JACC: ADVANCES VOL. 3, NO. 9, 2024

STATE-OF-THE-ART REVIEW

From Hospital to Home

Evidence-Based Care for Worsening Heart Failure

Suzanne Oskouie, MD,[a] Ambarish Pandey, MD, MSCS,[b] Andrew J. Sauer, MD,[c] Stephen J. Greene, MD,[d] Wilfried Mullens, MD, PhD,[e] Muhammad Shahzeb Khan, MD, MSc,[d] Kieran L. Quinn, MD, PhD,[f,g,h] Jennifer E. Ho, MD,[i] Nancy M. Albert, PhD,[j] Harriette GC. Van Spall, MD, MPH[k,l,m,n]

ABSTRACT

Heart failure (HF) is a leading cause of hospitalization in older adults. Patients are at high risk of readmission and death following hospitalization for HF. There is no standard approach of health care delivery during the hospital-to-home transition period, leaving missed opportunities in care optimization. In this review, we discuss contemporary randomized clinical trials that tested decongestion strategies, disease-modifying therapies, and health care services that inform the care of patients with worsening HF. We provide evidence-informed recommendations for optimizing therapies and improving outcomes during and following hospitalization for HF. These include adequate decongestion with loop diuretics and select sequential nephron blockade strategies based on early evaluation of diuretic response; initiation of disease-modifying pharmacotherapies prior to hospital discharge with close follow-up and optimization after discharge; cardiac rehabilitation; and transitional or palliative care referral post-hospitalization. Evidence-based implementation strategies to facilitate broad uptake include digital health tools and algorithm-driven optimization of pharmacotherapies. (JACC Adv 2024;3:101131) © 2024 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/).

Approximately 56 million people live with left-sided heart failure (HF) worldwide. Most of these individuals are older adults, and half are women.[1] HF continues to grow in prevalence and carries a significant health burden as one of the leading causes for hospitalization in adults 65 years of age or older. It is estimated that patients hospitalized for HF face an in-hospital mortality risk of 2 to 17%.[2] Following hospitalization for heart failure (HHF), patients face a 90-day and 1-year mortality risk of 10% and 28%, respectively.[2,3] Readmissions are common, estimated at 25% at 30 days and 36% at 90 days[2,3] (**Figure 1**). While approximately half of all readmissions following HHF are for worsening HF,[4] the proportion of readmissions for causes other than HF increases with increasing left ventricular

From the [a]Division of Cardiology, University of Arizona Sarver Heart Center, Tucson, Arizona, USA; [b]Division of Cardiology, UT Southwestern Medical Center, Dallas, Texas, USA; [c]Department of Cardiology, Saint Luke's Mid America Heart Institute, Kansas City, Missouri, USA; [d]Division of Cardiology, Duke University School of Medicine, Durham, North Carolina, USA; [e]Department of Cardiology, Ziekenhuis Oost-Limburg, Genk, Belgium; [f]Department of Medicine, Sinai Health System, University of Toronto, Toronto, Ontario, Canada; [g]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada; [h]Tammy Latner Centre for Palliative Care, Toronto, Ontario, Canada; [i]Division of Cardiology, Department of Medicine, Cardiovascular Institute, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA; [j]Research and Innovation- Nursing Institute and Kaufman Center for Heart Failure- Heart Vascular and Thoracic Institute, Cleveland Clinic, Cleveland, Ohio, USA; [k]Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada; [l]Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada; [m]Baim Institute for Clinical Research, Boston, Massachusetts, USA; and the [n]Research Institute of St. Joseph's Hospital Hamilton, Ontario, Canada.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received February 26, 2024; revised manuscript received May 2, 2024, accepted June 10, 2024.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2024.101131

ABBREVIATIONS AND ACRONYMS

eGFR = estimated glomerular filtration rate

GDMT = guideline-directed medical therapy

HF = heart failure

HFmrEF = heart failure with mid-range ejection fraction

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

HHF = hospitalization for heart failure

LVEF = left ventricular ejection fraction

RAASi = renin-angiotensin-aldosterone inhibitor

RCT = randomized controlled trial

ejection fraction (LVEF). The burden of HHF is not well characterized in low- and middle-income countries, where most people with HF live and where there has been an increase in age-standardized HF rates over the last 30 years.[1]

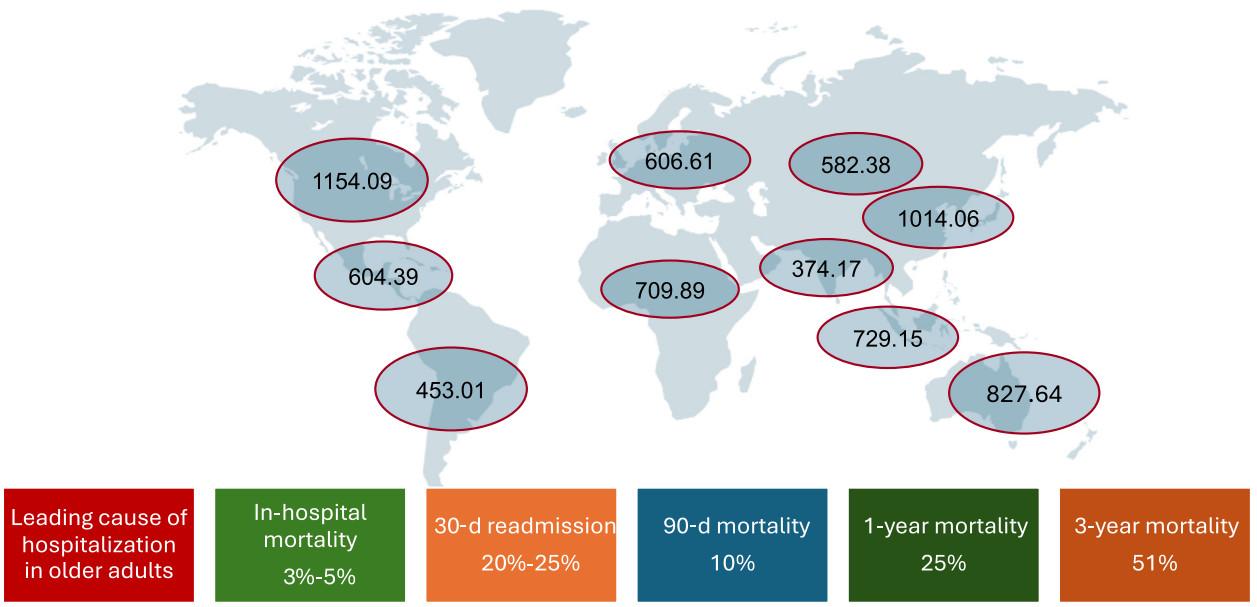
Hospitalization represents an opportunity to address the underlying causes of HF (Table 1),[5] relieve congestion, optimize medical therapies, facilitate recovery and rehabilitation, manage comorbidities, and tailor health care services to disease trajectory. It is also an opportunity to address the socioeconomic determinants of health.[6] Successful discharge planning involves care continuity to optimize therapies and support the patient's health care needs. In this review, we discuss evidence-based interventions to improve care and outcomes among those hospitalized for worsening HF.

HIGHLIGHTS

- Worsening heart failure requiring hospitalization portends high risk.
- Goals of hospitalization should include timely decongestion and safe initiation of disease-modifying therapies.
- Several strategies can be adopted to optimize tolerability of disease-modifying therapies.
- Select device therapies improve outcomes in severely symptomatic heart failure.
- Health services such as cardiac rehabilitation, transitional care, and palliative care can improve how patients function and feel.

THERAPIES FOR DECONGESTION. Prompt recognition of clinical congestion in worsening HF (Table 2) and complete decongestion should be priorities during hospitalization. Residual congestion at discharge is associated with an increased risk of readmission and death.[5] As HF advances, patients may develop resistance to loop diuretics, requiring high-dose intravenous (IV) boluses, infusions, or a combination of different diuretics. Diuretic intensification with an IV formulation that is 2.5 times the equivalent oral dose is associated with improved net diuresis and symptom relief,[8,9] but diuretic responsiveness may vary. Spot urine sodium levels less than 50 to 70 mmol/L 2 hours following IV diuretics may

FIGURE 1 Global Burden of Heart Failure



Regions circled in red represent prevalence estimates per 100,000 based on 2019 Global Burden of Disease Data. Not all 21 regions depicted. Data for mortality and readmission are from sources of international epidemiologic and clinical trials.[1-4] HF = heart failure; HHF = hospitalization for heart failure.

TABLE 1 Causes of Worsening Heart Failure

Acute
Medication nonadherence
Cardiac conditions
• Arrhythmia
• Uncontrolled hypertension
• Myocardial ischemia or infarction
• Mechanical complications of myocardial infarction
• Myocarditis
• Valvular dysfunction
Noncardiac conditions
• High output states
• Acute kidney injury
Insidious
• Worsening kidney disease
• Underlying disease progression
• Underuse of disease-modifying therapy
• Underdosing of diuretics

TABLE 2 Parameters of Congestion in HF

Symptoms
• Orthopnea
• Resting dyspnea
• Dyspnea on exertion
Physical exam
• Jugular vein distension
• Hepatojugular reflux
• Pulmonary rales
• S3
• Peripheral edema
• Hepatomegaly
Labs
• Increasing trend in NT-proBNP level
• Spot urine Na <70 mmol/L
Imaging
• Ultrasound with IVC >2.2 cm with <50% collapsibility
• >15 B-lines on lung imaging when scanning 28 sites
• Chest x-ray with interstitial or alveolar edema
Invasive
• PCWP >12 mm Hg
• CVP >5 mm Hg

Adapted with permission from ref.[7] Eur J Heart Fail.

CVP = central venous pressure; HF = heart failure; IVC = inferior vena cava; JVP = jugular venous pressure; Na = sodium; NT-proBNP = N-terminal pro-brain natriuretic peptide; PCWP = pulmonary capillary wedge pressure.

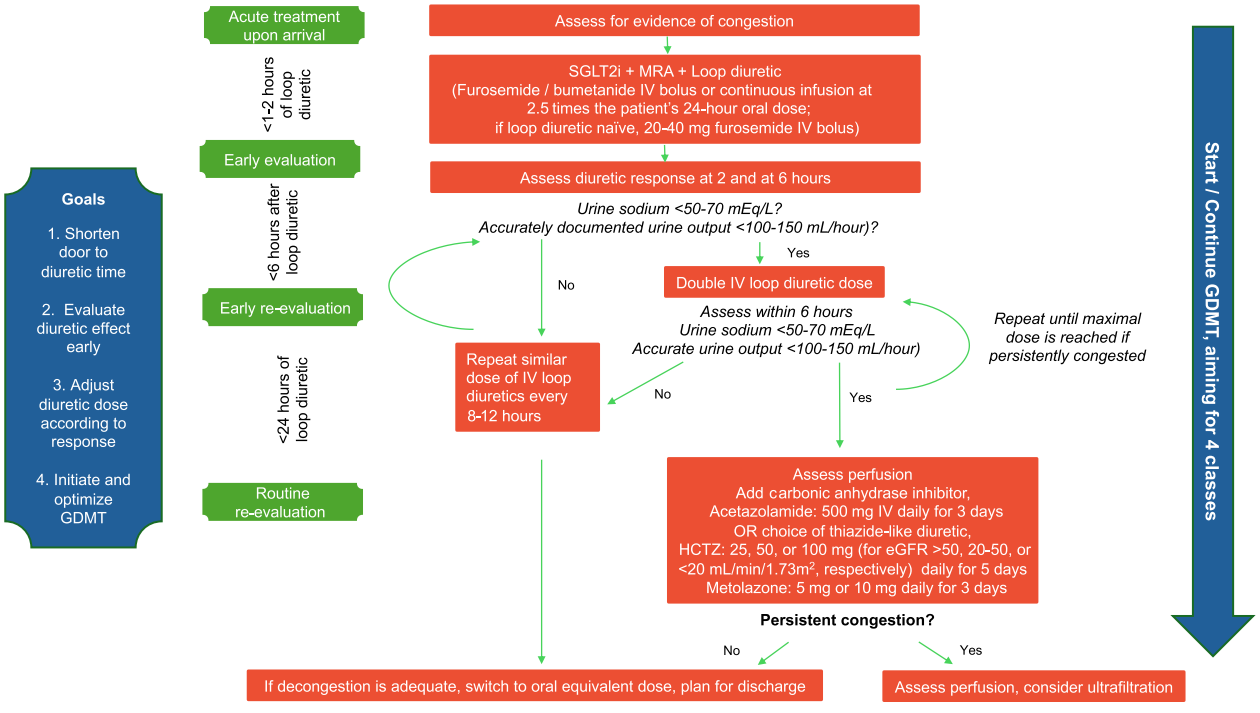
indicate inadequate natriuresis or diuretic resistance, suggesting a need to increase the diuretic dose.[10] A natriuresis-guided diuretic strategy in the PUSH-AHF (Pragmatic Urinary Sodium-based algoritHm in Acute Heart Failure) randomized controlled trial (RCT) improved mean 24-hour urine sodium excretion compared with standard of care without increased adverse effects.[11] Hemoconcentration can be another sign of diuretic effect, although it is not a target for decongestion. While associated with worsening kidney function, hemoconcentration is associated with a lower risk of mortality at 180 days.[12]

Loop diuretics are the mainstay of decongestion therapy. They should be titrated to the degree of congestion and maintained at the lowest effective dose required to achieve euvolemia quickly while avoiding volume depletion or metabolic derangements.[7] Among loop diuretics, the TRANSFORM-HF (ToRsemide compArisoN With furoSemide FOR Management of Heart Failure) RCT tested a strategy of torsemide vs oral furosemide for decongestion among hospitalized patients at a frequency and dosage determined by the treating clinician.[13] There was no difference in the primary outcome of mortality across LVEF categories in patients recently facing HHF after a median of 17.4 months follow up; the effect of torsemide on decongestion parameters was not evaluated.[13] Either loop diuretic remains a viable option for patients at risk for congestion following discharge.

Sequential nephron blockade, with diuretics targeting the proximal and distal parts of the nephron in addition to loop diuretics that target the loop of Henle, can improve decongestion during hospitalization (**Figure 2**). In the CLOROTIC (Safety and Efficacy of the Combination of Loop with Thiazide-Type Diuretics in Patients with Decompensated Heart Failure) RCT, oral hydrochlorothiazide added to IV furosemide among patients on high loop diuretic doses and evidence of diuretic resistance increased weight loss within 72 hours post randomization[14] (**Table 3**), relative to IV furosemide alone; however, it did not improve patient-reported dyspnea or post-discharge clinical events and was associated with worsening kidney function. Thiazide diuretics are also associated with hypokalemia and hyponatremia and should be used cautiously.[7]

In another evaluation of sequential nephron blockade, the addition of the carbonic anhydrase inhibitor acetazolamide at a dose of 500 mg IV achieved greater clinical decongestion than IV loop diuretic alone within 3 days in patients who were on <80 mg IV daily furosemide in the ADVOR (Acetazolamide in Decompensated Heart Failure with Volume Overload) RCT (**Table 3**); this was also associated with a reduced length of stay without increased risks.[15] However, adding IV acetazolamide did not improve patient-reported or clinical outcomes. The study did not include patients on high-dose loop diuretics or on sodium-glucose cotransporter 2 inhibitors (SGLT2is), limiting inferences in patients with resistance to high-dose loop diuretics.

FIGURE 2 Strategies to Effectively Decongest Patients Hospitalized for Worsening Heart Failure



Inpatient decongestion should begin with intravenous loop diuretic therapy starting early in admission. In absence of adequate natriuresis and diuresis within 6 hours, the loop diuretic dose can be increased, and add-on diuretic therapy can be added. This should be pursued until the patient is dry. Initiation and optimization of GDMT should occur in parallel, as additionally outlined in **Figure 2**. Adapted and modified with permission from Mullens et al.[7] eGFR = estimated glomerular filtration rate; GDMT = guideline-directed medical therapy; HCTZ = hydrochlorothiazide; IV = intravenous; MRA = mineralocorticoid receptor antagonist; RCT = randomized controlled trial; SGLT2i = sodium-glucose transport inhibitors; UOP = urine output.

SGLT2is represent another sequential nephron blockade strategy and are a safe early addition to loop diuretic therapy. Once daily empagliflozin not only improved clinical outcomes, but was also associated with better decongestion after 15, 30, and 90 days of treatment compared to placebo in the EMPULSE (EMPagliflozin for Patients Hospitalized with acUte Heart faiLure Who Have been StabilizEd) RCT[21] (**Table 3**). In a randomized comparison of dapagliflozin compared to metolazone (a thiazide), dapagliflozin did not improve decongestion but had a better safety profile than metolazone, which was associated with worsening kidney function.[17]

Other approaches such as low-dose dopamine or low-dose nesiritide demonstrated no improvement in kidney function or decongestion in clinical trials[29] (**Table 3**). Similarly, the use of vasopressin antagonists,[22,23] early and aggressive vasodilatory therapy,[28] and ultrafiltration[27] demonstrated no reduction in all-cause mortality or HHF. Consideration of these therapies should prompt referral for advanced HF care, as the underlying hemodynamics—refractory congestion and/or hypoperfusion—are indicators of advanced disease. Additional indicators of advanced HF include recurrent episodes of worsening HF, defibrillator shocks, persistent hyponatremia, progressive deterioration in kidney function, and intolerance to disease-modifying therapies.[5,30]

There is no clear evidence to support pulmonary artery (PA) catheter-guided decongestion in patients hospitalized for HF. In the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) RCT, addition of a PA catheter (targeting a pulmonary capillary wedge pressure of 15 mm Hg and a right atrial pressure of 8 mm Hg) to clinical assessment did not reduce the primary outcome of days alive and out of the hospital compared to clinical assessment alone after 6 months of follow-up.[31] There were more in-hospital adverse events in the PA catheter vs comparator group. The trial was unblinded and did not include patients on inotropes, although all patients had high diuretic requirements. Given the lack of RCT data to support its use in patients hospitalized for HF, hemodynamic

TABLE 3 Randomized Controlled Trials of Diuretic Therapy in Patients Hospitalized for HF

Trial Name No. Randomized (% Female) Intervention	Primary Outcome(s) and Effect Estimate(s) (95% CI Unless Otherwise Specified)	Method to Assess Decongestion (If Defined)	Safety Endpoint Estimate(s) (95% CI Unless Otherwise Specified) or Clinically Significant Adverse Events
Diuretic/aquaretic trials			
ADVOR[15] 519 (37%) IV Acetazolamide 500 mg once daily vs placebo for 3 days	Successful decongestion within 3 days of randomization without an indication for escalation of decongestive therapy RR: 1.46 (1.17-1.82), $P < 0.001$.	Clinical assessment of volume overload within 3 days after randomization using the congestion score without indication for escalation in therapy.	Combined renal safety (doubling of sCr, a decrease of ≥50% in eGFR, or renal-replacement therapy) 2.7% (acetazolamide) vs 0.8% (placebo), $P = 0.10$. Severe metabolic acidosis 0 patients Hypokalemia ($K^+ < 3$ mmol/L) 5.5% (acetazolamide) vs 3.9% (placebo), $P = 0.39$ Hypotension (systolic BP < 85 mm Hg) 6.6% (acetazolamide) vs 3.5% (placebo), $P = 0.11$
ATHENA-HF[16] 360 (36%) High-dose spironolactone (100 mg) vs placebo or 25 mg spironolactone (usual care) daily for 96 hours	Change in log NT-proBNP levels from baseline to 96 hours −0.55 (−0.92 to −0.18) (high-dose spironolactone) vs −0.49 (−0.98 to −0.14) (usual care), $P = 0.57$	Clinical congestion score, calculated by finding the sum of the individual scores for orthopnea, jugular venous distension, and pedal edema on a standardized 4-point scale ranging from 0 to 3.	Hyperkalemia (K^+>5.5 mmol/L) 0 patients (high dose spironolactone) vs 1 patient (usual care) Renal function change (sCr increase by 0.3 mg/dL) 28% (high-dose spironolactone) and 32% (usual care), $P = 0.42$
CLOROTIC[14] 230 (48%) HCTZ 25 mg (eGFR> 50 mL/min); 50 mg (eGFR 20-50 mL/min); 100 mg (eGFR <20 mL/min) daily for 5 days vs placebo	Adjusted change in body weight (kg) from baseline to 72 hours of randomization −2.3 kg (HCTZ) vs −1.5 kg (placebo), Adjusted mean difference: −1.14 (−1.84 to −0.42), $P = 0.002$. Change in patient-reported dyspnea from baseline to 72 hours of randomization using the VAS. Mean AUC: 960 (HCTZ) vs 720 (placebo), $P = 0.50$.	Clinical assessment of rales, edema, pleural effusion, and ascites at 72 hours and 96 hours.	Impaired renal function (increase in serum Cr > 26.5 μmol/L or decrease in eGFR >50%) 46.5% vs 17.2%, $P < 0.001$ Hypokalemia (K ≤ 2.5 mmol/L) 1.8% (HCTZ) vs 0 (placebo), $P = 0.245$ Hyponatremia (Na ≤125 mmol/L) 2.6% (HCTZ) vs 1.7% (placebo), $P = 0.682$
DAPA-RESIST[17] 61 (54%) Dapagliflozin 10 mg vs metolazone 5-10 mg daily for 3 days on background of requiring IV loop diuretics	Mean change in weight at 96 hours 3.0 ± 2.5 kg (dapagliflozin) vs 3.6 ± 2.0 kg (metolazone), mean difference 0.65 (−0.12 to 1.41), $P = 0.11$	Clinical assessment of volume overload within 3 days after randomization using the congestion score without indication for escalation in therapy.	Increase in sCr >0.3 mg/dL from baseline at 96 hours 32.5% (dapagliflozin) vs 29.7% (metolazone), $P < 0.01$ Hypokalemia (≤3.5 mmol/L) 50% (dapagliflozin) vs 63% (metolazone), $P = 0.44$ Hyperkalemia (≥5.5 mmol/L) 3% (dapagliflozin) vs 0 (metolaone), $P = 1.00$
DIURESIS-CHF[18] 34 (35%) Acetazolamide and low-dose loop diuretics vs high-dose loop diuretics Open-label oral spironolactone given upfront vs at discharge	Total natriuresis after 24 hours 264 ± 126 mmol (combinational therapy) vs 234 ± 133 mmol (loop diuretic monotherapy), $P = 0.515$ 314 ± 142 mmol (upfront spironolactone) vs 200 ± 91 mmol (delayed spironolactone), $P = 0.010$	Presence of ≥2 clinical signs of congestion (edema, ascites, jugular venous distension, or pulmonary congestion).	Increase in sCr by >0.3 mg/dL within 72 hours 28% (combinational treatment) vs 0 (high-dose loop diuretic), $P = 0.046$ Hyperkalemia: 6% (upfront) vs 11% (at discharge); Hypokalemia: 13% (upfront) vs 28% (at discharge) $P = 0.270$
DOSE[8] 308 (27%) Intravenous furosemide bolus every 12 hours vs continuous furosemide infusion Low intensification to equivalent of patient's daily oral diuretic dose vs high intensification to 2.5 times daily oral dose	Patient global assessment by VAS over 72 hours mean AUC, 4,236 ± 1,440 (furosemide bolus) and 4,373 ± 1,404 (continuous infusion), $P = 0.47$ mean AUC, 4,430 ± 1,401 (high-intensification) vs 4,171 ± 1,436 (low-intensification), $P = 0.06$	Jugular venous pressure of <8 cm of water, with no orthopnea and with trace peripheral edema or no edema.	Change in sCr from baseline to 72 hours (coprimary endpoint) 0.05 ± 0.3 mg per deciliter (furosemide bolus) and 0.07 ± 0.3 mg per deciliter (continuous infusion), $P = 0.45$ 0.08 ± 0.3 mg per deciliter (high-intensification) vs 0.04 ± 0.3 mg per deciliter (low-intensification), $P = 0.21$
EMPAG-HF[19] 60 (38%) Empagliflozin 25 mg daily vs placebo for 5 days	Cumulative urine output over 5 days Group difference estimation: 2,125 mL (840-3,550), $P = 0.003$ (higher urine output in the empagliflozin group)	-	Increase in sCr by >0.3 mg/dL 11.5% (empagliflozin) vs 32.1% (placebo) Urinary tract infection 3.3% (empagliflozin) vs 13.8% (placebo) Worsening heart failure 3.3% empagliflozin vs 13.8% (placebo) Worsening liver function 0 patients Stroke or transient ischemic attack 11.1% (empagliflozin) vs 0 (placebo) 30-day mortality 3.3% (empagliflozin) or 6.9% (placebo) None statistically significant

Continued on the next page

TABLE 3 Continued

Trial Name No. Randomized (% Female) Intervention	Primary Outcome(s) and Effect Estimate(s) (95% CI Unless Otherwise Specified)	Method to Assess Decongestion (If Defined)	Safety Endpoint Estimate(s) (95% CI Unless Otherwise Specified) or Clinically Significant Adverse Events
EMPA-RESPONSE-AHF[20] 80 (33%) Empagliflozin 10 mg/day vs placebo for 30 days	[a]Change in VAS dyspnea score Mean difference (80% CI): 0.31 (0.01-0.61), $P = 0.18$ [a]Diuretic response (weight change per 40 mg of furosemide) Mean difference (80% CI): −0.21 (−0.51 to 0.09), $P = 0.37$ [a]Percentage change in NT-proBNP Mean difference (80% CI): 0.12 (−0.18 to 0.42), $P = 0.63$ [a]Length of stay Mean difference (80% CI): −0.12, (−0.43 to 0.19) placebo group, $P = 0.58$	Presence of edema, rales, and/or congestion on chest radiograph	Adverse events leading to treatment discontinuation 7 patients (empagliflozin) vs 5 patients (placebo), $P = 0.36$ Serious adverse events 8 patients (empagliflozin) vs 11 patients (placebo), $P = 0.54$ Adverse events of special interest (hepatic injury, worsening renal function, metabolic acidosis, ketoacidosis, diabetic ketoacidosis) 4 patients (empagliflozin) vs 4 patients (placebo), $P = 0.29$
EMPULSE[21] 530 (34%) Empagliflozin 10 mg once daily vs placebo	Hierarchical composite of all-cause death, number of HF events, time to first heart failure event, or >5-point difference in change from baseline to 90-day Kansas City Cardiomyopathy Questionnaire Total Symptom Score Win ratio 1.36 (1.09-1.68), $P = 0.0054$	Weight loss at 15, 30, and 90 days Adjusted mean differences: −1.97 (−2.86 to −1.08) at 15 days −1.74 (−2.73 to −0.74) at 30 days −1.53 (−2.75 to −0.31) kg at 90 days Weight loss adjusted/40 mg IV furosemide or equivalent Adjusted mean difference: −2.31 (−3.77 to −0.85) at 15 d, −2.79 (−5.03 to −0.54) at 30 d, −3.18 (−6.08 to −0.28) at 90 days (all $P < 0.05$). The area under the curve (AUC) of change from baseline in log-transformed in N-terminal pro-B-type natriuretic peptide levels (over 30 days of treatment) Mean ratio: 0.90 (0.82-0.98), $P = 0.018$ Clinical congestion score Adjusted mean difference: −0.34 (−0.60 to −0.09), $P < 0.01$ at day 15 −0.23 (−0.47-0.02), $P = 0.067$ at day 90 Hemoconcentration (measured as changes in hematocrit) Adjusted mean difference: 1.71 (1.02-2.4) at 15 days 1.62 (0.88-2.35) at 30 days 1.94 (1.11-2.76) at 90 days All $P < 0.0001$	Any adverse event 70.0% (empagliflozin) vs 77.3% (placebo) Severe adverse events 15.0% (empagliflozin) vs 20.5% (placebo)
EVEREST[22] 4,133 (26%) Oral tolvaptan, 30 mg once daily for 60 days vs placebo	All-cause mortality HR: 0.98 (0.87-1.11), $P = 0.68$ Cardiovascular death or hospitalization for heart failure HR: 1.04 (0.95-1.14), $P = 0.55$	-	Adverse events requiring study drug discontinuation 6.5% (tolvaptan) vs 5.5% (placebo) driven primarily by thirst 7 patients(tolvaptan) vs 0 patients (placebo), $P = 0.02$ No other statistically significant differences.
PUSH-AHF[11] 310 (61%) Natriuresis-guided diuretic therapy based on urine sodium measurements vs usual care	Natriuresis at 24 hours Mean difference: 63 (18-109), $P = 0.0061$ Combined HHF or all-cause mortality HR 0.92 (0.62-1.38), $P = 0.698$	-	Doubling of sCr at 24 hours 0% (natriuresis-guided) vs 1% (usual care) Doubling of sCr at 48 hours 1% (natriuresis-guided) vs 2% (usual care) Worsening HF 9% (natriuresis-guided) vs 15% (usual care) No statistically significant differences.
SECRET of CHF[23] 250 (33%) Oral tolvaptan, 30 mg once daily for 3 days vs placebo	Change in self-assessed dyspnea at 8 and 16 hours by a 7-point Likert scale $P = 0.46$ and $P = 0.78$, respectively.	≥2 of the following: jugular venous distension, pitting edema, ascites, pulmonary congestion on chest x-ray and/or rales	No difference in clinically significant adverse events.
TACTICS-HF[24] 257 (34%) Tolvaptan 30 mg at 0, 24, ad 48 hours vs placebo	Proportion of patients defined as responders at 24 hours RR: 0.8 (95% CI not reported), $P = 0.32$	Clinical assessment of jugular venous pressure <8 cm water, no orthopnea, and trace peripheral edema or less	Worsening heart failure 23% (tolvaptan) vs 30% (placebo), $P = 0.21$ No change in duration of hospitalization, rehospitalization, or all cause death at 30 days
TRANSFORM-HF[13] 2,859 (37%) Torsemide or furosemide with investigator-selected dosage	All-cause mortality HR: 1.02 (0.89-1.18)	-	-

Continued on the next page

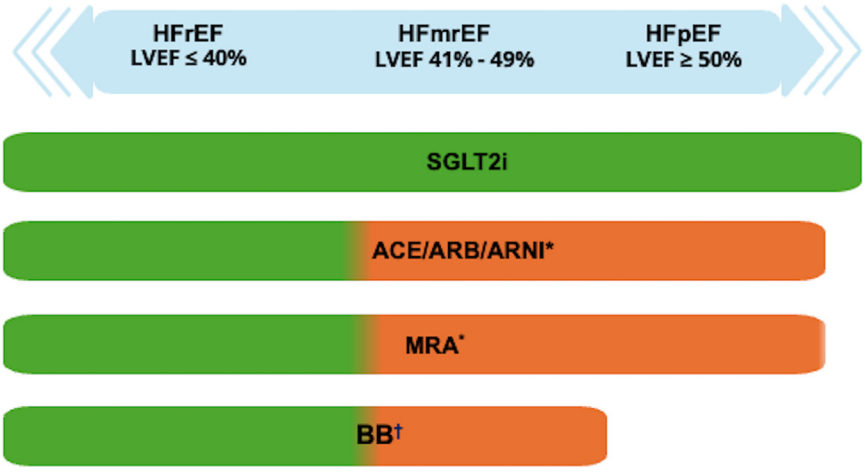
TABLE 3 Continued

Trial Name No. Randomized (% Female) Intervention	Primary Outcome(s) and Effect Estimate(s) (95% CI Unless Otherwise Specified)	Method to Assess Decongestion (If Defined)	Safety Endpoint Estimate(s) (95% CI Unless Otherwise Specified) or Clinically Significant Adverse Events
Ultrafiltration trials			
AVOID-HF[25] 224 (29%) Aquadex FlexFlow System; adjustments per protocol guidelines on the basis of vital signs and kidney function until decongestion achieved vs loop diuretics with adjustments per protocol guidelines on the basis of vital signs and kidney function	HF event within 90 days of hospital discharge HR: 0.66 (0.4-1.1)	Jugular venous pressure <8 cm H_2O, absence of dyspnea, and trace or no peripheral edema	Change in BUN, sCr, BUN/SCr, eGFR at 90 days −0.30 ± 0.42 (−0.60 to 0.00) (ultrafiltration) vs −0.26 ± 0.30 (−0.70 to 0.10) (loop diuretics), $P = 0.829$
CARRESS-HF[26] 188 (28%) Aquadex System 100 at a fixed rate of 200 ml/hour until decongestion achieved vs stepped pharmacologic therapy with diuretic agents dosed to maintain urine output 3-5 l/day	Change in sCr at 96 hours after randomization 0.23 ± 0.70 mg/dl (ultrafiltration) vs −0.04 ± 0.53 mg/dl (stepped pharmacologic therapy), $P = 0.003$ Change in weight at 96 hours after randomization 5.7 ± 3.9 kg (ultrafiltration) vs 5.5 ± 5.1 kg (stepped pharmacologic therapy), $P = 0.58$	Jugular venous pressure <8 cm H_2O, no more than trace peripheral edema, and the absence of orthopnea	Serious adverse events over 60 days of follow-up: 72% (ultrafiltration) vs 57% (pharmacologic therapy), $P = 0.03$ Driven by higher incidences of kidney failure, bleeding complications, and intravenous catheter-related complications
UNLOAD[27] 200 (31%) Aquadex System 100 with duration and rate determined by the treating physician vs IV diuretics	Weight loss at 48 hours after randomization 5.0 ± 3.1 kg (ultrafiltration) vs 3.1 ± 3.5 kg (standard care), $P = 0.001$ Dyspnea assessment at 48 hours after randomization 5.4 ± 1.1 (ultrafiltration) vs 5.2 ± 1.2 (standard care), $P = 0.5881$ Higher dyspnea score signifies worse symptoms	-	Increase in sCr by >0.3 mg/dL 14.4% (ultrafiltration) vs 7.7% (IV diuretics), $P = 0.528$ Change in electrolytes 1% (ultrafiltration) vs 12% (IV diuretics), $P = 0.018$ Driven by hypokalemia (K^+<3.5 meq/L) Episodes of hypotension 4% (ultrafiltration) vs 3% (IV diuretics), *P* value not provided
Vasodilation trials			
GALACTIC[28] 788 (37%) Early intensive and sustained vasodilation combining individualized doses of sublingual and transdermal nitrates, low-dose oral hydralazine for 48 hours, and rapid uptitration of ACEI, ARB, or ARNI vs usual care	Composite of all-cause mortality or rehospitalization for AHF at 180 days HR: 1.07 (0.83-1.39), $P = 0.59$	-	No difference in clinically significant adverse events
ROSE[29] 360 (27%) Low dose dopamine 2 μg/kg/min or low-dose nesiritide 0.005 mcg/kg/min without bolus vs placebo with standard background therapy	Cumulative urinary volume at 72 hours Treatment difference: 229 (−714 to 1,171), $P = 0.59$ (dopamine strategy) Treatment difference 279 (−618 to 1,176), $P = 0.49$ (nesiritide strategy) Change in cystatin-C at 72 hours Treatment difference: 0.01 (−0.08 to 0.10), $P = 0.72$ (dopamine strategy) Treatment difference: −0.04 (−0.13 to 0.05), $P = 0.36$ (nesiritide strategy)	Decongestion endpoints are defined as cumulative urine sodium excretion, weight change, change in NT-proBNP from randomization to 72 hours.	Increase in sCr >0.3 mg/dL 0 (−0.7 to 0.08) (dopamine) vs 0.02 (−0.4-0.08) (placebo), $P = 0.78$ 0.02 (−0.06 to 0.09) (nesiritide) vs 0.02 (−0.4 to 0.08) (placebo), $P = 0.90$ Worsening or persistent heart failure 9% (dopamine) vs 4% (placebo), $P = 0.14$ 5% (nesiritide) vs 4% (placebo), $P = 0.77$ Significant hypotension requiring discontinuation 0.9% (dopamine) vs 10.4% (placebo), $P < 0.001$ 18.8% (nesiritide) vs 10.4% (placebo), $P<0.07$%

[a]Not adjusted for multiple testing.

ACEI = angiotensin-converting enzyme inhibitor; ADVOR = Acetazolamide in Decompensated Heart Failure with Volume Overload; AHF = acute heart failure; ARB = angiotensin receptor blockers; ARNI = angiotensin-receptor neprilysin inhibitors; ATHENA-HF = Aldosterone Targeted NeuroHormonal Combined With Natriuresis Therapy -Heart Failure; AVOID-HF = Aquapheresis versus Intravenous Diuretics and Hospitalization for Heart Failure; AUC = area under the curve; CARRESS-HF = Cardiorenal Rescue Study in Acute Decompensated Heart Failure; CLOROTIC = Safety and Efficacy of the Combination of Loop with Thiazide-Type Diuretics in Patients with Decompensated Heart Failure; DAPA-RESIST = DAPAgliflozin Versus Thiazide Diuretic in Heart Failure in Patients with Heart Failure and Diuretic RESISTance; DIURESIS-CHF = Acetazolamide and Spironolactone to Increase Natriuresis in Congestive Heart Failure; DOSE = Diuretic Optimization Strategies Evaluation; eGFR = estimated glomerular filtration rate; EMPAG-HF = Effects of Early Empagliflozin Initiation on Diuresis and Kidney Function in Patients With Acute Decompensated Heart Failure; EMPA-RESPONSE-AHF = Randomized, double-blind, placebo-controlled, multicenter pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure; EMPULSE = A Multicenter, Randomized, Double-blind, 90-day Superiority Trial to Evaluate the Effect on Clinical Benefit, Safety and Tolerability of Once Daily Oral EMPagliflozin 10 mg Compared to Placebo, Initiated in Patients Hospitalized for acUte Heart faiLure (de Novo or Decompensated Chronic HF) Who Have Been StabilisEd; EVEREST = The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study; GALACTIC = Goal-Directed Afterload Reduction in Acute Congestive Cardiac Decompensation; HCTZ = hydrochlorothiazide; HF = heart failure; HHF = hospitalization for heart failure; IV = intravenous; NT-proBNP = N-terminal pro B-type natriuretic peptide; PUSH-AHF = Pragmatic Urinary Sodium-based treatment algoritHm in Acute Heart Failure; ROSE = Renal Optimization Strategies Evaluation in Acute Heart Failure; RR = relative risk; sCr = serum creatinine; SECRET of CHF = Study to Evaluate Challenging Responses to Therapy in Congestive Heart Failure; SGLT2i = sodium-glucose transporter-2 inhibitor; TACTICS-HF = Targeting Acute Congestion with Tolvaptan in Congestive Heart Failure; TRANSFORM-HF = ToRsemide compArisoN With furoSemide FOR Management of Heart Failure; UNLOAD = Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure; VAS = visual analog scale.

FIGURE 3 Recommendation for GDMT Initiation in Patients With HF



The SGLT2i has a Class I level of recommendation in the 2023 focused update of the 2021 European Society of Cardiology guidelines[34] in HFmrEF and HFpEF, though it holds a Class IIa level of recommendation for these conditions in the 2022 American College of Cardiology/American Heart Association/Heart Failure Society of America guidelines.[5] The evidence supporting the use of ACEI/ARB/ARNI and MRA is modest for HFpEF, with a reduction in HF hospitalizations.[35] There is no evidence to support the use of beta blockers in HFpEF,[35] and use should be limited unless other indications are present. Color legend: green = class of recommendation 1; orange = class of recommendation 2b. *Preferred as a first-line anti-hypertensive in HFmrEF and HFpEF. †In HFpEF, indications for beta blockers should be balanced against risk of chronotropic incompetence. ACEI = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; ARNI = angiotensin receptor-neprilysin inhibitors; BB = beta-blockers; COR = class of recommendation; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonists; RAASi = renin-angiotensin aldosterone inhibitors; SGLT2i = sodium-glucose transport inhibitors.

monitoring with a PA catheter has a class IIa recommendation with level C evidence in the American College of Cardiology/American Heart Association/Heart Failure Society of America guidelines[5] (Supplemental Table 1). Invasive hemodynamic monitoring may be useful in patients undergoing evaluation for mechanical circulatory support or transplant.[32,33]

DISEASE-MODIFYING THERAPIES. Decades of research inform our current guideline recommendations for instituting the four "pillars," or classes, of disease-modifying therapies in HFrEF, defined as HF with LVEF ≤40%. These guideline-directed medical therapy (GDMT) include: 1) beta-blockers (BB); 2) angiotensin receptor-neprilysin inhibitors (ARNI) or RAASi including angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blocker (ARB); 3) mineralocorticoid receptor antagonists (MRA); and 4) SGLT2i (Figure 3). In RCTs, these GDMT reduced all-cause death or the composite of cardiovascular (CV) death or HHF, largely in ambulatory patients, although consistent benefits across a range of endpoints have been demonstrated in patients hospitalized for HF (Table 4).[35] SGLT2i additionally has definitive evidence of a reduction in composite CV death or HHF in HFmrEF (LVEF 41-49%) and HFpEF (LVEF ≥50%),[42,43] driven primarily by a reduction in HHF as LVEF increases. No class of medication in any individual trial has reduced CV or all-cause death in HFpEF, likely due to an increased burden of noncardiac comorbidities and phenotypic heterogeneity in patients with higher LVEF.

The efficacy and safety of the four pillars of GDMT have largely been demonstrated in ambulatory HF,[5,35] but there is growing evidence to support the benefit of in-hospital initiation in worsening HF. The safety of continuing BB during hospitalization in HFrEF was demonstrated in a meta-analysis of five observational studies and one RCT in which cessation of BB was associated with an increase in in-hospital mortality, short-term mortality, and combined mortality and hospitalization.[44] The RALES (Randomized Aldactone Evaluation Study) RCT that demonstrated a reduction in all-cause mortality with spironolactone vs placebo in HFrEF included patients with NYHA functional class IV symptoms (Table 4).[45] In PIONEER-HF (comParIson of sacubitril-valsartaN vs Enalapril on Effect

TABLE 4 Select RCTs That Demonstrated Efficacy of GDMT in Patients With Worsening HF

Trial Name No. of Randomized (% Female)	Inclusion Criteria	Primary Outcome(s) and Effect Estimate(s) (95% CI Unless Otherwise Specified)	Safety Endpoint Estimate(s) (95% CI Unless Otherwise Specified) or Clinically Significant Adverse Events
ARNI			
PIONEER-HF[36] 881 (28%) Sacubitril-valsartan 97-103 mg twice a day vs enalapril 10 mg twice a day	Patients hospitalized for AHF	Time-averaged proportional change in the NT-proBNP concentration from baseline through weeks 4 and 8 Ratio of change: 0.76 (0.69-0.85)	Worsening renal function (an increase in the serum creatinine concentration of ≥0.5 mg per deciliter and a decrease in the estimated glomerular filtration rate of ≥25%) 2 patients (sacubitril-valsartan) vs 1 patient (enalapril) and 1 patient vs 1 patient, respectively Hyperkalemia 2 patients (sacubitril-valsartan) vs 4 patients (enalapril) Symptomatic hypotension 11 patients vs 11 patients Angioedema 0 patients (sacubitril-valsartan) vs 6 patients (enalapril)
PARAGLIDE-HF[37] 466 (52%) Sacubitril-valsartan titrated to a target of 97-103 mg twice a day vs Valsartan titrated to a target of 160 mg twice a day	Patients with a diagnosis of HF, LVEF >40%, elevated NT-proBNP during HHF or within 30 days of worsening HF event	Time-averaged proportional change in NT-proBNP from baseline to weeks 4 and 8 Ratio of change: 0.85 (0.73-0.999)	Symptomatic hypotension 20.9% (sacubitril-valsartan) vs 16.8% (valsartan), OR 1.31 (0.96-1.77), $P = 0.09$ Worsening renal function 20.9% (sacubitril-valsartan) vs 27.1% (valsartan), OR 0.71 (0.54-0.94), $P = 0.017$ Hyperkalemia 18.5% vs 18.1%, OR 1.03 (0.75-1.40), $P = 0.87$.
MRA			
RALES[14] 1,663 (27%) Spironolactone 25 mg daily vs placebo	NYHA III-IV HF and LVEF<35%	All-cause death RR: 0.70 (0.60-0.82)	Adverse events: Serious hyperkalemia 2% (spironolactone) vs 1% (placebo), $P = 0.042$ Gynecomastia in men 10% (spironolactone) vs 1% (placebo), $P < 0.001$.
SGLT2i			
SOLOIST-WHF[38] 1,222 (34%) Sotagliflozin 200 mg once daily with a dose increase to 400 mg as tolerated vs placebo	Patients with type 2 DM who were recently hospitalized for worsening HF	Total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure HR: 0.67 (0.52-0.85), $P < 0.001$	Adverse events of special interest: Diabetic ketoacidosis 0.3% (sotagliflozin) vs 0.7% (placebo) Severe hypoglycemia 1.5% (sotagliflozin) vs 0.3% (placebo) Bone fracture 2.0% (sotagliflozin) vs 1.5% (placebo) Adverse event leading to amputation 0.7% (sotagliflozin) vs 0.2% (placebo) None statistically significant
EMPULSE-HF[21,39] 530 (34%) Empagliflozin 10 mg once daily vs placebo	Patients hospitalized with acute de novo or decompensated chronic HF	Composite of death, number of heart failure events, time to first heart failure event, and change in KCCQ-TSS Win ratio: 1.36 (1.09-1.68)	Volume depletion 12.7% (empagliflozin) vs 10.2% (placebo) Symptomatic hypotension 1.2% (empagliflozin) vs 1.5% (placebo) Hypoglycemia 1.9% (empagliflozin) vs 1.5% (placebo)
Soluble Cyclic GMP Stimulator			
VICTORIA[40] 5,050 (24%) Vericiguat starting at 2.5 mg daily, increased to 5 mg daily, then 10 mg daily vs placebo	Patients who have NYHA II-IV HF with EF<45% with hospitalization for HF in the past year or intravenous diuretic use within the previous 3 months; elevated natriuretic peptide within 30 days before randomization	Composite of death from cardiovascular causes or first hospitalization for heart failure HR: 0.90 (0.82-0.98)	Symptomatic hypotension 9.1% (vericiguat) vs 7.9% (placebo), $P = 0.12$ Syncope 4.0% (vericiguat) vs 3.5% (placebo)
IV Iron			
AFFIRM-AHF[41] 3,065 (34%) IV ferric carboxymaltose 500 mg-2,000 mg vs placebo	Patients hospitalized for acute HF who were clinically stable with serum ferritin <100 ng/L or serum ferritin 100-299 ng/L and transferrin saturation <20%	Hierarchical composite of death after 12 months, hospitalizations for heart failure in 12 months, or change from baseline to 6 months in 6-minute walk test Unmatched win ratio: 1.10 (99% CI: 0.99-1.23)	Serious adverse events during treatment 27% (ferric carboxymaltose) vs 26.2% (placebo)

AFFIRM-AHF = Study to Compare Ferric Carboxymaltose with Placebo in Patients with Acute Heart Failure and Iron Deficiency; AHF = acute heart failure; ARB = angiotensin receptor blocker; ARNI = angiotensin-receptor neprilysin inhibitors; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; EMPULSE-HF = EMPagliflozin for Patients Hospitalized with acUte Heart failure Who Have been StabilizEd; GDMT = guideline-directed medical therapy; HF = heart failure; HR = hazard ratio; IV = intravenous; KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire, Total Symptom Score; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PARAGLIDE-HF = Prospective comparison of ARNI with ARB Given following stabiLization in Decompensated HFpEF; PIONEER-HF = ComParIson of sacubitril-valsartaN versus Enalapril on Effect on nt-pRo-bnp in patients stabilized from an acute Heart Failure episode; RALES = Randomized Aldactone Evaluation Study; RR = relative risk; SBP = systolic blood pressure; SGLT2i = sodium-glucose transport inhibitors; SOLOIST-WHF = Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post-Worsening Heart Failure; VICTORIA = VerICiguaT global study in subjects with heart failure with reduced ejection fraction.

TABLE 5 Strategies to Optimize GDMT Use in the Setting of Common Clinical Barriers

>50% Increase in Creatinine
Address underlying cause, commonly volume depletion or congestion
Discontinue nephrotoxic medications
Consider halving RAASi and re-evaluate
As a last resort, if creatinine continues to increase, discontinue RAASi
Hyperkalemia and RAASi/MRA
Confirm that blood sample is not hemolyzed
Address underlying cause of hyperkalemia (ie, K+ supplements, metabolic acidosis, rhabdomyolysis, hypocalcemia)
Ensure SGLT2i is on medication regimen
Recommend dietary reduction of K+ intake
Prescribe K+ binders
Adjust MRA dose, then, if needed, RAASi dose
As a last resort, discontinue MRA and re-challenge in 2-4 weeks if K+ normalizes
Symptomatic hypotension and BB/RAASi
Correct volume depletion or congestion
Deprescribe antihypertensive medications other than HF GDMT
Stagger timing of BB and RAASi to avoid simultaneous peak effect
Switch from carvedilol to bisoprolol or metoprolol XL
Decrease RAASi/BB dose
Switch ARNI to ACEI/ARB
Euglycemic DKA and SGLT2i
To prevent DKA, hold SGLT2i in the setting of significant dehydrating illness or major surgery, then resume
Discontinue SGLT2i if DKA occurs
Do not use SGT2i in type 1 diabetes mellitus
Genital mycotic infections and SGLT2i
To prevent mycotic infections, counsel on daily genital hygiene
Treat genital infection with single dose of fluconazole
Discontinue SGLT2i after recurrent genital infection
Unaffordability
Prescribe generic drugs when possible
Prescribe higher-dose pills split in pieces
Prescribe longer-duration prescriptions
Recommend discount or online pharmacies (eg, CostPlusDrugs)

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin-receptor neprilysin inhibitors; BB = beta blockers; BP = blood pressure; DKA = diabetic ketoacidosis; GDMT = guideline-directed medical therapy; HF = heart failure; K+ = potassium; MRA = mineralocorticoid receptor antagonists; RAASi = renin-angiotensin aldosterone inhibitors; SGLT2i = sodium-glucose transport inhibitors.

on nt-pRo-bnp in patients stabilized from an acute Heart Failure episode) RCT, the ARNI sacubitril-valsartan led to a greater reduction in N-terminal pro-B-type natriuretic peptide (NT-proBNP) (Table 4)[36] than enalapril among patients hospitalized for decompensated HFrEF.[36] The benefit of ARNI in patients hospitalized for HF with an ejection fraction >40% was shown in PARAGLIDE-HF (Prospective comparison of ARNI with ARB Given following stabi-Lization in Decompensated HFpEF) RCT, demonstrating a greater reduction in NT-proBNP concentration (Table 4) compared to valsartan; however, there was an increased incidence of hypotension in the ARNI group, however.[37]

In the EMPULSE RCT of patients hospitalized for HF across LVEF categories, the SGLT2i empagliflozin relative to placebo led to an improvement (Table 4) in the primary composite outcome of death from any cause, the number of HF events and time to first HF event, and change in the Kansas City Cardiomyopathy Questionnaire Total Symptom Score at 90 days.[39] In the SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post-Worsening Heart Failure) RCT, sotagliflozin, a combined SGLT1/SGLT2 inhibitor, reduced the primary composite endpoint of total number of deaths from CV causes and hospitalizations and urgent visits for HF compared to placebo in patients with diabetes who were hospitalized for worsening HF (Table 4).[38] Sotagliflozin was associated with increased diarrhea and severe hypoglycemia vs placebo.

Some interventions have shown modest or equivocal benefits. In patients with HFrEF who were hospitalized for HF within the preceding 6 months, the VICTORIA (VerICiguaT global study in subjects with heart failure with reduced ejection fraction) RCT demonstrated that, relative to placebo, the soluble guanylate cyclase stimulator, vericiguat, modestly decreased the primary composite outcome of CV death or HHF (Table 4), driven by a reduction in HHF.[40] In patients experiencing HHF with concomitant iron deficiency, IV iron has not shown consistent benefit. In the AFFIRM-AHF (Study to Compare Ferric Carboxymaltose with Placebo in Patients with Acute Heart Failure and Iron Deficiency), IV ferric carboxymaltose did not reduce total HHF and CV death (Table 4).[41] The eart-FID (Heart Failure with Iron Deficiency) RCT was similarly neutral for the primary endpoints of composite HHF, CV death, and 6-minute walk distance among ambulatory patients with HF.[46]

PRACTICAL TIPS TO OPTIMIZE MEDICAL THERAPIES. Despite high-quality evidence, disease-modifying therapies in HF have been underutilized or used at suboptimal doses. Medical comorbidities, adverse effects frailty, and cost are common reasons for underutilization, and implementation strategies have varied in success (Table 5).

Kidney dysfunction. Among patients with HF, those with kidney disease are at the highest risk of adverse outcomes and are paradoxically undertreated.[47,48] Chronic kidney disease (CKD) has little implication for the use of BB but is often considered a limiting factor in the use of other classes of HF therapies. In RCTs, RAASi, MRA, and SGLT2i have demonstrated consistent efficacy through to CKD

TABLE 6 Guidance for Improving GDMT in the Setting of Changes in Kidney Function and Serum Potassium Based on Current Evidence

Class of Therapy	Recommended Action Based on Kidney Parameters Increase in Serum Cr (%) eGFR (mL/min/1.73 m^2) Serum K^+ (mmol/L)		
	Continue	**Continue With Caution or Decrease Dose**	**May Hold**
ACEI/ARB	<50% 25 mL/min/1.73 m^2 <5.0 mmol/L Uptitrate and evaluate kidney function and electrolytes	50-100% 20-25 mL/min/1.73 m^2 5.0-5.5 mmol/L Evaluate clinical status and other causes of WKF. Consider halving ARB and re-evaluate	>100% <20 mL/min/1.73 m^2 >5.5 mmol/L Evaluate clinical status and other causes of WKF[a]
MRA	<50% 30 mL/min/1.73 m^2 <5.0 mmol/L Uptitrate and evaluate kidney function and electrolytes.	50-100% 20-30 mL/min/1.73 m^2 5.0-5.5 mmol/L Evaluate clinical status and other causes of WKF. Consider halving MRA and re-evaluate.	>100% <20 mL/min/1.73 m^2 >5.5 mmol/L- dose decrease >6.0 mmol/L - discontinue Evaluate clinical status and other causes of WKF.[a]
SGLT2i	<50% 20 mL/min/1.73 m^2 N/A Continue SGLT2i and reevaluate kidney function regularly.	50-100% <20 mL/min/1.73 m^2 N/A Continue SGLT2i; evaluate other causes in parallel.	>100% <20 mL/min/1.73 m^2 N/A Large increases in Cr are unexpected; evaluate clinical status and other causes of WKF[a] before holding. May choose to continue and monitor if eGFR stabilizes.
ARNI	<50% 30 mL/min/1.73 m^2 <5.0 mmol/L Uptitrate and evaluate kidney function and electrolytes.	50-100% 20-30 mL/min/1.73 m^2 5.0-5.5 mmol/L Evaluate clinical status and other causes of WKF.[a] Consider halving dose.	>100% <20 mL/min/1.73 m^2 >5.5 mmol/L Evaluate clinical status and other causes of WKF.[a]

Adapted with permission from Beldhuis et al.[47] [a]Re-challenge in 2 to 4 weeks (if possible at lower dose) if renal function has improved.

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin-receptor blockers; ARNI = angiotensin-receptor neprilysin inhibitors; eGFR = estimated glomerular filtration rate; MRA = mineralocorticoid receptor antagonist; sCr = serum creatinine; SGLT2i = sodium-glucose transport inhibitors; WKF = worsening kidney function.

stage 3B, with some trials including patients with an estimated glomerular filtration rate (eGFR) as low as 20 or 30 mL/min/1.73 m^2 [47]; of note, these classes improve outcomes in CKD as well as HF.[47]

The most recent Kidney Disease Improving Global Outcomes guidelines[49] favor continuation of RAASi in patients with HF unless the creatinine increases by >30%, and even then, to address other underlying causes of kidney injury and hold RAASi only as a last resort. An increase in serum creatinine by >50% or above 3.5 mg/dL has been proposed as a threshold at which to withhold RAASi therapy (**Table 6**); treatment may be reinitiated at a lower dose if kidney function improves after two to 4 weeks of withholding therapy.[48] In patients with severe kidney disease, hydralazine and isosorbide dinitrate (H-ISDN) are commonly used instead of ACEI/ARB/ARNI. However, there are no RCT data to suggest the benefit of hydralazine-isosorbide dinitrate compared to placebo in patients with advanced kidney disease, and this practice holds a Class IIb recommendation with Level of Evidence: C in the ACC/AHA/HFSA guidelines.[5]

SGLT2i could be continued in the setting of reduced eGFR if renal replacement therapy is not imminent. In secondary analysis of the DAPA-HF (Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure) trial, patients on SGLT2i with reductions in eGFR below the threshold of trial recruitment had better outcomes than those who received placebo.[50]

Hyperkalemia. RAASi and MRA use require close monitoring for hyperkalemia, particularly in the setting of kidney dysfunction, and hyperkalemia may be mitigated through the use of SGLT2i.[51] Patients with mild hyperkalemia can be treated without a change in RAASi or MRA therapies if other causes of hyperkalemia are addressed.[49] For persistent hyperkalemia without a reversible cause, potassium binders can be introduced.[52] Downtitration of RAASi is associated with an increased risk of cardiorenal events,[53] and in the case of MRA, an increase in all-cause mortality,[54] but may be considered with persistent hyperkalemia. A serum potassium >6.0 mEq/L should prompt withholding of therapy.[47] Even so, a rechallenge is recommended at 2 to 4 weeks if kidney function and/or potassium have improved[52] (**Table 6**).

Hypotension. Hypotension on hospital discharge is a poor prognostic indicator that should prompt evaluation of underlying causes and, when appropriate, discussion of advanced therapies or advanced care planning.[55] Common causes of symptomatic

TABLE 7 Proposed Criteria for Referral of Patients With Advanced Heart Failure to Specialized Palliative Care

Disease-based
Complication of advanced/refractory heart failure
Cardiorenal syndrome
Persistent malignant arrhythmias
Implantable cardioverter-defibrillator shocks
Cardiac cachexia
Inability to tolerate or resistant to guideline-directed therapies
Multiorgan failure
Presence of one or more life-threatening diseases in addition to heart failure
Advanced cardiac therapies
Chronic inotropes
Meets criteria but is not a candidate for mechanical circulatory support or cardiac transplant.
Hospital utilization
≥2 emergency room visits within the past 3 months
≥2 hospitalizations within the last 3 months
Needs-based
Symptom distress
Severe physical symptoms
Severe emotional symptoms
Severe spiritual or existential distress
Dependent on ≥3 basic activities of daily living
Refractory symptoms requiring palliative sedation
Request for hastened death/assisted suicide
Decision-making and social support
Hospice referral/discussion
Discussion regarding withdrawal/de-escalation of life-prolonging interventions
Patient/family/care team request Assistance with goals of care discussions/decision-making/care planning
Assistance with goals of care discussions/decision-making/care planning
Time-based
Clinician estimated life expectancy of ≤6 months

Table based on recommendations from ref.[82], J Am Coll Cardiol.

hypotension include volume depletion or congestion and medications. Antihypertensive medications other than GDMT should be discontinued. As HF advances, RAASi/ARNI and BB doses can be staggered to avoid simultaneous peak effect. When necessary, doses of ARNI can be downtitrated and subsequently switched to ACEI/ARB.[37] SGLT2is and MRAs have minimal blood pressure effect at the doses used in HF and are reasonable to maintain without dose adjustment. The downtitration and discontinuation of GDMT should be a last resort and considered only after addressing other causes of hypotension. GDMT remains associated with improved outcomes in patients with hypotension, though this effect is attenuated when hypotension is compounded by significant kidney dysfunction.[55]

Second-line therapies such as ivabradine (if the patient is in sinus rhythm) or digoxin—both of which reduce HHF in ambulatory HFrEF—may be considered in the setting of hypotension that limits use of first-line GDMT classes, but these have not been tested in hospitalized patients.[56,57] Vericiguat should not be considered among second-line therapies in the setting of hypotension, as such patients may be more prone to progressive symptomatic hypotension and syncope.[57]

Euglycemic diabetic ketoacidosis and genitourinary infections. Diabetic ketoacidosis occurs in around 0.25% of patients on SGLT2i[58] and is most often seen in patients with insulin-dependent and autoimmune diabetes misdiagnosed as type 2 diabetes. It is an indication to stop treatment.[58] Dehydrating illness and fasting states are risk factors for euglycemic diabetic ketoacidosis,[58] prompting the recommendation for patients to temporarily hold SGLT2i in these settings, with re-initiation as soon as fluid and dietary intake resumes.

The risk of genital mycotic infections with SGLT2i is small and occurs primarily in diabetics due to glycosuria; this risk can be mitigated with daily genital hygiene, prompt recognition of symptoms, and treatment with a single dose of fluconazole.[59] Recurrent infections or Fournier's gangrene, a rare, serious complication of mycotic infections warrant cessation of SGLT2i.[59]

Frailty or older age. The average patient hospitalized for HF in high-income countries ranges from over 60 to 75 years old; most have complex comorbidities, and over 50% are frail.[3,60,61] Frailty, defined as a state of increased vulnerability due to reduced physiologic reserve, plays an important role in the progression of HF and is a risk marker for death.[62] Neither frailty nor older age should be a reason to withhold HF therapy.[63] In the GUIDE-IT (Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment in Heart Failure) post-hoc analysis, participants with a high frailty burden had a significantly lower likelihood of being initiated on GDMT or having dose escalation than nonfrail participants.[62]

Cost and complexity. Clinicians could help offset the cost of medications by substituting proprietary for generic medications in each class, prescribing therapies for longer duration, or prescribing higher dose pills that can be divided; these strategies can minimize prescription fill costs for any given dose of medication. U.S. initiatives such as Cost Plus Drugs Company can allow for savings by bypassing the high administrative costs and pharmaceutical intermediaries.[64] Medications that do not improve health status can be deprescribed to simplify regimens, increase adherence, and avoid prescribing

TABLE 8 Implementation Trials for Transitional Care

Trial Name No. of Randomized (% Female)	Intervention	Primary Outcome and Efficacy Estimate (95% CI Unless Otherwise Specified)
CONNECT-HF[86] 5,746 (33.3%)	Hospital and postdischarge quality improvement initiative with regular education of clinicians by a trained group of HF and quality improvement experts; audit and feedback on HF process measures vs usual care	Composite HF readmission or all-cause mortality Adjusted HR: 0.92 (0.81-1.05) Composite HF care quality score 3.3% (−0.8% to 7.3%)
PACT-HF[3] 2,494 (50.4%)	In-hospital education, structured discharge summary, primary care visit within a week of discharge; nurse-led home visits and heart function clinic visits for high-risk patients vs usual transitional care as per clinician's discretion	Composite all-cause readmission, ED visit, or death at 3 months HR: 0.99 (0.83-1.19) Composite all-cause readmission or ED visit at 30 days HR: 0.93 (0.73-1.18)
STRONG-HF[87] 1,078 (38.6%)	Initiation of GDMT in hospital and postdischarge optimization of therapies, with the goal of achieving 100% of the target GDMT doses within 2 weeks of discharge; 4 outpatient appointments over the 2 post discharge months to monitor clinical status, laboratory parameters, and NT-proBNP levels vs usual care as per local physician follow-up	Composite HF readmission or all-cause mortality by day 180 Adjusted RR: 0.66 (0.50-0.86)

CONNECT-HF = Care Optimization Through Patient and Hospital Engagement Clinical Trial for HF; ED = emergency department; GDMT = guideline-directed medical therapy; HF = heart failure; HR = hazard ratio; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PACT-HF = Patient-Centered Care Transitions in HF; RR = relative risk; STRONG-HF = Safety, Tolerability and efficacy of Rapid Optimization, helped by NT-proBNP and GDF-15, of HF therapies.

cascades, in which an adverse drug reaction is treated with an additional medication.[65]

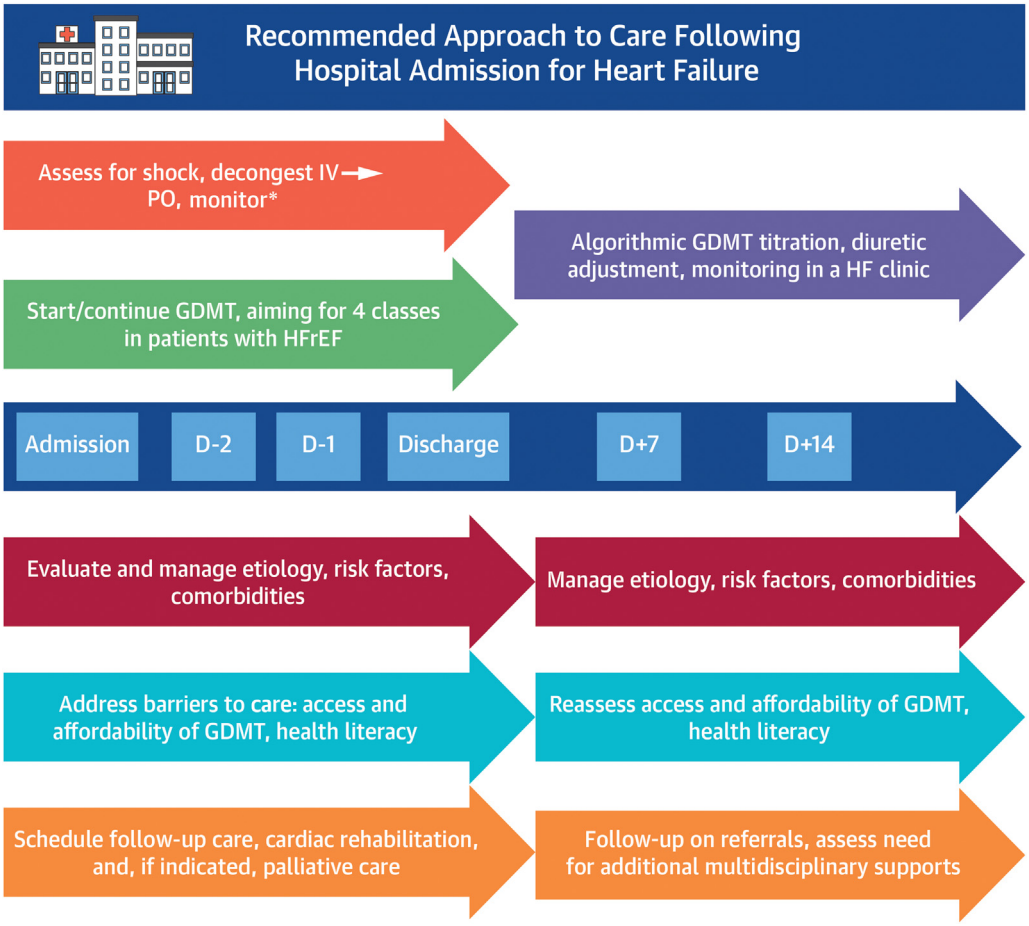
DEVICE THERAPIES. Most large RCTs on implantable device therapies have been conducted in ambulatory patients, but trials that included patients with NYHA class IV HF can be informative for treatment of worsening HF.

Cardiac resynchronization therapy (CRT) has been shown in high-quality RCTs to reduce all-cause mortality and HF events in patients with left bundle branch block and an LVEF ≤35%; this intervention is given a class I indication in patients with symptomatic HF and QRS ≥150 ms.[5] Subgroup analyses from RCTs suggest benefit in females at an even lower QRS duration, and some guidelines set a lower QRS threshold for referral in females[66] (Supplemental Table 1). The 3-arm COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure) trial showed that CRT alone or CRT with an implantable cardioverter defibrillator decreased the primary endpoint of time to any-cause death or hospitalization in patients with advanced HF, LVEF ≤35%, and QRS of ≥120 ms compared with patients receiving GDMT alone at a median of 12 months.[67] In the CARE-HF (Cardiac Resynchronization-Heart Failure) RCT, CRT decreased time to all-cause death or unplanned hospitalization in patients with NYHA functional class III or IV symptoms, echocardiographic ventricular dyssynchrony, and a QRS of ≥120 ms relative to medical therapy alone at a mean follow-up of 29.4 months.[68]

The use of permanently implanted PA sensors with PA-guided therapy in ambulatory patients has not had consistent effects, and RCTs have not been placebo-controlled.[5,60] In the CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure) trial, remote assessment of PA pressures in addition to standard care reduced HF-related hospitalizations at 6 months in patients with HF across LVEF and a prior hospitalization.[60] In contrast, the GUIDE-HF (Haemodynamic-GUIDEd management of Heart Failure) RCT, demonstrated that hemodynamic-guided management of patients with NYHA class II to IV symptoms did not reduce the composite endpoint of mortality and total HF events at 12 months.[61] Thus, this implantable device carries a Class IIb indication in the ACC/AHA/HFSA due to conflicting data[5] (Supplemental Table 1).

Additional device interventions such as transcatheter edge-to-edge repair (TEER) for symptomatic severe mitral[69,70] or tricuspid valve regurgitation[71] may improve either clinical or health status outcomes in select patients. The effect of mitral TEER on clinical outcomes differed in 2 pivotal unblinded RCTs without procedure-control, likely due to different baseline characteristics of patients in the 2 trials.[69,70] Tricuspid TEER improved a hierarchical composite of clinical endpoints, driven by an improvement in self-reported health status, but the trial was unblinded with no procedure-control group.[71] These interventions do not have a Class I indication in international guidelines for ambulatory

CENTRAL ILLUSTRATION **Steps to Optimize Care Following Admission for Heart Failure**



Oskouie S, et al. JACC Adv. 2024;3(9):101131.

Attention must be given to addressing precipitating causes, ensuring adequate decongestion, optimizing disease-modifying GDMT, and ensuring continuity of care to optimize GDMT following discharge. *Algorithm for decongestion is discussed in Figure 2. D-1 = 1 day prior to discharge; D-2 = 2 days prior to discharge; D+7 = 7 days following discharge; D+14 = 14 days following discharge; GDMT = guideline-directed medical therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; IV = intravenous; PO = by mouth.

patients. There is an unmet need for procedure-controlled device trials and tools to identify patients who will benefit most from these therapies.[72]

Well-designed RCTs with procedure control groups have demonstrated the neutral effect of interatrial shunt devices on clinical and patient-reported outcomes in ambulatory patients with severely symptomatic HF.[73,74] The effect of other device therapies such as cardiac contractility modulation[75] and baroreceptor stimulation[76] have been investigated on surrogate and/or patient-reported outcomes in small unblinded trials among patients with advanced symptoms. While results appear promising, adequately-powered double-blinded outcomes RCTs could better inform clinical practice; both interventions are acknowledged as areas with evidence gaps in the guidelines and do not have a level of recommendation.[5,9]

POST-HOSPITALIZATION SERVICES.

Cardiac rehabilitation. Frailty and functional decline increase during HHF due to physical inactivity and inadequate nutritional support. Cardiac rehabilitation can improve outcomes. The REHAB-HF (Rehabilitation Therapy in Older Acute Heart Failure Patients) RCT showed that early, transitional, tailored, progressive rehabilitation intervention among hospitalized patients with decompensated HF improved

physical function, exercise capacity, and quality of life,[77] with the greatest benefit in patients who had the highest frailty burden at baseline.[78] Data from small RCTs have demonstrated benefit in HFpEF, where pharmacotherapy options are more limited; this is currently under investigation in a multicenter RCT.[79]

Palliative care. Patients with HF prefer an adequately supported death at home,[80] but commonly die in the hospital, receiving intensive and invasive care in the last weeks of life.[81] In a retrospective cohort of approximately 400,000 adults who died of HF, ambulatory palliative care was independently associated with lower odds of in-hospital death.[81] Palliative care consultation remains underutilized, however.[82] A consensus study of international experts identified 25 referral criteria within categories of "disease-based," "needs-based," and "time-based,"[82] which have yet to be validated (**Table 7**). Palliative care referral is currently recommended in patients with features of advanced HF, manifested by NYHA functional class III/IV symptoms and recurrent hospitalizations despite optimal GDMT, as well as end-organ dysfunction, malignant arrhythmias, poor functional capacity, or high-risk on the Seattle Heart Failure Model or HF survival score.[5] Clinical phenotypes based on comorbidities are more effective than LVEF at predicting death within 6 months following HHF; patients with concomitant chronic lung disease are at the highest risk.[83] In a comparative effectiveness study of risk prediction tools validated in HHF, a simple 3-variable index based on length of hospitalization, preceding emergency department visits, and natriuretic peptide levels had the best performance for predicting 30-day death.[84] These tools could be used to guide palliative care referrals.

Transitional care. Transitional care services shown in explanatory trials[85] to reduce all-cause mortality and readmission in HF were not shown in pragmatic settings to improve clinical outcomes, although they improve patient-reported outcomes. Pragmatic trials that have had neutral effect on clinical outcomes following hospitalization for HF include the PACT-HF (Patient-Centered Care Transitions in HF) pragmatic stepped-wedge RCT of nurse-home visits and HF clinics vs usual care[3]; and the ONNECT-HF (Care Optimization Through Patient and Hospital Engagement Clinical Trial for HF) RCT of quality improvement and audit-feedback on quality indicators[86] (**Table 8**). These interventions did not improve the uptake of HF pharmacotherapies, but did improve discharge preparedness and quality of life.[3,88] Transitional care approaches that include algorithm-driven optimization of pharmacotherapies within the context of a HF discharge clinic can improve clinical outcomes and uptake, as seen in the STRONG-HF (Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP testinG, of Heart Failure Therapies) RCT (**Table 8**).[87] As such, recent society guidelines recommend upfront initiation with timely optimization of GDMT doses.[5,30,34] Decision support and reminders in electronic health records, as well as digital nudges to patients, can optimize GDMT initiation and intensification.[89]

TABLE 9 Checklist for Improving Outcomes Following Hospitalization for Heart Failure

Clinical optimization
❑ Decongest
❑ Address precipitating factors
❑ Address comorbidities
❑ Deprescribe unnecessary therapy
❑ Initiate GDMT pillars
Discharge preparation
❑ Switch from IV to oral therapies
❑ Ensure adequate decongestion with stable oral dose for 2 days prior to discharge
❑ Address barriers to GDMT access or uptake
❑ Provide education
Transitional care
❑ Schedule postdischarge follow-up visit, ideally in an HF clinic to optimize GDMT
❑ Refer to cardiac rehabilitation
❑ If appropriate, refer to palliative care
Evidence-based implementation
❑ Use implementation strategies that have been shown to improve uptake of evidence-based treatments or clinical outcomes (eg, digital nudges to patients, EHR alerts to clinicians, frequent visits for GDMT uptitration).

EHR = electronic health record; GDMT = guideline-directed medical therapy; HF = heart failure; IV = intravenous.

CONCLUSIONS

Among patients with HF, worsening HF is common and portends a high risk of recurrent decompensation and death. Strategies to improve outcomes during and after HHF include complete decongestion prior to discharge, early initiation and optimization of disease-modifying therapies, and comprehensive ambulatory care that optimizes therapies and refers appropriate patients for advanced HF services (**Central Illustration**, **Table 9**). Finally, proven-effective implementation strategies informed by pragmatic trials with validated outcome measures should be adopted to minimize bias so that all those living with the disease may benefit from research advancements.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Sauer has received research funding from Abbott, Boston Scientific, and Edwards Lifesciences; and speaking and advising compensation from Acorai, Story Health, Boston Scientific, General Prognostics, Abbott, Impulse Dynamics, Bayer, and Biotronik. Dr Greene has received research support from the Duke University Department of Medicine Chair's Research Award, American Heart Association (#929502), Amgen, AstraZeneca, Bristol Myers Squibb, Cytokinetics, Merck, Novartis, Pfizer, and Sanofi; has served on advisory boards or as consultant for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim/Lilly, Bristol Myers Squibb, Corteria, CSL Vifor, Cytokinetics, Lexicon, Roche Diagnostics, Merck, PharmaIN, Sanofi, scPharmaceuticals, Tricog Health, and Urovant Pharmaceuticals; and has received speaker fees from Bayer, Boehringer Ingelheim, Cytokinetics, Lexicon, and Roche Diagnostics. Dr Albert received research funding from AstraZeneca and Novartis within the last 2 years and is a consultant to American Regent, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Merck, and Roche. Dr Spall is funded by the Canadian Institutes of Health Research and has research support from Medtronic and educational grants from Novartis and Boehringer Ingelheim. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Harriette GC. Van Spall, McMaster University, 20 Copeland Avenue, David Braley Research Building, Suite C3-117, Hamilton, Ontario L8L 0A3, Canada. E-mail: harriette.vanspall@phri.ca. X handle: @hvanspall.

REFERENCES

1. Wei S, Miranda JJ, Mamas MA, Zühlke LJ, Kontopantelis E, Thabane L, Van Spall HGC. Sex differences in the Etiology and burden of heart failure across Country income level: analysis of 204 countries and Territories 1990-2019. *Eur Heart J Qual Care Clin Outcomes*. 2022;9(7):662–672. https://doi.org/10.1093/ehjqcco/qcac088

2. Rosano GMC, Seferovic P, Savarese G, et al. Impact analysis of heart failure across European countries: an ESC-HFA position paper. *ESC Heart Fail*. 2022;9:2767–2778. https://doi.org/10.1002/ehf2.14076

3. Van Spall HGC, Lee SF, Xie F, et al. Effect of patient-Centered transitional care services on clinical outcomes in patients hospitalized for heart failure: the PACT-HF randomized clinical trial. *JAMA*. 2019;321:753–761. https://doi.org/10.1001/jama.2019.0710

4. Bozkurt B, Savarese G, Adamsson Eryd S, et al. Mortality, outcomes, costs, and Use of Medicines following a first heart failure hospitalization: EVOLUTION HF. *JACC Heart Fail*. 2023;11:1320–1332. https://doi.org/10.1016/j.jchf.2023.04.017

5. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: Executive summary: a Report of the American College of cardiology/American heart association Joint Committee on clinical practice guidelines. *J Am Coll Cardiol*. 2022;79:1757–1780. https://doi.org/10.1016/j.jacc.2021.12.011

6. Averbuch T, Mohamed MO, Islam S, et al. The association between socioeconomic status, Sex, Race/Ethnicity and in-hospital mortality among patients hospitalized for heart failure. *J Card Fail*. 2022;28:697–709. https://doi.org/10.1016/j.cardfail.2021.09.012

7. Mullens W, Damman K, Harjola VP, et al. The use of diuretics in heart failure with congestion - a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2019;21:137–155. https://doi.org/10.1002/ejhf.1369

8. Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med*. 2011;364:797–805. https://doi.org/10.1056/NEJMoa1005419

9. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599–3726. https://doi.org/10.1093/eurheartj/ehab368

10. Averbuch T, Damman K, Van Spall HGC. Urinary sodium: worth its salt? *Eur Heart J Qual Care Clin Outcomes*. 2022;8(7):701–702. https://doi.org/10.1093/ehjqcco/qcac015

11. Ter Maaten JM, Beldhuis IE, van der Meer P, et al. Natriuresis-guided diuretic therapy in acute heart failure: a pragmatic randomized trial. *Nat Med*. 2023;29:2625–2632. https://doi.org/10.1038/s41591-023-02532-z

12. Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. *Circulation*. 2010;122:265–272. https://doi.org/10.1161/circulationaha.109.933275

13. Mentz RJ, Anstrom KJ, Eisenstein EL, et al. Effect of torsemide vs furosemide after discharge on all-cause mortality in patients hospitalized with heart failure: the TRANSFORM-HF randomized clinical trial. *JAMA*. 2023;329:214–223. https://doi.org/10.1001/jama.2022.23924

14. Trulls JC, Morales-Rull JL, Casado J, et al. Combining loop with thiazide diuretics for decompensated heart failure: the CLOROTIC trial. *Eur Heart J*. 2023;44:411–421. https://doi.org/10.1093/eurheartj/ehac689

15. Mullens W, Dauw J, Martens P, et al. Acetazolamide in acute decompensated heart failure with volume Overload. *N Engl J Med*. 2022;387:1185–1195. https://doi.org/10.1056/NEJMoa2203094

16. Butler J, Anstrom KJ, Felker GM, et al. Efficacy and safety of spironolactone in acute heart failure: the ATHENA-HF randomized clinical trial. *JAMA Cardiol*. 2017;2:950–958. https://doi.org/10.1001/jamacardio.2017.2198

17. Ern Yeoh S, Osmanska J, Petrie MC, et al. Dapagliflozin versus metolazone in heart failure resistant to loop diuretics. *Eur Heart J*. 2023;44(31):2966–2977. https://doi.org/10.1093/eurheartj/ehad341

18. Verbrugge FH, Martens P, Ameloot K, et al. Acetazolamide to increase natriuresis in congestive heart failure at high risk for diuretic resistance. *Eur J Heart Fail*. 2019;21:1415–1422. https://doi.org/10.1002/ejhf.1478

19. Schulze PC, Bogoviku J, Westphal J, et al. Effects of early empagliflozin initiation on diuresis and kidney function in patients with acute decompensated heart failure (EMPAG-HF). *Circulation*. 2022;146:289–298. https://doi.org/10.1161/circulationaha.122.059038

20. Damman K, Beusekamp JC, Boorsma EM, et al. Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF). *Eur J Heart Fail*. 2020;22:713–722. https://doi.org/10.1002/ejhf.1713

21. Biegus J, Voors AA, Collins SP, et al. Impact of empagliflozin on decongestion in acute heart failure: the EMPULSE trial. *Eur Heart J*. 2023;44:41–50. https://doi.org/10.1093/eurheartj/ehac530

22. Konstam MA, Gheorghiade M, Burnett JC Jr, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA*. 2007;297:1319–1331. https://doi.org/10.1001/jama.297.12.1319

23. Konstam MA, Kiernan M, Chandler A, et al. Short-term effects of tolvaptan in patients with acute heart failure and volume Overload. *J Am Coll Cardiol*. 2017;69:1409–1419. https://doi.org/10.1016/j.jacc.2016.12.035

24. Felker GM, Mentz RJ, Cole RT, et al. Efficacy and safety of tolvaptan in patients hospitalized with acute heart failure. *J Am Coll Cardiol*. 2017;69:1399–1406. https://doi.org/10.1016/j.jacc.2016.09.004

25. Costanzo MR, Negoianu D, Jaski BE, et al. Aquapheresis versus intravenous diuretics and hospitalizations for heart failure. *JACC Heart Fail*. 2016;4:95–105. https://doi.org/10.1016/j.jchf.2015.08.005

26. Bart BA, Goldsmith SR, Lee KL, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med*. 2012;367:2296–2304. https://doi.org/10.1056/NEJMoa1210357

27. Costanzo MR, Ronco C, Abraham WT, et al. Extracorporeal ultrafiltration for fluid Overload in

heart failure: current status and Prospects for Further research. *J Am Coll Cardiol*. 2017;69:2428-2445. https://doi.org/10.1016/j.jacc.2017.03.528

28. Kozhuharov N, Goudev A, Flores D, et al. Effect of a strategy of comprehensive vasodilation vs usual care on mortality and heart failure Rehospitalization among patients with acute heart failure: the GALACTIC randomized clinical trial. *JAMA*. 2019;322:2292-2302. https://doi.org/10.1001/jama.2019.18598

29. Chen HH, Anstrom KJ, Givertz MM, et al. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. *JAMA*. 2013;310:2533-2543. https://doi.org/10.1001/jama.2013.282190

30. Ezekowitz JA, O'Meara E, McDonald MA, et al. 2017 comprehensive update of the Canadian cardiovascular society guidelines for the management of heart failure. *Can J Cardiol*. 2017;33:1342-1433. https://doi.org/10.1016/j.cjca.2017.08.022

31. Binanay C, Califf RM, Hasselblad V, et al. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. *JAMA*. 2005;294:1625-1633. https://doi.org/10.1001/jama.294.13.1625

32. Garan AR, Kanwar M, Thayer KL, et al. Complete hemodynamic profiling with pulmonary artery catheters in Cardiogenic shock is associated with lower in-hospital mortality. *JACC Heart Fail*. 2020;8:903-913. https://doi.org/10.1016/j.jchf.2020.08.012

33. Rossello X, Vila M, Rivas-Lasarte M, Ferrero-Gregori A, Sans-Roselló J, Duran-Cambra A, Sionis A. Impact of pulmonary artery catheter Use on short- and long-term mortality in patients with Cardiogenic shock. *Cardiology*. 2017;136:61-69. https://doi.org/10.1159/000448110

34. McDonagh TA, Metra M, Adamo M, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2023;44(37):3627-3639. https://doi.org/10.1093/eurheartj/ehad195

35. Van Spall HGC, Averbuch T, Damman K, Voors AA. Risk and risk reduction in trials of heart failure with reduced ejection fraction: absolute or relative? *Eur J Heart Fail*. 2021;23:1437-1444. https://doi.org/10.1002/ejhf.2248

36. Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med*. 2019;380:539-548. https://doi.org/10.1056/NEJMoa1812851

37. Mentz RJ, Ward JH, Hernandez AF, et al. Angiotensin-neprilysin inhibition in patients with mildly reduced or preserved ejection fraction and worsening heart failure. *J Am Coll Cardiol*. 2023;82:1-12. https://doi.org/10.1016/j.jacc.2023.04.019

38. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med*. 2021;384:117-128. https://doi.org/10.1056/NEJMoa2030183

39. Voors AA, Angermann CE, Teerlink JR, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. *Nat Med*. 2022;28:568-574. https://doi.org/10.1038/s41591-021-01659-1

40. Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2020;382:1883-1893. https://doi.org/10.1056/NEJMoa1915928

41. Ponikowski P, Kirwan BA, Anker SD, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. *Lancet*. 2020;396:1895-1904. https://doi.org/10.1016/s0140-6736(20)32339-4

42. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;385:1451-1461. https://doi.org/10.1056/NEJMoa2107038

43. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;381:1609-1620. https://doi.org/10.1056/NEJMoa1908655

44. Prins KW, Neill JM, Tyler JO, Eckman PM, Duval S. Effects of beta-blocker Withdrawal in acute decompensated heart failure: a systematic review and meta-analysis. *JACC Heart Fail*. 2015;3:647-653. https://doi.org/10.1016/j.jchf.2015.03.008

45. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341:709-717. https://doi.org/10.1056/nejm199909023411001

46. Mentz RJ, Garg J, Rockhold FW, et al. Ferric carboxymaltose in heart failure with iron deficiency. *N Engl J Med*. 2023;389:975-986. https://doi.org/10.1056/NEJMoa2304968

47. Beldhuis IE, Lam CSP, Testani JM, Voors AA, Van Spall HGC, Ter Maaten JM, Damman K. Evidence-based medical therapy in patients with heart failure with reduced ejection fraction and chronic kidney disease. *Circulation*. 2022;145:693-712. https://doi.org/10.1161/circulationaha.121.052792

48. Mullens W, Martens P, Testani JM, et al. Renal effects of guideline-directed medical therapies in heart failure: a consensus document from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2022;24:603-619. https://doi.org/10.1002/ejhf.2471

49. Navaneethan SD, Zoungas S, Caramori ML, et al. Diabetes management in chronic kidney disease: Synopsis of the 2020 KDIGO clinical practice guideline. *Ann Intern Med*. 2021;174:385-394. https://doi.org/10.7326/m20-5938

50. Chatur S, Vaduganathan M, Claggett BL, et al. Dapagliflozin in patients with heart failure and deterioration in estimated glomerular filtration rate to <25ml/min/1.73m(2). *J Am Coll Cardiol*. 2023;82(19):1854-1863. https://doi.org/10.1016/j.jacc.2023.08.026

51. Neuen BL, Oshima M, Agarwal R, et al. Sodium-glucose cotransporter 2 inhibitors and risk of hyperkalemia in people with type 2 diabetes: a meta-analysis of individual participant data from randomized, controlled trials. *Circulation*. 2022;145:1460-1470. https://doi.org/10.1161/circulationaha.121.057736

52. Butler J, Anker SD, Lund LH, et al. Patiromer for the management of hyperkalemia in heart failure with reduced ejection fraction: the DIAMOND trial. *Eur Heart J*. 2022;43:4362-4373. https://doi.org/10.1093/eurheartj/ehac401

53. Kanda E, Rastogi A, Murohara T, et al. Clinical impact of suboptimal RAASi therapy following an episode of hyperkalemia. *BMC Nephrol*. 2023;24:18. https://doi.org/10.1186/s12882-022-03054-5

54. Martens P, Kooij J, Maessen L, Dauw J, Dupont M, Mullens W. The importance of developing hyperkalaemia in heart failure during long-term follow-up. *Acta Cardiol*. 2021;76:589-597. https://doi.org/10.1080/00015385.2020.1748346

55. Izumi K, Kohno T, Goda A, et al. Low blood pressure and guideline-directed medical therapy in patients with heart failure with reduced ejection fraction. *Int J Cardiol*. 2023;370:255-262. https://doi.org/10.1016/j.ijcard.2022.10.129

56. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet*. 2010;376:875-885. https://doi.org/10.1016/s0140-6736(10)61198-1

57. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med*. 1997;336:525-533. https://doi.org/10.1056/nejm199702203360801

58. Ata F, Yousaf Z, Khan AA, et al. SGLT-2 inhibitors associated euglycemic and hyperglycemic DKA in a multicentric cohort. *Sci Rep*. 2021;11:10293. https://doi.org/10.1038/s41598-021-89752-w

59. Rangaswami J, Bhalla V, de Boer IH, et al. Cardiorenal Protection with the Newer Antidiabetic Agents in patients with diabetes and chronic kidney disease: a Scientific statement from the American heart association. *Circulation*. 2020;142:e265-e286. https://doi.org/10.1161/cir.0000000000000920

60. Abraham WT, Adamson PB, Bourge RC, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet*. 2011;377:658-666. https://doi.org/10.1016/s0140-6736(11)60101-3

61. Zile MR, Mehra MR, Ducharme A, et al. Hemodynamically-guided management of heart failure across the ejection fraction Spectrum: the GUIDE-HF trial. *JACC Heart Fail*. 2022;10:931-944. https://doi.org/10.1016/j.jchf.2022.08.012

62. Khan MS, Segar MW, Usman MS, et al. Frailty, guideline-directed medical therapy, and outcomes in HFrEF: from the GUIDE-IT trial. *JACC Heart Fail*. 2022;10:266-275. https://doi.org/10.1016/j.jchf.2021.12.004

63. Pandey A, Kitzman D, Whellan DJ, et al. Frailty among older decompensated heart failure patients: prevalence, association with patient-Centered outcomes, and Efficient Detection methods. *JACC Heart Fail*. 2019;7:1079-1088. https://doi.org/10.1016/j.jchf.2019.10.003

64. Narendrula A, Lang J, Mossialos E. Generic cardiology drug prices: the potential benefits of the Marc Cuban cost plus drug company model. *Front Pharmacol*. 2023;14:1179253. https://doi.org/10.3389/fphar.2023.1179253

65. Krishnaswami A, Steinman MA, Goyal P, et al. Deprescribing in older adults with cardiovascular disease. *J Am Coll Cardiol*. 2019;73:2584–2595. https://doi.org/10.1016/j.jacc.2019.03.467

66. Chung MK, Patton KK, Lau CP, et al. 2023 HRS/APHRS/LAHRS guideline on cardiac physiologic pacing for the avoidance and mitigation of heart failure. *Heart Rhythm*. 2023;20:e17–e91. https://doi.org/10.1016/j.hrthm.2023.03.1538

67. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med*. 2004;350:2140–2150. https://doi.org/10.1056/NEJMoa032423

68. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. 2005;352:1539–1549. https://doi.org/10.1056/NEJMoa050496

69. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. 2018;379:2307–2318. https://doi.org/10.1056/NEJMoa1806640

70. Obadia JF, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med*. 2018;379:2297–2306. https://doi.org/10.1056/NEJMoa1805374

71. Sorajja P, Whisenant B, Hamid N, et al. Transcatheter repair for patients with tricuspid regurgitation. *N Engl J Med*. 2023;388:1833–1842. https://doi.org/10.1056/NEJMoa2300525

72. Mullens W, Dauw J, Gustafsson F, et al. Integration of implantable device therapy in patients with heart failure. A clinical consensus statement from the Heart Failure Association (HFA) and European Heart Rhythm Association (EHRA) of the European Society of Cardiology (ESC). *Eur J Heart Fail*. 2024;26:483–501. https://doi.org/10.1002/ejhf.3150

73. Rodés-Cabau J, Lindenfeld J, Abraham WT, et al. Interatrial shunt therapy in advanced heart failure: outcomes from the open-label cohort of the RELIEVE-HF trial. *Eur J Heart Fail*. 2024;26(4):1078–1089. https://doi.org/10.1002/ejhf.3215

74. Shah SJ, Borlaug BA, Chung ES, et al. Atrial shunt device for heart failure with preserved and mildly reduced ejection fraction (REDUCE LAP-HF II): a randomised, multicentre, blinded, sham-controlled trial. *Lancet*. 2022;399:1130–1140. https://doi.org/10.1016/s0140-6736(22)00016-2

75. Abraham WT, Kuck KH, Goldsmith RL, et al. A randomized controlled trial to evaluate the safety and efficacy of cardiac contractility modulation. *JACC Heart Fail*. 2018;6:874–883. https://doi.org/10.1016/j.jchf.2018.04.010

76. Zile MR, Lindenfeld J, Weaver FA, Zannad F, Galle E, Rogers T, Abraham WT. Baroreflex activation therapy in patients with heart failure and a reduced ejection fraction: long-term outcomes. *Eur J Heart Fail*. 2024;26(4):1051–1061. https://doi.org/10.1002/ejhf.3232

77. Kitzman DW, Whellan DJ, Duncan P, et al. Physical rehabilitation for older patients hospitalized for heart failure. *N Engl J Med*. 2021;385:203–216. https://doi.org/10.1056/NEJMoa2026141

78. Pandey A, Kitzman DW, Nelson MB, et al. Frailty and effects of a Multidomain physical rehabilitation intervention among older patients hospitalized for acute heart failure: a secondary analysis of a randomized clinical trial. *JAMA Cardiol*. 2023;8:167–176. https://doi.org/10.1001/jamacardio.2022.4903

79. Sachdev V, Sharma K, Keteyian SJ, et al. Supervised exercise Training for chronic heart failure with preserved ejection fraction: a Scientific statement from the American heart association and American College of cardiology. *Circulation*. 2023;147:e699–e715. https://doi.org/10.1161/cir.0000000000001122

80. Heyland DK, Dodek P, Rocker G, et al. What matters most in end-of-life care: perceptions of seriously ill patients and their family members. *CMAJ*. 2006;174:627–633. https://doi.org/10.1503/cmaj.050626

81. Van Spall HGC, Hill AD, Fu L, Ross HJ, Fowler RA. Temporal Trends and Sex differences in intensity of healthcare at the end of life in adults with heart failure. *J Am Heart Assoc*. 2021;10:e018495. https://doi.org/10.1161/JAHA.120.018495

82. Chang YK, Allen LA, McClung JA, et al. Criteria for referral of patients with advanced heart failure for Specialized palliative care. *J Am Coll Cardiol*. 2022;80:332–344. https://doi.org/10.1016/j.jacc.2022.04.057

83. Gevaert AB, Tibebu S, Mamas MA, et al. Clinical phenogroups are more effective than left ventricular ejection fraction categories in stratifying heart failure outcomes. *ESC Heart Fail*. 2021;8:2741–2754. https://doi.org/10.1002/ehf2.13344

84. Van Spall HG, Averbuch T, Lee SF, Oz UE, Mamas MA, Januzzi JL, Ko DT. The LENT index predicts 30 day outcomes following hospitalization for heart failure. *ESC Heart Fail*. 2021;8:518–526. https://doi.org/10.1002/ehf2.13109

85. Van Spall HGC, Rahman T, Mytton O, et al. Comparative effectiveness of transitional care services in patients discharged from the hospital with heart failure: a systematic review and network meta-analysis. *Eur J Heart Fail*. 2017;19:1427–1443. https://doi.org/10.1002/ejhf.765

86. DeVore AD, Granger BB, Fonarow GC, et al. Effect of a hospital and Postdischarge quality improvement intervention on clinical outcomes and quality of care for patients with heart failure with reduced ejection fraction: the CONNECT-HF randomized clinical trial. *JAMA*. 2021;326:314–323. https://doi.org/10.1001/jama.2021.8844

87. Mebazaa A, Davison B, Chioncel O, et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. *Lancet*. 2022;400(10367):1938–1952. https://doi.org/10.1016/s0140-6736(22)02076-1

88. Averbuch T, Lee SF, Zagorski B, Mebazaa A, Fonarow GC, Thabane L, Van Spall HGC. Effect of a transitional care model following hospitalization for heart failure: 3-year outcomes of the Patient-Centered Care Transitions in Heart Failure (PACT-HF) randomized controlled trial. *Eur J Heart Fail*. 2024;26(3):652–660. https://doi.org/10.1002/ejhf.3134

89. Mukhopadhyay A, Reynolds HR, Phillips LM, et al. Cluster-randomized trial comparing ambulatory Decision support tools to improve heart failure care. *J Am Coll Cardiol*. 2023;81:1303–1316. https://doi.org/10.1016/j.jacc.2023.02.005

KEY WORDS decongestion, heart failure, hospitalization, implementation, transitional care

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