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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

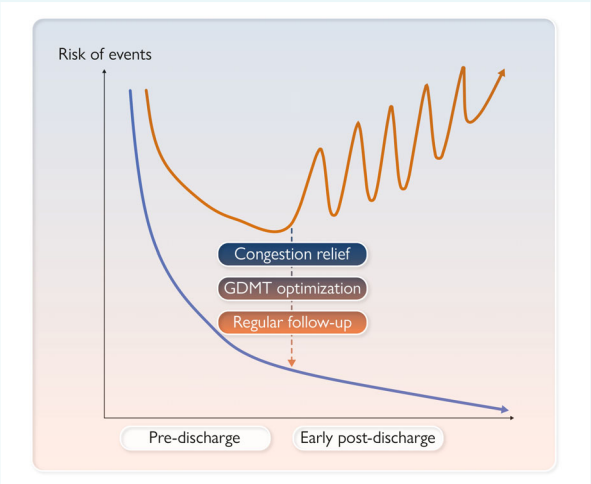

Figure 1 Determinants of better outcome after discharge. Optimal decongestion, optimization of guideline-directed medical therapy (GDMT) and intensive post-discharge monitoring reduce mortality and new heart failure events after discharge.

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*.

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]

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.

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

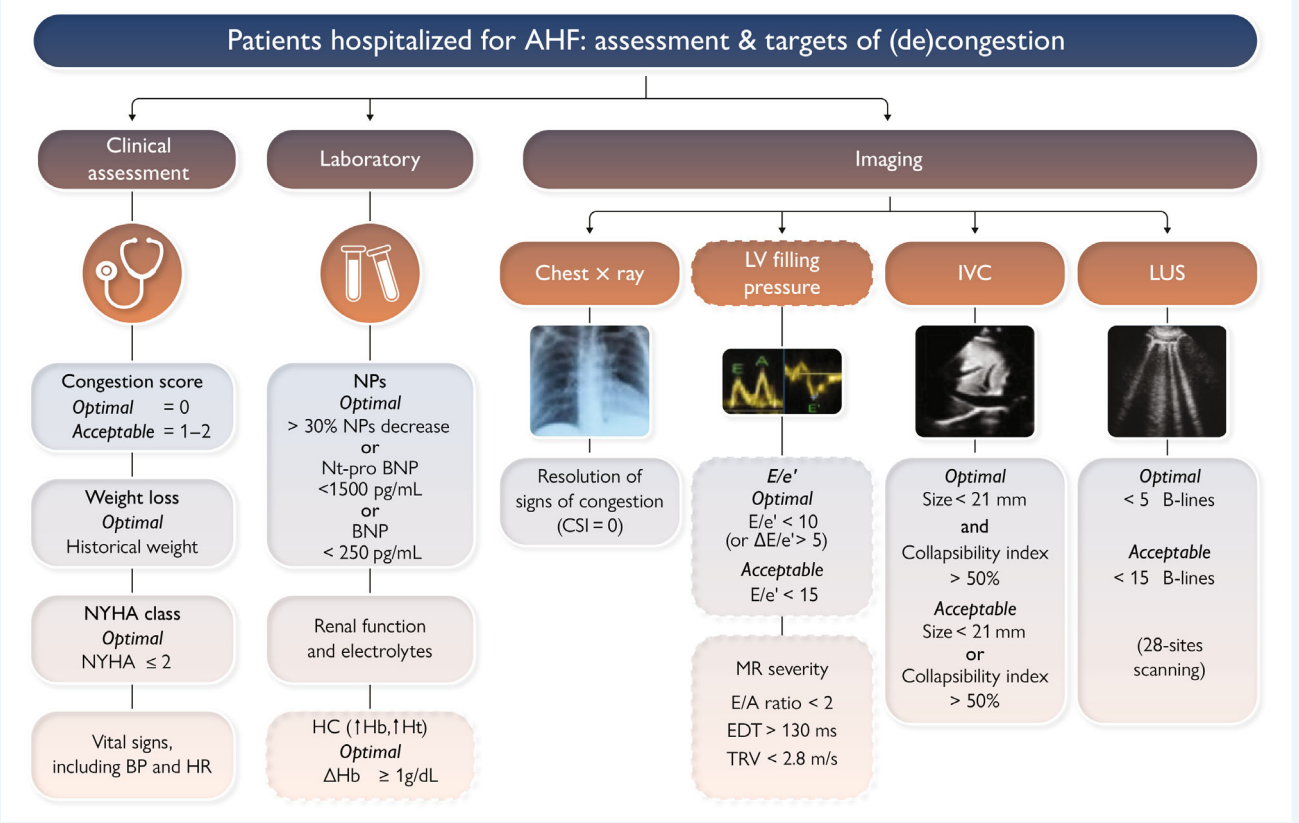

Figure 2 Assessment and targets of decongestion during the pre-discharge phase. Clinical, laboratory and imaging factors to assess before discharge and relative targets are reported. AHF, acute heart failure; BP, blood pressure; BNP, B-type natriuretic peptide; CSI, congestion score index; EDT, E-wave 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

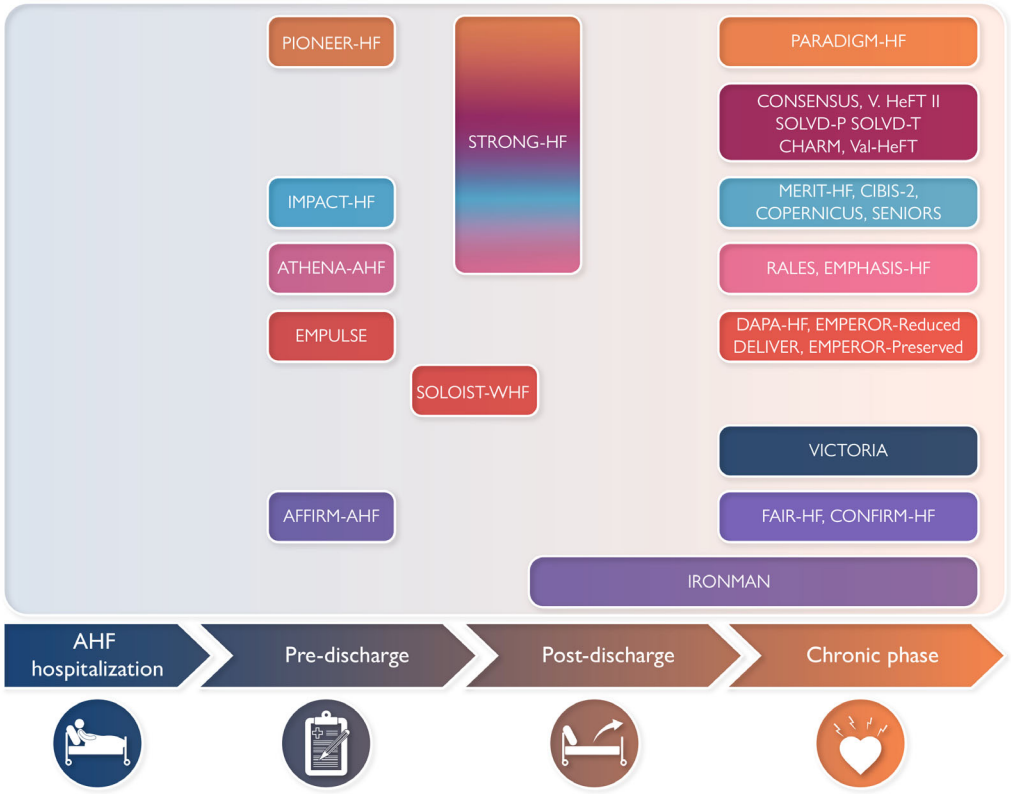

Figure 3 Randomized clinical trials in different hospitalization phases. Studies including pre-discharge, early post-discharge and late post-discharge heart failure populations are reported. AHF, acute heart failure.

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,

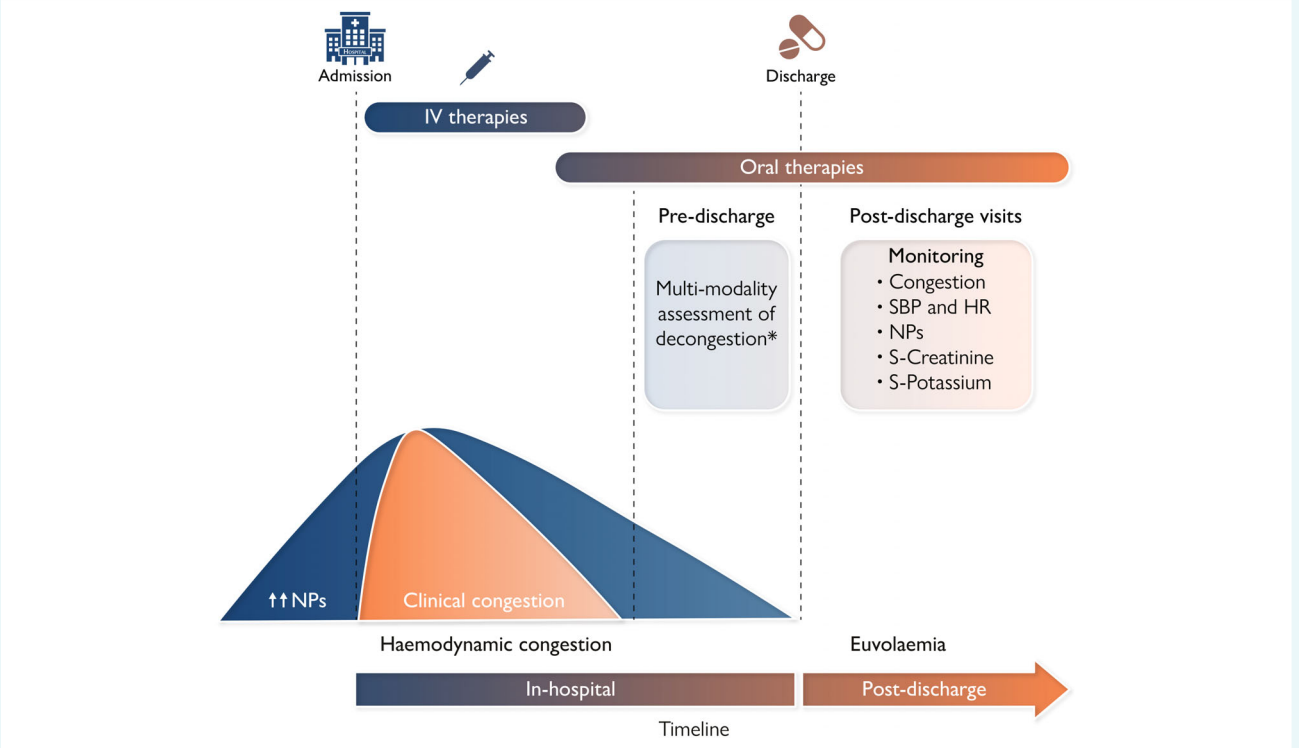

Figure 4 Management of heart failure patients according to hospitalization phase. During hospitalization, in presence of clinical congestion, intravenous (IV) therapies are needed. Assessment of decongestion and optimization of oral therapies (purple arrows) before discharge and at early follow-up visits 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.

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