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CONTEMPORARY REVIEW

Acute Heart Failure Is a Malignant Process: But We Can Induce Remission

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ABSTRACT: Acute heart failure is a common and increasingly prevalent condition, affecting >10 million people annually. For those patients who survive to discharge, early readmissions and death rates are >30% everywhere on the planet, making it a malignant condition. Beyond these adverse outcomes, it represents one of the largest drivers of health care costs globally. Studies in the past 2 years have demonstrated that we can induce remissions in this malignant process if therapy is instituted rapidly, at the first acute heart failure episode, using full doses of all available effective medications. Multiple studies have demonstrated that this goal can be achieved safely and effectively. Now the urgent call is for all stakeholders, patients, physicians, payers, politicians, and the public at large to come together to address the gaps in implementation and enable health care providers to induce durable remissions in patients with acute heart failure.

Key Words: acute heart failure ■ medications ■ remission induction

> *Malignant (definition from the* Merriam-Webster Dictionary*): adjective; tending to produce death or deterioration*

Acute heart failure (AHF) is a common condition.[1–4] In the present article, we will first review the definition, epidemiology, cause, and outcomes of AHF. We will show that AHF is a malignant condition associated with severe short-term and midterm adverse outcomes globally. We then examine the treatments available for AHF and their impact on these adverse outcomes. Finally, we propose a framework for the future approach to patients with AHF that may dramatically improve outcomes and possibly induce a remission in this malignant process.

DEFINITION

In part the lack of progress in AHF research over the past decades can be attributed to its subjective definition. Most authors[5–7] define it as a sudden worsening of symptoms and signs of congestion associated with some cardiac abnormality requiring emergency treatment. Some add to the definition the need for admission, whereas others add requirements for intravenous therapy. However, compared with other acute cardiovascular conditions, such as myocardial infarction, aortic dissection, or pulmonary embolism, where electrocardiographic data, imaging data, and biomarkers can confirm or refute the diagnosis with high certainty, no such imaging or blood test exists for the diagnosis of AHF. Although elevated natriuretic peptides are important in diagnosing AHF and a lack of increase in natriuretic peptides can rule out AHF with high certainty,[8] increased natriuretic peptides can also be caused by other disease states, most notably chronic stable heart failure (HF). Hence, natriuretic peptides by themselves are not specific for AHF. Chest x-ray signs of congestion, on the other hand, are highly specific but lack sensitivity.[9] Therefore, despite years of research, no single biomarker or imaging technique has been found to be both specific and sensitive to the diagnosis of AHF; and its diagnosis remains subjective and based mostly on symptoms, clinical assessments, and ruling out of other reasons for acute congestion, such an acute coronary syndrome, arrhythmia, or infection.

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Nonstandard Abbreviations and Acronyms

AHF	acute heart failure
GDMT	guideline-directed medical therapy

EPIDEMIOLOGY AND CAUSE

It is estimated that >60 million people experience HF globally[10]; however, how many of them are admitted with AHF is not known, partially because of the lack of objective criteria for the diagnosis of AHF. In the United States, 4.5 to 4.9/1000 people are admitted for HF as a primary diagnosis every year,[11] putting the number of AHF admissions in the United States at 1.5 million yearly, ≈25% of patients with HF. Applying the same ratios globally, one would assume that AHF is the cause of at least 20 million hospital admission per year.

Several registries have outlined the possible causes for an AHF event.[12–20] Acute coronary syndromes, valvular heart diseases, arrhythmias, especially atrial fibrillation, infections, uncontrolled hypertension, and nonadherence with medication prescriptions are the most commonly identified precipitants. However, in about half the patients, no causes were identified, whereas in up to a quarter, >1 cause was noted. The identification of potential causes for AHF is important for 2 reasons. First, it provides prognostic information. For instance, AHF following an acute coronary syndrome or infection is associated with higher short-term mortality than AHF associated with atrial fibrillation or uncontrolled hypertension.[21,22] Second, some of these causes may have therapeutic implications, as described later. Valvular heart disease is frequently associated with AHF.[23] AHF may result from either a new or a worsening acute valvular lesion, or it may be attributable to combined precipitants (such as an infection or arrhythmia) in a patient with significant valvular heart disease. The severity of the AHF event associated with valvular heart disease may vary from mild to frank cardiogenic shock.

Given the prognostic and therapeutic importance of the different causes of AHF (detailed later), it is recommended that some workup of patients with AHF should be undertaken after the initial stabilization to determine whether such precipitants have contributed to the AHF event.[4] This should include at a minimum a full evaluation of blood hematology and chemistry, a chest x-ray, heart rhythm monitoring, and echocardiography. These may be followed by ischemia evaluation. With respect to valvular heart disease, the evaluation is especially difficult because of the rapid variation in loading conditions and the presence of combined valvular lesions. Additional tests may be needed depending on the clinical presentation, such as exploring possible pulmonary embolism or various infections. The identification of precipitating factors may enable the delivery of specific treatments directed toward the underlying causes of AHF.

Prognosis and Outcomes

Across the globe in multiple real-life registries, AHF has been shown to be associated with significant short- and medium-term adverse outcomes.[24] The longer-term prognosis of patients with HF is similar to or worse than the most common cancers, with ≈50% mortality in 5 years,[25] and the 6-month rate of readmission or death after an AHF admission is at least 30% (describe later), rivaling the short-term prognosis of most cancers. Recent analysis of the national readmission database[26] describes a 90-day readmission rate of >30%, with numbers only increasing in recent years (Table). In a community hospital-based registry, Philbin et al[27] found the mortality rate during 6 months of follow-up after an AHF admission to be 16%, and 43% of patients had at least 1 readmission. The median time to an event was 41 days from the discharge. Those numbers are consistent with registries from all over the world. In the EuroHeart Failure survey program,[28] the mortality rate was 13.5% within 12 weeks, and the rate of readmission was 24%. In Italy, a nationwide survey on AHF in cardiology ward services[29] found that within 6 months of an AHF admission, mortality was 12.8%, and the readmission rate was 38.1%. In a Swedish registry,[30] the death rates for HF with preserved ejection fraction, HF with midrange ejection fraction, and HF with reduced ejection fraction 30 days after an AHF admission were 2.9%, 2.1%, and 2.8%, respectively, and 1-year mortality rates were 17.4%, 14.2%, and 15.4%, respectively. In a Spanish registry[31] during the 90-day postdischarge period, 11% of patients died and 32.2% were readmitted; the combined end point of readmission or death occurred in 37.4% of patients. Similar numbers have been reported across Asia. In the Korean AHF registry,[32] the 6-month mortality rate for patients after an AHF admission was 12.4%, with a rate of HF readmission of 17.9% over the same period. In a Malaysian registry conducted in a single general hospital over 1 year,[33] the mortality rates for 30 and 90 days were 13% and 17%, respectively, whereas the readmission rates for 30 to 90 days were 11% and 14%, respectively. In an Indian national heart registry,[34] the death rates at 90 days from an AHF admission were 14.2% (14.9% and 13.9% in women and men, respectively). The readmission rate during 90-day follow-up was 8.4%. The Cardiology Society of India-Kerala Acute Heart Failure Registry[35] mortality rates at 90 days after an AHF admission were 11.6%. In another India-based registry,[36] the combined end point of rehospitalization

Table. Mortality and Readmission Rates for AHF: A Global Perspective

Region	Study, registry, survey, or database	Mortality rate, %	Readmission rate, %
United States	National Readmission Database	N/A	18.2 (30 d)
	Khan et al (2021)[26]		31.2 (90 d)
United States	Philbin et al (1999)[27]	16 (6 mo)	43 (6 mo)
Europe	EuroHeart Failure survey	13.5 (12 wk)	24 (12 wk)
	Cleland et al (2003)[28]		
Italy	Tavazzi et al (2006)[29]	12.8 (6 mo)	38.1 (6 mo)
Sweden	SwedeHF Registry	14.2–17.4 (1 y)	2.1–2.9 (30 d)
	Koh et al (2017)[30]		
Spain	EAHFE Registry	11.4 (90 d)	32.2 (90 d)
	Miró et al (2019)[31]		
South Korea	KorAHF registry	3.3 (30 d)	7.0 (30 d)
	Lee et al (2017)[32]	8.4 (90 d)	13.5 (90 d)
		12.4 (180 d)	17.9 (180 d)
Malaysia	Ling et al (2020)[33]	13.1 (30 d)	11.2 (30 d)
		16.8 (90 d)	14 (90 d)
India	NHFR	14.2 (90 d)	8.4 (90 d)
	Harikrishnan et al (2022)[34]		
India	CSI-KHFR	11.6 (90 d)	N/A
	Joseph et al (2022)[35]		
India	AFAR study	26.3 (6 mo)	39.5% (6 mo for readmission or death)
	Seth et al (2015)		
Japan	Kyoto Congestive Heart Failure registry	4.1–9.6 (180 d)	2.8%–21.2% (180 d)
	Shiba et al (2022)[37]		
Argentina	Argentine SAC Registry	12.8 (90 d)	24.5% (90 d)
	Fairman et al (2009)[38]		
Africa	THESUS-HF	17.8 (6 mo)	15.4% (60 d for death or readmission)
	Damasceno et al (2012)[39]		

AFAR indicates Acute Failure Registry; AHF, acute heart failure; CSI-KHFR, Cardiology Society of India-Kerala Acute Heart Failure Registry; EAHFE, Epidemiology of Acute Heart Failure in Emergency Departments; KorAHF, Korean AHF; N/A, not applicable; NHFR, National Heart Failure Registry; SAC, Society of Cardiology; SwedeHF, Swedish Heart Failure; and THESUS-HF, Sub-Saharan Africa Survey of Heart Failure.

or death was 39.5% within 6 months after discharge from an AHF admission. Mortality was 26.3% over the same period. Similar rates were also reported in the Kyoto AHF registry from Japan.[37] Similar results were also reported in South America. An Argentinian national registry[38] found that after an AHF event, readmissions occurred in 24.5%, and 12.8% of patients died within 90 days. Last, in the Sub-Saharan Africa Survey of Heart Failure,[39] the rate of death or readmission at 60 days was 15.4%, whereas the 6-month mortality rate was 17.8%. A recent review has suggested that 13.2% of patients with AHF are readmitted within 30 days and 35.7% are readmitted within 1 year; 30-day mortality is 7.6%, and 1-year mortality is 23.3%.[40]

The combined findings of these registries demonstrate that, despite many differences in patients' characteristics, age, background disease, and treatment, morbidity and mortality rates after an AHF admission are high and are similar across the globe. Mortality within 90 days of an AHF event is consistently ≈10% to 15%, and readmission rates are 20% to 30% and higher, in the United States, in Europe, and across Asia, Africa, and South America. AHF is therefore a malignant disease affecting the whole planet. In places where registries and data are available longitudinally, it seems that these severe adverse outcomes have not decreased over the past decades, and may have even increased, especially in the United States.[26]

Treatment of AHF

Despite these staggering numbers and associated costs, until recently no therapies had been shown to improve these dire outcomes. Because of this lack of effective therapy, of the 90 pages of the 2022 Heart Failure Clinical Practice Guidelines, only 3 were dedicated to AHF, despite the fact that most adverse outcomes in patients with HF occur during or immediately

after an AHF event. These guidelines recommend that patients with AHF are diuresed with loop diuretics intravenously and then orally with careful monitoring of symptoms and signs of HF, fluid balance, and weight (level of evidence 1b). In those who are nonresponsive, an intensified diuretic regimen, including either more loop diuretics or a second-line diuretic, may be considered (level of evidence 2b). Intravenous vasodilators may be used to relieve congestion in selected patients, especially those without hypotension (level of evidence 2b). Additional treatments may be considered in patients in shock or at risk of shock. Furthermore, it is recommended that guideline-directed medical therapy (GDMT) should be continued or started in those with lower ejection fraction.[4] In addition, some workup to assess the presence of possible precipitating factors should be undertaken (previously described). When such workup identifies potential precipitants, those should be addressed as much as possible. In some cases, the therapeutic implications are straightforward, such as is the case of an acute myocardial infraction, infections, such as a pneumonia, or pulmonary embolism. In other cases, evidence is lacking to help the physician decide on the best therapeutic approach, as is the case with some valvular lessions.

Treatment for Patients During the First Days of Admission for AHF Has Not Been Shown to Improve Outcomes

About 20 years ago, it was suggested that the treatment of AHF can be divided into 3 major stages[1]: first, the initial stabilization, then the first few days in the hospital, and finally before and after discharge.

The interventions administered to patients during the first hours of admission for AHF are based on little evidence. The most common treatment administered is intravenous furosemide or other types of loop diuretics. This practice is endorsed by all guidelines. For instance, the 2022 Heart Failure Clinical Practice Guidelines[4] include a level 1 recommendation for diuretics in the initial treatment of AHF, but with level B-NR evidence (nonrandomized studies). Nonetheless, the use of intravenous loop diuretics to decrease congestion in patients with AHF during the initial first few hours of admission is important for symptom relief. The effect of this therapy on short- and longer-term outcomes is, however, not known. Keeping loop diuretics as a background therapy, studies have been done throughout the years to assess the addition of other treatments early in the AHF admission. Two small studies[41,42] suggested an early benefit of intravenous nitrates on oxygenation and need for mechanical ventilation for early myocardial infarction in patients with pulmonary edema; however, a recent study has shown that those strategies do not improve short-term outcomes.[43] Noninvasive ventilation was also proposed as a way to improve both patients' symptoms and outcomes in the immediate stabilization of AHF; however, a prospective study[44] has shown that noninvasive ventilation improves patients' dyspnea but has no effect on short-term outcomes. Therefore, as of now, guidelines recommend the use of diuretics as the first-line treatment of patients with AHF. Other therapies, such as intravenous vasodilators and noninvasive ventilation, can be considered for symptom improvement, but these interventions do not seem to improve short-term outcomes.

After the initial stabilization, multiple treatments have been proposed to further improve patients' symptoms beyond the first hours of admission. Although many of the interventions studied do show improvement in symptoms and signs, especially of congestion, none has been shown to improve patients' outcomes. The focus of many of these studies was decongestion. In the diuretic strategies in patients with acute decompensated heart failure (DOSE) trial assessing different diuretic strategies during an admission for AHF,[45] the authors compared bolus with continuous infusion of loop diuretics and a high- versus low-dose loop diuretic strategy in a 2-by-2 factorial design. Comparing bolus versus continuous infusion, the study did not show any significant difference in patients' global assessment of symptoms or in the mean change in creatinine level. For the second comparison of a high- versus a low-dose strategy, there was a nonsignificant trend toward greater improvement in patients' global assessment of symptoms in the high-dose group. However, with respect to outcomes, death, rehospitalization, or emergency department visit occurred in 42% of subjects within the 60-day follow-up period, with no significant difference between the groups, comparing continuous diuretics versus bolus (hazard ratio [HR], 1.15 [95% CI, 0.83–1.60]; P=0.41) or the high-dose loop diuretics group and the low-dose group (HR, 0.83 [95% CI, 0.60–1.16]; P=0.28). In the ADVOR (Acetazolamide in Decompensated Heart Failure With Volume Overload) study,[46] successful decongestion occurred in 42.2% of patients in the acetazolamide group and in 30.5% in the placebo group. Acetazolamide treatment was associated with higher cumulative urine output and natriuresis, findings consistent with better diuretic efficiency. However, symptoms were not improved with respect to EuroQol 5-dimension visual analog scale at day 4, a prespecified secondary end point. In fact, EuroQol 5-dimension visual analog scale improved numerically more in control, with mean changes of 10.3 versus 9.4 points. Nor was there reduction in readmission; death from any cause or rehospitalization for HF occurred in 29.7% of the patients in the acetazolamide group and in 27.8% of the patients in the placebo group through 3

months of follow-up (*P*=not significant). Similar results were seen study in the CLOROTIC (Combining Loop With Thiazide Diuretics for Decompensated Heart Failure) study,[47] which randomized 230 patients with AHF and a history of dependence on furosemide, 80 to 240 mg/d, for at least a month to hydrochlorothiazide or placebo. The study showed a significant 0.8-kg higher weight loss at 72 hours in the active group, but there were no improvements in patients' dyspnea and there was an increase in renal impairment and hypokalemia in the active group. The risk of HF readmissions (37.7% versus 34.5%) and death (20.2% versus 16.4%) at 90 days were numerically higher in the active group. In the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan),[48] the aquaretic agent tolvaptan significantly improved secondary end points of day 1 patient-assessed dyspnea, day 1 body weight, and day 7 edema. As for the primary outcomes, within a median of 9.9 months, 25.9% in the tolvaptan group and 26.3% in the placebo group died, whereas the composite of cardiovascular death or hospitalization for HF occurred in 42% in the tolvaptan group and 40.2% in the placebo group. In the PROTECT (Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized With Acute Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function),[49] rolofylline was not beneficial with respect to the primary success/no change/failure end point compared with placebo. More patients in the rolofylline group than in the placebo group met the criteria for treatment success (40.6% versus 36.0%), but the proportion of treatment failures was also higher in the rolofylline group compared with the placebo group (21.8% versus 19.8%). Within 60 days, 30.7% of the patients in the rolofylline group compared with 31.9% of the patients assigned to placebo died or were readmitted for cardiovascular or renal causes (*P*=not significant). Rates of death over a period of 180 days were similar: 17.9% in the rolofylline group and 17.4% in the placebo group (*P*=not significant).

In the CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure),[50] patients were randomly assigned to a strategy of stepped pharmacologic therapy or ultrafiltration. There was no significant difference between pharmacologic therapy and ultrafiltration with respect to mean weight loss 96 hours after enrollment (*P*=0.58). Also, the rate of clinical decongestion at 96 hours was low but similar in the 2 treatment groups (9% with pharmacologic therapy and 10% with ultrafiltration). Mortality rates were 17% in the ultrafiltration group, compared with 13% in the pharmacologic therapy group, whereas the composite rate of death or rehospitalization for HF was similar in both groups (38% and 35%, respectively).

Equally, vasodilators administered during the first few days after an AHF admission have not demonstrated effects on outcomes. In the GALACTIC (Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure) study,[51] the improvement of dyspnea, as assessed at levels of 60° and 20° on day 2 and day 6, and reduction of NT-proBNP (N-terminal pro-B-type natriuretic peptide) concentration were not significantly different between groups. Similarly, all-cause mortality or adjudicated AHF rehospitalization through day 180 occurred in 30.6% in the early intensive and sustained vasodilation group and 27.8% in the usual care group (adjusted HR, 1.07 [95% CI, 0.83–1.39]; *P*=0.59). Two large studies examined the effects of natriuretic peptide agonists in AHF. In the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure)[52] examining the effects of nesiritide in AHF, there was a small increase in the number of patients reporting improvement in dyspnea at both the 6- and 24-hour time points; however, this finding did not meet the prespecified criteria for statistical significance. The rates of rehospitalization for HF or death from any cause at 30 days were 9.4% in the nesiritide group compared with 10.1% in the placebo group (*P*=0.31). In the TRUE-AHF (Trial to Evaluate the Efficacy and Safety of Ularitide [Urodilatin] Intravenous Infusion in Patients Suffering From Acute Decompensated Heart Failure),[53] patients with AHF were assigned to receive a continuous intravenous infusion of either ularitide at a dose of 15 ng per kilogram of body weight per minute or matching placebo for 48 hours, in addition to accepted therapy. There were greater reductions of NT-proBNP in the ularitide than the placebo group. Death from cardiovascular causes occurred in 21.7% of patients in the ularitide group versus 21.0% in the placebo group (HR, 1.03 [95% CI, 0.85–1.25]; *P*=0.75). Other vasodilators or agents with mainly vasodilating properties were studied. The VERITAS (Value of Endothelin Receptor Inhibition With Tezosentan in Acute Heart Failure Study)[54] examined the effects of the endothelin antagonist tezosentan in AHF. In this study, tezosentan did not improve dyspnea more than placebo, and the mortality rates or worsening HF at 7 days in the combined trials was 26% in both treatment groups. In the second RELAX-AHF-2 (Relaxin in Acute Heart Failure) trial,[55] there was no significant difference in the 5-day rate of worsening HF, which occurred in 6.9% of patients in the serelaxin group and in 7.7% of the placebo group. The death rate at 180 days was similar in the serelaxin group and the placebo group (11.2% and 11.9%, respectively), as was the incidence of death from cardiovascular causes or rehospitalization for HF or renal failure (24.3% and 24.9%, respectively).

Similar results have been seen with inotropic agents. In the OPTIME-CHF (Outcomes of a Prospective Trial

of Intravenous Milrinone for Exacerbation of Chronic Heart Failure),[56] patients with an acute exacerbation of chronic HF were randomly assigned to receive a 48-hour infusion of either milrinone, 0.5 μg/kg per minute initially, or saline placebo. Both groups had the same reduction in HF scale score from baseline to day 3. The milrinone and placebo groups did not differ significantly for in-hospital mortality (3.8% versus 2.3%; $P=0.19$), 60-day mortality (10.3% versus 8.9%; $P=0.41$), or the composite incidence of death or readmission (35.0% versus 35.3%; $P=0.92$). The SURVIVE (Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support) study[57] was a randomized, double-blind trial comparing the efficacy and safety of intravenous levosimendan with dobutamine in patients hospitalized with acute decompensated HF. Although in the levosimendan group there was a greater decrease in B-type natriuretic peptide level at 24 hours that persisted through 5 days compared with the dobutamine group, there was not any difference between the groups in the secondary end points: all-cause mortality at 31 days, number of days alive and out of the hospital, patient global assessment, and patient assessment of dyspnea at 24 hours. All-cause mortality at 180 days occurred in 26% of patients in the levosimendan group and 28% of patients in the dobutamine group ($P=0.40$). In another phase 3 trial of levosimendan, the REVIVE (Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy) trial,[58] the short-term effects of levosimendan were assessed. Patient dyspnea improvement was more pronounced in the levosimendan group at 6, 24, and 48 hours and at 3 and 5 days, and the same improvement was seen for the patient global assessment. However, levosimendan was associated with more frequent hypotension and cardiac arrhythmias during the infusion period, and there was a numerically higher risk of early death across the 2 trials that persisted at day 90 (49 of 350 on a regimen of levosimendan versus 40 of 350 on a regimen of placebo). In the ATOMIC-AHF (Acute Treatment With Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure) trial,[59] omecamtiv mecarbil did not improve dyspnea relief compared with placebo or any of the secondary outcomes studied. All-cause rehospitalization within 30 days occurred in 12.9% of the omecamtiv mecarbil–treated patients and 15.5% in the placebo group, with no significant differences in rates of death (2.6% versus 3.3%, respectively). Finally, in a strategy study, the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness),[60] patients were assigned to receive therapy guided by clinical assessment and a pulmonary artery catheter or clinical assessment alone. Therapy in both groups led to substantial reduction in symptoms, jugular venous pressure, and edema. Use of the pulmonary artery catheter did not significantly affect the primary end point of days alive and out of the hospital during the first 6 months, mortality, or the number of days hospitalized.

The results of these studies have been disappointing to the HF research community and patients. They demonstrate that no intervention to date given during the first days of a hospital admission for AHF, not treatments to reduce congestion, nor vasodilators nor inotropes, nor strategies combining them, improves short- or medium-term outcomes of patients with AHF.

Rapid Introduction of GDMT After an AHF Event Improves Long-Term Outcomes

In recent years, a dramatic shift has occurred in our ability to improve the outcomes of patients after an AHF admission through early implementation of GDMT. First, several retrospective analyses have suggested that patients treated with higher doses of GDMT have better outcomes after AHF.[61] Then, in the span of 2 years between November 2020 to November 2022, 5 major studies were presented and published showing that interventions that reduce neurohormonal adrenergic activation led to substantial improvements in patient outcomes. Early implementation and up-titration to full recommended doses of 4 classes of medications, mineralocorticoid receptor antagonists, β-blockers, renin-angiotensin system inhibitors or angiotensin receptor/neprilysin inhibitors (ARNis), and sodium-glucose cotransporter-2 inhibitors, have been shown to dramatically reduce death and/or HF events during the first 60 to 180 days after an AHF event with striking HRs of 0.49 to 0.62.[62–66] At the American Heart Association meeting in November 2020, 2 studies were presented and published simultaneously. In the first study, AFFIRM-AHF (A Randomized, Double-Blind Placebo Controlled Trial Comparing the Effect of Intravenous Ferric Carboxymaltose on Hospitalizations and Mortality in Iron Deficient Patients Admitted for Acute Heart Failure),[66] patients admitted for AHF with left ventricular ejection fraction <50%, high natriuretic peptides, and iron deficiency were randomized to receive intravenous ferric carboxymaltose or placebo. After 1 year, the primary end point of total hospitalizations for HF and cardiovascular death showed borderline significance (rate ratio [RR], 0.79 [95% CI, 0.62–1.01]; $P=0.059$). The effect was more significant for the end point of first HF hospitalization or cardiovascular death (HR, 0.80 [95% CI, 0.66–0.98]; $P=0.030$). Furthermore, the effects were more pronounced in patients recruited before the COVID-19 epidemic. Patients with AHF with iron deficiency represent >70% of patients with AHF. Simultaneously, the SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart

Failure) study was presented and published.[62] In this study, patients with diabetes and a recent admission for AHF were randomized during the admission or within 72 hours of discharge to receive placebo or the sodium-glucose cotransporter-1 and sodium-glucose cotransporter-2 blocker sotagliflozin. Patients were enrolled without left ventricular ejection fraction limitation. The study was discontinued before its planned sample size was reached because of financial reasons after only 1222 of the planned 4000 patients were enrolled. Despite this substantially reduced sample size, the SOLOIST-WHF study met both its revised and original end points. The rate of cardiovascular death, HF readmissions, or HF urgent visits (revised primary end point) was lower in the sotagliflozin group than in the placebo group (51.0 versus 76.3 events/100 patient-years; RR, 0.67 [95% CI, 0.52–0.85]; $P<0.001$). In addition, the original primary end point of the trial (the first occurrence of either death from cardiovascular causes or hospitalization for HF) was also significantly affected, with an HR of 0.71 (95% CI, 0.56–0.89), as was the effect on quality of life, as measured by the Kansas City Cardiomyopathy Questionnaire score, with a 4.1 (95% CI, 1.3–7.0) point difference. In the PIONEER-HF (Comparison of Sacubitril-Valsartan Versus Enalapril on Effect on NT-proBNP in Patients Stabilized From an Acute Heart Failure Episode) study,[64] patients with HF with reduced ejection fraction who were hospitalized for AHF were randomly assigned to receive sacubitril-valsartan or enalapril. The primary end point, the time-averaged reduction in the NT-proBNP concentration, was significantly greater in the sacubitril-valsartan group than in the enalapril group. Because the study was only powered to changes in NT-proBNP, only 881 patients were enrolled and follow-up was limited to only 8 weeks. Despite the limited size and follow-up, the use of angiotensin receptor/neprilysin inhibitor was associated with a relative 39% reduction in 8-week risk of cardiovascular or HF readmission compared with enalapril (16.3% enalapril versus 9.8% sacubitril/valsartan). In the EMPULSE (Empagliflozin 10 mg Compared to Placebo, Initiated in Patients Hospitalized for Acute Heart Failure [de Novo or Decompensated Chronic HF] Who Have Been Stabilized) study,[63] the sodium-glucose cotransporter 2 inhibitor empagliflozin was compared with placebo in patients at the end of an AHF admission. Again, the study was small: only 530 patients with a diagnosis of AHF regardless of ejection fraction were enrolled and randomly assigned to receive empagliflozin, 10 mg, once daily or placebo. Treatment and follow-up were also limited to 90 days. To evaluate the range of clinical benefit, the investigators chose a hierarchical composite of death from any cause, number of HF events, and time to first HF event, or a ≥5-point difference in change from baseline in the Kansas City Cardiomyopathy Questionnaire total symptom score at 90 days, assessed using a win ratio. The study showed that patients treated with empagliflozin had signicant clinical benefit compared with placebo (stratified win ratio, 1.36 [95% CI, 1.09–1.68]; $P=0.0054$). In addition, there was a 35% reduction in 90-day cardiovascular death or HF event (HR, 0.65 [95% CI, 0.43–0.99]; $P=0.042$[67]). Finally, the STRONG-HF (Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies) trial[65] was a randomized, prospective clinical trial designed to assess the safety and efficacy of a rapid up-titration of GDMT before and after discharge from an admission for AHF. Patients were randomly assigned (1:1) to either usual care (discharge and follow-up according to the local practice until day 90 after randomization) or high-intensity care. In the high-intensity group, patients were administered 50% of maximally recommended doses of β-blocker, renin-angiotensin system inhibitor, and mineralocorticoid receptor antagonist before discharge and full doses at 2 weeks from discharge under strict safety follow-up that included 4 postdischarge visits within 6 weeks. The study enrolled 1078 patients of the planned 1800 patients as it was stopped by the data safety and monitoring committee because of a larger than expected difference in the primary end point (180-day HF hospitalization or death) between groups. At 180 days, risk of HF readmission or all-cause death was lower in the high-intensity care group compared with the usual care group (15.2% versus 23.3%, respectively; $P=0.0021$). The secondary end point of change from baseline to day 90 in EuroQol 5-dimension visual analog scale was markedly improved in the high-intensity care group (10.72 [0.88] versus 7.22 [0.90]; $P<0.0001$).

Treatment effects in these studies (Figure) are larger than those seen in chronic HF studies with the same medications, and therefore when combined with the high event rate after AHF, they are associated with a low number of patients needed to treat to prevent rehospitalization and prolong survival. In fact, we have recently calculated that the number needed to treat of some HF medications when administered for a few months after an AHF event was equal or lower to the number needed to treat in chronic HF studies over a few years of exposure.[68] These improvements were for the most part also accompanied by significant improvements in short-term quality of life.

These substantial new discoveries have largely surprised the scientific community and, apparently, investigators planning those studies. For instance, the sotagliflozin study[62] met its initially prespecified primary end point despite being stopped early because of financial reasons after only 1222 patients were enrolled (and its primary end point changed before the database lock because the investigators did not think the originally planned one could be met). Both the sacubitril/

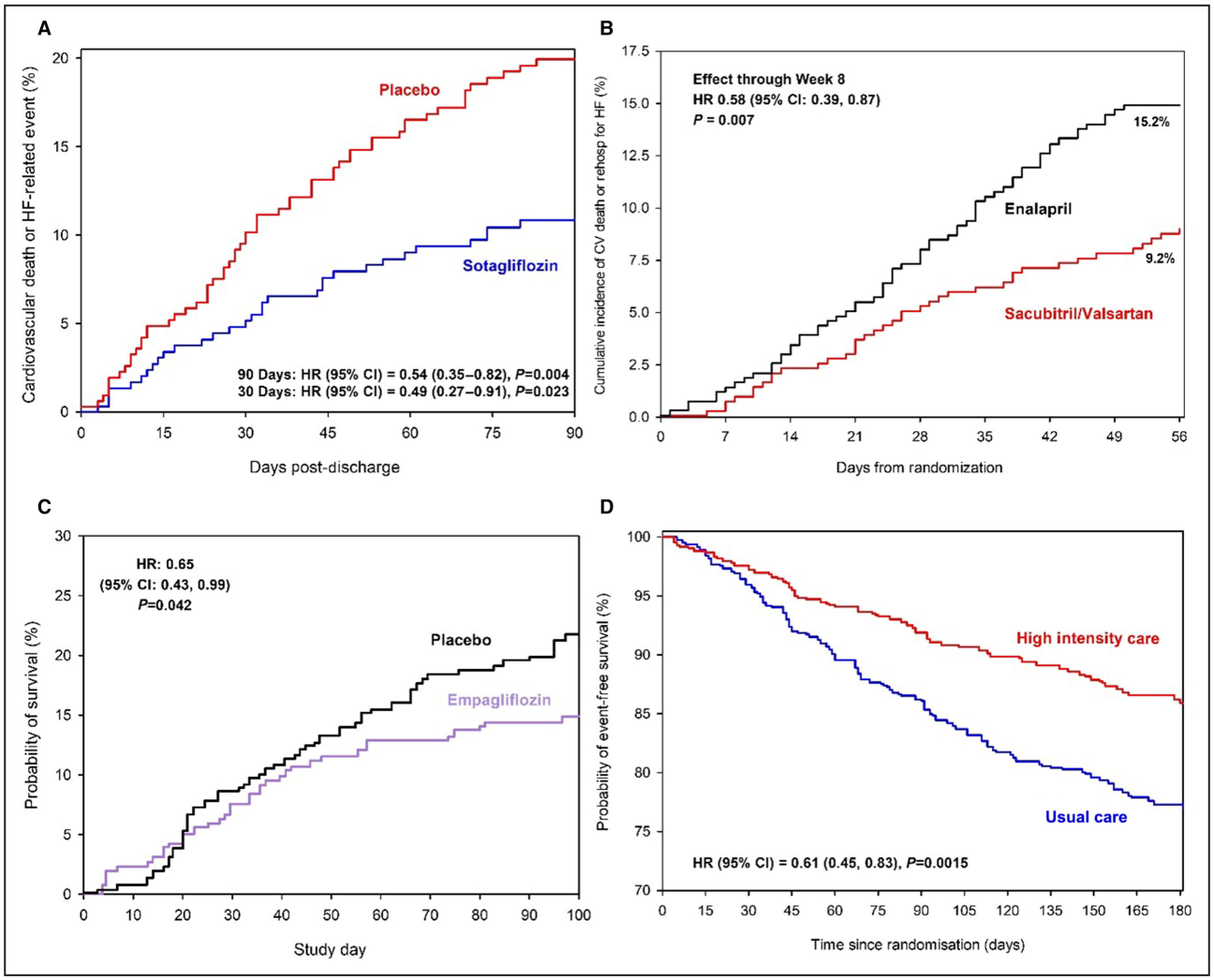

Figure. Effects on outcomes in selected recent studies targeting patients after an acute heart failure (HF) episode.
A, SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure) study: cardiovascular (CV) death and HF-related events over the first 90 days after discharge (Bertram Pitt, personal communication, presented at American Heart Association 2022). **B**, PIONEER-HF (Comparison of Sacubitril-Valsartan Versus Enalapril on Effect on NT-proBNP in Patients Stabilized From an Acute Heart Failure Episode) study: the composite of CV death or rehospitalization for HF (from the study by Morrow et al[64]). **C**, EMPULSE (Empagliflozin 10 mg Compared to Placebo, Initiated in Patients Hospitalized for Acute Heart Failure [de Novo or Decompensated Chronic HF] Who Have Been Stabilized) study: time to all-cause death or first HF event (from the study by Voors[67]). **D**, STRONG-HF (Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies) trial: CV death or HF readmission through 180 days after randomization (from the study by Mebazaa et al[65]). HR indicates hazard ratio.

valsartan study and the empagliflozin study were powered to nonoutcome end points, probably because the investigators did not think the studies were large enough to show a benefit on hard outcomes, only to find they had sufficient power to find statistically significant treatment effects on these outcomes in a post hoc analysis.[63,64] The STRONG-HF study was stopped by the data safety and monitoring board after ≈1000 patients were enrolled because of a larger-than-expected effect on death or HF readmission.[65]

Some have suggested that enhanced follow-up after discharge by itself would be important in preventing the severe adverse outcomes observed in patients after an AHF admission. However, well-powered large studies in which such enhanced follow-up was used but without structured GDMT up-titration did not result in better outcomes,[69–72] suggesting that GDMT up-titration is a critical component in improving patients' outcomes.

Although a new study combining these approaches (the main 4 pillars of HF therapy rapidly up-titrated in a specific HF follow program versus control) will probably never be conducted (because of ethical concerns of denying lifesaving therapies to patients with AHF), we can safely assume that an early up-titration of quadruple therapy (angiotensin receptor/neprilysin inhibitors,

sodium-glucose cotransporter-2 inhibitors, β-blockers, and mineralocorticoid receptor antagonists) plus intravenous iron when indicated would reduce rates of death and HF readmission in the first months after an AHF event by at least 50%.

Additional Considerations During the Admission and Predischarge

In some cases, the treatment implications of precipitating factors discovered during the AHF admission workup are less clear (eg, with valvular heart disease).[23] Because no prospective randomized studies have been conducted examining interventions in patients with AHF and valvular heart disease, and patients with severe valvular heart diseases are commonly excluded from AHF randomized trials, strong recommendations cannot be made, especially with respect to timing and type of procedures. However, because patients with AHF with valvular heart disease are sick with multiple comorbidities and end organ dysfunction, it is likely that percutaneous treatments will be preferred to surgical interventions; some studies are being planned to address those even in patients with cardiogenic shock. Regardless, after being discharged from AHF admission, patients should be considered for a multidisciplinary management program, including cardiologists, a general practitioner, a nurse specialized in HF treatment, plus other personnel.[73,74] A network meta-analysis has suggested that nurse home visits were effective in reducing all-cause mortality and all-cause readmission compared with usual care.[75,76] A special emphasis should be given to the issue of adherence. As previously stated, nonadherence is one of the most quoted reasons for an AHF event, but the estimates of its occurrence vary widely, possibly because in most cases adherence is estimated by patients' self-report and not by objective measures, such as medication blood levels. A 2016 review in the *Journal of the American Heart Association* (*JAHA*) covering 57 studies has found that adherence interventions in patients with HF both reduced mortality and reduced readmissions (odds ratio, 0.79 [95% CI, 0.71–0.89]), with low heterogeneity. This suggests that nonadherence is a driver of AHF events and that it can be modified by appropriate treatment.[77] A recent analysis that examined technological interventions to improve adherence showed only limited benefit,[78] suggesting that a more complex intervention focusing on patients through specific HF clinics may be needed to improve adherence.

Does Preventing AHF Readmission Induce a Remission?

Patients who are admitted with AHF are at risk of repeated AHF admission and death in the 6 to 12 months following an admission.[79–83] Most analyses have shown a *dose-response* association with the number of admissions increasing the risk of mortality, and the risk of mortality being higher after each subsequent admission (ie, the risk of death after the fourth admission in a year is substantially higher than the risk of death after the first admission). Moreover, the risk of recurrent AHF or death increases as the time from the most recent admission is shorter (ie, patients who have not been admitted for a year have a lower risk of admission than those who had an AHF admission in the past 6 months, which, in turn, led to a lower risk for AHF readmission or death if the AHF admission happened in the past 3 months).[84] Hence, preventing an AHF admission may reduce the chance of another admission and dying. Therefore, it is possible that applying GDMT therapy early after an AHF admission and reducing the risk of readmissions early may prevent mortality beyond the immediate effect on mortality (albeit none of which was statistically significant) observed in the SOLOIST-WHF, EMPULSE, PIONEER-HF, and STRONG-HF studies.[62–65] If prevention of one AHF event may prevent the next one and reduce mortality, then patients who have not had an AHF event for 6 months can be defined as *HF in remission*.

A Possible Road Map to the Future

The analogy to oncology is reflected in the terminology proposed in the universal definition of HF, describing the early stages of the HF patient journey as those at risk and with pre-HF analogous to precancerous conditions.[85] Once patients develop AHF, they have equal or more short-term adverse outcomes as the most common cancers; hence, the AHF admission can be termed a malignant condition. Recent evidence shows that these outcomes can be modified by GDMT, available in any country, many of which are generic and relatively inexpensive, with treatment effects that are at least comparable to most chemotherapy and with much milder adverse effects. Therefore, applying GDMT in AHF may induce a remission in the malignant process (ie, patients remain alive and progression free [no repeated AHF admission] for at least 6 months). As each AHF event is associated with more events and mortality, preventing initial events will likely also improve long-term survival. Hence, those who improve on treatment can be thought of being in HF in remission.[85]

If AHF is a malignant condition and safe, effective treatment options exist to allow patients to enter durable remissions, why is this not widely practiced? The lack of clinical implementation cannot be blamed on lack of clinical evidence or shortage of affordable treatment options. We propose that it is a lack of dedicated resources, infrastructure, and organization of

HF management that likely plays a key role. HF therapy is organized around long-term periodic care (ie, seeing patients every few months). If we are to enable induction of remission in patients with HF who decompensate into malignant AHF, health care providers globally would need to adopt an oncological approach to care in patients before and after hospitalization for AHF. During an AHF event and the first weeks after it, the best medical therapy available should be quickly and safely up-titrated under stringent frequent follow-up, with the same urgency as with a patient diagnosed with a lethal malignancy. For this goal, specific dedicated post-AHF clinics may be a possible way to advance such therapy. Such outpatient oncological care centers are in existence in many health care systems globally and hence implementation of postdischarge AHF transitional care clinics, using the oncological service as a blueprint, should be feasible. Although studies examining such enhanced follow-up by themselves did not demonstrate significant benefits, it is highly likely that such post-AHF care when combined with rapid GDMT up-titration would lead to improved patient outcomes. This concept will be tested in the ROBUST-HF (Registry of Best Up-Titration Strategies in Acute Heart Failure) initiative, in which sites globally will attempt to initiate post-AHF clinics specifically targeting patients who are not optimally treated at discharge. Yet, in real life globally, including the United States and Europe, patients are seen several weeks to months after discharge from AHF, as part of their long-term care, and are usually treated by few medications at suboptimal doses,[86] despite important prior efforts, such as Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure[87] and Get With The Guidelines–Heart Failure.[88,89] One can only imagine the public outcry if a patient diagnosed with a malignant treatable cancer had his/her treatment delayed for weeks and months after diagnosis, only to be treated with half the proven chemotherapeutic regimen and even that in low doses.

In summary, AHF is a commonly occurring malignant condition. Beyond the adverse outcomes, it represents one of the largest drivers of health care costs globally. Studies in the past 2 years have demonstrated that we can induce remissions in this malignant process if full therapy is instituted rapidly, at the first AHF episode, using full doses of all available effective medications. We have shown that this goal can be achieved safely and effectively. Now the urgent call is for all stakeholders (patients, physicians, payers, politicians, and the public at large) to come together to address the gaps in implementation and enable health care providers to induce durable remissions in patients with AHF, reducing its staggering economic and health cost.

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REFERENCES

1. Cotter G, Moshkovitz Y, Milovanov O, Salah A, Blatt A, Krakover R, Vered Z, Kaluski E. Acute heart failure: a novel approach to its pathogenesis and treatment. *Eur J Heart Fail*. 2002;4:227–234. doi: 10.1016/S1388-9842(02)00017-X
2. Kimmoun A, Takagi K, Gall E, Ishihara S, Hammoum P, El Bèze N, Bourgeois A, Chassard G, Pegorer-Sfes H, Gayat E, et al. Temporal trends in mortality and readmission after acute heart failure: a systematic review and meta-regression in the past four decades. *Eur J Heart Fail*. 2021;23:420–431. doi: 10.1002/ejhf.2103
3. McDonagh TA, Metra M, Adamo M, Baumbach A, Böhm M, Burri H, Čelutkiene J, Chioncel O, Cleland JGF, Coats AJS, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic

heart failure. *Eur Heart J*. 2021;42:3599–3726. doi: 10.1093/eurheartj/ehab368
4. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145:E895–E1032. doi: 10.1161/CIR.0000000000001063
5. Arrigo M, Jessup M, Mullens W, Reza N, Shah AM, Sliwa K, Mebazaa A. Acute heart failure. *Nat Rev Dis Primers*. 2020;6:16. doi: 10.1038/s41572-020-0151-7
6. Kurmani S, Squire I. Acute heart failure: definition, classification and epidemiology. *Curr Heart Fail Rep*. 2017;14:385–392. doi: 10.1007/s11897-017-0351-y
7. Tomasoni D, Lombardi CM, Sbolli M, Cotter G, Metra M. Acute heart failure: more questions than answers. *Prog Cardiovasc Dis*. 2020;63:599–606. doi: 10.1016/j.pcad.2020.04.007
8. Januzzi JL, Chen-Tournoux AA, Moe G. Amino-terminal pro-B-type natriuretic peptide testing for the diagnosis or exclusion of heart failure in patients with acute symptoms. *Am J Cardiol*. 2008;101:S29–S38. doi: 10.1016/j.amjcard.2007.11.017
9. Allen CJ, Guha K, Sharma R. How to improve time to diagnosis in acute heart failure—clinical signs and chest X-ray. *Card Fail Rev*. 2015;1:69–74. doi: 10.15420/cfr.2015.1.2.69
10. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, Abbastabar H, Abd-Allah F, Abdela J, Abdelalim A, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease study 2017. *Lancet*. 2018;392:1789–1858. doi: 10.1016/S0140-6736(18)32279-7
11. Agarwal MA, Fonarow GC, Ziaeian B. National trends in heart failure hospitalizations and readmissions from 2010 to 2017. *JAMA Cardiol*. 2021;6:952–956. doi: 10.1001/jamacardio.2020.7472
12. Spreafico M, Gasperoni F, Barbati G, Ieva F, Scagnetto A, Zanier L, Iorio A, Sinagra G, Di Lenarda A. Adherence to disease-modifying therapy in patients hospitalized for HF: findings from a community-based study. *Am J Cardiovasc Drugs*. 2020;20:179–190. doi: 10.1007/s40256-019-00367-z
13. Sun LY, Tu JV, Coutinho T, Turek M, Rubens FD, McDonnell L, Tulloch H, Eddeen AB, Mielniczuk LM. Sex differences in outcomes of heart failure in an ambulatory, population-based cohort from 2009 to 2013. *CMAJ*. 2018;190:E848–E854. doi: 10.1503/cmaj.180177
14. Oliva F, Mortara A, Cacciatore G, Chinaglia A, Di Lenarda A, Gorini M, Metra M, Senni M, Maggioni AP, Tavazzi L. Acute heart failure patient profiles, management and in-hospital outcome: results of the Italian Registry on Heart Failure Outcome. *Eur J Heart Fail*. 2012;14:1208–1217. doi: 10.1093/eurjhf/hfs117
15. Logeart D, Isnard R, Resche-Rigon M, Seronde MF, de Groote P, Jondeau G, Galinier M, Mulak G, Donal E, Delahaye F, et al. Current aspects of the spectrum of acute heart failure syndromes in a real-life setting: the OFICA study. *Eur J Heart Fail*. 2013;15:465–476. doi: 10.1093/eurjhf/hfs189
16. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, Nodari S, Lam CSP, Sato N, Shah AN, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol*. 2014;63:1123–1133. doi: 10.1016/j.jacc.2013.11.053
17. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, Ferrari R, Piepoli MF, Delgado Jimenez JF, Metra M, et al. European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *Eur J Heart Fail*. 2016;18:613–625. doi: 10.1002/ejhf.566
18. Chioncel O, Mebazaa A, Maggioni AP, Harjola VP, Rosano G, Laroche C, Piepoli MF, Crespo-Leiro MG, Lainscak M, Ponikowski P, et al. Acute heart failure congestion and perfusion status—impact of the clinical classification on in-hospital and long-term outcomes; insights from the ESC-EORP-HFA heart failure long-term registry. *Eur J Heart Fail*. 2019;21:1338–1352. doi: 10.1002/ejhf.1492
19. Javaloyes P, Miró Ò, Gil V, Martín-Sánchez FJ, Jacob J, Herrero P, Takagi K, Alquézar-Arbé A, López Díez MP, Martín E, et al. Clinical phenotypes of acute heart failure based on signs and symptoms of perfusion and congestion at emergency department presentation and their relationship with patient management and outcomes. *Eur J Heart Fail*. 2019;21:1353–1365. doi: 10.1002/ejhf.1502
20. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, Hochadel M, Komajda M, Lassus J, Lopez-Sendon JL, et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J*. 2006;27:2725–2736. doi: 10.1093/eurheartj/ehl193
21. Vorilhon C, Chenaf C, Mulliez A, Pereira B, Clerfond G, Authier N, Jean F, Motreff P, Citron B, Eschalier A, et al. Heart failure prognosis and management in over-80-year-old patients: data from a French national observational retrospective cohort. *Eur J Clin Pharmacol*. 2015;71:251–260. doi: 10.1007/s00228-014-1794-7
22. Wang TD, Huang ST, Wang CY, Lin FJ, Chen HM, Hsiao FY. Nationwide trends in incidence, healthcare utilization, and mortality in hospitalized heart failure patients in Taiwan. *ESC Heart Fail*. 2020;7:3653–3666. doi: 10.1002/ehf2.12892
23. Chioncel O, Adamo M, Nikolaou M, Parissis J, Mebazaa A, Yilmaz MB, Hassager C, Moura B, Bauersachs J, Harjola VP, et al. Acute heart failure and valvular heart disease: a scientific statement of the Heart Failure Association, the Association for Acute CardioVascular Care and the European Association of Percutaneous Cardiovascular Interventions of the European Society of Cardiology. *Eur J Heart Fail*. 2023;25:1025–1048. doi: 10.1002/ejhf.2918
24. Greene SJ, Fonarow GC, Vaduganathan M, Khan SS, Butler J, Gheorghiade M. The vulnerable phase after hospitalization for heart failure. *Nat Rev Cardiol*. 2015;12:220–229. doi: 10.1038/nrcardio.2015.14
25. Zannad F, Cotter G, Alonso Garcia A, George S, Davison B, Figtree G, Prasad K, Rockhold F, Schilsky RL, Stockbridge N, et al. What can heart failure trialists learn from oncology trialists? *Eur Heart J*. 2021;42:2373–2383. doi: 10.1093/eurheartj/ehab236
26. Khan MS, Sreenivasan J, Lateef N, Abougergi MS, Greene SJ, Ahmad T, Anker SD, Fonarow GC, Butler J. Trends in 30- and 90-day readmission rates for heart failure. *Circ Heart Fail*. 2021;14:E008335. doi: 10.1161/CIRCHEARTFAILURE.121.008335
27. Philbin EF, Rocco TA, Lindenmuth NW, Ulrich K, Jenkins PL. Clinical outcomes in heart failure: report from a community hospital-based registry. *Am J Med*. 1999;107:549–555. doi: 10.1016/S0002-9343(99)00309-5
28. Cleland JGF, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, Dietz R, Gavazzi A, Hobbs R, Korewicki J, et al. The EuroHeart Failure survey programme—a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. *Eur Heart J*. 2003;24:442–463. doi: 10.1016/S0195-668X(02)00823-0
29. Tavazzi L, Maggioni AP, Lucci D, Cacciatore G, Ansalone G, Oliva F, Porcu M. Nationwide survey on acute heart failure in cardiology ward services in Italy. *Eur Heart J*. 2006;27:1207–1215. doi: 10.1093/eurheartj/ehi845
30. Koh AS, Tay WT, Teng THK, Vedin O, Benson L, Dahlstrom U, Savarese G, Lam CSP, Lund LH. A comprehensive population-based characterization of heart failure with mid-range ejection fraction. *Eur J Heart Fail*. 2017;19:1624–1634. doi: 10.1002/ejhf.945
31. Miró Ò, Padrosa J, Takagi K, Gayat É, Gil V, Llorens P, Martín-Sánchez FJ, Herrero-Puente P, Jacob J, Montero MM, et al. Influence of the length of hospitalisation in post-discharge outcomes in patients with acute heart failure: results of the LOHRCA study. *Eur J Intern Med*. 2019;70:24–32. doi: 10.1016/j.ejim.2019.08.007
32. Lee SE, Lee HY, Cho HJ, Choe WS, Kim H, Choi JO, Jeon ES, Kim MS, Kim JJ, Hwang KK, et al. Clinical characteristics and outcome of acute heart failure in Korea: results from the Korean Acute Heart Failure Registry (KorAHF). *Korean Circ J*. 2017;47:341–353. doi: 10.4070/kcj.2016.0419
33. Ling HS, Chung BK, Chua PF, Gan KX, Ho WL, Ong EYL, Kueh CHS, Chin YP, Fong AYY. Acute decompensated heart failure in a non cardiology tertiary referral centre, Sarawak general hospital (SGH-HF). *BMC Cardiovasc Disord*. 2020;20:511. doi: 10.1186/s12872-020-01793-7
34. Harikrishnan S, Bahl A, Roy A, Mishra A, Prajapati J, Manjunath CN, Sethi R, Guha S, Satheesh S, Dhaliwal RS, et al. Clinical profile and 90 day outcomes of 10 851 heart failure patients across India: National Heart Failure Registry. *ESC Heart Fail*. 2022;9:3898–3908. doi: 10.1002/ehf2.14096
35. Joseph S, Panniyammakal J, Abdullakutty J, Vaikathuseril LJ, Joseph J, Mattummal S, Punnose E, Unni G, Natesan S, Sivadasanpillai H. The Cardiology Society of India-Kerala Acute Heart Failure Registry: poor adherence to guideline-directed medical therapy. *Eur Heart J*. 2022;43:908–915. doi: 10.1093/eurheartj/ehab793
36. Seth S, Khanal S, Ramakrishnan S, Gupta N, Bahl VK. Epidemiology of acute decompensated heart failure in India: the AFAR study

(Acute Failure registry study). *J Pract Cardiovasc Sci*. 2015;1:35. doi: 10.4103/2395-5414.157563
37. Shiba M, Kato T, Morimoto T, Yaku H, Inuzuka Y, Tamaki Y, Ozasa N, Seko Y, Yamamoto E, Yoshikawa Y, et al. Changes in BNP levels from discharge to 6-month visit predict subsequent outcomes in patients with acute heart failure. *PLoS One*. 2022;17:e0263165. doi: 10.1371/journal.pone.0263165
38. Fairman E, Mtsac J, Rodriguez L, Blanco P, Guetta J, Fernández S, Marturano M, Botto F, Borracci R. 2007 National registry of admissions due to heart failure. *Rev Argent Cardiol*. 2009;77:33–39.
39. Damasceno A, Mayosi BM, Sani M, Ogah OS, Mondo C, Ojji D, Dzudie A, Kouam C, Suliman A, Schrueder N, et al. The causes, treatment, and outcome of acute heart failure in 1006 Africans from 9 countries. *Arch Intern Med*. 2012;172:1386–1394. doi: 10.1001/archinternmed.2012.3310
40. Foroutan F, Rayner DG, Ross HJ, Ehler T, Srivastava A, Shin S, Malik A, Benipal H, Yu C, Alexander Lau TH, et al. Global comparison of readmission rates for patients with heart failure. *J Am Coll Cardiol*. 2023;82:430–444. doi: 10.1016/j.jacc.2023.05.040
41. Cotter G, Metzkor E, Kaluski E, Faigenberg Z, Miller R, Simovitz A, Shaham O, Marghitay D, Koren M, Blatt A, et al. Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. *Lancet*. 1998;351:389–393. doi: 10.1016/S0140-6736(97)08417-1
42. Sharon A, Shpirer I, Kaluski E, Moshkovitz Y, Milovanov O, Polak R, Blatt A, Simovitz A, Shaham O, Faigenberg Z, et al. High-dose intravenous isosorbide-dinitrate is safer and better than Bi-PAP ventilation combined with conventional treatment for severe pulmonary edema. *J Am Coll Cardiol*. 2000;36:832–837. doi: 10.1016/S0735-1097(00)00785-3
43. Freund Y, Cachanado M, Delannoy Q, Laribi S, Yordanov Y, Gorlicki J, Chouihed T, Féral-Pierssens AL, Truchot J, Desmettre T, et al. Effect of an emergency department care bundle on 30-day hospital discharge and survival among elderly patients with acute heart failure: the ELISABETH randomized clinical trial. *JAMA*. 2020;324:1948–1956. doi: 10.1001/jama.2020.19378
44. Gray AJ, Goodacre S, Newby DE, Masson MA, Sampson F, Dixon S, Crane S, Elliott M, Nicholl J; 3CPO Study Investigators. A multicentre randomised controlled trial of the use of continuous positive airway pressure and non-invasive positive pressure ventilation in the early treatment of patients presenting to the emergency department with severe acute cardiogenic pulmonary oedema: the 3CPO trial. *Health Technol Assess*. 2009;13:1–106. doi: 10.3310/hta13330
45. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, et al. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med*. 2011;364:797–805. doi: 10.1056/NEJMoa1005419
46. Mullens W, Dauw J, Martens P, Verbrugge FH, Nijst P, Meekers E, Tartaglia K, Chenot F, Moubayed S, Dierckx R, et al. Acetazolamide in acute decompensated heart failure with volume overload. *N Engl J Med*. 2022;387:1185–1195. doi: 10.1056/NEJMoa2203094
47. Trullàs JC, Morales-Rull JL, Casado J, Carrera-Izquierdo M, Sánchez-Marteles M, Conde-Martel A, Dávila-Ramos MF, Llácer P, Salamanca-Bautista P, Pérez-Silvestre J, et al. Combining loop with thiazide diuretics for decompensated heart failure: the CLOROTIC trial. *Eur Heart J*. 2023;44:411–421. doi: 10.1093/eurheartj/ehac689
48. Konstam MA, Gheorghiade M, Burnett JC, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST outcome trial. *JAMA*. 2007;297:1319–1331. doi: 10.1001/jama.297.12.1319
49. Massie BM, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, Weatherley BD, Cleland JGF, Givertz MM, Voors A, et al. Rolofylline, an adenosine A1-receptor antagonist, in acute heart failure. *N Engl J Med*. 2010;363:1419–1428. doi: 10.1056/NEJMoa0912613
50. Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA, Redfield MM, Deswal A, Rouleau JL, LeWinter MM, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med*. 2012;367:2296–2304. doi: 10.1056/NEJMoa1210357
51. Kozhuharov N, Goudev A, Flores D, Maeder MT, Walter J, Shrestha S, Gualandro DM, De Oliveira Junior MT, Sabti Z, Müller B, 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. doi: 10.1001/jama.2019.18598
52. O'Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, Heizer GM, Komajda M, Massie BM, McMurray JJV, et al. Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med*. 2011;365:32–43. doi: 10.1056/NEJMoa1100171
53. Packer M, O'Connor C, McMurray JJV, Wittes J, Abraham WT, Anker SD, Dickstein K, Filippatos G, Holcomb R, Krum H, et al. Effect of ularitide on cardiovascular mortality in acute heart failure. *N Engl J Med*. 2017;376:1956–1964. doi: 10.1056/NEJMoa1601895
54. McMurray JJV, Teerlink JR, Cotter G, Bourge RC, Cleland JGF, Jondeau G, Krum H, Metra M, O'Connor CM, Parker JD, et al. Effects of tezosentan on symptoms and clinical outcomes in patients with acute heart failure: the VERITAS randomized controlled trials. *JAMA*. 2007;298:2009–2019. doi: 10.1001/jama.298.17.2009
55. Metra M, Teerlink JR, Cotter G, Davison BA, Felker GM, Filippatos G, Greenberg BH, Pang PS, Ponikowski P, Voors AA, et al. Effects of serelaxin in patients with acute heart failure. *N Engl J Med*. 2019;381:716–726. doi: 10.1056/NEJMoa1801291
56. Cuffe MS, Califf RM, Adams KF, Benza R, Bourge R, Colucci WS, Massie BM, O'Connor CM, Pina I, Quigg R, et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA*. 2002;287:1541–1547. doi: 10.1001/jama.287.12.1541
57. Mebazaa A, Nieminen MS, Packer M, Cohen-Solal A, Kleber FX, Pocock SJ, Thakkar R, Padley RJ, Põder P, Kivikko M. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE randomized trial. *JAMA*. 2007;297:1883–1891. doi: 10.1001/jama.297.17.1883
58. Packer M, Colucci W, Fisher L, Massie BM, Teerlink JR, Young J, Padley RJ, Thakkar R, Delgado-Herrera L, Salon J, et al. Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure. *JACC Heart Fail*. 2013;1:103–111. doi: 10.1016/j.jchf.2012.12.004
59. Teerlink JR, Felker GM, McMurray JJV, Ponikowski P, Metra M, Filippatos GS, Ezekowitz JA, Dickstein K, Cleland JGF, Kim JB, et al. Acute treatment with omecamtiv mecarbil to increase contractility in acute heart failure: the ATOMIC-AHF study. *J Am Coll Cardiol*. 2016;67:1444–1455. doi: 10.1016/j.jacc.2016.01.031
60. Hill JA, Pauly DF, Olitsky DR, Russell S, O'Connor CM, Patterson B, Elkayam U, Khan S, Stevenson LW, Brooks K, et al. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. *JAMA*. 2005;294:1625–1633. doi: 10.1001/jama.294.13.1625
61. Gayat E, Arrigo M, Littnerova S, Sato N, Parenica J, Ishihara S, Spinar J, Müller C, Harjola VP, Lassus J, et al. Heart failure oral therapies at discharge are associated with better outcome in acute heart failure: a propensity-score matched study. *Eur J Heart Fail*. 2018;20:345–354. doi: 10.1002/ejhf.932
62. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, Lewis JB, Riddle MC, Voors AA, Metra M, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med*. 2021;384:117–128. doi: 10.1056/NEJMoa2030183
63. Voors AA, Angermann CE, Teerlink JR, Collins SP, Kosiborod M, Biegus J, Ferreira JP, Nassif ME, Psotka MA, Tromp J, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. *Nat Med*. 2022;28:568–574. doi: 10.1038/s41591-021-01659-1
64. Morrow DA, Velazquez EJ, Devore AD, Desai AS, Duffy CI, Ambrosy AP, Gurmu Y, Mccague K, Rocha R, Braunwald E. Clinical outcomes in patients with acute decompensated heart failure randomly assigned to sacubitril/valsartan or enalapril in the PIONEER-HF trial. *Circulation*. 2019;139:2285–2288. doi: 10.1161/CIRCULATIONAHA.118.039331
65. Mebazaa A, Davison B, Chioncel O, Cohen-Solal A, Diaz R, Filippatos G, Metra M, Ponikowski P, Sliwa K, Voors AA, 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;400:1938–1952. doi: 10.1016/S0140-6736(22)02076-1
66. Ponikowski P, Kirwan BA, Anker SD, McDonagh T, Dorobantu M, Drozdz J, Fabien V, Filippatos G, Göhring UM, Keren A, 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. doi: 10.1016/S0140-6736(20)32339-4
67. Voors AA. EMPULSE—EFFICACY and safety of Empagliflozin in hospitalized heart failure patients: main results from the EMPULSE trial.

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68. Cotter G, Davison B, Cohen-Solal A, Freund Y, Mebazaa A. Targeting the "vulnerable" period—first 3–6 months after an acute heart failure admission—the light gets brighter. *Eur J Heart Fail*. 2023;25:30–34. doi: 10.1002/ejhf.2754
69. Van Spall HGC, Lee SF, Xie F, Oz UE, Perez R, Mitoff PR, Maingi M, Tjandrawidjaja MC, Heffernan M, Zia MI, 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. doi: 10.1001/jama.2019.0710
70. Jaarsma T, Van Der Wal MHL, Lesman-Leegte I, Luttik ML, Hogenhuis J, Veeger NJ, Sanderman R, Hoes AW, Van Gilst WH, Lok DJA, et al. Effect of moderate or intensive disease management program on outcome in patients with heart failure: Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure (COACH). *Arch Intern Med*. 2008;168:316–324. doi: 10.1001/archinternmed.2007.83
71. Devore AD, Granger BB, Fonarow GC, Al-Khalidi HR, Albert NM, Lewis EF, Butler J, Piña IL, Allen LA, Yancy CW, 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. doi: 10.1001/jama.2021.8844
72. Logeart D, Berthelot E, Bihry N, Eschalier R, Salvat M, Garcon P, Eicher JC, Cohen A, Tartiere JM, Samadi A, et al. Early and short-term intensive management after discharge for patients hospitalized with acute heart failure: a randomized study (ECAD-HF). *Eur J Heart Fail*. 2022;24:219–226. doi: 10.1002/ejhf.2357
73. Li M, Li Y, Meng Q, Li Y, Tian X, Liu R, Fang J. Effects of nurse-led transitional care interventions for patients with heart failure on healthcare utilization: a meta-analysis of randomized controlled trials. *PLoS One*. 2021;16:e0261300. doi: 10.1371/journal.pone.0261300
74. Raat W, Smeets M, Janssens S, Vaes B. Impact of primary care involvement and setting on multidisciplinary heart failure management: a systematic review and meta-analysis. *ESC Heart Fail*. 2021;8:802–818. doi: 10.1002/ehf2.13152
75. Van Spall HGC, Rahman T, Mytton O, Ramasundarahettige C, Ibrahim Q, Kabali C, Coppens M, Brian Haynes R, Connolly S. 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. doi: 10.1002/ejhf.765
76. Thodi M, Bistola V, Lambrinou E, Keramida K, Nikolopoulos P, Parissis J, Farmakis D, Filippatos G. A randomized trial of a nurse-led educational intervention in patients with heart failure and their caregivers: impact on caregiver outcomes. *Eur J Cardiovasc Nurs*. 2022:zvac118. doi: 10.1093/eurjcn/zvac118
77. Ruppar TM, Cooper PS, Mehr DR, Delgado JM, Dunbar-Jacob JM. Medication adherence interventions improve heart failure mortality and readmission rates: systematic review and meta-analysis of controlled trials. *J Am Heart Assoc*. 2016;5:e002606. doi: 10.1161/JAHA.115.002606
78. Cheng C, Donovan G, Al-Jawad N, Jalal Z. The use of technology to improve medication adherence in heart failure patients: a systematic review of randomised controlled trials. *J Pharm Policy Pract*. 2023;16:81. doi: 10.1186/s40545-023-00582-9
79. Setoguchi S, Stevenson LW, Schneeweiss S. Repeated hospitalizations predict mortality in the community population with heart failure. *Am Heart J*. 2007;154:260–266. doi: 10.1016/j.ahj.2007.01.041
80. Lee DS, Austin PC, Stukel TA, Alter DA, Chong A, Parker JD, Tu JV. "Dose-dependent" impact of recurrent cardiac events on mortality in patients with heart failure. *Am J Med*. 2009;122:162–169.e1. doi: 10.1016/j.amjmed.2008.08.026
81. Huusko J, Tuominen S, Studer R, Corda S, Proudfoot C, Lassenius M, Ukkonen H. Recurrent hospitalizations are associated with increased mortality across the ejection fraction range in heart failure. *ESC Heart Fail*. 2020;7:2406–2417. doi: 10.1002/ehf2.12792
82. Lindmark K, Boman K, Stålhammar J, Olofsson M, Lahoz R, Studer R, Proudfoot C, Corda S, Fonseca AF, Costa-Scharplatz M, et al. Recurrent heart failure hospitalizations increase the risk of cardiovascular and all-cause mortality in patients with heart failure in Sweden: a real-world study. *ESC Heart Fail*. 2021;8:2144–2153. doi: 10.1002/ehf2.13296
83. Solomon SD, Dobson J, Pocock S, Skali H, McMurray JJV, Granger CB, Yusuf S, Swedberg K, Young JB, Michelson EL, et al. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. *Circulation*. 2007;116:1482–1487. doi: 10.1161/CIRCULATIONAHA.107.696906
84. Bello NA, Claggett B, Desai AS, McMurray JJV, Granger CB, Yusuf S, Swedberg K, Pfeffer MA, Solomon SD. Influence of previous heart failure hospitalization on cardiovascular events in patients with reduced and preserved ejection fraction. *Circ Heart Fail*. 2014;7:590–595. doi: 10.1161/CIRCHEARTFAILURE.113.001281
85. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, Anker SD, Atherton J, Böhm M, Butler J, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. *Eur J Heart Fail*. 2021;23:352–380. doi: 10.1002/ejhf.2115
86. Laveau F, Hammoudi N, Berthelot E, Belmin J, Assayag P, Cohen A, Damy T, Duboc D, Dubourg O, Hagege A, et al. Patient journey in decompensated heart failure: an analysis in departments of cardiology and geriatrics in the greater Paris university hospitals. *Arch Cardiovasc Dis*. 2017;110:42–50. doi: 10.1016/j.acvd.2016.05.009
87. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, O'Connor CM, Pieper K, Jie LS, Yancy C, et al. Association between performance measures and clinical outcomes for patients hospitalized with heart failure. *JAMA*. 2007;297:61–70. doi: 10.1001/jama.297.1.61
88. Hong Y, LaBresh KA. Overview of the American Heart Association "Get With the Guidelines" programs: coronary heart disease, stroke, and heart failure. *Crit Pathw Cardiol*. 2006;5:179–186. doi: 10.1097/01.hpc.0000243588.00012.79
89. LaBresh KA, Gliklich R, Liljestrand J, Peto R, Ellrodt AG. Using "Get With the Guidelines" to improve cardiovascular secondary prevention. *Jt Comm J Qual Saf*. 2003;29:539–550. doi: 10.1016/S1549-3741(03)29064-X