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References

1. RYBELSUS® (summary of product characteristics). Bagsværd, Denmark: Novo Nordisk A/S; June 2022. **2.** Rosenstock J, Allison D, Birkenfeld AL, et al. Effect of additional oral semaglutide vs sitagliptin on glycated hemoglobin in adults with type 2 diabetes uncontrolled with metformin alone or with sulfonylurea: the PIONEER 3 randomized clinical trial. *JAMA*. 2019;321(15):1466-1480. **3.** Rodbard HW, Rosenstock J, Canani LH, et al. Oral semaglutide versus empagliflozin in patients with type 2 diabetes uncontrolled on metformin: the PIONEER 2 trial. *Diabetes Care*. 2019;42(12):2272-2281. **4.** Pratley R, Amod A, Hoff ST,et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. *Lancet*. 2019;394(10192):39-50.

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CONSENSUS STATEMENT

Pre-discharge and early post-discharge management of patients hospitalized for acute heart failure: A scientific statement by the Heart Failure Association of the ESC

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Acute heart failure is a major cause of urgent hospitalizations. These are followed by marked increases in death and rehospitalization rates, which then decline exponentially though they remain higher than in patients without a recent hospitalization. Therefore, optimal management of patients with acute heart failure before discharge and in the early post-discharge phase is critical. First, it may prevent rehospitalizations through the early detection and effective treatment of residual or recurrent congestion, the main manifestation of decompensation. Second, initiation at pre-discharge and titration to target doses in the early post-discharge period, of guideline-directed medical therapy may improve both short- and long-term outcomes. Third, in chronic heart failure, medical treatment is often left unchanged, so the acute heart failure hospitalization presents an opportunity for implementation of therapy. The aim of this scientific statement by the Heart Failure Association of the European Society of Cardiology is to summarize recent findings that have implications for clinical management both in the pre-discharge and the early post-discharge phase after a hospitalization for acute heart failure.

Keywords Acute heart failure • Pre-discharge • Early post-discharge • Management • Prognosis

Preamble

Acute heart failure (AHF) is a frequent and life-threatening condition. It is a leading cause of hospitalizations and is associated with high mortality and rehospitalization rates.[1–8] According to the 2021 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic heart failure (HF), management of patients hospitalized for AHF can be divided into three stages having different goals and requiring different approaches: pre-hospital/early hospital (immediate), in-hospital (intermediate), and pre-discharge/early post-discharge.[9] Pre-hospital and in-hospital phases are mainly focused on the diagnosis and identification of the aetiology, patient stabilization, monitoring of vital signs, empirical treatment of congestion and/or hypoperfusion, and initiation of evidence-based treatments.[9,10] Pre-discharge and early post-discharge management strategies are beginning to be studied in trials, but implementation is more challenging. A significant proportion of patients with AHF are discharged with persistent congestion, which is known to be associated with a higher risk of readmission and mortality.[3] The risk of readmissions and death is highest in the first weeks after discharge and decreases exponentially thereafter. In addition, patient follow-up is often absent or woefully insufficient in this phase, exposing patients to an increased risk. Finally, medical treatment established in the pre- and early post-discharge phases remains generally unchanged during subsequent consultations making these phases critical, not only for the increased risk, but also for the suboptimal treatment[2,11,12] (*Figure 1*).

Improvement of early post-discharge and long-term outcomes by optimizing pre- and post-discharge management of patients with AHF is a major unmet need. This scientific statement of the Heart Failure Association (HFA) of the ESC aims to provide a summary of current evidence about pre-discharge and early post-discharge management of patients hospitalized for AHF. Of note, this document refers to acute decompensated heart failure (ADHF) and acute pulmonary oedema since they are the most common clinical presentations of AHF and those where we have evidence from prospective clinical trials. The two other clinical presentations of AHF, cardiogenic shock and right HF,[9] are excluded from this consensus article and are extensively considered in other statements.[13,14] Recommendations for clinical practice can be found in the 2021 ESC guidelines for the treatment of HF.[9]

Impact of acute heart failure hospitalizations on subsequent outcome

In-hospital mortality of patients admitted for AHF ranges between 4% and 10%.[3,4,15] Post-discharge 1-year mortality is much greater, averaging 25–30% and more than one third of patients are readmitted in the first 6 months after discharge.[4,6,9,11,16–19] Compared to patients who are not hospitalized, those hospitalized for AHF have a more than six-fold increase in the risk of death in the first month after discharge. This is followed by an almost exponential decrease in mortality but there is a persistent two-fold increase in the risk for up to 2 years after discharge.[11] Each readmission is associated with higher rates of subsequent rehospitalizations, emergency visits and death.[1,11,15,20] The increase in the risk of death may be up to 12 to 16-fold in patients who have had multiple hospitalizations or longer ones, compared to that of patients recently admitted to the hospital due to AHF.[11] AHF could be the first manifestation of HF, referred to as 'new-onset HF' or 'de-novo HF', or a more commonly decompensation of a chronic condition. Patients with de-novo HF may have a higher in-hospital mortality, but may have lower post-discharge mortality and readmissions because of the beneficial effect of new treatment initiation.[4,15,21]

Pre-discharge assessment

During the pre-discharge phase, a multiparametric evaluation, including clinical assessment and use of biomarkers and imaging, is mandatory in order to: (1) exclude or minimize persistent congestion; (2) optimize guideline-directed medical therapy (GDMT); (3) plan post-discharge management, including up-titration of the

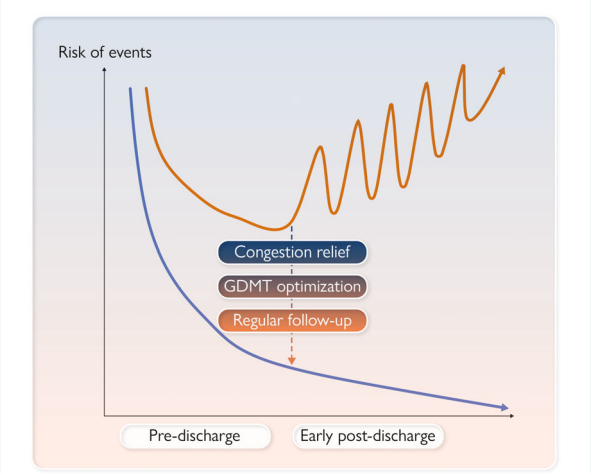

Figure 1 Determinants of better outcome after discharge. Optimal decongestion, optimization of guideline-directed medical therapy (GDMT) and intensive post-discharge monitoring reduce mortality and new heart failure events after discharge.

GDMT and specific post-discharge programmes (i.e., rehabilitation, home-visiting programmes) (*Figure 1*).

Factors related to an increased risk of residual congestion at discharge and/or early readmission after discharge are reported in *Table 1*.

Table 1 Risk factors of residual congestion at discharge and/or for heart failure readmission

Clinical factors
• NYHA class >2
• ≥ 1 HF hospitalization within 6 months
• Low blood pressure (SBP <90 mmHg)
Factors related to therapies
• GDMT discontinuation during hospitalization
• Intolerance to GDMT
• High diuretic dose
Laboratory exams
• Renal dysfunction
• Electrolyte disturbance
• High NP levels
• Anaemia
ECG and imaging
• QRS duration >130 ms without CRT
• Ventricular arrhythmias
• LVEF <20%
• High pulmonary pressure
• High LV filling pressures
• Moderate/severe tricuspid regurgitation
• IVC >21 mm
• B-lines >15
Comorbidities
• Diabetes mellitus
• Valvular heart disease
• Coronary artery disease
• Atrial fibrillation
• Pulmonary disease
• Frailty

CRT, cardiac resynchronization therapy; ECG, electrocardiogram; GDMT, guideline-directed medical therapy; HF, heart failure; IVC, inferior vena cava; LV, left ventricular; LVEF, left ventricular ejection fraction; NP, natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.

Clinical assessment

Clinical assessment is useful to detect signs of congestion,[22–26] but the accuracy of physical examination for the detection of congestion is low.[23,27–29] Several congestion scores (CS) including symptoms (dyspnoea, orthopnoea, fatigue) and signs of HF (rales, peripheral oedema, jugular vein distension, hepatomegaly) have been proposed.[27] A CS and a simplified CS are reported in online supplementary *Table S1*.[22,30] In a post hoc analysis of the EVEREST (Efficacy of Vasopressin Antagonism in HF Outcome Study with Tolvaptan) trial, mild (CS 1–2) and severe congestion (CS >2) at discharge were associated with an incremental risk of readmission and mortality at 1 year after HF hospitalization.[22] Body weight and New York Heart Association (NYHA) functional class should also be assessed before discharge and integrated with other clinical evaluations (*Figure 2*).

Measurement of blood pressure and heart rate is mandatory both for prognostic stratification and for personalization of GDMT.[24,25,31] Patients with hypotension may be less likely to tolerate angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) and, even less, angiotensin receptor–neprilysin inhibitors (ARNI).[32–34] Patients with congestion may not tolerate early introduction of beta-blockers.

Signs of congestion and hypoperfusion may be present at the time of discharge and are associated with worse outcomes.[3,9,15,35–37] An analysis of the ESC-EUROObservational Research Programme (EORP)-Heart Failure Association (HFA) HF Long-Term Registry showed signs of residual congestion in 30.9% of the patients discharged after an AHF hospitalization.[3]

Laboratory measurements

Natriuretic peptides (NPs) have a major role in the diagnosis, risk stratification, and management of patients with AHF.[9,38–40] They are important markers of congestion.[39,41,42] In addition to their values at the time of discharge, the change in NP concentration

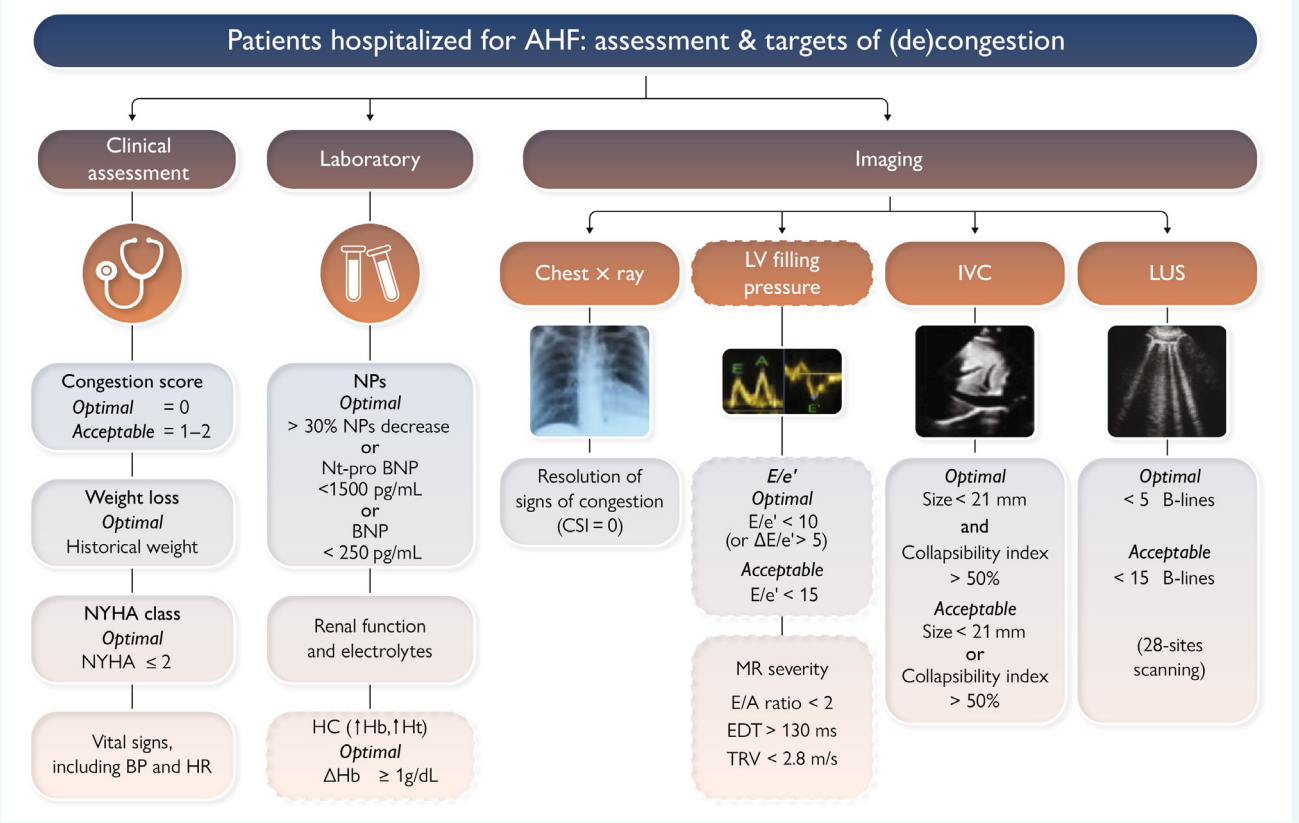

Figure 2 Assessment and targets of decongestion during the pre-discharge phase. Clinical, laboratory and imaging factors to assess before discharge and relative targets are reported. AHF, acute heart failure; BP, blood pressure; BNP, B-type natriuretic peptide; CSI, congestion score index; EDT, E-wave deceleration time; Hb, haemoglobin; HC, haemoconcentration; HR, heart rate; Ht, haematocrit; IVC, inferior vena cava; LUS, lung ultrasound; LV, left ventricular; NP, natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; TRV, tricuspid regurgitation velocity.

during hospitalization is a powerful predictor of post-discharge outcome[39,41–44] (*Figure 2*). Current ESC HF guidelines recommend measurement of NPs both at time of hospitalization and before discharge.[9]

The prognostic value of both absolute levels and relative changes of B-type natriuretic peptide (BNP)/N-terminal proBNP (NT-proBNP) at discharge has been studied in patients with AHF.[41,45,46] The ELAN-HF (European Collaboration on Acute Decompensated HF) score, which was developed from data collected from seven European cohorts of patients admitted with AHF, found that both the absolute discharge NT-proBNP level and the percentage reduction of NT-proBNP at discharge were strong predictors of 180-day mortality. The study showed that the 180-day cumulative mortality rate was 4.1% among patients with an absolute NT-proBNP discharge level of <1500 pg/ml. This mortality rate more than doubled to 10% when the NT-proBNP discharge level was between 1500 and 5000 pg/ml and then again doubled to 24% when the NT-proBNP discharge level was between 5001 and 15 000 pg/ml. Patients with a NT-proBNP discharge level of >15 000 pg/ml had a mortality rate of 41%. In addition, the study found that patients with a NT-proBNP reduction of ≤30% had twice the 180-day cumulative mortality rate compared to patients with a NT-proBNP reduction of >30%.[47] These findings suggest that measuring absolute levels and changes in NT-proBNP at discharge can help identify patients at high risk of mortality and facilitate appropriate management strategies.

Prospective randomized trials assessing the efficacy of a strategy based on measurements of NT-proBNP levels to guide therapy in high-risk patients with HF have failed to show a significant benefit compared to usual care.[48,49] More recently, serial measurements of NT-proBNP were performed during frequent follow-up visits for GDMT initiation and up-titration in patients assigned to high-intensity care, compared to a usual care group. Such a strategy was associated with a higher likelihood of reaching target doses of GDMT and with reduced all-cause mortality and HF rehospitalizations.[50] Although this trial was not designed to exclusively assess the clinical impact of NT-proBNP measurements, it supports their use in a strategy of GDMT optimization in patients with a recent hospitalization for AHF.

Emerging biomarkers, such as carbohydrate antigen 125 (CA125) and adrenomedullin may complement NPs in the future.[38,51–56]

Haemoconcentration may be useful since it reflects a relative reduction in plasma volume. Its occurrence during AHF hospitalization is associated with better outcomes.[57,58] However, it may be influenced by iron status, which may also change during hospitalization.[59,60] Further studies are needed to assess the role of haemoconcentration as a marker of successful decongestion.

Diuretic response may be assessed through urinary sodium and/or urine volume measurements as recommended by the guidelines for the first 24 h to guide diuretic dosing.[9,61,62] Randomized prospective clinical trials are ongoing to assess the impact of these measurements on post-discharge outcomes.[63–67]

Myocardial, kidney and liver injury should be monitored during hospitalization with the use of traditional biomarkers (e.g., cardiac troponin, creatinine, cystatin C, transaminases, bilirubin, gamma-glutamyl transpeptidase).[9,38,42,44] The significance of trajectories in serum creatinine measurements during hospitalization and their relationship with concomitant treatment have been recently reviewed in position papers by the HFA as well as in the ESC HF guidelines.[9,68,69] Assessment of renal function before discharge is important as kidney dysfunction may limit the use of GDMT, particularly with renin–angiotensin–aldosterone system (RAAS) inhibitors or ARNI[9,25,68] (*Figure 2*). A transient decline in estimated glomerular filtration rate (eGFR), averaging 3–4 ml/min/1.73 m^2, may occur after the initiation of sodium–glucose cotransporter 2 (SGLT2) inhibitors, though this has no adverse prognostic value.[70–74] An appropriate interpretation of changes in markers of kidney function is essential during the treatment of HF. Even though worsening renal function is associated with worse outcome on a population level, the interpretation of such changes within the appropriate clinical context helps to correctly assess risk and determine further treatment strategies.[75] Unnecessary fear of worsening kidney function is a leading cause of not attaining decongestion in AHF and of insufficient dosing of GDMT in general.

Neurohormonal activation, urine flow rate, and the effect of arginine vasopressin on the urea transporter in the collecting duct can lead to enhanced proximal and distal tubular reabsorption, resulting in increased levels of blood urea nitrogen (BUN) in AHF. Moreover, increased urea concentrations may also result from increased protein breakdown. Hence, elevated BUN levels can serve as an indicator of neurohormonal activation and nutritional status, regardless of any decline in eGFR.[9,76] Consequently, even in patients with eGFR ≥45 ml/min/1.73 m^2, higher levels of BUN are associated with a greater risk of post-discharge mortality.

Serum electrolytes should be closely monitored during an AHF hospitalization.[9] Both hypo- and hyperkalaemia are associated with poorer outcomes[77,78] (*Figure 2*). New potassium-lowering agents, patiromer or sodium zirconium cyclosilicate, improving hyperkalaemia, may favour initiation or up-titration of RAAS inhibitors.[9,79]

Measurements of serum ferritin and transferrin saturation during an AHF event are also mandated by current ESC guidelines as detection of iron deficiency is an indication for iron replacement therapy prior to discharge to reduce HF rehospitalizations.[9,59]

Imaging

At pre-discharge, comprehensive imaging has a major role for the detection of residual congestion.

Chest X-ray may be useful to detect pulmonary congestion, pleural effusion, need and response to treatments (online supplementary *Table S2*). However, the main measurements of congestion include echocardiographic signs of increased left ventricular (LV) filling pressures, B-lines by lung ultrasound (LUS) and inferior vena cava (IVC) size and collapsibility. Transmitral flow velocity and tissue Doppler annular velocities (septal and lateral e' and average E/e' ratio) and left atrial volume are cornerstones as measurements related with LV filling pressure in chronic HF, while their performance may be less powerful in acute setting.[80]

Mitral regurgitation severity and tricuspid regurgitation velocity may be useful in a multiparametric approach to assess response to medical therapy and residual congestion before discharge.[3,81]

Inferior vena cava imaging and LUS may be easily assessed at bedside with portable devices. They provide a reliable estimation of right atrial pressure and lung congestion, respectively, and rapidly reflect changes in volume status in response to treatment. Persistently dilated IVC with low collapsibility index before discharge predicts greater risk of readmission.[82] Notably, dilated IVC is a marker of systemic, but not pulmonary congestion. The number of B-lines indicates the severity of pulmonary congestion. A recent expert consensus document reported different image acquisition methods and showed that the 28 scanning-site LUS technique provides a precise quantification of extravascular lung water: less than 5 B-lines indicate no congestion; 16 to 30 B-lines detected in the entire lung indicate moderate pulmonary congestion; and >30 B-lines are signs of severe pulmonary oedema. The eight-region LUS technique is a semiquantitative technique. A positive region is defined by the presence of ≥3 B-lines in a longitudinal plane between two ribs and ≥2 positive regions on each lung suggest significant pulmonary congestion.[83,84] (online supplementary *Table S3*). Residual pulmonary congestion as assessed with LUS at discharge is strongly associated with adverse outcomes.[85–87] In a systematic review including 13 studies, the presence of ≥15 B-lines on 28-zone LUS at discharge identified patients at a more than five-fold risk for HF readmission or death.[88] LUS has also been used to guide treatment in randomized controlled trials showing the efficacy of this strategy to reduce HF rehospitalizations.[89–91]

Imaging should be integrated with clinical evaluation and biomarkers in a multimodal assessment strategy to guide therapy and timing of discharge.[92] Clinical improvement may occur whilst tissue/haemodynamic congestion still persists, and the combined use of several tools may increase the sensitivity of detecting residual congestion.[23,85,92] The use of imaging may be particularly important at sites with limited availability of NP measurements for quick decision making and serial follow-up.[40,93] Integration of clinical assessment, laboratory exams and imaging is presented in *Figure 2*.

Pre-discharge optimization of treatment

In patients admitted with AHF, neurohormonal modulators and SGLT2 inhibitors should be administered or continued, if used previously, as their beneficial effects persist during hospitalization (see below).[9] However, patients with haemodynamic instability, namely hypotension due to low cardiac output, and/or persistently reduced eGFR (<20–30 ml/min/1.73 m^2) may be intolerant to higher doses and especially, beta-blockers may need to be used with caution. Significant symptomatic hypotension and severe kidney dysfunction were also major exclusion criteria within most randomized clinical trials, so there is no indication for GDMT in patients with low systolic blood pressure, that is, <100 mmHg, and severe renal dysfunction, that is, with an eGFR <20–30 ml/min/1.73 m^2.[9] These patients represent a significant proportion of patients with HF, especially those with a recent decompensation or in advanced stages.[94–96] Medical treatment need to be reviewed with respect to its efficacy and safety before discharge after an AHF hospitalization.

Diuretics

Loop diuretics are universally recommended in patients with HF to treat and prevent signs and symptoms of congestion. Notably, early evaluation of diuretic effect and appropriate dosing according to natriuresis and diuresis are recommended during AHF hospitalization. Complete decongestion while carefully monitoring renal function and electrolytes, is the target.[9,61,97] Several studies showed that high doses of loop diuretic are associated with an increased risk of mortality, even after multivariate adjustment or propensity matching.[9,68,69,98,99] Potential bias remains as sicker patients are more likely to receive higher doses of loop diuretics. Nevertheless, inappropriately high doses of diuretics might result in electrolyte disturbances, further neurohormonal activation, accelerated kidney function decline, dehydration and hypotension.[68,98,100] Therefore, it is generally advised to use the lowest possible dose of diuretics that keeps the patient free of congestion and this is particularly important at the pre-discharge phase.[9,61]

Many measurements have been proposed to guide diuretic treatment, including laboratory exams, that is, urinary sodium and volume, haemoconcentration, biomarkers, that is, NPs and CA125, and imaging modalities, that is, LUS and echo-Doppler measurements. However, evidence from results of prospective trials is still insufficient to recommend a specific strategy to be applied before discharge.[9,97]

In the recent ADVOR (Acetazolamide in Decompensated HF with Volume Overload) trial, acetazolamide, added to standard therapy with furosemide, improved congestion, compared to furosemide alone, in patients hospitalized for AHF with signs of congestion. This was associated with a 1-day shorter length of hospital stay with no effects on mortality and HF readmission.[101] Aquaretics and, namely vasopressin antagonists such as tolvaptan, may also be useful in improving congestion status, above all in hyponatraemic patients.[102,103]

Guideline-directed medical therapy

Current practice

Guideline-directed medical therapy has shown to improve survival and reduce HF hospitalization, and is therefore recommended in patients with AHF. As pointed out below, there is evidence supporting both implementation of GDMT during AHF hospitalization and the early start of this treatment, if not ongoing and not contraindicated, before discharge.[9,97]

Real-life registries show significant gaps in the use and dosing of GDMT both in outpatients and in patients hospitalized for AHF.[104–106] A recent registry (VICTORIA [Vericiguat Global Study in Subjects with HF with Reduced Ejection Fraction]), including 1695 patients hospitalized for worsening HF with reduced ejection fraction (HFrEF) from 51 sites in the US and Canada, showed that, among eligible patients, 33%, 25% and 55% were not prescribed ACEi/ARB/ARNI, beta-blockers or mineralocorticoid receptor antagonists (MRA), respectively; and 89% were not prescribed ARNI. In-hospital rates of initiation/dose increase were 20% for ACEi/ARB, 4% for ARNI, 20% for beta-blockers, 22% for MRA. Overall, 17% and 28% of eligible patients were prescribed triple therapy prior to admission and at discharge, respectively, and only 1% had triple therapy at target doses at both admission and discharge.[107] Further, multiple registries show that the likelihood of further optimization of GDMT is very low after discharge.[12,108–112] Thus, hospitalization for AHF is a key opportunity to optimize GDMT, with an improvement in post-discharge quality of life and outcome (*Figures 3* and *4*).[12,104,113–117]

Early benefits of guideline directed medical therapy

Multiple studies show that the beneficial effects of GDMT start early after their initiation. Thus, there is evidence supporting initiation of GDMT before discharge, if not ongoing at this time, and its up-titration when possible.

A recent analysis of the SOLVD (Studies of Left Ventricular Dysfunction) Treatment trial showed that the reduction in all-cause death or HF hospitalizations with enalapril versus placebo was significant as early as 30 days after randomization (hazard ratio [HR] 0.49, 95% confidence interval [CI] 0.33–0.73) and was of borderline significance already at 14 days (HR 0.65, 95% CI 0.39–1.06).[118] The favourable effects of carvedilol on mortality and hospitalizations became apparent as early as 14 to 21 days following initiation of treatment in the COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) trial.[119] A recent analysis of MRA trials showed early achievement of significant beneficial effects also with these drugs. A significant reduction in cardiovascular death or hospitalization was observed at 19 days after randomization in the pooled cohort of HFrEF trials, RALES (Randomized Aldactone Evaluation Study) and EMPHASIS-HF (Eplerenone in Patients With Systolic Heart Failure and Mild Symptoms), and, similarly, as early as 7 days in patients enrolled in EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study).[120]

Consistently, available data show that patients who are on neurohormonal antagonists and continue them during an AHF hospitalization have better outcome.[121–123] A randomized prospective trial

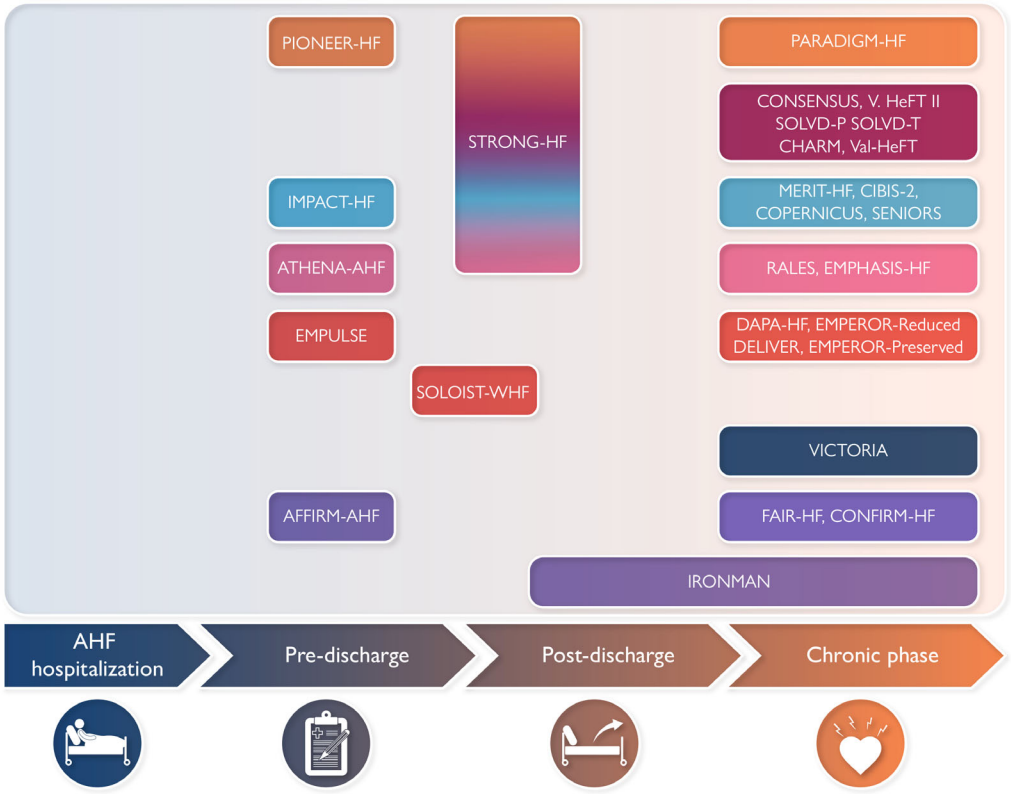

Figure 3 Randomized clinical trials in different hospitalization phases. Studies including pre-discharge, early post-discharge and late post-discharge heart failure populations are reported. AHF, acute heart failure.

confirmed the beneficial effects of executing ongoing beta-blocker therapy in patients with decompensated HF.[124]

In PIONEER-HF (Comparison of Sacubitril-Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode), in-hospital sacubitril/valsartan, compared to enalapril, led to a greater reduction in NT-proBNP levels (primary endpoint of the trial). Rehospitalizations for HF and a composite endpoint of serious clinical events, including death, rehospitalization for HF, implantation of a LV assist device, and inclusion on the list for heart transplantation, were also reduced by in-hospital use of sacubitril/valsartan versus enalapril (HR 0.56, 95% CI 0.37–0.84 and HR 0.54, 95% CI 0.37–0.79, respectively). Rates of untoward events did not differ significantly between the two groups.[125,126]

The beneficial effects of SGLT2 inhibitors occurred early after randomization in clinical trials, 28 days with dapagliflozin in DAPA-HF (Dapagliflozin And Prevention of Adverse-outcomes in HF), 12 and 18 days with empagliflozin in EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic HF With Reduced Ejection Fraction) and EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic HF With Preserved Ejection Fraction), respectively, with an early improvement in quality of life and symptoms.[127–131] Considering their tolerability in patients with low blood pressure, their favourable effects on renal function and their efficacy, irrespective of LV ejection fraction (LVEF) and background HF therapy, early administration of SGLT2 inhibitors is recommended.[9,97,114]

The EMPA-RESPONSE-AHF (Effects of Empagliflozin on Clinical Outcomes in Patients with Acute Decompensated HF) trial and the larger EMPULSE (A Study to Test the Effect of Empagliflozin in Patients Who Are in Hospital for AHF) trial confirmed the efficacy and tolerability of empagliflozin in patients with AHF.[132,133] In EMPULSE, empagliflozin, at the fixed dose of 10 mg, was started soon after initial stabilization in patients with acute decompensated HF, regardless of their LVEF. The primary outcome of the trial was clinical benefit, defined as a hierarchical composite of death from any cause, number of HF events and time to first HF event, or a 5 point or greater difference in change from baseline in the Kansas City Cardiomyopathy Questionnaire total symptom score at 90 days, as assessed using a win ratio. More patients treated with empagliflozin had clinical benefit compared with placebo (stratified win ratio, 1.36; 95% CI 1.09–1.68; $p = 0.0054$).[133] Consistently, dapagliflozin had beneficial effects on outcome when started during or shortly after an AHF hospitalization in the DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction HF) trial.[134] The DICTATE-AHF (Dapagliflozin in AHF) trial is investigating whether early initiation of dapagliflozin may facilitate decongestion, improve natriuresis,

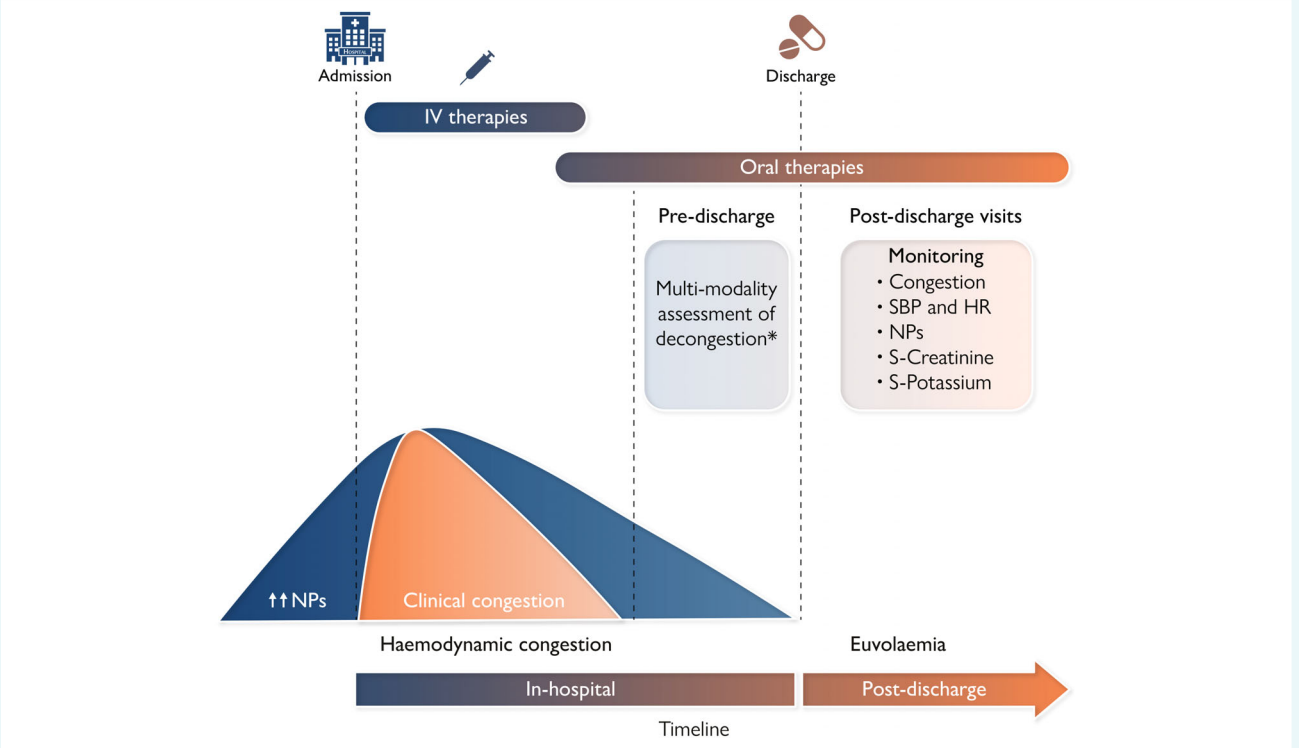

Figure 4 Management of heart failure patients according to hospitalization phase. During hospitalization, in presence of clinical congestion, intravenous (IV) therapies are needed. Assessment of decongestion and optimization of oral therapies (purple arrows) before discharge and at early follow-up visits are also needed. This algorithm is not provided by the European Society of Cardiology guidelines, but it is a proposal from the authors. HR, heart rate; NP, natriuretic peptide; SBP, systolic blood pressure. *See *Figure 2*.

and facilitate safe transition to beneficial outpatient therapy in patients with type 2 diabetes hospitalized with hypervolaemic AHF.[135]

Vericiguat may have a role since, although the VICTORIA trial did not include inpatients with AHF,[136] its criteria can be applicable in 40% of patients admitted due to AHF.[137]

Dose titration

Few data were available, until recently, regarding the efficacy and safety of GDMT titration in patients with recent worsening of HF. Bistola *et al.*[138] analysed data from 2345 patients from BIOSTAT-CHF (A systems BIOlogy Study to TAilored Treatment in Chronic HF). Up-titration of either ACEi/ARB or beta-blockers was associated with a reduced risk of all-cause hospitalization that was larger, compared to no treatment, when ≥50% target doses were achieved, in patients with LVEF <50%.

More recently, STRONG-HF (Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of HF Therapies) has shown the beneficial effects of a strategy of treatment implementation in patients with recent AHF regardless of LVEF.[50] STRONG-HF was a multinational, open-label, prospective, randomized clinical trial to assess the safety and efficacy of a high-intensity care strategy, before discharge and in the following weeks after discharge, compared with usual care, in patients recently hospitalized for AHF. The high-intensity care strategy consisted of up-titration of GDMT (ACEi/beta-blocker/MRA, not ARNI or SGLT2 inhibitor) to 100% of recommended doses within 2 weeks of discharge with, then, four scheduled outpatient visits, at 1, 2, 3 and 6 weeks after randomization, with careful monitoring of clinical status and laboratory values, including NT-proBNP concentrations.[50] The study met its primary endpoint with a lower occurrence at 180 days of the primary endpoint of HF readmission or all-cause death in the high-intensity care versus the usual group (adjusted risk difference 8.1%, 95% CI 2.9−13.2; $p = 0{\cdot}0021$; risk ratio 0.66, 95% CI 0.50−0.86). The intensive treatment strategy was also associated with a significant reduction in NT-proBNP concentrations and an improvement in symptoms and quality of life with a similar incidence of serious adverse events.[50]

Thus, dose titration, in addition to prosecution or initiation of all the four cornerstones of GDMT, may reduce mortality and rehospitalizations in patients with recent AHF.

Practical considerations

The data outlined above show that the beneficial effects of GDMT on outcome and, in the case of SGLT2 inhibitors, also on symptoms, occur early after their initiation in patients with HF. These drugs are also well tolerated as soon as the patients are on oral treatment and the use of higher doses, close to the target ones shown as effective in clinical trials, is associated with better outcomes. All four fundamental GDMTs should first be started and then titrated

to target doses as early as possible in patients hospitalized for HF. Notable exceptions are patients with contraindications, including severe chronic kidney disease and, for ACEi/ARB/ARNI, patients with hypotension or hyperkalaemia. Clinical inertia surely has a major role in the lack of prescription of GDMT and should be overcome by proper implementation of current guidelines.

Treatment of comorbidities

Pre-discharge management of cardiovascular (i.e., atrial fibrillation, chronic coronary syndrome, valvular heart disease) and non-cardiovascular (i.e., diabetes, thyroid disorder, frailty and cachexia, iron deficiency and anaemia, lung disease, renal failure, electrolyte imbalance) comorbidities is needed. Comorbidities have been extensively considered in the 2021 ESC HF guidelines.[9] No specific aspect is related with pre-discharge assessment, except for the indication, based on the results of AFFIRM-AHF for ferric carboxymaltose to reduce rehospitalizations in patients with AHF and iron deficiency.[9,59] Similarly to AFFIRM-AHF, IRONMAN (Effectiveness of Intravenous Iron Treatment versus Standard Care in Patients with HF and Iron Deficiency) showed a reduction in the primary endpoint of recurrent hospital admissions for HF and cardiovascular death which was of borderline statistical significance (rate ratio 0.82, 95% CI 0.66–1.02) and reached statistical significance in a pre-specified COVID-19 analysis. This trial enrolled mainly outpatients, although 14% were hospitalized at the time of recruitment.[139]

Recently, a new frailty score was developed by the HFA to identify high-risk patients.[140] Specific treatments, including rehabilitation/exercise programmes, if possible, should be considered especially in patients with more severe disease, frailty, or with several comorbidities.[9]

Early post-discharge assessment

The early post-discharge phase has been termed as the 'vulnerable phase' due to its association with high rates of mortality and rehospitalizations which then decrease almost exponentially after the first weeks.[2] Management of the transition from inpatient to outpatient care is therefore crucial.[2,141,142]

Causes of readmissions

The pathophysiology of early readmission is typically related to persistent congestion at the time of discharge (see sections above).[2] Close monitoring of the patients, including changes in body weight, fluid status, renal function and NP plasma levels may detect decompensation at an early stage and prevent readmissions.[142–145] Other risk factors for decompensation include incomplete recovery from acute illness, namely an infection, deconditioning during the previous hospitalization, poor social support, or poor adherence to the prescribed drug regimen.[142,146]

Prognostic variables

Variables predictive of post-discharge decompensation include socio-demographic factors, such as higher age, poor socio-economic support, clinical signs, such as hypotension and signs of congestion, laboratory exams, such as electrolyte abnormalities, iron deficiency, kidney or liver dysfunction, biomarkers, namely NPs and troponin (*Table 1*).[9,97,142,144,147] Among electrolytes, the role of hypochloraemia has emerged with new or persistent hypochloraemia (serum chloride <96 mEq/L) 14 days after hospital admission being independently associated with reduced survival.[147]

Novel biomarker-driven prognostic models to predict morbidity and mortality have been recently proposed with NT-proBNP and high-sensitivity cardiac troponin T (hs-cTnT). These, in addition to a shorter time since last HF hospitalization, longer time since HF diagnosis and NYHA class III or IV, are predictors of major events in both patients with HFrEF and with HF and mildly reduced and preserved ejection fraction.[148,149] Other clinical predictors of major events were lower systolic blood pressure, higher heart rate and peripheral oedema in patients with HFrEF and comorbidities such as chronic obstructive pulmonary disease, insulin-treated diabetes and low haemoglobin, in patients with LVEF >40%.[148,149]

Early post-discharge assessments should therefore include reassessment of clinical parameters, blood pressure, heart rate, body weight, signs of congestion, laboratory exams, including renal and liver function, electrolytes, iron status, NPs and possibly hs-cTnT, as prognostic markers. Imaging may help if congestion is suspected. Specific causes of HF, such as coronary artery disease or valvular heart disease, should also be addressed.

In the STRONG-HF trial, clinical evaluation (signs, symptoms and vital signs, including blood pressure and heart rate) and laboratory tests (serum creatinine, serum potassium and NT-proBNP) were evaluated at 1, 2, 3 and 6 weeks after discharge (*Figure 4*).[45]

Early post-discharge management

Post-discharge follow-up visits

The 2021 HF ESC guidelines recommend one early follow-up visit within 1 to 2 weeks after discharge.[9] More frequent, up to at least four, post-discharge visits within 6 weeks after discharge, with GDMT up-titration, led to a reduction in rehospitalizations for HF or all-cause death in STRONG-HF regardless of LVEF.[50] Treatment titration likely had a major role as frequent visits alone have been unsuccessful in reducing events.[117,150–153] Thus, both GDMT start and titration and frequent post-discharge visits were shown as effective to reduce major events in these high-risk patients (*Figure 4*).

Disease management models

Patients discharged from hospital must be enrolled in a multidisciplinary management programme, including cardiologists, a general practitioner, a nurse specialized in HF treatment, plus other personnel.[9,154,155] In the COACH (Comparison of Outcomes and Access to Care for HF) trial, among patients with AHF who were seeking emergency care, the use of a validated point-of-care tool for risk stratification in the emergency department to support clinicians in making decisions about discharging or admitting patients,

combined with the provision of standardized transitional care, led to a 12% lower risk of death from any cause or hospitalization for cardiovascular causes within 30 days after presentation than usual care.[156] This tool was used to ascertain whether patients had a low, intermediate, or high risk of death within 7 days or within 30 days.[157] Patients at low risk were recommended to be discharged early and to receive standardized transitional care while patients at high risk had to be admitted to the hospital. Patients who were discharged early had access to a standardized transitional care clinic, staffed with a nurse supervised by a cardiologist. The clinic provided outpatient care for up to 30 days after discharge from the emergency department or hospital and this programme reduced post-discharge event rate.[156] However, the COACH trial is only an example of disease management model in patients admitted due to AHF. Different tools have been previously reported to help in patient disposition and possibly improve outcomes.[158]

In a previous study, Lee *et al.*[159] related the type of transition care with outcome in patients with HF evaluated at emergency departments. Early collaborative care by a cardiologist and a primary care physician further reduced mortality compared to primary care alone.

A network meta-analysis including 53 randomized trials demonstrated that nurse home visits were the most effective strategy to reduce all-cause mortality and all-cause readmission compared to usual care[160] as well as caregiver outcomes.[161] Introducing nurse-led HF clinics in Swedish primary care settings led to a decrease in the need for in-hospital care and provided high quality person-centred care.[162] Importantly, while home visits and HF clinics reduced all-cause hospitalizations and mortality, educational programmes alone did not.[160,163]

Finally, all these disease management models need to be contextualized since huge differences may exist among different health systems.

Pre-discharge counselling

A randomized trial including 223 patients hospitalized for AHF showed that the addition of 1 h one-on-one teaching session with a nurse educator at the time of hospital discharge resulted in improved clinical outcomes (i.e., HF readmission), increased self-care measure adherence, and reduced cost of care.[164] Ensuring patient comprehension has a major role.[165]

Therefore, pre-discharge counselling and patient education, possibly involving the caregivers, may be helpful for improving disease awareness, therapeutic adherence and response to treatment, and avoiding HF rehospitalizations.

Non-invasive home telemonitoring

Telemonitoring remotely provides digital health information to support and optimize patients' care. It may be particularly suitable for patients' follow-up in the early post-discharge phase. Its role has become more relevant after the COVID-19 pandemic.[166–168]

Phone calls allow assessment of symptoms, body weight, heart rate, and blood pressure, collected by the patient, and may be useful to guide therapy or have clinical visits and other measurements, such as biomarkers and/or echocardiography. Phone calls are also useful to check adherence to medications, answer patient's questions and them in recognizing the symptoms that are related to decompensation and the side effects of drug therapy.

The results of controlled clinical trials of telemonitoring strategies were mostly neutral. However, as with biomarker-guided therapy, these neutral results were likely caused by optimal treatment also occurring in the control group, as may be expected when tertiary care centres are involved.[169–174] The Telemedical Interventional Management in HF II (TIM-HF2) trial showed a reduction in unplanned cardiovascular hospitalizations or all-cause mortality in patients undergoing remote management versus usual care.[173] Centre and patient selection was based on the results of the previous, neutral, trial with the exclusion, based on these data, of patients with major depression.[171,173]

Invasive haemodynamic telemonitoring

An increase in LV filling pressure precedes most episodes of AHF decompensation. Early detection of such changes should allow early treatment and possibly prevention of hospitalizations.[175] Lung congestion has been monitored by intrathoracic impedance monitoring with either dedicated devices or implantable defibrillators.[176–178] The mostly neutral results of prospective trials have not led to specific recommendations, yet.[9] Better results were obtained with invasive pulmonary artery pressure (PAP) monitoring.

In the CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III HF Patients) trial, wireless PAP monitoring with the CardioMEMS™ system led to a lower risk of HF hospitalization at 6-month follow-up (HR 0.70, 95% CI 0.60–0.84; $p < 0.001$) compared with standard care, in patients with NYHA class III and a previous hospital admission for HF, irrespective of LVEF.[179] The efficacy of this system was maintained at 18-month follow-up.[180] These results were confirmed in a prospective observational study including 234 NYHA class III patients and showing a 62% reduction in events in 12 months after CardioMEMS™ implantation compared with the 12 months before (0.60 vs. 1.55 events/patient-year; HR 0.38, 95% CI 0.31–0.48; $p < 0.0001$).[181] The larger GUIDE-HF (haemodynamic-GUIDEed management of HF) trial was designed to evaluate whether the efficacy of wireless PAP monitoring could be extended to patients with HF across the spectrum of symptom severity (NYHA functional class II to IV), with either a recent HF hospitalization or elevated NPs. The trial was neutral for the primary endpoint of all-cause mortality and total HF events at 12 months. However, in a pre-specified COVID-19 sensitivity analysis, primary events were reduced with invasive monitoring, primarily through a lower HF hospitalization rate.[182] GUIDE-HF results suggest that wireless PAP monitoring may be useful in a subgroup of patients at high risk for HF event and with high PAP at baseline whereas patients with low PAP have little possibility of short-term gain.

A novel device for wireless PAP monitoring (Cordella™) is under investigation in the PROACTIVE-HF (Prospective,

Multi-Center, Randomized, Controlled, Single Blind Clinical Trial Evaluating the Safety and Efficacy of the Cordella™ Pulmonary Artery Sensor System in NYHA Class III HF Patients) trial.[183]

Thus, LV filling pressure monitoring may allow prompt treatment of the haemodynamic changes leading to congestion before clinical signs become manifest, possibly preventing an episode of worsening HF.

The association between haemodynamic-guided HF management and reduction of HF hospitalizations was also reported in observational studies.[181,184]

Rehabilitation programmes post-hospitalization

Exercise rehabilitation programmes reduce all-cause and HF hospitalizations, improve exercise tolerance and health-related quality of life in all patients with HF, regardless of their LVEF.[185–189] In a retrospective cohort study on 40 364 patients, exercise rehabilitation was associated with 42% lower odds of all-cause mortality (odds ratio 0.58, 95% CI 0.54–0.62), 26% lower odds of hospitalization (0.74, 95% CI 0.71–0.77), 37% lower odds of incident stroke (0.63, 95% CI 0.51–0.79), and 53% lower odds of incident atrial fibrillation (0.47, 95% CI 0.4–0.55) compared to controls.[190] However, the role of rehabilitation on mortality remains still disputed. Long-term adherence is one of the main issues of exercise programmers. In this context, telemedicine may play a major role.[191]

Post-discharge rehabilitation programmes, preferably residential in hospital, should be considered also in old and frail patients, as well as in those with more severe disease or comorbidities.[192]

Concluding remarks

In conclusion, the early post-discharge phase after an AHF hospitalization is characterized by an extremely high risk of death and rehospitalizations, with a 5 to more than 10-fold increase in the rate of these events, compared to that of the patients who do not have an episode of decompensation. In addition, treatment started during and immediately after an AHF decompensation has a high likelihood of being continued in the long term without further changes. Thus, management of the pre-discharge and early post-discharge phase after an AHF hospitalization is based on prompt recognition and treatment of congestion, the major cause of rehospitalization, as well as to optimization of GDMT, the major driver of better long-term prognosis.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conflict of interest: M.M. reports personal fees from Actelion, Amgen, AstraZeneca, Abbott Vascular, Bayer, Servier, Edwards Therapeutics, Livanova, Vifor Pharma, WindTree Therapeutics, as member of Trials' Committees or advisory boards or for speeches at sponsored meetings in the last 3 years. M.A. reports speaker fees from Abbott Vascular and Medtronic. A.M. has received grants from Roche Diagnostics, Abbott Laboratories, 4TEEN4, and Windtree Therapeutics; honoraria for lectures from Roche Diagnostics, Bayer, and MSD; is a consultant for Corteria Pharmaceuticals, S-form Pharma, FIRE-1, Implicity, 4TEEN4, and Adrenomed; and is coinventor of a patent on combination therapy for patients having acute or persistent dyspnoea. A.B.G. has received honoraria for lectures and/or advisory from Abbott, AstraZeneca, Boehringer Ingelheim, Novartis, Roche Diagnostics, V-wave, Vifor. S.D.A. declares grants and personal fees from Vifor and Abbott Vascular, and personal fees for consultancies, trial committee work and/or lectures from Actimed, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bioventrix, Brahms, Cardiac Dimensions, Cardior, Cordio, CVRx, Edwards, Farraday, Impulse Dynamics, Janssen, Novartis, Occlutech, Pfizer, Respicardia, Servier, Vectorious, and V-Wave; he is named co-inventor of two patent applications regarding MR-proANP (DE 102007010834 & DE 102007022367), but he does not benefit personally from the related issued patents. M.B. is supported by the Deutsche Forschungsgemeinschaft (German Research Foundation; TTR 219, project No. 322900939) and reports personal fees from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Medtronic, Novartis, Servier, and Vifor. J.B. serves as a consultant to Abbott, Adrenomed, Amgen, Array, AstraZeneca, Bayer, Berlin Cures, Boehringer Ingelheim, Bristol-Myers Squib, CVRx, G3 Pharmaceutical, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, Novo Nordisk, Occlutech, Relypsa, Roche, Sanofi, SC Pharma, V-Wave Limited, and Vifor. G.F. reports lecture fees and/or committee member contributions in clinical trials sponsored by Bayer, Medtronic, Vifor, Servier, Novartis, Amgen, and Boehringer Ingelheim, and research support from the European Union. E.A.J. reports research grants and personal fees from Vifor Pharma, personal fees from Bayer, Novartis, Abbott, Boehringer Ingelheim, Pfizer, Servier, AstraZeneca, Berlin Chemie, Cardiac Dimensions, Takeda and Gedeon Richter. L.H.L. reports grants from AstraZeneca, Vifor, Boston Scientific, Boehringer Ingelheim, Novartis; consulting fees from Merck, Vifor, AstraZeneca, Bayer, Pharmacosmos, MedScape, Sanofi, Lexicon, Myokardia, Boehringer Ingelheim, Servier; speakers honoraria from Abbott, MedScape, Radcliffe, AstraZeneca, Novartis; shareholder in AnaCardio. B.M. reports advisory or speaker fees from AstraZeneca, Bayer, Boehringer Ingelheim, Ely Lilly, Servier, Novartis, Vifor Pharma. W.M. received research grants/consultancy fees from Novartis, Vifor, Medtronic, Abbott, AstraZeneca, Boehringer Ingelheim. P.P. has received consulting fees from Boehringer Ingelheim, AstraZeneca, Vifor Pharma, Amgen, Servier, Novartis, Bayer, MSD, Pfizer, Cibiem, Impulse Dynamics, Renal Guard Solutions, and BMS; he has also received honoraria from Boehringer Ingelheim, AstraZeneca, Vifor Pharma, Amgen, Servier, Novartis, Berlin Chemie, Bayer, Pfizer, Impulse Dynamics, Renal Guard Solutions, BMS, and Abbott Vascular for lectures, presentations, speakers' bureaus, manuscript writing, or educational events. A.R. reports speaker honoraria fees from Bayer, Pfizer, Roche. G.S. reports grants and personal fees from Vifor, AstraZeneca, grants and non-financial support from Boehringer Ingelheim, personal fees from Società Prodotti Antibiotici, Roche, Servier, GENESIS, Cytokinetics, Medtronic, grants from Novartis, Boston Scientific, PHARMACOSMOS, Merck, outside the submitted work. A.J.S.C. reports personal fees from AstraZeneca, Bayer, Boehringer Ingelheim, Menarini, Novartis, Nutricia, Servier, Vifor, Abbott, Actimed, Arena, Cardiac Dimensions, Corvia, CVRx, Enopace, ESN Cleer, Faraday, Gore, Impulse Dynamics, and Respicardia, outside the submitted work. All other authors have nothing to disclose.

References

1. Gheorghiade M, Pang PS. Acute heart failure syndromes. *J Am Coll Cardiol*. 2009;**53**:557–573. https://doi.org/10.1016/j.jacc.2008.10.041
2. 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. https://doi.org/10.1038/nrcardio.2015.14

3. Chioncel O, Mebazaa A, Maggioni AP, Harjola VP, Rosano G, Laroche C, et al.; ESC-EORP-HFA Heart Failure Long-Term Registry Investigators. 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. https://doi.org/10.1002/ejhf.1492
4. Butt JH, Fosbol EL, Gerds TA, Andersson C, McMurray JJV, Petrie MC, et al. Readmission and death in patients admitted with new-onset versus worsening of chronic heart failure: Insights from a nationwide cohort. *Eur J Heart Fail*. 2020;**22**:1777–1785. https://doi.org/10.1002/ejhf.1800
5. Chioncel O, Collins SP, Ambrosy AP, Pang PS, Antohi EL, Iliescu VA, et al. Improving postdischarge outcomes in acute heart failure. *Am J Ther*. 2018;**25**:e475–e486. https://doi.org/10.1097/MJT.0000000000000791
6. Kimmoun A, Takagi K, Gall E, Ishihara S, Hammoum P, El Beze N, 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. https://doi.org/10.1002/ejhf.2103
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. https://doi.org/10.1016/j.pcad.2020.04.007
8. Hariharaputhiran S, Peng Y, Ngo L, Ali A, Hossain S, Visvanathan R, et al. Long-term survival and life expectancy following an acute heart failure hospitalization in Australia and New Zealand. *Eur J Heart Fail*. 2022;**24**:1519–1528. https://doi.org/10.1002/ejhf.2595
9. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2022;**24**:4–131. https://doi.org/10.1002/ejhf.2333
10. Mebazaa A, Yilmaz MB, Levy P, Ponikowski P, Peacock WF, Laribi S, et al. Recommendations on pre-hospital & early hospital management of acute heart failure: A consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergency Medicine. *Eur J Heart Fail*. 2015;**17**:544–558. https://doi.org/10.1002/ejhf.289
11. Solomon SD, Dobson J, Pocock S, Skali H, McMurray JJ, Granger CB, et al. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. *Circulation*. 2007;**116**:1482–1487. https://doi.org/10.1161/CIRCULATIONAHA.107.696906
12. Rao VN, Murray E, Butler J, Cooper LB, Cox ZL, Fiuzat M, et al. In-hospital initiation of sodium-glucose cotransporter-2 inhibitors for heart failure with reduced ejection fraction. *J Am Coll Cardiol*. 2021;**78**:2004–2012. https://doi.org/10.1016/j.jacc.2021.08.064
13. Chioncel O, Parissis J, Mebazaa A, Thiele H, Desch S, Bauersachs J, et al. Epidemiology, pathophysiology and contemporary management of cardiogenic shock – a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2020;**22**:1315–1341. https://doi.org/10.1002/ejhf.1922
14. Harjola VP, Mebazaa A, Celutkiene J, Bettex D, Bueno H, Chioncel O, et al. Contemporary management of acute right ventricular failure: A statement from the Heart Failure Association and the Working Group on Pulmonary Circulation and Right Ventricular Function of the European Society of Cardiology. *Eur J Heart Fail*. 2016;**18**:226–241. https://doi.org/10.1002/ejhf.478
15. Chioncel O, Mebazaa A, Harjola VP, Coats AJ, Piepoli MF, Crespo-Leiro MG, et al.; ESC Heart Failure Long-Term Registry Investigators. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: The ESC Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2017;**19**:1242–1254. https://doi.org/10.1002/ejhf.890
16. Metra M, Teerlink JR. Heart failure. *Lancet*. 2017;**390**:1981–1995. https://doi.org/10.1016/S0140-6736(17)31071-1
17. Tromp J, Bamadhaj S, Cleland JGF, Angermann CE, Dahlstrom U, Ouwerkerk W, et al. Post-discharge prognosis of patients admitted to hospital for heart failure by world region, and national level of income and income disparity (REPORT-HF): A cohort study. *Lancet Glob Health*. 2020;**8**:e411–e422. https://doi.org/10.1016/S2214-109X(20)30004-8
18. O'Connor CM, Abraham WT, Albert NM, Clare R, Gattis Stough W, Gheorghiade M, et al. Predictors of mortality after discharge in patients hospitalized with heart failure: An analysis from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Am Heart J*. 2008;**156**:662–673. https://doi.org/10.1016/j.ahj.2008.04.030
19. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, 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. https://doi.org/10.1002/ejhf.566
20. Setoguchi S, Stevenson LW, Schneeweiss S. Repeated hospitalizations predict mortality in the community population with heart failure. *Am Heart J*. 2007;**154**:260–266. https://doi.org/10.1016/j.ahj.2007.01.041
21. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, 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. https://doi.org/10.1093/eurheartj/ehl193
22. Ambrosy AP, Pang PS, Khan S, Konstam MA, Fonarow GC, Traver B, et al.; EVEREST Trial Investigators. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: Findings from the EVEREST trial. *Eur Heart J*. 2013;**34**:835–843. https://doi.org/10.1093/eurheartj/ehs444
23. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JE, Cleland JG, et al. Assessing and grading congestion in acute heart failure: A scientific statement from the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. *Eur J Heart Fail*. 2010;**12**:423–433. https://doi.org/10.1093/eurjhf/hfq045
24. Rosano GMC, Allen LA, Abdin A, Lindenfeld J, O'Meara E, Lam CSP, et al. Drug layering in heart failure: Phenotype-guided initiation. *JACC Heart Fail*. 2021;**9**:775–783. https://doi.org/10.1016/j.jchf.2021.06.011
25. Rosano GMC, Moura B, Metra M, Bohm M, Bauersachs J, Ben Gal T, et al. Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2021;**23**:872–881. https://doi.org/10.1002/ejhf.2206
26. Rosano GMC, Vitale C, Adamo M, Metra M. Roadmap for the management of heart failure patients during the vulnerable phase after heart failure hospitalizations: How to implement excellence in clinical practice. *J Cardiovasc Med (Hagerstown)*. 2022;**23**:149–156. https://doi.org/10.2459/JCM.0000000000001221
27. Girerd N, Seronde MF, Coiro S, Chouihed T, Bilbault P, Braun F, et al. Integrative assessment of congestion in heart failure throughout the patient journey. *JACC Heart Fail*. 2018;**6**:273–285. https://doi.org/10.1016/j.jchf.2017.09.023
28. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. *JAMA*. 1989;**261**:884–888. https://doi.org/10.1001/jama.1989.03420060100040
29. Van Aelst LNL, Arrigo M, Placido R, Akiyama E, Girerd N, Zannad F, et al. Acutely decompensated heart failure with preserved and reduced ejection fraction present with comparable haemodynamic congestion. *Eur J Heart Fail*. 2018;**20**:738–747. https://doi.org/10.1002/ejhf.1050
30. Rubio-Gracia J, Demissei BG, Ter Maaten JM, Cleland JG, O'Connor CM, Metra M, et al. Prevalence, predictors and clinical outcome of residual congestion in acute decompensated heart failure. *Int J Cardiol*. 2018;**258**:185–191. https://doi.org/10.1016/j.ijcard.2018.01.067
31. Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, et al. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. *JAMA*. 2006;**296**:2217–2226. https://doi.org/10.1001/jama.296.18.2217
32. Cautela J, Tartiere JM, Cohen-Solal A, Bellemain-Appaix A, Theron A, Tibi T, et al. Management of low blood pressure in ambulatory heart failure with reduced ejection fraction patients. *Eur J Heart Fail*. 2020;**22**:1357–1365. https://doi.org/10.1002/ejhf.1835
33. Maggioni AP, Anker SD, Dahlstrom U, Filippatos G, Ponikowski P, Zannad F, et al. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2013;**15**:1173–1184. https://doi.org/10.1093/eurjhf/hft134
34. Vader JM, Givertz MM, Starling RC, McNulty SE, Anstrom KJ, Desvigne-Nickens P, et al.; LIFE Investigators. Tolerability of sacubitril/valsartan in patients with advanced heart failure: Analysis of the LIFE trial run-in. *JACC Heart Fail*. 2022;**10**:449–456. https://doi.org/10.1016/j.jchf.2022.04.013
35. Nohria A, Tsang SW, Fang JC, Lewis EF, Jarcho JA, Mudge GH, et al. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. *J Am Coll Cardiol*. 2003;**41**:1797–1804. https://doi.org/10.1016/s0735-1097(03)00309-7
36. Javaloyes P, Miro O, Gil V, Martin-Sanchez FJ, Jacob J, Herrero P, et al.; ICA-SEMES Research Group. 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. https://doi.org/10.1002/ejhf.1502
37. Rivas-Lasarte M, Maestro A, Fernandez-Martinez J, Lopez-Lopez L, Sole-Gonzalez E, Vives-Borras M, et al. Prevalence and prognostic impact of subclinical pulmonary congestion at discharge in patients with acute heart failure. *ESC Heart Fail*. 2020;**7**:2621–2628. https://doi.org/10.1002/ehf2.12842
38. Bayes-Genis A, Aimo A, Jhund P, Richards M, de Boer RA, Arfsten H, et al. Biomarkers in heart failure clinical trials. A review from the Biomarkers Working

Group of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2022;**24**:1767–1777. https://doi.org/10.1002/ejhf.2675
39. Mueller C, McDonald K, de Boer RA, Maisel A, Cleland JGF, Kozhuharov N, et al. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. *Eur J Heart Fail*. 2019;**21**:715–731. https://doi.org/10.1002/ejhf.1494
40. Bayes-Genis A, Januzzi JL, Richards AM, Arfsten H, de Boer RA, Emdin M, et al. The 'Peptide for Life' Initiative: A call for action to provide equal access to the use of natriuretic peptides in the diagnosis of acute heart failure across Europe. *Eur J Heart Fail*. 2021;**23**:1432–1436. https://doi.org/10.1002/ejhf.2293
41. Bettencourt P, Azevedo A, Pimenta J, Frioes F, Ferreira S, Ferreira A. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. *Circulation*. 2004;**110**:2168–2174. https://doi.org/10.1161/01.CIR.0000144310.04433.BE
42. Nunez J, de la Espriella R, Rossignol P, Voors AA, Mullens W, Metra M, et al. Congestion in heart failure: A circulating biomarker-based perspective. A review from the Biomarkers Working Group of the Heart Failure Association, European Society of Cardiology. *Eur J Heart Fail*. 2022;**24**:1751–1766. https://doi.org/10.1002/ejhf.2664
43. Metra M, Nodari S, Parrinello G, Specchia C, Brentana L, Rocca P, et al. The role of plasma biomarkers in acute heart failure. Serial changes and independent prognostic value of NT-proBNP and cardiac troponin-T. *Eur J Heart Fail*. 2007;**9**:776–786. https://doi.org/10.1016/j.ejheart.2007.05.007
44. Metra M, Cotter G, Davison BA, Felker GM, Filippatos G, Greenberg BH, et al.; RELAX-AHF Investigators. Effect of serelaxin on cardiac, renal, and hepatic biomarkers in the Relaxin in Acute Heart Failure (RELAX-AHF) development program: Correlation with outcomes. *J Am Coll Cardiol*. 2013;**61**:196–206. https://doi.org/10.1016/j.jacc.2012.11.005
45. O'Brien RJ, Squire IB, Demme B, Davies JE, Ng LL. Pre-discharge, but not admission, levels of NT-proBNP predict adverse prognosis following acute LVF. *Eur J Heart Fail*. 2003;**5**:499–506. https://doi.org/10.1016/s1388-9842(03)00098-9
46. Bayes-Genis A, Lopez L, Zapico E, Cotes C, Santalo M, Ordonez-Llanos J, et al. NT-ProBNP reduction percentage during admission for acutely decompensated heart failure predicts long-term cardiovascular mortality. *J Card Fail*. 2005;**11**:S3–S8. https://doi.org/10.1016/j.cardfail.2005.04.006
47. Salah K, Kok WE, Eurlings LW, Bettencourt P, Pimenta JM, Metra M, et al. A novel discharge risk model for patients hospitalised for acute decompensated heart failure incorporating N-terminal pro-B-type natriuretic peptide levels: A European coLlaboration on Acute decompeNsated Heart Failure: ELAN-HF score. *Heart*. 2014;**100**:115–125. https://doi.org/10.1136/heartjnl-2013-303632
48. Felker GM, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuzat M, Houston-Miller N, et al. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: A randomized clinical trial. *JAMA*. 2017;**318**:713–720. https://doi.org/10.1001/jama.2017.10565
49. Stienen S, Salah K, Moons AH, Bakx AL, van Pol P, Kortz RAM, et al. NT-proBNP (N-terminal pro-B-type natriuretic peptide)-guided therapy in acute decompensated heart failure: PRIMA II randomized controlled trial (Can NT-ProBNP-Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?). *Circulation*. 2018;**137**:1671–1683. https://doi.org/10.1161/CIRCULATIONAHA.117.029882
50. Mebazaa A, Davison B, Chioncel O, Cohen-Solal A, Diaz R, Filippatos G, 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. https://doi.org/10.1016/S0140-6736(22)02076-1
51. Nunez J, Nunez E, Bayes-Genis A, Fonarow GC, Minana G, Bodi V, et al. Long-term serial kinetics of N-terminal pro B-type natriuretic peptide and carbohydrate antigen 125 for mortality risk prediction following acute heart failure. *Eur Heart J Acute Cardiovasc Care*. 2017;**6**:685–696. https://doi.org/10.1177/2048872616649757
52. Nunez J, de la Espriella R, Minana G, Santas E, Llacer P, Nunez E, et al. Antigen carbohydrate 125 as a biomarker in heart failure: A narrative review. *Eur J Heart Fail*. 2021;**23**:1445–1457. https://doi.org/10.1002/ejhf.2295
53. Nunez J, Llacer P, Garcia-Blas S, Bonanad C, Ventura S, Nunez JM, et al. CA125-guided diuretic treatment versus usual care in patients with acute heart failure and renal dysfunction. *Am J Med*. 2020;**133**:370–80.e4. https://doi.org/10.1016/j.amjmed.2019.07.041
54. Meijers WC, Bayes-Genis A, Mebazaa A, Bauersachs J, Cleland JGF, Coats AJS, et al. Circulating heart failure biomarkers beyond natriuretic peptides: Review from the Biomarker Study Group of the Heart Failure Association (HFA), European Society of Cardiology (ESC). *Eur J Heart Fail*. 2021;**23**:1610–1632. https://doi.org/10.1002/ejhf.2346
55. Voors AA, Kremer D, Geven C, Ter Maaten JM, Struck J, Bergmann A, et al. Adrenomedullin in heart failure: Pathophysiology and therapeutic application. *Eur J Heart Fail*. 2019;**21**:163–171. https://doi.org/10.1002/ejhf.1366
56. Pandhi P, Ter Maaten JM, Emmens JE, Struck J, Bergmann A, Cleland JG, et al. Clinical value of pre-discharge bio-adrenomedullin as a marker of residual congestion and high risk of heart failure hospital readmission. *Eur J Heart Fail*. 2020;**22**:683–691. https://doi.org/10.1002/ejhf.1693
57. van der Meer P, Postmus D, Ponikowski P, Cleland JG, O'Connor CM, Cotter G, et al. The predictive value of short-term changes in hemoglobin concentration in patients presenting with acute decompensated heart failure. *J Am Coll Cardiol*. 2013;**61**:1973–1981. https://doi.org/10.1016/j.jacc.2012.12.050
58. Breidthardt T, Weidmann ZM, Twerenbold R, Gantenbein C, Stallone F, Rentsch K, et al. Impact of haemoconcentration during acute heart failure therapy on mortality and its relationship with worsening renal function. *Eur J Heart Fail*. 2017;**19**:226–236. https://doi.org/10.1002/ejhf.667
59. Ponikowski P, Kirwan BA, Anker SD, McDonagh T, Dorobantu M, Drozdz J, et al.; AFFIRM-AHF Investigators. 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
60. Loncar G, Obradovic D, Thiele H, von Haehling S, Lainscak M. Iron deficiency in heart failure. *ESC Heart Fail*. 2021;**8**:2368–2379. https://doi.org/10.1002/ehf2.13265
61. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, 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
62. Mullens W, Verbrugge FH, Nijst P, Tang WHW. Renal sodium avidity in heart failure: From pathophysiology to treatment strategies. *Eur Heart J*. 2017;**38**:1872–1882. https://doi.org/10.1093/eurheartj/ehx035
63. Damman K, Ter Maaten JM, Coster JE, Krikken JA, van Deursen VM, Krijnen HK, et al. Clinical importance of urinary sodium excretion in acute heart failure. *Eur J Heart Fail*. 2020;**22**:1438–1447. https://doi.org/10.1002/ejhf.1753
64. Biegus J, Zymlinski R, Testani J, Marciniak D, Zdanowicz A, Jankowska EA, et al. Renal profiling based on estimated glomerular filtration rate and spot urine sodium identifies high-risk acute heart failure patients. *Eur J Heart Fail*. 2021;**23**:729–739. https://doi.org/10.1002/ejhf.2053
65. Dauw J, Lelonek M, Zegri-Reiriz I, Paredes-Paucar CP, Zara C, George V, et al. Rationale and design of the Efficacy of a Standardized Diuretic Protocol in Acute Heart Failure study. *ESC Heart Fail*. 2021;**8**:4685–4692. https://doi.org/10.1002/ehf2.13666
66. Ter Maaten JM, Beldhuis IE, van der Meer P, Krikken JA, Coster JE, Nieuwland W, et al. Natriuresis-guided therapy in acute heart failure: Rationale and design of the Pragmatic Urinary Sodium-based treatment algoritHm in Acute Heart Failure (PUSH-AHF) trial. *Eur J Heart Fail*. 2022;**24**:385–392. https://doi.org/10.1002/ejhf.2385
67. Martens P, Chen HH, Verbrugge FH, Testani JT, Mullens W, Tang WHW. Assessing intrinsic renal sodium avidity in acute heart failure: Implications in predicting and guiding decongestion. *Eur J Heart Fail*. 2022;**24**:1978–1987. https://doi.org/10.1002/ejhf.2662
68. Mullens W, Damman K, Testani JM, Martens P, Mueller C, Lassus J, et al. Evaluation of kidney function throughout the heart failure trajectory – a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2020;**22**:584–603. https://doi.org/10.1002/ejhf.1697
69. Mullens W, Martens P, Testani JM, Tang WHW, Skouri H, Verbrugge FH, 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
70. McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, et al.; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;**381**:1995–2008. https://doi.org/10.1056/NEJMoa1911303
71. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al.; EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;**383**:1413–1424. https://doi.org/10.1056/NEJMoa2022190
72. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Bohm M, et al.; EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;**385**:1451–1461. https://doi.org/10.1056/NEJMoa2107038
73. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al.; DELIVER Trial Committees and Investigators. Dapagliflozin in heart

failure with mildly reduced or preserved ejection fraction. *N Engl J Med*. 2022;**387**:1089–1098. https://doi.org/10.1056/NEJMoa2206286
74. Adamson C, Docherty KF, Heerspink HJL, de Boer RA, Damman K, Inzucchi SE, et al. Initial decline (dip) in estimated glomerular filtration rate after initiation of dapagliflozin in patients with heart failure and reduced ejection fraction: Insights from DAPA-HF. *Circulation*. 2022;**146**:438–449. https://doi.org/10.1161/CIRCULATIONAHA.121.058910
75. Metra M, Davison B, Bettari L, Sun H, Edwards C, Lazzarini V, et al. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. *Circ Heart Fail*. 2012;**5**:54–62. https://doi.org/10.1161/CIRCHEARTFAILURE.111.963413
76. Metra M, Cotter G, Gheorghiade M, Dei Cas L, Voors AA. The role of the kidney in heart failure. *Eur Heart J*. 2012;**33**:2135–2142. https://doi.org/10.1093/eurheartj/ehs205
77. Rossignol P, Lainscak M, Crespo-Leiro MG, Laroche C, Piepoli MF, Filippatos G, et al.; Heart Failure Long-Term Registry Investigators Group. Unravelling the interplay between hyperkalaemia, renin-angiotensin-aldosterone inhibitor use and clinical outcomes. Data from 9222 chronic heart failure patients of the ESC-HFA-EORP Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2020;**22**:1378–1389. https://doi.org/10.1002/ejhf.1793
78. Nunez J, Bayes-Genis A, Zannad F, Rossignol P, Nunez E, Bodi V, et al. Long-term potassium monitoring and dynamics in heart failure and risk of mortality. *Circulation*. 2018;**137**:1320–1330. https://doi.org/10.1161/CIRCULATIONAHA.117.030576
79. Butler J, Anker SD, Lund LH, Coats AJS, Filippatos G, Siddiqi TJ, 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
80. Lancellotti P, Galderisi M, Edvardsen T, Donal E, Goliasch G, Cardim N, et al. Echo-Doppler estimation of left ventricular filling pressure: Results of the multicentre EACVI Euro-Filling study. *Eur Heart J Cardiovasc Imaging*. 2017;**18**:961–968. https://doi.org/10.1093/ehjci/jex067
81. Kajimoto K, Sato N, Takano T; investigators of the Acute Decompensated Heart Failure Syndromes (ATTEND) registry. Functional mitral regurgitation at discharge and outcomes in patients hospitalized for acute decompensated heart failure with a preserved or reduced ejection fraction. *Eur J Heart Fail*. 2016;**18**:1051–1059. https://doi.org/10.1002/ejhf.562
82. Goonewardena SN, Gemignani A, Ronan A, Vasaiwala S, Blair J, Brennan JM, et al. Comparison of hand-carried ultrasound assessment of the inferior vena cava and N-terminal pro-brain natriuretic peptide for predicting readmission after hospitalization for acute decompensated heart failure. *JACC Cardiovasc Imaging*. 2008;**1**:595–601. https://doi.org/10.1016/j.jcmg.2008.06.005
83. Picano E, Pellikka PA. Ultrasound of extravascular lung water: A new standard for pulmonary congestion. *Eur Heart J*. 2016;**37**:2097–2104. https://doi.org/10.1093/eurheartj/ehw164
84. Platz E, Jhund PS, Girerd N, Pivetta E, McMurray JJV, Peacock WF, et al.; Study Group on Acute Heart Failure of the Acute Cardiovascular Care Association and the Heart Failure Association of the European Society of Cardiology. Expert consensus document: Reporting checklist for quantification of pulmonary congestion by lung ultrasound in heart failure. *Eur J Heart Fail*. 2019;**21**:844–851. https://doi.org/10.1002/ejhf.1499
85. Coiro S, Rossignol P, Ambrosio G, Carluccio E, Alunni G, Murrone A, et al. Prognostic value of residual pulmonary congestion at discharge assessed by lung ultrasound imaging in heart failure. *Eur J Heart Fail*. 2015;**17**:1172–1181. https://doi.org/10.1002/ejhf.344
86. Gargani L, Pang PS, Frassi F, Miglioranza MH, Dini FL, Landi P, et al. Persistent pulmonary congestion before discharge predicts rehospitalization in heart failure: A lung ultrasound study. *Cardiovasc Ultrasound*. 2015;**13**:40. https://doi.org/10.1186/s12947-015-0033-4
87. Platz E, Campbell RT, Claggett B, Lewis EF, Groarke JD, Docherty KF, et al. Lung ultrasound in acute heart failure: Prevalence of pulmonary congestion and short- and long-term outcomes. *JACC Heart Fail*. 2019;**7**:849–858. https://doi.org/10.1016/j.jchf.2019.07.008
88. Platz E, Merz AA, Jhund PS, Vazir A, Campbell R, McMurray JJ. Dynamic changes and prognostic value of pulmonary congestion by lung ultrasound in acute and chronic heart failure: A systematic review. *Eur J Heart Fail*. 2017;**19**:1154–1163. https://doi.org/10.1002/ejhf.839
89. Rivas-Lasarte M, Alvarez-Garcia J, Fernandez-Martinez J, Maestro A, Lopez-Lopez L, Sole-Gonzalez E, et al. Lung ultrasound-guided treatment in ambulatory patients with heart failure: A randomized controlled clinical trial (LUS-HF study). *Eur J Heart Fail*. 2019;**21**:1605–1613. https://doi.org/10.1002/ejhf.1604
90. Mhanna M, Beran A, Nazir S, Sajdeya O, Srour O, Ayesh H, et al. Lung ultrasound-guided management to reduce hospitalization in chronic heart failure: A systematic review and meta-analysis. *Heart Fail Rev*. 2022;**27**:821–826. https://doi.org/10.1007/s10741-021-10085-x
91. Pivetta E, Goffi A, Nazerian P, Castagno D, Tozzetti C, Tizzani P, et al. Lung ultrasound integrated with clinical assessment for the diagnosis of acute decompensated heart failure in the emergency department: A randomized controlled trial. *Eur J Heart Fail*. 2019;**21**:754–766. https://doi.org/10.1002/ejhf.1379
92. Moura B, Aimo A, Al-Mohammad A, Flammer A, Barberis V, Bayes-Genis A, et al. Integration of imaging and circulating biomarkers in heart failure: A consensus document by the Biomarkers and Imaging Study Groups of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2021;**23**:1577–1596. https://doi.org/10.1002/ejhf.2339
93. Seferović PM, Vardas P, Jankowska EA, Maggioni AP, Timmis A, Milinković I, et al. The Heart Failure Association Atlas: Heart failure epidemiology and management statistics 2019. *Eur J Heart Fail*. 2021;**23**:906–914. https://doi.org/10.1002/ejhf.2143
94. Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, et al. Advanced heart failure: A position statement of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2018;**20**:1505–1535. https://doi.org/10.1002/ejhf.1236
95. Patel RB, Fonarow GC, Greene SJ, Zhang S, Alhanti B, DeVore AD, et al. Kidney function and outcomes in patients hospitalized with heart failure. *J Am Coll Cardiol*. 2021;**78**:330–343. https://doi.org/10.1016/j.jacc.2021.05.002
96. Pagnesi M, Lombardi CM, Chiarito M, Stolfo D, Baldetti L, Loiacono F, et al. Prognostic impact of the updated 2018 HFA-ESC definition of advanced heart failure: Results from the HELP-HF registry. *Eur J Heart Fail*. 2022;**24**:1493–1503. https://doi.org/10.1002/ejhf.2561
97. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, 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. https://doi.org/10.1161/CIR.0000000000001063
98. Damman K, Kjekshus J, Wikstrand J, Cleland JG, Komajda M, Wedel H, et al. Loop diuretics, renal function and clinical outcome in patients with heart failure and reduced ejection fraction. *Eur J Heart Fail*. 2016;**18**:328–336. https://doi.org/10.1002/ejhf.462
99. Kapelios CJ, Laroche C, Crespo-Leiro MG, Anker SD, Coats AJS, Diaz-Molina B, et al.; Heart Failure Long-Term Registry Investigators Group. Association between loop diuretic dose changes and outcomes in chronic heart failure: Observations from the ESC-EORP Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2020;**22**:1424–1437. https://doi.org/10.1002/ejhf.1796
100. Ter Maaten JM, Martens P, Damman K, Dickstein K, Ponikowski P, Lang CC, et al. Higher doses of loop diuretics limit uptitration of angiotensin-converting enzyme inhibitors in patients with heart failure and reduced ejection fraction. *Clin Res Cardiol*. 2020;**109**:1048–1059. https://doi.org/10.1007/s00392-020-01598-w
101. Mullens W, Dauw J, Martens P, Verbrugge FH, Nijst P, Meekers E, et al.; ADVOR Study Group. Acetazolamide in acute decompensated heart failure with volume overload. *N Engl J Med*. 2022;**387**:1185–1195. https://doi.org/10.1056/NEJMoa2203094
102. Konstam MA, Gheorghiade M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, et al.; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. 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
103. Konstam MA, Kiernan M, Chandler A, Dhingra R, Mody FV, Eisen H, et al.; SECRET of CHF Investigators, Coordinators, and Committee Members. 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
104. Greene SJ, Butler J, Fonarow GC. In-hospital initiation of quadruple medical therapy for heart failure: Making the post-discharge vulnerable phase far less vulnerable. *Eur J Heart Fail*. 2022;**24**:227–229. https://doi.org/10.1002/ejhf.2382
105. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, et al. Medical therapy for heart failure with reduced ejection fraction: The CHAMP-HF registry. *J Am Coll Cardiol*. 2018;**72**:351–366. https://doi.org/10.1016/j.jacc.2018.04.070
106. Greene SJ, Fonarow GC, DeVore AD, Sharma PP, Vaduganathan M, Albert NM, et al. Titration of medical therapy for heart failure with reduced ejection fraction. *J Am Coll Cardiol*. 2019;**73**:2365–2383. https://doi.org/10.1016/j.jacc.2019.02.015
107. Greene SJ, Ezekowitz JA, Anstrom KJ, Demyanenko V, Givertz MM, Pina IL, et al. Medical therapy during hospitalization for heart failure with reduced ejection fraction: The VICTORIA registry. *J Card Fail*. 2022;**28**:1063–1077. https://doi.org/10.1016/j.cardfail.2022.02.011

108. Carnicelli AP, Lippmann SJ, Greene SJ, Mentz RJ, Greiner MA, Hardy NC, et al. Sacubitril/valsartan initiation and postdischarge adherence among patients hospitalized for heart failure. *J Card Fail*. 2021;**27**:826–836. https://doi.org/10.1016/j.cardfail.2021.03.012
109. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al.; OPTIMIZE-HF Investigators and Coordinators. Prospective evaluation of beta-blocker use at the time of hospital discharge as a heart failure performance measure: Results from OPTIMIZE-HF. *J Card Fail*. 2007;**13**:722–731. https://doi.org/10.1016/j.cardfail.2007.06.727
110. Curtis LH, Mi X, Qualls LG, Check DK, Hammill BG, Hammill SC, et al. Transitional adherence and persistence in the use of aldosterone antagonist therapy in patients with heart failure. *Am Heart J*. 2013;**165**:979–986.e1. https://doi.org/10.1016/j.ahj.2013.03.007
111. Gattis WA, O'Connor CM, Gallup DS, Hasselblad V, Gheorghiade M; IMPACT-HF Investigators and Coordinators. Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure: Results of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial. *J Am Coll Cardiol*. 2004;**43**:1534–1541. https://doi.org/10.1016/j.jacc.2003.12.040
112. Kaplon-Cieslicka A, Benson L, Chioncel O, Crespo-Leiro MG, Coats AJS, Anker SD, et al.; Heart Failure Association (HFA) of the European Society of Cardiology (ESC) and the ESC Heart Failure Long-Term Registry Investigators. A comprehensive characterization of acute heart failure with preserved versus mildly reduced versus reduced ejection fraction – insights from the ESC-HFA EORP Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2022;**24**:335–350. https://doi.org/10.1002/ejhf.2408
113. Greene SJ, Butler J, Fonarow GC. Simultaneous or rapid sequence initiation of quadruple medical therapy for heart failure-optimizing therapy with the need for speed. *JAMA Cardiol*. 2021;**6**:743–744. https://doi.org/10.1001/jamacardio.2021.0496
114. Tomasoni D, Fonarow GC, Adamo M, Anker SD, Butler J, Coats AJS, et al. Sodium-glucose co-transporter 2 inhibitors as an early, first-line therapy in patients with heart failure and reduced ejection fraction. *Eur J Heart Fail*. 2022;**24**:431–441. https://doi.org/10.1002/ejhf.2397
115. Gayat E, Arrigo M, Littnerova S, Sato N, Parenica J, Ishihara S, 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. https://doi.org/10.1002/ejhf.932
116. Carubelli V, Lombardi C, Specchia C, Peveri G, Oriecuia C, Tomasoni D, et al. Adherence and optimization of angiotensin converting enzyme inhibitor/angiotensin II receptors blockers and beta-blockers in patients hospitalized for acute heart failure. *ESC Heart Fail*. 2021;**8**:1944–1953. https://doi.org/10.1002/ehf2.13223
117. Sharma A, Verma S, Bhatt DL, Connelly KA, Swiggum E, Vaduganathan M, et al. Optimizing foundational therapies in patients with HFrEF: How do we translate these findings into clinical care? *JACC Basic Transl Sci*. 2022;**7**:504–517. https://doi.org/10.1016/j.jacbts.2021.10.018
118. Lam PH, Packer M, Fonarow GC, Faselis C, Allman RM, Morgan CJ, et al. Early effects of starting doses of enalapril in patients with chronic heart failure in the SOLVD Treatment trial. *Am J Med*. 2020;**133**:e25–e31. https://doi.org/10.1016/j.amjmed.2019.06.053
119. Krum H, Roecker EB, Mohacsi P, Rouleau JL, Tendera M, Coats AJ, et al.; Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group. Effects of initiating carvedilol in patients with severe chronic heart failure: Results from the COPERNICUS study. *JAMA*. 2003;**289**:712–718. https://doi.org/10.1001/jama.289.6.712
120. Bedrouni W, Sharma A, Pitt B, Lam CSP, Ni J, Ferreira JP, et al. Timing of statistical benefit of mineralocorticoid receptor antagonists among patients with heart failure and post-myocardial infarction. *Circ Heart Fail*. 2022;**15**:e009295. https://doi.org/10.1161/CIRCHEARTFAILURE.121.009295
121. Gilstrap LG, Fonarow GC, Desai AS, Liang L, Matsouaka R, DeVore AD, et al. Initiation, continuation, or withdrawal of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and outcomes in patients hospitalized with heart failure with reduced ejection fraction. *J Am Heart Assoc*. 2017;**6**:e004675. https://doi.org/10.1161/JAHA.116.004675
122. Metra M, Torp-Pedersen C, Cleland JG, Di Lenarda A, Komajda M, Remme WJ, et al.; COMET Investigators. Should beta-blocker therapy be reduced or withdrawn after an episode of decompensated heart failure? Results from COMET. *Eur J Heart Fail*. 2007;**9**:901–909. https://doi.org/10.1016/j.ejheart.2007.05.011
123. 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
124. Jondeau G, Neuder Y, Eicher JC, Jourdain P, Fauveau E, Galinier M, et al.; B-CONVINCED Investigators. B-CONVINCED: Beta-blocker CONtinuation Vs. INterruption in patients with Congestive heart failure hospitalizED for a decompensation episode. *Eur Heart J*. 2009;**30**:2186–2192. https://doi.org/10.1093/eurheartj/ehp323
125. Morrow DA, Velazquez EJ, DeVore AD, Desai AS, Duffy CI, Ambrosy AP, et al. 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. https://doi.org/10.1161/CIRCULATIONAHA.118.039331
126. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, et al.; PIONEER-HF Investigators. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med*. 2019;**380**:539–548. https://doi.org/10.1056/NEJMoa1812851
127. Berg DD, Jhund PS, Docherty KF, Murphy SA, Verma S, Inzucchi SE, et al. Time to clinical benefit of dapagliflozin and significance of prior heart failure hospitalization in patients with heart failure with reduced ejection fraction. *JAMA Cardiol*. 2021;**6**:499–507. https://doi.org/10.1001/jamacardio.2020.7585
128. Packer M, Anker SD, Butler J, Filippatos G, Ferreira JP, Pocock SJ, et al. Effect of empagliflozin on the clinical stability of patients with heart failure and a reduced ejection fraction: The EMPEROR-Reduced trial. *Circulation*. 2021;**143**:326–336. https://doi.org/10.1161/CIRCULATIONAHA.120.051783
129. Packer M, Butler J, Zannad F, Filippatos G, Ferreira JP, Pocock SJ, et al. Effect of empagliflozin on worsening heart failure events in patients with heart failure and preserved ejection fraction: EMPEROR-Preserved trial. *Circulation*. 2021;**144**:1284–1294. https://doi.org/10.1161/CIRCULATIONAHA.121.056824
130. Kosiborod MN, Angermann CE, Collins SP, Teerlink JR, Ponikowski P, Biegus J, et al. Effects of empagliflozin on symptoms, physical limitations, and quality of life in patients hospitalized for acute heart failure: Results from the EMPULSE trial. *Circulation*. 2022;**146**:279–288. https://doi.org/10.1161/CIRCULATIONAHA.122.059725
131. Butler J, Siddiqi TJ, Filippatos G, Ferreira JP, Pocock SJ, Zannad F, et al. Early benefit with empagliflozin in heart failure with preserved ejection fraction: Insights from the EMPEROR-Preserved trial. *Eur J Heart Fail*. 2022;**24**:245–248. https://doi.org/10.1002/ejhf.2420
132. Damman K, Beusekamp JC, Boorsma EM, Swart HP, Smilde TDJ, Elvan A, 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
133. Voors AA, Angermann CE, Teerlink JR, Collins SP, Kosiborod M, Biegus J, 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
134. Cunningham JW, Vaduganathan M, Claggett BL, Kulac IJ, Desai AS, Jhund PS, et al. Dapagliflozin in patients recently hospitalized with heart failure and mildly reduced or preserved ejection fraction. *J Am Coll Cardiol*. 2022;**80**:1302–1310. https://doi.org/10.1016/j.jacc.2022.07.021
135. Cox ZL, Collins SP, Aaron M, Hernandez GA, Iii ATM, Davidson BT, et al. Efficacy and safety of dapagliflozin in acute heart failure: Rationale and design of the DICTATE-AHF trial. *Am Heart J*. 2021;**232**:116–124. https://doi.org/10.1016/j.ahj.2020.10.071
136. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, et al.; VICTORIA Study Group. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2020;**382**:1883–1893. https://doi.org/10.1056/NEJMoa1915928
137. Khan MS, Xu H, Fonarow GC, Lautsch D, Hilkert R, Allen LA, et al. Applicability of vericiguat to patients hospitalized for heart failure in the United States. *JACC Heart Fail*. 2023;**11**:211–223. https://doi.org/10.1016/j.jchf.2022.11.007
138. Bistola V, Simitsis P, Parissis J, Ouwerkerk W, van Veldhuisen DJ, Cleland JG, et al. Association between up-titration of medical therapy and total hospitalizations and mortality in patients with recent worsening heart failure across the ejection fraction spectrum. *Eur J Heart Fail*. 2021;**23**:1170–1181. https://doi.org/10.1002/ejhf.2219
139. Kalra PR, Cleland JGF, Petrie MC, Thomson EA, Kalra PA, Squire IB, et al.; IRONMAN Study Group. Intravenous ferric derisomaltose in patients with heart failure and iron deficiency in the UK (IRONMAN): An investigator-initiated, prospective, randomised, open-label, blinded-endpoint trial. *Lancet*. 2022;**400**:2199–2209. https://doi.org/10.1016/S0140-6736(22)02083-9
140. Vitale C, Jankowska E, Hill L, Piepoli M, Doehner W, Anker SD, et al. Heart Failure Association/European Society of Cardiology position paper on frailty in patients with heart failure. *Eur J Heart Fail*. 2019;**21**:1299–1305. https://doi.org/10.1002/ejhf.1611

141. Njoroge JN, Cheema B, Ambrosy AP, Greene SJ, Collins SP, Vaduganathan M, et al. Expanded algorithm for managing patients with acute decompensated heart failure. *Heart Fail Rev*. 2018;**23**:597–607. https://doi.org/10.1007/s10741-018-9697-9
142. Metra M, Gheorghiade M, Bonow RO, Dei Cas L. Postdischarge assessment after a heart failure hospitalization: The next step forward. *Circulation*. 2010;**122**:1782–1785. https://doi.org/10.1161/CIRCULATIONAHA.110.982207
143. Blair JE, Khan S, Konstam MA, Swedberg K, Zannad F, Burnett JC Jr, et al.; EVEREST Investigators. Weight changes after hospitalization for worsening heart failure and subsequent re-hospitalization and mortality in the EVEREST trial. *Eur Heart J*. 2009;**30**:1666–1673. https://doi.org/10.1093/eurheartj/ehp144
144. Blair JE, Pang PS, Schrier RW, Metra M, Traver B, Cook T, et al.; EVEREST Investigators. Changes in renal function during hospitalization and soon after discharge in patients admitted for worsening heart failure in the placebo group of the EVEREST trial. *Eur Heart J*. 2011;**32**:2563–2572. https://doi.org/10.1093/eurheartj/ehr238
145. Dunlay SM, Gheorghiade M, Reid KJ, Allen LA, Chan PS, Hauptman PJ, et al. Critical elements of clinical follow-up after hospital discharge for heart failure: Insights from the EVEREST trial. *Eur J Heart Fail*. 2010;**12**:367–374. https://doi.org/10.1093/eurjhf/hfq019
146. Krumholz HM. Post-hospital syndrome – an acquired, transient condition of generalized risk. *N Engl J Med*. 2013;**368**:100–102. https://doi.org/10.1056/NEJMp1212324
147. Ter Maaten JM, Damman K, Hanberg JS, Givertz MM, Metra M, O'Connor CM, et al. Hypochloremia, diuretic resistance, and outcome in patients with acute heart failure. *Circ Heart Fail*. 2016;**9**:e003109. https://doi.org/10.1161/CIRCHEARTFAILURE.116.003109
148. Pocock SJ, Ferreira JP, Gregson J, Anker SD, Butler J, Filippatos G, et al. Novel biomarker-driven prognostic models to predict morbidity and mortality in chronic heart failure: The EMPEROR-Reduced trial. *Eur Heart J*. 2021;**42**:4455–4464. https://doi.org/10.1093/eurheartj/ehab579
149. Pocock SJ, Ferreira JP, Packer M, Zannad F, Filippatos G, Kondo T, et al. Biomarker-driven prognostic models in chronic heart failure with preserved ejection fraction: The EMPEROR-Preserved trial. *Eur J Heart Fail*. 2022;**24**:1869–1878. https://doi.org/10.1002/ejhf.2607
150. Hernandez AF, Greiner MA, Fonarow GC, Hammill BG, Heidenreich PA, Yancy CW, et al. Relationship between early physician follow-up and 30-day readmission among Medicare beneficiaries hospitalized for heart failure. *JAMA*. 2010;**303**:1716–1722. https://doi.org/10.1001/jama.2010.533
151. DeVore AD, Granger BB, Fonarow GC, Al-Khalidi HR, Albert NM, Lewis EF, 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
152. Jaarsma T, van der Wal MH, Lesman-Leegte I, Luttik ML, Hogenhuis J, Veeger NJ, et al.; Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure (COACH) Investigators. 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. https://doi.org/10.1001/archinternmed.2007.83
153. Van Spall HGC, Lee SF, Xie F, Oz UE, Perez R, Mitoff PR, 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
154. Li M, Li Y, Meng Q, Li Y, Tian X, Liu R, et al. 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. https://doi.org/10.1371/journal.pone.0261300
155. 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. https://doi.org/10.1002/ehf2.13152
156. Lee DS, Straus SE, Farkouh ME, Austin PC, Taljaard M, Chong A, et al.; COACH Trial Investigators. Trial of an intervention to improve acute heart failure outcomes. *N Engl J Med*. 2023;**388**:22–32. https://doi.org/10.1056/NEJMoa2211680
157. Lee DS, Stitt A, Austin PC, Stukel TA, Schull MJ, Chong A, et al. Prediction of heart failure mortality in emergent care: A cohort study. *Ann Intern Med*. 2012;**156**:767–775, W-261, W-262. https://doi.org/10.7326/0003-4819-156-11-201206050-00003
158. Miro O, Rossello X, Platz E, Masip J, Gualandro DM, Peacock WF, et al.; Study Group on Acute Heart Failure of the Acute Cardiovascular Care Association of the European Society of Cardiology. Risk stratification scores for patients with acute heart failure in the emergency department: A systematic review. *Eur Heart J Acute Cardiovasc Care*. 2020;**9**:375–398. https://doi.org/10.1177/2048872620930889
159. Lee DS, Stukel TA, Austin PC, Alter DA, Schull MJ, You JJ, et al. Improved outcomes with early collaborative care of ambulatory heart failure patients discharged from the emergency department. *Circulation*. 2010;**122**:1806–1814. https://doi.org/10.1161/CIRCULATIONAHA.110.940262
160. Van Spall HGC, Rahman T, Mytton O, Ramasundarahettige C, Ibrahim Q, Kabali C, 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
161. Thodi M, Bistola V, Lambrinou E, Keramida K, Nikolopoulos P, Parissis J, et al. 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*. https://doi.org/10.1093/eurjcn/zvac118. Published online ahead of print 13/12/22
162. Liljeroos M, Stromberg A. Introducing nurse-led heart failure clinics in Swedish primary care settings. *Eur J Heart Fail*. 2019;**21**:103–109. https://doi.org/10.1002/ejhf.1329
163. Jonkman NH, Westland H, Groenwold RH, Agren S, Anguita M, Blue L, et al. What are effective program characteristics of self-management interventions in patients with heart failure? An individual patient data meta-analysis. *J Card Fail*. 2016;**22**:861–871. https://doi.org/10.1016/j.cardfail.2016.06.422
164. Koelling TM, Johnson ML, Cody RJ, Aaronson KD. Discharge education improves clinical outcomes in patients with chronic heart failure. *Circulation*. 2005;**111**:179–185. https://doi.org/10.1161/01.CIR.0000151811.53450.B8
165. Oh S, Choi H, Oh EG, Lee JY. Effectiveness of discharge education using teach-back method on readmission among heart failure patients: A systematic review and meta-analysis. *Patient Educ Couns*. 2023;**107**:107559. https://doi.org/10.1016/j.pec.2022.11.001
166. Brahmbhatt DH, Cowie MR. Remote management of heart failure: An overview of telemonitoring technologies. *Card Fail Rev*. 2019;**5**:86–92. https://doi.org/10.15420/cfr.2019.5.3
167. Cleland JGF, Clark RA, Pellicori P, Inglis SC. Caring for people with heart failure and many other medical problems through and beyond the COVID-19 pandemic: The advantages of universal access to home telemonitoring. *Eur J Heart Fail*. 2020;**22**:995–998. https://doi.org/10.1002/ejhf.1864
168. Task Force for the management of COVID-19 of the European Society of Cardiology. ESC guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic: Part 2 – care pathways, treatment, and follow-up. *Eur Heart J*. 2022;**43**:1059–1103. https://doi.org/10.1093/eurheartj/ehab697
169. Frederix I, Caiani EG, Dendale P, Anker S, Bax J, Bohm A, et al. ESC e-Cardiology Working Group Position Paper: Overcoming challenges in digital health implementation in cardiovascular medicine. *Eur J Prev Cardiol*. 2019;**26**:1166–1177. https://doi.org/10.1177/2047487319832394
170. Chaudhry SI, Mattera JA, Curtis JP, Spertus JA, Herrin J, Lin Z, et al. Telemonitoring in patients with heart failure. *N Engl J Med*. 2010;**363**:2301–2309. https://doi.org/10.1056/NEJMoa1010029
171. Koehler F, Winkler S, Schieber M, Sechtem U, Stangl K, Bohm M, et al.; Telemedical Interventional Monitoring in Heart Failure Investigators. Impact of remote telemedical management on mortality and hospitalizations in ambulatory patients with chronic heart failure: The Telemedical Interventional Monitoring in Heart Failure study. *Circulation*. 2011;**123**:1873–1880. https://doi.org/10.1161/CIRCULATIONAHA.111.018473
172. Koehler F, Koehler K, Deckwart O, Prescher S, Wegscheider K, Winkler S, et al. Telemedical Interventional Management in Heart Failure II (TIM-HF2), a randomised, controlled trial investigating the impact of telemedicine on unplanned cardiovascular hospitalisations and mortality in heart failure patients: Study design and description of the intervention. *Eur J Heart Fail*. 2018;**20**:1485–1493. https://doi.org/10.1002/ejhf.1300
173. Koehler F, Koehler K, Deckwart O, Prescher S, Wegscheider K, Kirwan BA, et al. Efficacy of telemedical interventional management in patients with heart failure (TIM-HF2): A randomised, controlled, parallel-group, unmasked trial. *Lancet*. 2018;**392**:1047–1057. https://doi.org/10.1016/S0140-6736(18)31880-4
174. Cleland JG, Louis AA, Rigby AS, Janssens U, Balk AH; TEN-HMS Investigators. Noninvasive home telemonitoring for patients with heart failure at high risk of recurrent admission and death: The Trans-European Network-Home-Care Management System (TEN-HMS) study. *J Am Coll Cardiol*. 2005;**45**:1654–1664. https://doi.org/10.1016/j.jacc.2005.01.050
175. Zile MR, Bennett TD, St John Sutton M, Cho YK, Adamson PB, Aaron MF, et al. Transition from chronic compensated to acute decompensated

heart failure: Pathophysiological insights obtained from continuous monitoring of intracardiac pressures. *Circulation*. 2008;**118**:1433–1441. https://doi.org/10.1161/CIRCULATIONAHA.108.783910

176. Conraads VM, Tavazzi L, Santini M, Oliva F, Gerritse B, Yu CM, et al. Sensitivity and positive predictive value of implantable intrathoracic impedance monitoring as a predictor of heart failure hospitalizations: The SENSE-HF trial. *Eur Heart J*. 2011;**32**:2266–2273. https://doi.org/10.1093/eurheartj/ehr050
177. Landolina M, Perego GB, Lunati M, Curnis A, Guenzati G, Vicentini A, et al. Remote monitoring reduces healthcare use and improves quality of care in heart failure patients with implantable defibrillators: The Evolution of Management Strategies of Heart Failure Patients With Implantable Defibrillators (EVOLVO) study. *Circulation*. 2012;**125**:2985–2992. https://doi.org/10.1161/CIRCULATIONAHA.111.088971
178. Shochat MK, Shotan A, Blondheim DS, Kazatsker M, Dahan I, Asif A, et al. Non-invasive lung IMPEDANCE-guided preemptive treatment in chronic heart failure patients: A randomized controlled trial (IMPEDANCE-HF trial). *J Card Fail*. 2016;**22**:713–722. https://doi.org/10.1016/j.cardfail.2016.03.015
179. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, et al.; CHAMPION Trial Study Group. 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
180. Abraham WT, Stevenson LW, Bourge RC, Lindenfeld JA, Bauman JG, Adamson PB, et al.; CHAMPION Trial Study Group. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: Complete follow-up results from the CHAMPION randomised trial. *Lancet*. 2016;**387**:453–461. https://doi.org/10.1016/S0140-6736(15)00723-0
181. Angermann CE, Assmus B, Anker SD, Asselbergs FW, Brachmann J, Brett ME, et al.; MEMS-HF Investigators. Pulmonary artery pressure-guided therapy in ambulatory patients with symptomatic heart failure: The CardioMEMS European Monitoring Study for Heart Failure (MEMS-HF). *Eur J Heart Fail*. 2020;**22**:1891–1901. https://doi.org/10.1002/ejhf.1943
182. Lindenfeld J, Zile MR, Desai AS, Bhatt K, Ducharme A, Horstmanshof D, et al. Haemodynamic-guided management of heart failure (GUIDE-HF): A randomised controlled trial. *Lancet*. 2021;**398**:991–1001. https://doi.org/10.1016/S0140-6736(21)01754-2
183. Mullens W, Sharif F, Dupont M, Rothman AMK, Wijns W. Digital health care solution for proactive heart failure management with the Cordella Heart Failure System: Results of the SIRONA first-in-human study. *Eur J Heart Fail*. 2020;**22**:1912–1919. https://doi.org/10.1002/ejhf.1870
184. Dauw J, Sokolski M, Middleton JT, Nijst P, Dupont M, Forouzan O, et al. Ambulatory haemodynamic-guided management reduces heart failure hospitalizations in a multicentre European heart failure cohort. *ESC Heart Fail*. 2022;**9**:3858–3867. https://doi.org/10.1002/ehf2.14056
185. Edelmann F, Gelbrich G, Dungen HD, Frohling S, Wachter R, Stahrenberg R, et al. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: Results of the Ex-DHF (Exercise Training in Diastolic Heart Failure) pilot study. *J Am Coll Cardiol*. 2011;**58**:1780–1791. https://doi.org/10.1016/j.jacc.2011.06.054
186. Nolte K, Herrmann-Lingen C, Wachter R, Gelbrich G, Dungen HD, Duvinage A, et al. Effects of exercise training on different quality of life dimensions in heart failure with preserved ejection fraction: The Ex-DHF-P trial. *Eur J Prev Cardiol*. 2015;**22**:582–593. https://doi.org/10.1177/2047487314526071
187. Flynn KE, Pina IL, Whellan DJ, Lin L, Blumenthal JA, Ellis SJ, et al.; HF-ACTION Investigators. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA*. 2009;**301**:1451–1459. https://doi.org/10.1001/jama.2009.457
188. Taylor RS, Walker S, Smart NA, Piepoli MF, Warren FC, Ciani O, et al.; ExTraMATCH II Collaboration. Impact of exercise rehabilitation on exercise capacity and quality-of-life in heart failure: Individual participant meta-analysis. *J Am Coll Cardiol*. 2019;**73**:1430–1443. https://doi.org/10.1016/j.jacc.2018.12.072
189. Taylor RS, Walker S, Smart NA, Piepoli MF, Warren FC, Ciani O, et al.; ExTraMATCH II Collaboration. Impact of exercise-based cardiac rehabilitation in patients with heart failure (ExTraMATCH II) on mortality and hospitalisation: An individual patient data meta-analysis of randomised trials. *Eur J Heart Fail*. 2018;**20**:1735–1743. https://doi.org/10.1002/ejhf.1311
190. Buckley BJR, Harrison SL, Fazio-Eynullayeva E, Underhill P, Sankaranarayanan R, Wright DJ, et al. Cardiac rehabilitation and all-cause mortality in patients with heart failure: A retrospective cohort study. *Eur J Prev Cardiol*. 2021;**28**:1704–1710. https://doi.org/10.1093/eurjpc/zwab035
191. Ramachandran HJ, Jiang Y, Tam WWS, Yeo TJ, Wang W. Effectiveness of home-based cardiac telerehabilitation as an alternative to phase 2 cardiac rehabilitation of coronary heart disease: A systematic review and meta-analysis. *Eur J Prev Cardiol*. 2022;**29**:1017–1043. https://doi.org/10.1093/eurjpc/zwab106
192. Hansen D, Abreu A, Ambrosetti M, Cornelissen V, Gevaert A, Kemps H, et al. Exercise intensity assessment and prescription in cardiovascular rehabilitation and beyond: Why and how: A position statement from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. *Eur J Prev Cardiol*. 2022;**29**:230–245. https://doi.org/10.1093/eurjpc/zwab007