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STATE OF THE ART REVIEW
Heart failure and cardiomyopathies

Acute heart failure: current pharmacological treatment and perspectives

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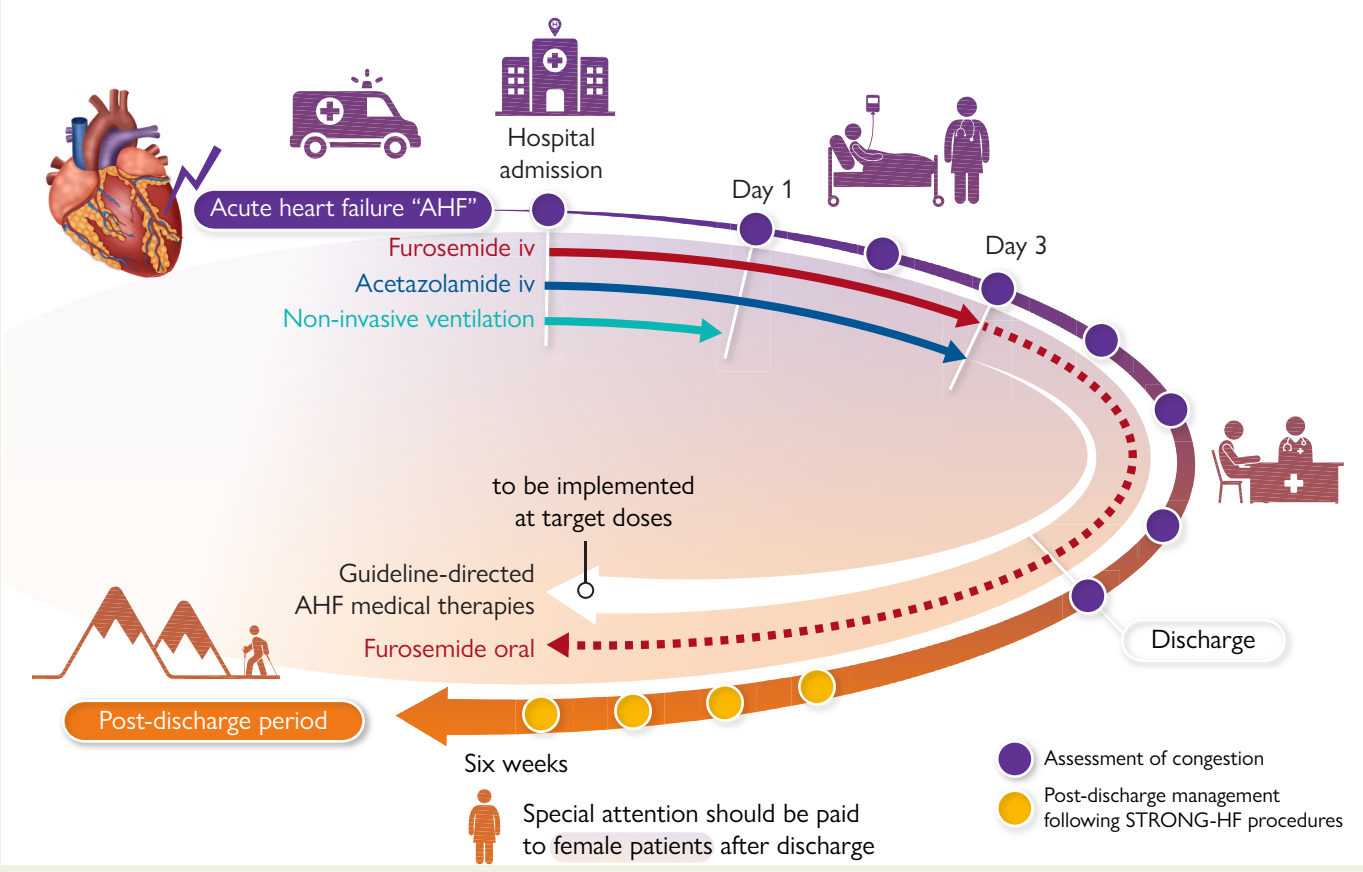
Graphical Abstract



Schematic representation of management of acute heart failure (AHF) patients from hospital admission to post-discharge period. Assessment of congestion includes clinical signs and symptoms (fatigue, dyspnoea, orthopnoea, oedema, and body weight), ultrasound assessment (lung, pleura, inferior vena cava, and ascites), and biology (natriuretic peptides and haematocrit). i.v., intravenous.

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Abstract

Acute heart failure (AHF) represents the most frequent cause of unplanned hospital admission in patients older than 65 years. Symptoms and clinical signs of AHF (e.g. dyspnoea, orthopnoea, oedema, jugular vein distension, and variation of body weight) are mostly related to systemic venous congestion secondary to various mechanisms including extracellular fluids, increased ventricular filling pressures, and/or auto-transfusion of blood from the splanchnic into the pulmonary circulation. Thus, the initial management of AHF patients should be mostly based on decongestive therapies on admission followed, before discharge, by rapid implementation of guideline-directed oral medical therapies for heart failure. The therapeutic management of AHF requires the identification and rapid diagnosis of the disease, the diagnosis of the cause (or triggering factor), the evaluation of severity, the presence of comorbidities, and, finally, the initiation of a rapid treatment. The most recent guidelines from ESC and ACC/AHA/HFSA have provided updated recommendations on AHF management. Recommended pharmacological treatment for AHF includes diuretic therapy aiming to relieve congestion and achieve optimal fluid status, early and rapid initiation of oral therapies before discharge combined with a close follow-up. Non-pharmacological AHF management requires risk stratification in the emergency department and non-invasive ventilation in case of respiratory failure. Vasodilators should be considered as initial therapy in AHF precipitated by hypertension. On the background of recent large randomized clinical trials and international guidelines, this state-of-the-art review describes current pharmacological treatments and potential directions for future research in AHF.

Keywords Acute heart failure • Assessment of congestion • Decongestion therapy • Non-invasive ventilation • Guideline-directed medical therapy

Introduction

Acute heart failure (AHF), defined as the new onset or recurrence of signs of heart failure (HF), represents the most frequent cause of unplanned hospital admission, worldwide, in patients older than 65.[1] Acute heart failure symptoms include dyspnoea, fatigue, pulmonary rales, peripheral oedema, and distended jugular veins at physical examination. Two clinical situations are described in AHF patients as follows: (i) the very frequent 'acutely decompensated HF', where symptoms of congestion appear and/or worsen in patients with known history of HF, and (ii) *de novo* AHF characterized by the occurrence of symptoms of congestion in patients without history of HF.[2,3] Symptoms and clinical signs of AHF are mostly related to systemic venous congestion secondary to various mechanisms including accumulation of extracellular fluids, increased ventricular filling pressures, and/or auto-transfusion of blood from the splanchnic into the pulmonary circulation.[4] Thus, the initial management of AHF patients is mostly based on decongestive therapies on admission which should be followed, before discharge, by rapid implementation of guideline-directed oral medical therapies for HF.[5] Despite significant scientific and clinical progress occurring in recent years, AHF remains associated with poor outcomes, including very high readmission rates and/or high mortality.

This state-of-the-art review describes current pharmacological treatments and perspectives in AHF. It will however not cover cardiogenic shock, the less frequent but most severe form of AHF, defined as low blood pressure associated with low cardiac output, altered end-organ perfusion, which requires specific treatment[6,7] and is outside the scope of the present work.

Epidemiology and prevalence

Acute heart failure is a major and global public health issue, and the pathophysiologic abnormalities occurring with HF significantly impact patient's quality of life. The epidemiology of HF has been the subject of large epidemiological studies (with cardiac measurements largely derived from Caucasian populations) and pivotal clinical trials [e.g. the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial[8]]. Even if a comprehensive picture of acute and chronic HF occurring globally cannot be achieved, it is important to note the enormous burden the syndrome imposes on the patients, their families, and the health care systems. Global data on AHF are limited, mainly due to the differential coding of the syndrome precluding an exact estimation of the prevalence and comparison between regions. Each year, in USA and Europe, 1 million patients in both continents are hospitalized with the diagnosis of AHF.[2,3] The prevalence of AHF appears to be heterogeneous across the world, and it may be higher in countries where chronic HF is more prevalent.[2,3] Despite the differences in diagnostic criteria, most studies estimated that over half of all HF patients in the general population have a preserved left ventricular ejection fraction (LVEF) and that the proportion of this HF phenotype is increasing due to the aging of the population and the increasing prevalence of cardiometabolic disorders.[9] In-hospital mortality of AHF reaches 4%, and rises to 10% within 60 to 90 days after hospital discharge and further increases to 25%–30% at 1 year.[10–14] A recent large meta-analysis demonstrated a steady decrease in mortality related to AHF over the last three decades while readmissions remain unacceptably high (10%–30% at 30 days and 46% at 1 year) with similar results in surveys and in trials.[15] Notably, Kimmoun *et al.*[15] showed that HF readmissions remain high in the USA and Asia but continue to decrease in Europe.

Congestion in acute heart failure

Systemic venous congestion is the central feature of AHF and due to redistribution of blood from the splanchnic to the pulmonary circulation and/or to abnormal intravascular and interstitial fluid accumulation.[16,17] Systemic venous congestion may be associated with hypoperfusion due to poor cardiac function but can also occur in many patients with preserved cardiac output and/or LVEF. Systemic congestion is the pathophysiological cornerstone of AHF leading to organ dysfunction, including the kidneys, liver, lungs, and gut. Organ dysfunction during AHF is associated with an increased risk of death.[18] Impairment of renal function in AHF is often secondary to increased central venous pressure leading to renal venous hypertension and

higher renal interstitial pressure resulting in decreased glomerular filtration rate and oliguria. Increased central venous pressure also contributes to liver congestion which must be suspected in case of abdominal pain, elevation of alkaline phosphatase, bilirubin, and/or γ-glutamyl transferase.[19] Hypoxic hepatitis can be observed in the most severe form of AHF, particularly in the setting of cardiogenic shock. Elevation of ventricular filling pressures leads to increased ventricular wall tension, myocardial stretch, and progressive worsening in cardiac contractility.[1] Elevation of the filling pressure in the left atrium increases the hydrostatic pressure in the upstream pulmonary capillaries increasing fluid filtration rate to the pulmonary interstitium to the alveoli. Finally, the drainage capacities of the lymphatic system of the pleural cavities are rapidly exceeded by the elevation of the venous pressure, causing fluid shifts to the pleural cavities which manifest as pleural effusions. Finally, high venous central pressure leads to increased abdominal pressure and to splanchnic congestion with the direct consequence of alteration of intestinal permeability, impaired nutrient absorption and malnutrition, increased oxygen gradient from the base to the apex of the villi causing epithelial injury, which results in extravasation of endotoxins which enhance inflammatory milieu and the progression to end-organ dysfunction.[20,21]

Clinical tools

A universally accepted diagnostic algorithm for quantification of congestion and identification of precise therapeutic targets is lacking. However, it is known that unresolved congestion, occurring in 40% of patients at hospital discharge, is an independent predictor of poor outcomes.[22] *Figure 1* proposes a contemporary way to assess congestion measured by clinical variables, biomarkers, and imaging. Signs and symptoms of congestion are late manifestations of increased cardiac filling pressures.[23]

The use of natriuretic peptides (NPs) to assess volume status and guide decongestive therapies is useful, though fluid overload may not the sole cause of increased levels of these biomarkers,[24,25] particularly in patients with impaired renal function. Fluid removal is often associated with reduction of plasma NP levels with a decrease >30% at Day 5 being a good prognostic marker.[26] Serum creatinine (sCr) is the most widely used biomarker to guide fluid removal due to the belief that its level reflects both renal filtration function and tubular status.[27,28] Of note, sCr may be altered in the days and weeks following hospitalization for AHF due to many mechanisms including diuretic therapies; it often returns eventually to baseline values and should not be considered as an indicator of poor prognosis.[29–32] Therefore, some suggest to use the term of 'permissive hypercreatininemia' in HF.[33] Therefore, the terms worsening renal function, acute kidney injury, and increased sCr cannot be used interchangeably.

Contemporary indices of congestion

In daily practice, congestion may be assessed by clinical signs and symptoms, imaging, and biological markers.[34] Few additional tools to assess congestion and guide the use of 'decongestive' therapies are yet available. A comprehensive echocardiogram is the gold standard for evaluating volume status and left ventricular (LV) filling pressures at baseline and before discharge. The analysis of LV filling pressure by transmitral flow and early diastolic tissue wave (E/e') ratio provides useful details on LV pressure and volume overload. The diameter of the inferior vena cava (IVC) is typically measured from the long-axis subxiphoid view between 5 and 30 mm from the IVC and right atrial junction during end-expiration and after sniff (*Figure 1*). Inferior vena cava diameter and per cent change during inspiration are correlated with right atrial pressure.[35] The accuracy of IVC measurements is influenced by the presence of a prominent Eustachian valve, patient's position, and operator's experience (*Figure 1*). Despite its limitations, echocardiography outperforms congestion scores for the prediction of short- and medium-term readmissions.[36,37]

Direct blood volume (BV) analysis can be done using the indicator-dilution method via the standardized technique using intravenous injection of a known dose of I-131 labelled albumin.[38] The unknown variable (BV) can then be measured using a known concentration of the injectate in a known volume and the concentration of the injectate in the unknown volume to be calculated.[39] A nuclear medicine technique that can accurately measure a radioisotope tracer concentration in fluid samples using the indicator-dilution technique was approved by the Food and Drug Administration (FDA) in 1998 and can provide BV results in ≤90 min (BVA-100 blood volume analyzer; Daxor Corporation Inc., New York, NY). Multiple studies have confirmed that the BVA-100 can assess BV and determine the causes of its abnormalities.[40–42] Although BVA is user-friendly and can be repeated, independent validation in randomized controlled trials to demonstrate incremental benefit and favourable cost–benefit ratio is needed.

Extravascular lung water (ELW) reflects the water content of the lung interstitium, determined by lung permeability and cardiac filling pressures. Lung ultrasound (LUS) is increasingly used for ELW assessment through the analysis of B-line artefacts (*Figure 1*).[43] According to a recent meta-analysis, three or more B-lines in two or more bilateral lung zones can be considered diagnostic for pulmonary oedema (sensitivity, 94%; specificity, 92%).[44] A B-line score cut-off ≥ 15 is significantly correlated with clinical congestion scores, E/E' ratio, N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, increased LV filling pressure, larger LV volumes, LV mass index, left atrial volume index, tricuspid regurgitation velocity, and estimated systolic pulmonary artery pressure (PAP).[45]

The CardioMEMS™ PAP sensor was tested in the CHAMPION trial (CardioMEMS™ Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in Class III Heart Failure).[46] The PAP-guided HF management was associated with a 28% and 37% fewer HF hospitalization after 6 and 15 months, respectively, compared to clinically-driven therapy.[46] The benefits of PAP-guided therapy occurred regardless of LVEF and have been replicated in clinical practice.[47–49] In patients implanted with the CardioMEMS device, PAP can be measured at least daily in both outpatient and hospital settings. The pre-COVID-19 impact analysis of the Hemodynamic-GUIDEd Management of Heart Failure (GUIDE-HF), a multicentre, prospective, single-blind study where 1000 New York Heart Association (NYHA) class II–IV HF patients with either elevated NT-proBNP [or B-type natriuretic peptide (BNP)] and/or a prior HF hospitalization were randomized to either PAP-based HF therapy or standard care, indicated a benefit of PAP-guided management on the primary outcome, primarily driven by lower HF hospitalization rates.[44]

In HF patients with cardiac implantable electronic devices (CIEDs) from the manufacturer Boston Scientific (Boston, MA, USA), the MultiSENSE (Multisensor Chronic Evaluation in Ambulatory Heart Failure Patients) study showed that the HeartLogic multiparameter index, combining heart sounds (S1 and S3), thoracic impedance, respiration, heart rate, and activity, emerged as a timely predictor of impending HF decompensation[50] with a warning time of ∼34 days. In addition to MultiSENSE, other studies have been conducted for risk stratification of HF patients based on combinations of data obtainable from CIEDs.[51] However, limitations of the HeartLogic algorithm include inability to stratify the risk of HF patients with preserved LVEF and of those lacking an indication for CIEDs. Ongoing research efforts are focused on the development of wearable devices that can detect non-invasive parameters similar to those collected

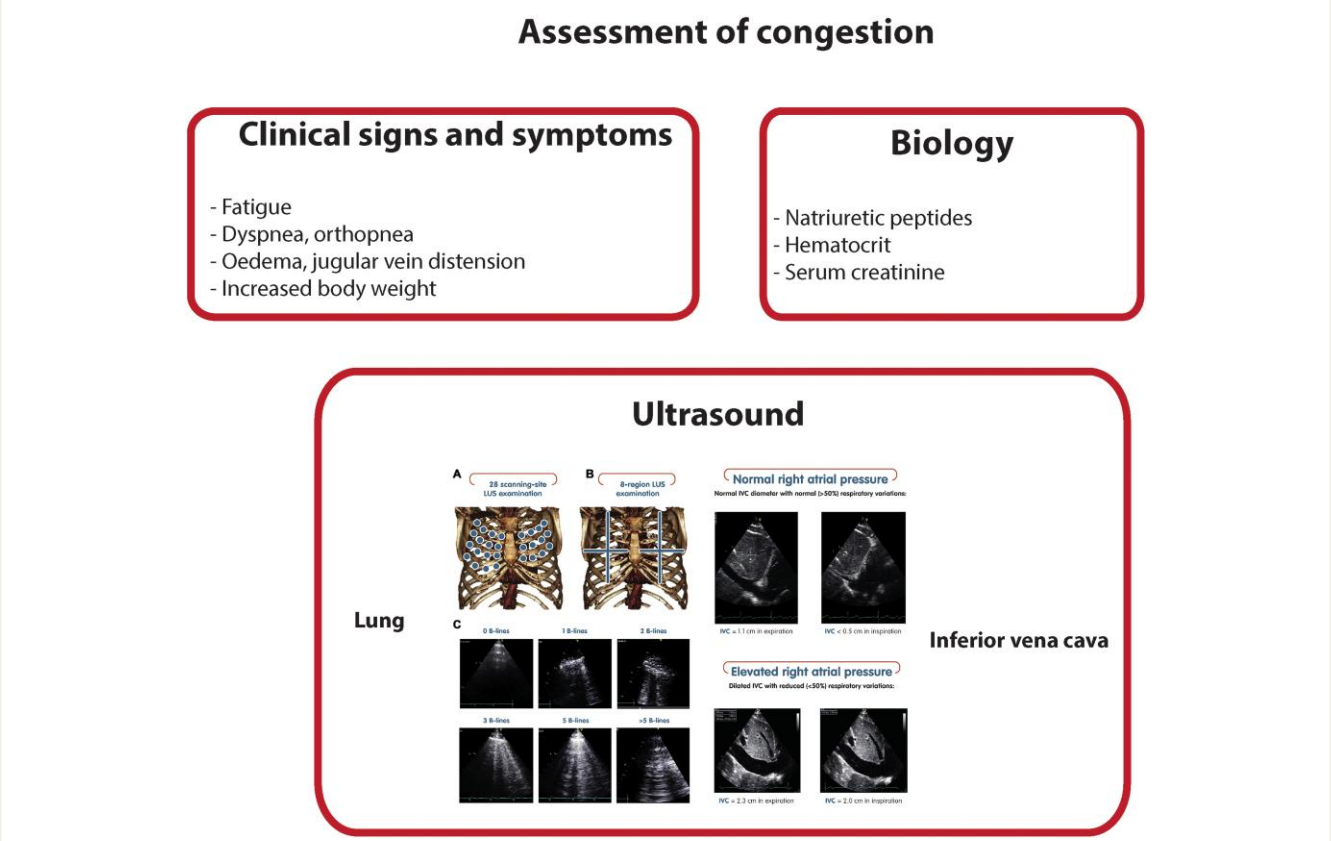

Figure 1 Assessment of congestion (clinical, biology, and ultrasonography). Lung ultrasound and quantification of inferior vena cava diameters through respiratory cycles. (*A* and *B*) Two techniques for quantifying pulmonary congestion using lung ultrasound (LUS). With the 28 scanning-site LUS technique, a precise quantification of extravascular lung water can be achieved; 16 to 30 comets (also called B-lines) detected in the entire lung are evocative of moderate pulmonary congestion, and >30 comets are evocative of severe pulmonary congestion. 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, which suggest significant pulmonary congestion. Lung ultrasound lasts <5 min using both techniques. (*C*) Upper images: normally aerated lung and regular interstitium, the only image that can be visualized below the pleural line is the reflection of the chest wall from the probe to the parietal pleura (A lines), or a few vertical artefacts can be detected (images with one and two lung comets). (*C*) Bottom images: progressive extravascular lung water accumulation as shown by the increasing number of lung comets. Right panels: right atrial pressures can be assessed with IVC diameters as shown in the upper and lower right panels. Reproduced with permission from Girerd *et al.*[16]

by the CIEDs to enable the timely implementation of therapies that can effectively prevent HF decompensation.

Therapeutic management and treatments of acute heart failure

In general, the therapeutic management of AHF is based on the identification and rapid diagnosis of the disease, the diagnosis of the cause (or triggering factor), the evaluation of the severity, the existence of comorbidities and finally, the initiation of a rapid treatment. Latest guidelines from ESC and ACC/AHA/HFSA have provided updated recommendations on AHF management, summarized in *Table 1*.[49,52]

Treatment according to aetiology of acute heart failure

Management of AHF differs according to the conditions which have triggered it. As recommended by the 2021 ESC HF guidelines, an initial step of the management of AHF patients is to search for specific causes summarized under the CHAMPIT acronym as follows: acute coronary syndrome, hypertensive emergency, rapid arrhythmias or severe bradycardia/conduction disturbance, acute mechanical causes (e.g. pulmonary embolism), infection (e.g. myocarditis and endocarditis), and tamponade.[52] Other aetiologies, less frequent, include valvular disease, peri-partum cardiomyopathy, hypertensive disorders, and thyroid disease. Thus, specific aetiological therapies should be implemented as early as possible.

Decongestive therapies

The goal of decongestive therapies is to treat fluid overload and hopefully achieve optimal fluid status. Currently, diuretics are the mainstay of decongestive therapies. However, determination of the optimal diuretic strategy remains challenging especially when worsening renal function, diuretic resistance, and electrolyte disturbances occur. Thorough knowledge of the pharmacokinetics and—dynamics of diuretics are mandatory to use them effectively.[54] The site of action and cellular mechanisms of different diuretics are listed in *Figure 2*.

Despite the use of intravenous loop diuretics, many patients are discharged with residual clinical signs of volume overload, a strong predictor of poor outcome.[1,55] Although sequential nephronal blockade has been suggested as a more effective decongestive strategy which can attenuate tubular adaptation to loop diuretics, convincing evidence of the optimal diuretic agents, dosing schedule, and route of administration is lacking.[52–54] *Figure 3* shows the contemporary management and recommendations of 2022 AHA/ACC/HFSA guidelines on the use of diuretics as decongestive therapy in AHF.[53]

Diuretic response

Decrease in body weight, net fluid total loss, or total urinary output following administration of loop diuretics is defined as a favourable response to the diuretic and natriuretic effect of these medications. Diuretic resistance is defined as a failure to increase diuresis and natriuresis output to relieve volume overload, oedema, or congestion despite optimal doses of a loop diuretic.[57,58] Qualitatively, pathologic diuretic resistance can be defined as an unsatisfactory rate of diuresis/natriuresis despite an adequate diuretic regimen in a hypervolaemic patient.[59]

Furthermore, diuretic response should always be interpreted considering the dose and type of the diuretic agent administered as well as the degree of volume overload and kidney function. Currently, net fluid output and changes in body weight are frequently used, though they only capture changes in total body water and not in extracellular sodium accumulation. Furthermore, body weight data are misleading as measurements are performed by different people, on different scales at variable time-points. Fluctuations in weight might also not represent changes in volume redistribution.[60]

As the objective of diuretic therapy is to eliminate excessive sodium (and accompanying water), the measurement of urinary sodium content has experienced a renewed interest as a better indicator for diuretic response.[61–64] In addition to measuring sodium in a continuous urinary collection, a spot urine sample 1–2 h following loop diuretic administration has been shown to have an excellent correlation with total urine sodium output in a 6 h urine collection.[65] Therefore, this strategy might allow the clinician to determine loop diuretic response in a timely fashion, allowing for faster and more frequent adjustments in therapy. Despite persistent increased urinary volume output (diuresis), renal sodium output (natriuresis) diminishes over time, due to increased renal sodium reabsorption while facing low sodium intake. Therefore, increasingly hypotonic urine is produced during consecutive days of loop diuretic therapy, depending upon altered renal haemodynamics, differential substrate delivery (sodium and/or diuretics), neurohormonal factors, and structural kidney abnormalities, including arginine vasopressin action. The use of urinary sodium following a first administration of loop diuretics to guide diuretic therapy has now been incorporated in the European guidelines for the diagnosis and treatment of HF.[52]

Diuretic utilization

Guidelines recommend the use of intravenous loop diuretics in AHF, as the gastrointestinal absorption of oral diuretics will be diminished in AHF due to bowel oedema.[52,54] Optimal dosing and timing of intravenous loop diuretics are of pivotal importance. Loop diuretics must achieve a threshold concentration at their renal site of action to induce effective natriuresis.[57] Over 95% of the loop diuretics are bound to albumin, do not undergo glomerular filtration, and reach their target site by active secretion from the blood into the urine by the organic acid transporters present in the proximal tubules.[66] Hypoalbuminaemia leads to a decreased secretion of loop diuretics into the tubules and reduces their diuretic effect. Afterwards, a log-linear increase in the dose is necessary to achieve the ceiling of urinary sodium excretion. Similarly, multiple administrations can cause additional natriuresis, as this increases the duration of time above a natriuretic threshold. These pharmacologic characteristics lead to the following recommendation in the ESC guidelines for the treatment of AHF[52]: (i) diuretic naïve patients with AHF should receive a dose of intravenous furosemide of at least 20–40 mg furosemide equivalent; (ii) higher doses should be considered in patient with pre-existing kidney dysfunction which is associated with a downward and rightward shift in the dose–response curve; and (iii) patients previously treated with oral diuretics are likely to require higher initial intravenous loop diuretic doses. An intravenous dose ranging between 400 and 600 mg furosemide vs. 10–15 mg bumetanide is generally considered as the maximal total daily dose as the diuretic ceiling effect is reached.[54,59] Generally, loop diuretics are given in multiple doses (two to three times daily). Intravenous loop diuretics should be administered as early as possible, since early institution of intravenous loop diuretic therapy could be associated with lower in-hospital mortality.[67] In the DOSE-AHF trial, no difference in improved global assessment of dyspnoea was seen between continuous infusion vs. bolus injection.[57] If bolus injections are given, these should be administered at least at 6 h intervals, to maximize the time the diuretic tubular concentration is adequate to trigger a natriuretic response.

A satisfactory diuretic response can be defined as a urine sodium content > 50–70 mEq/L at 2 h and/or by a urine output > 100–150 mL/h during the first 6 h[52,54] after administration. If there is an insufficient diuretic response, the loop diuretic dose should be doubled, with a repeated assessment of diuretic response. This strategy, based on early and frequent assessment of diuretic response, is currently being tested in two prospective randomized clinical trials.[68,69] Finally, a transient increased in sCr after initiation of decongestive therapy can be observed, which may not represent acute kidney injury but rather a haemodynamically-driven event that should not prompt discontinuation of diuretics or other life-saving therapies.[70]

If the diuretic response remains inadequate, e.g. <100 mL hourly diuresis despite doubling loop diuretic dose and reaching the maximal amount of loop diuretics (200 mg intravenous furosemide equivalents three times a day), concomitant administration of other diuretics with different tubular sites of action, such as thiazides or acetazolamide, may be considered. It was recently shown that increased natriuresis is strongly related to successful decongestion with the combination of furosemide and acetazolamide in AHF.[71] However, this combination requires careful monitoring of serum electrolytes and renal function. A multicentre, randomized, double-blind, phase IV clinical trial of the diuretic effects of Acetazolamide in Decompensated heart failure with Volume OveRload (ADVOR) investigated if combination therapy with intravenous acetazolamide improves loop diuretic response in decompensated heart failure patients.[72] ADVOR showed that the addition of intravenous acetazolamide to loop diuretic in patients admitted for AHF was associated with a greater incidence of successful decongestion defined as the absence of signs of volume overload (i.e. no more than trace oedemas, no residual pleural effusion, and no residual ascites), within 3 days after initiation of decongestive therapy and at discharge; benefits were seen in all AHF regardless of LVEF.[71,73] Furthermore, addition of intravenous acetazolamide to loop diuretics was safe and associated with a reduced hospital stay though not associated with change in death from any cause or rehospitalization for HF during 3 months of follow-up.[73] New diuretic agents to treat congestion and to improve quality of life and survival are needed in AHF.

Table 1 Head to head comparison between recommendations for the initial treatment of acute heart failure recommended by ESC[52] and ACC/AHA/HFSA[53] with class (green: is recommended or is indicated, orange: should be considered, red: is not recommended) and level (A: data derived from multiple randomized clinical trials or meta-analyses, B: data derived from a single randomized clinical trial or large non-randomized studies, C: consensus of opinion of the experts and/or small studies, retrospective studies, registries) of recommendations

ESC guidelines				ACC/AHA/HFSA guidelines		
Treatment class	Recommendations	Class	Level	Recommendations	COR	LOE
Oxygen and ventilatory support	Oxygen is recommended in patients with $SpO_2 < 90\%$ or $PaO_2 < 60$ mmHg to correct hypoxaemia	I	C			
	Intubation is administration or non-invasive ventilation	I	C			
	Non-invasive positive pressure ventilation should be considered in patients with respiratory distress (respiratory rate > 25 breaths/min, $SpO_2 < 90\%$) and started as soon as possible in order to decrease respiratory distress and reduce the rate of endotracheal intubation	IIa	B			
Diuretics	Intravenous loop diuretics are recommended for all patients with AHF admitted with signs/symptoms of fluid overload to improve symptoms	I	C	Patients with HF admitted with evidence of significant fluid overload should be promptly treated with intravenous loop diuretics to improve symptoms and reduce morbidity	1	B-NR
	Combination of loop diuretics with thiazide-type diuretic should be considered in patients with resistant oedema who do not respond to an increase in loop diuretics	IIa	B	In patients hospitalized with HF when diuresis is inadequate to relieve symptoms and signs of congestion, it is reasonable to intensify the diuretic regimen using either as follows: (i) higher doses of intravenous loop diuretics or (ii) addition of a second diuretic	2a	B-NR
Vasodilators	In patients with AHF and SBP > 110 mmHg, i.v. vasodilators may be considered as initial therapy to improve symptoms and reduce congestion	IIb	B	In patients who are admitted with decompensated HF, in the absence of systemic hypotension, intravenous nitroglycerine or nitroprusside may be considered as an adjuvant to diuretic therapy for relief of dyspnoea	2b	B-NR
Inotropic agents	Inotropic agents may be considered in patients with SBP < 90 mmHg and evidence of hypoperfusion who do not respond to standard treatment, including fluid challenge, to improve peripheral perfusion and maintain end-organ perfusion	IIb	C	In patients with cardiogenic shock, intravenous inotropic support should be used to maintain systemic perfusion and preserve end-organ performance	1	B-NR
	Inotropic agents are not recommended routinely, due to safety concerns, unless the patient has symptomatic hypotension and evidence of hypoperfusion	III	C			
Vasopressors	A vasopressor, preferably norepinephrine, may be considered in patients with cardiogenic shock to increase blood pressure and vital organ perfusion	IIb	B			
Others drugs	Thromboembolic prophylaxis (e.g. with LMWH) is recommended in patients not already anticoagulated and with no contraindications to anticoagulation, to reduce the risk of deep venous thrombosis and pulmonary embolism	I	A	In patients hospitalized with HF, prophylaxis for VTE is recommended to prevent venous thromboembolic disease	1	B-R
	Routine use of opiates is not recommended, unless in selected patients with severe/intractable pain or anxiety	III	C			
Follow-up visit after discharge	An early follow-up visit is recommended at 1–2 weeks after discharge to assess signs of congestion, drug tolerance and start and/or up titrate evidence-based therapy	I	C	In patients being discharged after hospitalization for worsening HF, an early follow-up, generally within 7 days of hospital discharge is reasonable to optimize care and reduce rehospitalization	2a	B-NR

AHF, acute heart failure; B-NR, level B non-randomised; B-R, level B randomised; COR, class of recommendation; HF, heart failure; LOE, level of evidence; LMWH, low-molecular-weight heparin; SBP, systolic blood pressure; VTE, venous thromboembolism.

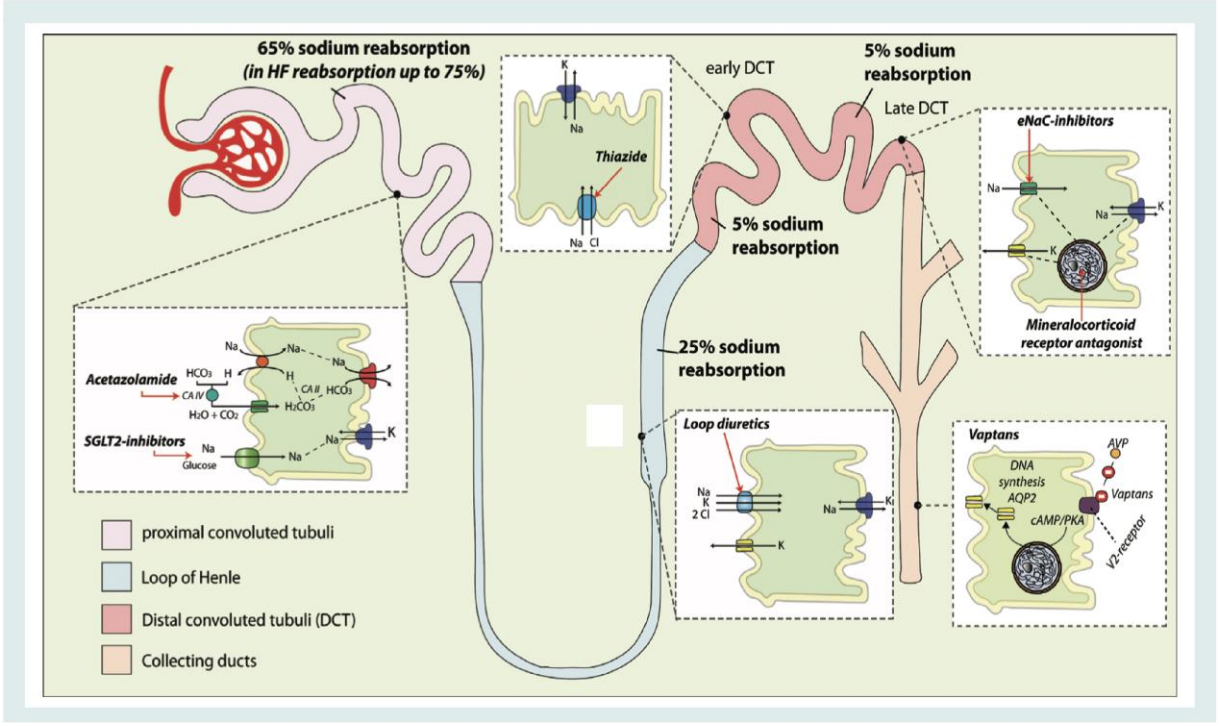

Figure 2 Local and systemic action of diuretics. Reproduced with permission from Mullens *et al.*[54] HF, heart failure

Recently, the multicentre placebo controlled randomized CLOROTIC trial (Combining Loop with Thiazide Diuretics for Decompensated Heart Failure) evaluated if the addition of hydrochlorothiazide (HCTZ) to loop diuretics in patients with AHF leads to improved decongestion.[74] Co-primary endpoints were weight loss and dyspnoea improvement at 72 h. There was a beneficial effect on weight loss, with no changes in patient-reported dyspnoea 72 h after randomization.[74] Additionally, there were no differences in mortality or rehospitalizations.[74] Concerning side effects, hypokalaemia was more frequent in the intervention group. In 2020, the Comparison of Oral or Intravenous Thiazides vs. Tolvaptan in Diuretic Resistant Decompensated Heart Failure (the 3T trial) showed that combination of high-dose of intravenous furosemide with oral metolazone, or intravenous chlorothiazide or tolvaptan in AHF patients with diuretic resistance, resulted in improved diuretic efficacy as defined by more greater weight loss at 48 h without detectable between-group difference.[75] Finally, recently, Mentz *et al.*[76] in a pragmatic trial entitled the Torsemide Comparison with Furosemide for Management of Heart Failure (TRANSFORM-HF) that aimed to overcome traditional HF trial challenges and to compare the effect of torsemide (loop diuretic with beneficial effects on cardiac fibrosis, aldosterone production, sympathetic activation, ventricular remodelling, and NP) vs. furosemide after discharge on all-cause mortality in patients with HF. In this randomized clinical trial, torsemide compared with furosemide did not result in a difference in all-cause mortality 1 year after an episode of AHF. However, results must be interpreted with great caution given loss of follow-up, participant cross-over, and non-adherence.

Vasopressin receptor antagonists

Tolvaptan is an oral selective arginine V2 receptor antagonist preventing the activation of the aquaporin system and impairing the ability of AVP-mediated reabsorption of free water in the kidney to reabsorb water.[77] Randomized controlled clinical trials have failed to demonstrate benefit of tolvaptan on HF hospitalizations and mortality at 60 days after discharge.[77–79] Tolvaptan does not have an indication for hyponatraemia specifically in the setting of HF in the USA and Europe.[52,53]

Vasodilators

Despite clinical evidence suggesting haemodynamic and clinical improvement, there have been limited data on the benefits of intravenous infusion of vasodilators on long-term outcomes. Drugs with a dual arteriolar and venous effects like sodium nitroprusside (SNP) appear to contribute to the immediate haemodynamic response of the drug.[80] Dilatation of the arterial resistance vessels as well as direct reduction in wall stress reduce LV afterload and allow the severely compromised LV to eject more blood. Importantly, these agents work preferentially in advanced HF with reduced ejection fraction (HFrEF) with dilated ventricles [i.e. highest wall tension = (pressure × radius)/(2 × wall thickness)]. The venodilator effect increases venous capacitance and reduces congestion. Both effects lead to an increase in cardiac output in patients with HF and often reduce the basal tachycardia (see Supplementary data online, *Figure S1*).

In case of advanced HF, SNP maybe administered in critical care settings with careful invasive haemodynamic monitoring due to the risk of inducing hypotension. A large retrospective, non-randomized case–control series showed that SNP can be safely administered to achieve haemodynamic improvement in patients presenting with advanced low-output HF.[81] The use of SNP according to a clinical protocol based on achieving a target mean arterial pressure is associated with more haemodynamic improvement that may facilitate the institution of a more aggressive oral vasodilator regimen beyond standard

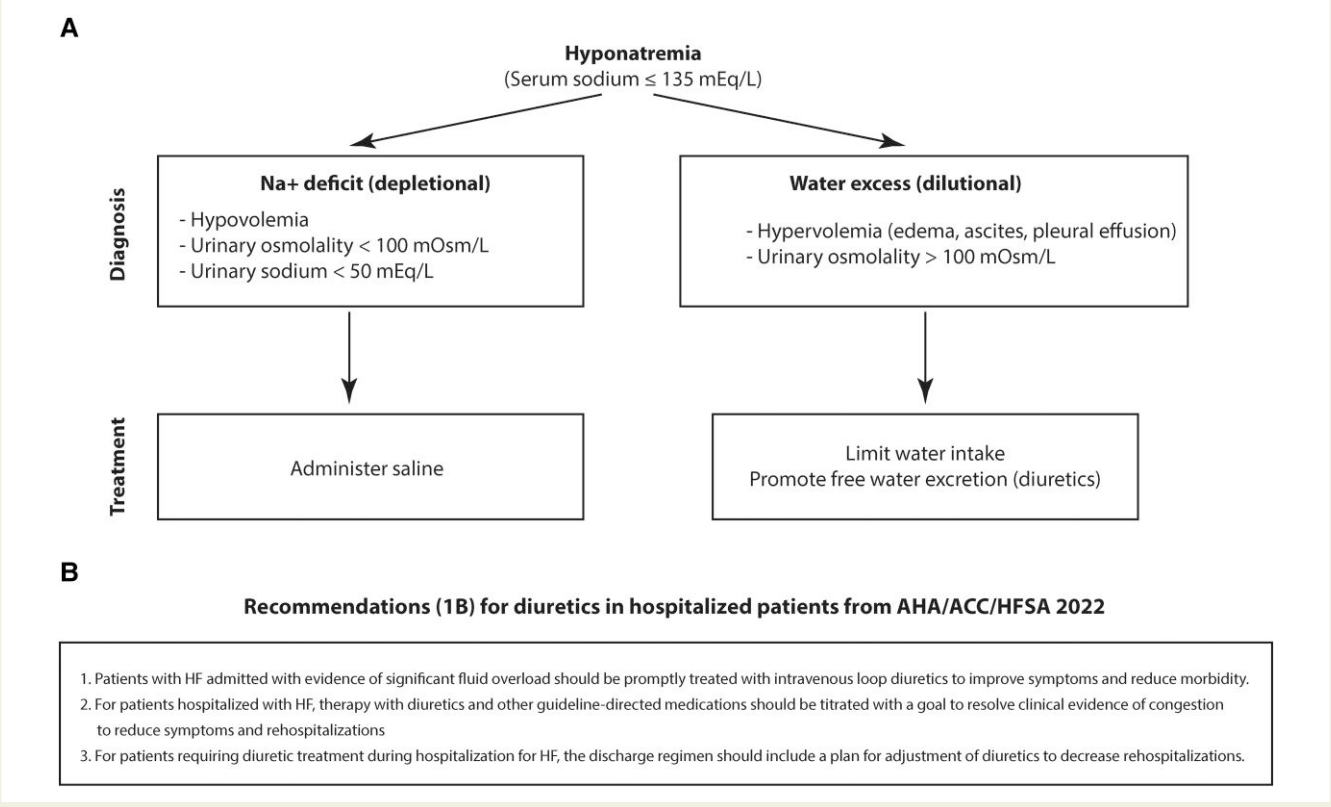

Figure 3 Acute heart failure: (*A*) management and (*B*) recommendations for decongestive therapy to manage hyponatraemia. AVP, arginine vasopressin. Adapted from Verbrugge *et al.*[56] HF, heart failure

neurohormonal antagonists at the time of discharge.[82,83] Taken together, the use of SNP was associated with significantly lower all-cause mortality and fewer clinical adverse events at long-term follow-up, irrespective of the use of inotropic therapy or underlying renal function.[81] However, two recent large randomized clinical trials failed to demonstrate benefit of vasodilators in AHF patients on mortality and readmission rate.[84,85] An important issue with SNP is that prolonged use beyond 72 h can lead to cyanide poisoning, particularly in patients with impaired renal function.[86]

In the Early and Comprehensive Care Bundle in Elderly for Acute Heart Failure: A Stepped Wedge Cluster Randomized Trial (ELISABETH), among older patients admitted to the emergency department (ED) for AHF, the use of a guideline-based comprehensive care bundle, including early intravenous nitrate boluses and management of precipitating factors, such as acute coronary syndrome, infection, or atrial fibrillation did not result in a reduced number of days alive at 30 days compared to usual care.[85] In the Goal-directed Afterload Reduction in Acute Congestive Cardiac Decompensation (GALACTIC) randomized clinical trial in patients hospitalized for AHF with dyspnoea, a strategy of early intensive vasodilation (including sublingual and transdermal glyceryl trinitrate) did not improve all-cause mortality and AHF rehospitalization at 180 days. Taken together, these results suggest that in the absence of hypertension, the use of vasodilators in AHF patients was not associated with better outcomes when compared to loop diuretic therapy alone.[52] Recent ESC HF guidelines indicated that titrated intravenous vasodilators can be considered in case of high systolic blood pressure in AHF patients. Care should be taken to avoid hypotension.[52]

Other therapeutic measures

Hyponatraemia is a frequent therapeutic challenge in AHF (*Figure 3*). Of note, a pseudo-hyponatraemia may occur in hyperglycaemia. In case of true hyponatraemia, physicians should first measure osmolarity to assess that it is reduced to confirm the true dilutional hyponatraemia, the most common type of low serum sodium levels in HF. 'Depletional hyponatraemia' (=deficit in Na^+) is due to various mechanisms including diuretic agents that enhance sodium excretion, associated with potassium/magnesium losses, malnutrition, diarrhoea, vomiting. Hence, hyponatraemia is common, for instance, with use of thiazides, begins soon after initiation of thiazides, may be severe, and is more likely to occur in elderly females. Isotonic saline with potassium/magnesium may often restore normal serum sodium levels. In contrast, 'dilutional hyponatraemia' is related to increased water retention due to increased osmotic and non-osmotic release of arginine vasopressin (AVP) and insufficient tubular flow through diluting (distal) segments of the nephron. Hyponatraemia may be corrected by improving distal nephron flow (loop diuretics with or without hypertonic saline, acetazolamide, renin-angiotensin system blockers, inotropes, or vasodilator therapy) or by administration of a vasopressin antagonist. Regardless of the mechanisms, distally working diuretics (thiazide-type, amiloride, mineralocorticoid receptor antagonists) should be stopped and plasma K^+ and Mg^{++} restored.[56]

Non-invasive ventilation

Application of a positive airway pressure by three modalities (continuous positive airway pressure, non-invasive pressure support ventilation,

or high-flow nasal cannula) in conscious AHF patients can reduce the need for endotracheal intubation and decreases the risk of ventilator-associated pneumonia.[87] The latest ESC guidelines recommended non-invasive ventilation as Class IIa recommendations with a level of evidence B in AHF patients with respiratory distress (defined as respiratory rate > 25/min and/or SpO_2 < 90%).[52]

Morphine and anxiolytic treatments

Acute heart failure is a stressful situation for patients due to the progressive respiratory failure frequently induced. To reduce anxiety and dyspnoea and to improve vasoconstriction accompanying hypertensives crises, morphine and short half-life benzodiazepines (e.g. midazolam) have been tested. In the multicentre, open-label, and randomized controlled Midazolam versus Morphine (MIMO) trial, the authors compared efficacy and safety of both molecules in AHF patients admitted to the ED.[88] Although the number of randomized patients was too small to make definitive conclusions, mortality was similar in both groups, and serious adverse events were more common in the morphine group, confirming results of previous studies.[89–91] Routine use of opiates in AHF patients is currently not recommended.[52]

Risk stratification and early follow-up after discharge

Surprisingly, 30-day risk of readmission has not decreased over time in AHF patients[92,93] underscoring the need for new approaches to improve outcomes. The decision to admit or discharge an AHF patient presenting to the ED is mainly based on clinical judgement, with a risk of inaccuracy in prognostication leading to low-risk patients being hospitalized and high-risk patients being discharged.[94] Risk stratification could help ED physicians to improve clinical decision making in AHF patients'.[94] By combining a validated point-of-care tool for risk stratification in the ED to support clinicians' decisions about admissions or discharge of AHF patients, with the provision of standardized transitional care, Lee *et al.*[95] observed a reduction of 12% in the risk of death from any cause or hospitalization for cardiovascular causes within 30 days after an AHF episode. This risk remained lower at 20 months after the AHF episode.

Post-discharge therapies and implementation of oral therapies

The latest North American and European guidelines for chronic HF recommended that guideline-directed medical therapy (GDMT) for HF includes beta-blocker, renin-angiotensin system inhibitors and mineralocorticoid receptor antagonists for HFrEF, and sodium-glucose cotransporter 2 inhibitors for all HF patients regardless of LVEF, with the aim of improving survival and preventing recurrent HF hospitalizations.[96] Concerning AHF, after the initial phase when patients recover from severe congestion, hypoxaemia, and/or organ dysfunction, the next step is to organize a seamless transition from hospital to home. Indeed, discharge to home is associated with high rates of early readmission and death, the 'vulnerable' post-discharge phase.[97] To improve this critically important issue, guidelines recommend the continuation of the home HF medications provided that haemodynamic instability is absent. Furthermore, implementation of oral GDMT as soon as possible is highly recommended. Recently, four studies improved our understanding on how to optimally implement GDMT for HF before and after discharge (*Table 2*).[5,98–101] The multinational randomized trial Empagliflozin in Patients Hospitalized With Acute Heart Failure Who Have Been Stabilized (EMPULSE) trial showed that initiation of empagliflozin (at a dose of 10 mg orally daily) in patients hospitalized for AHF was associated with improved symptoms, physical limitations, and quality of life soon after discharge.[98,99] The Effect of Sotagliflozin ion Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure trial (SOLOIST-WHF), a double-blind trial including type 2 diabetes mellitus patients admitted for worsening HF, found that sotagliflozin therapy initiated before or shortly after discharge resulted with better outcomes at 18 months, including deaths from cardiovascular causes, hospitalizations, and urgent visits for AHF.[100] The Comparison of Sacubitril-Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Decompensated Heart Failure Episode (PIONEER-HF) showed that initiation of sacubitril/valsartan therapy in patients stabilized after treatment of AHF was associated with a greater reduction in the NT-proBNP concentration and of the risk of cardiovascular death or HF readmission when compared to enalapril therapy.[101] Death and rehospitalization rates between groups were similar. Finally, the Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies (STRONG-HF), a multinational open-label randomized trial, recently showed that an early and intensive treatment strategy consisting of rapid GDMT establishment and up-titration 2 days before discharge from an episode of AHF, was safe and beneficial with reduced 180-day HF readmission and/or all-cause death.[5] The close follow-up with clinical exam and biological tests including plasma NT-proBNP, at each visit, allowed safe rapid up-titration of oral HF medications with almost no side effects.[5]

Implementation of iron supplementation therapies

Iron deficiency is common in AHF patients and is associated with poor outcomes.[102,103] Therefore, diagnosis and treatment of iron deficiency after an AHF episode are highly recommended.[52] The A Randomised, Double-blind Placebo Controlled Trial Comparing the Effect of Intravenous Ferric Carboxymaltose on Hospitalisations and Mortality in Iron Deficient Subjects Admitted for Acute Heart Failure (AFFIRM-HF) trial was designed to evaluate the effect of carboxymaltose compared with placebo on outcomes in patients with iron deficiency with a reduced LVEF (<50%) after an episode of AHF.[104] The authors observed that treatment with ferric carboxymaltose was safe and reduced the risk of HF hospitalizations, with no apparent effect on the risk of cardiovascular death. A new trial, Effectiveness of Intravenous Iron Treatment versus Standard Care in Patients with Heart Failure and Iron Deficiency (IRONMAN) confirmed, on a COVID-19 pre-specified analysis, a reduction in the risk of the primary endpoint with ferric derisomaltose vs. control and a greater improvement of the overall Minnesota Living with Heart Failure Questionnaire at 4-month follow-up.[105]

The *Graphical Abstract* summarizes main principles of the therapeutic management of AHF patients, from pre-admission to post-discharge period, based on the most recent guidelines and important trials. Of note, post-discharge management of congestion remains a difficult task for physicians. To improve clinical outcomes, a wide range of monitoring strategies (invasive and non-invasive) to prevent HF

Table 2 Trials showing benefits of heart failure medications at and after discharge of acute heart failure

Study name	Type	Intervention	Primary outcome	Duration of intervention and follow-up	Number of patients	Main results	Impact on mortality
EMPagliflozin in patients hospitalized with acUte heart failure who have been StabilisEd **EMPULSE study**[98,99] NCT04157751	Randomized clinical trial	Patients admitted for acute *de novo* or decompensated chronic HF 2 groups – Empagliflozin 10 mg once daily – Placebo	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	90 days	530 patients	Better clinical benefit in empagliflozin group (stratified win ratio, 1.36; 95% CI 1.09–1.68; $P = .0054$)	Yes (4.2% in empagliflozin group vs. 8.3% in placebo group)
Comparison of Sacubitril-Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode **PIONEER-HF study**[101] NCT02554890	Randomized clinical trial	HFrEF patients admitted for acute decompensated HF 2 groups – Sacubitril (97 mg) + valsartan (103 mg) twice daily – Enalapril 10 mg twice daily	Time-averaged proportional change in the NT-proBNP concentration from baseline through weeks 4 and 8	60 days	881 patients	Reduced time-averaged in the NT-proBNP concentration in the sacubitril/valsartan group: (i) reduced geometric mean of values at weeks 4 and 8 to the baseline (0.53 in the sacubitril/valsartan group vs. 75 in the enalapril group (per cent change, −46.7% vs. −25.3%; ratio of change with sacubitril/valsartan vs. enalapril, 0.71; 95% CI 0.63–0.81; $P < .001$). (ii) Greater reduction in the NT-proBNP concentration with sacubitril/valsartan at 1 week (ratio of change, 0.76; 95% CI 0.69–0.85). No difference of worsening renal function, hyperkalaemia, symptomatic hypotension, and angioedema between groups.	No (2.3% in sacubitril–valsartan group vs. 3.4% in enalapril group, HR 0.66 (0.30–1.48))
Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure **SOLOIST-WHF**[100] NCT03521934	Randomized clinical trial	Type 2 diabetes mellitus patients recently hospitalized for worsening HF 2 groups – Sotagliflozin 200 mg once daily – Placebo	Total number of deaths from cardiovascular causes and hospitalizations and urgent visits for HF (first and subsequent events)	18 months	1222 patients	Lower mortality from cardiovascular causes and hospitalizations and urgent visits for HF in the sotagliflozin group ($n = 245$) vs. placebo group ($n = 355$). Lower rate of mortality from cardiovascular causes and hospitalizations and urgent visits for HF in the sotagliflozin group vs.	No (10.6% in sotagliflozin groups vs. 12.5% in placebo group (HR 0.84, 95% CI 0.58–1.22)

Continued

Table 2 *Continued*

Study name	Type	Intervention	Primary outcome	Duration of intervention and follow-up	Number of patients	Main results	Impact on mortality
						placebo group (51.0 vs. 76.3; HR 0.67; 95% CI 0.52–0.85; $P < .001$). Reduced rate of death from cardiovascular causes in the sotagliflozin group vs. placebo group (10.6 vs. 12.5; HR 0.84; 95% CI 0.58–1.22) Reduced rate of death from any cause in the sotagliflozin group vs. placebo group (13.5 vs. 16.3; HR 0.82; 95% CI 0.59–1.14).	
Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure **STRONG-HF**[5] NCT03412201	Randomized clinical trial	Patients admitted to hospital with acute HF not treated with full doses of guideline-directed drug treatment 2 groups – Usual care: usual local practice – High-intensity care: up-titration of treatments to 100% of recommended doses within 2 weeks of discharge and four scheduled outpatient visits over the 2 months after discharge	180-day readmission to hospital due to HF or all-cause death	180 days	1078 patients	During the first 90 days of the study, patients in the high-intensity care group had a mean of 4.8 visits (SD 1.0) vs. 1.0 visits (0.3) in the usual care group. By Day 90, blood pressure, pulse, NYHA class, body weight, and NT-proBNP concentration had decreased more in the high-intensity care group than in the usual care group Heart failure readmission or all-cause death up to Day 180 occurred in 74 of 506 patients in the high-intensity care group and 109 (23.3%) of 502 patients in the usual care 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). More adverse events by 90 days occurred in the high-intensity care group (223 [41%] of 542) than in the usual care group (158 [29%] of 536) but similar incidences of serious adverse events (88 [16%] vs. 92 [17%]) and fatal adverse events (25 [5%] vs. 32 [6%]).	No (4.3% in high-intensity care group vs. 5.7% in usual care group at Day 90 with adjusted risk ratio 0.76 (0.45–1.29) (8.5% in high-intensity care group vs. 10% in usual care group at Day 180 with adjusted risk ratio 0.84 (0.56–1.26)

CI, confidence interval; HR, hazard ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; HF, heart failure; HFrEF, heart failure with reduced ejection fraction.

Table 3 Drugs being tested in ongoing trials in acute heart failure

Therapeutic class	Drug name	Trial name	NCT number	Intervention	Primary outcomes	Number of patients expected	Country
Sodium-glucose cotransporter inhibitors	Dapagliflozin	Efficacy and Safety of Dapagliflozin in Acute Heart Failure (DICTATE-AHF)	NCT04298229	RCT Dapagliflozin 10 mg vs. placebo	Cumulative change in weight (kg)	240	USA
		Dapagliflozin and Effect on Cardiovascular Events in Acute Heart Failure—Thrombolysis in Myocardial Infarction 68 (DAPA ACT HF-TIMI 68)	NCT04363697	RCT Dapagliflozin vs. placebo	Cardiovascular death or worsening heart failure	2400	USA
		Effect of Dapagliflozin in Patients With Acute Heart Failure (DAPA-RESPONSE-AFH)	NCT05406505	RCT Dapagliflozin 10 mg vs. placebo	Change in dyspnoea (visual analogue scale)	100	Egypt
	Empagliflozin	Early Treatment With Sodium-glucose Co-transporter 2 Inhibitor in High-risk Patients With Acute Heart Failure (EMPA-AHF)	NCT05392764	RCT Empagliflozin 10 mg vs. placebo	A hierarchical composite endpoint consisting of death within 90 days, heart failure rehospitalization within 90 days, WHF during hospitalization, and urine output up to 48 h after treatment initiation, assessed by the win ratio	500	Japan
	Canagliflozin	Canagliflozin in Patients With Acute Decompensated Heart Failure	NCT05364190	Open label Canagliflozin 100 mg vs. placebo	The cumulative mean of daily diuresis which is define as total urine output in 24 h during the hospitalization period.	180	Egypt
Other	Digoxin	Digoxin Short Term Treatment Assessment Randomized Trial in AHF (DIG-STA-AHF)	NCT02544815	RCT Digoxin 0.25 mg per day vs. placebo for 3 days	Change in patient-reported dyspnoea as quantified by the area under the curve of visual analogue scale scores (0–100 mm scale) from baseline to Day 3.	500	Tunisia

RCT, randomized clinical trial.

decompensation and to guide decongestion are available. Recently, a systematic review and meta-analysis, including randomized controlled trials, found that, compared to standard therapy, a device-based remote monitoring strategy for haemodynamic-guided management of patients with chronic HF is associated with a reduction of all-cause death and HF hospitalizations.[106] Thus, future studies will determine the best strategy and monitoring in guiding the long-term management of patients with HF.

Future directions for research on acute heart failure pharmacological treatments

Several clinical trials around the world are currently underway in AHF. Main molecules being studied are sodium-glucose cotransporter inhibitors, which are associated with a decreased risk of worsening HF events, cardiovascular deaths, and improved symptoms when used in HFrEF[107–109] regardless of the existence of diabetes, raising expectations for the future of AHF patients. Main clinical studies (randomized and open-label studies) are summarized in *Table 3*. As described above, congestion is still present in many patients discharged home from an AHF episode and congestion is the main reason of unscheduled readmission in outpatient HF clinics and ED in the following weeks. As intravenous diuretics showed limited benefits in preventing HF readmission, research should therefore focus on developing enteral or parenteral novel therapies that may markedly reduce congestion and prevent episodes of short-term readmission. Those therapies should be tested in worsening HF episodes seen at outpatient centre or in hospital. In addition, AHF with preserved LVEF is highly present in old patients and patients with metabolic disorders; novel therapies should also be assessed on those patients. Furthermore, research should focus on the best way to combine agents that will reduce and prevent congestion with guideline-directed HF medications to cure HF and have patients back to 'normal' uneventful life.

Conclusion

To conclude, AHF is a worldwide and frequent syndrome associated with poor outcomes. Signs and symptoms are related to systemic venous congestion due to the accumulation of extracellular fluids related to increased ventricular filling pressures. Intravenous diuretics are considered as the cornerstone of therapeutic management of AHF associated with non-invasive ventilation if needed. The 2023 focused update of those guidelines yet recommends an intensive strategy of initiation and rapid up-titration of evidence-based treatment before discharge and during frequent and careful follow-up visits in the first 6 weeks following a HF hospitalization is recommended to reduce the risk of HF rehospitalization or death.[110]

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

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