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Authors
Cheema, Baljash
Ambrosy, Andrew P
Kaplan, Rachel M
et al.

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Lessons learned in acute heart failure

Baljash Cheema[1], **Andrew P. Ambrosy**[2,3], **Rachel M. Kaplan**[1], **Michele Senni**[4], **Gregg C. Fonarow**[5], **Ovidiu Chioncel**[6], **Javed Butler**[7,*], **Mihai Gheorghiade**[1]

[1]Northwestern University, Feinberg School of Medicine, Chicago, IL, USA

[2]Duke University Medical Center, Durham, NC, USA

[3]Duke Clinical Research Institute, Durham, NC, USA

[4]Cardiovascular Department, Papa Giovannni XXIII Hospital, Bergamo, Italy

[5]Ahmanson-UCLA Cardiomyopathy Center, Ronald Reagan-UCLA Medical Center, Los Angeles, CA, USA

[6]Institute of Emergency for Cardiovascular Diseases 'Prof. C.C. Iliescu', Cardiology 1, UMF Carol Davila, Bucharest, Romania

[7]Stony Brook University, Stony Brook, NY, USA

Abstract

Acute heart failure (HF) is a global pandemic with more than one million admissions to hospital annually in the US and millions more worldwide. Post-discharge mortality and readmission rates remain unchanged and unacceptably high. Although recent drug development programmes have failed to deliver novel therapies capable of reducing cardiovascular morbidity and mortality in patients hospitalized for worsening chronic HF, hospitalized HF registries and clinical trial databases have generated a wealth of information improving our collective understanding of the HF syndrome. This review will summarize key insights from clinical trials in acute HF and hospitalized HF registries over the last several decades, focusing on improving the management of patients with HF and reduced ejection fraction.

Keywords

Acute heart failure; Clinical trial; Registry

Introduction

Each year, over one million patients in the US and Europe are admitted for heart failure (HF).[1–7] Presentation to the healthcare system for treatment of HF portends a grave

*Corresponding author. Health Sciences Center, T-16, Room 080, Stony Brook University, Stony Brook, NY 11794, USA. Tel: +1 631 444 1066, Fax: +1 631 444 1054, javed.butler@stonybrook.edu.

Supplementary Information

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Conflict of interest

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prognosis, and myocardial injury may occur before, during, or shortly after hospitalization in the vulnerable phase leading to disease progression.[8–11] Post-discharge event rates remain exceptionally high. Although global clinical trials and national hospitalized HF registries have not led to the development of new therapies to improve mortality and readmissions in patients with acute HF, they have significantly improved our understanding of patients with this complex syndrome.[5] The goal of this review is to summarize important lessons from clinical trials in acute HF and hospitalized HF registries over the last several decades with a focus on improving management surrounding the time of hospitalization in patients with HF and reduced ejection fraction (HFrEF). We have combined these lessons into Table 1 and provided a detailed summary of the key trials and registries in the Supplementary material online, Table S1.

Characteristics and risk factors for acute heart failure

A total of 80% of patients hospitalized for HF have a prior history of HF, and more than 50% of patients have a preserved ejection fraction (EF). The majority of patients are hypertensive or normotensive on admission with an identifiable trigger for hospitalization found in 60%, the most common being respiratory infections, ischemia, arrhythmias, and medication non-compliance.[12] Several major co-morbidities are highly prevalent among patients hospitalized for HFrEF, including diabetes (40%), coronary artery disease (CAD, 60%), and atrial fibrillation (40%).[13] In OPTIMIZE-HF and ADHERE, higher serum creatinine, lower systolic blood pressure, advanced age, and elevated blood urea nitrogen were associated with the highest mortality.[14,15] In EVEREST, patients with lower admission Kansas City Cardiomyopathy Questionnaire (KCCQ) scores, higher natriuretic peptides (NPs), hyponatraemia, tachycardia at discharge, hypotension at discharge, absence of beta-blocker (BB) therapy at discharge, a history of diabetes, or a history of arrhythmia had the highest risk of poor quality of life or mortality.[16] Even though the vast majority of patients respond to diuretic therapy and are discharged with minimal resting signs and symptoms of congestion, even patients with minimal or absent congestion suffer from high event rates.[13,14,17,18]

Understanding congestion

Congestion manifests as dyspnoea and/or oedema from high left ventricular filling pressures and is the most common reason patients present to the healthcare system for HF therapy.[19,20] It may be due to a gradual absolute increase in intravascular volume and/or a rapid relative redistribution of fluid from capacitance vessels to the effective circulation. Haemodynamic congestion, evidenced by elevated filling pressures and/or NP elevation, may exist with or without overt signs and symptoms of clinical congestion. Over time, subclinical haemodynamic congestion may progress to clinical congestion requiring hospital admission, whereas it is hypothesized that intervention in subclinical stage may prevent this.[21,22] Residual haemodynamic congestion despite resolution of clinical congestion at the time of hospital discharge may in part contribute to the high HF readmission rates, stressing the overall importance of properly assessing and addressing filling pressures.[22,23]

Managing congestion

Appropriately managing congestion in patients with acute HF requires a thorough evaluation, keeping in mind the concept of haemodynamic congestion. In Figure 1, we give a mechanistic approach to the patient with acute HF, and in Figure 2 we provide a visual summary of the recommendations given with US and European society guidelines for acute HF. Table 2 summarizes common ways of measuring congestion and the advantages and disadvantages with each, and Table 3 provides a grading system for congestion.[24–27] Proper evaluation is required not only on admission but throughout the hospital course, prior to discharge, and in the early post-discharge period to avoid inadequate decongestion and reduce the early event rate related to congestion.[28]

In-hospital phase

Over 90% of patients admitted for HF receive intravenous loop diuretics, though various strategies have been employed regarding dosing, frequency, and duration.[29] The DOSE-AHF trial investigated bolus vs. continuous dosing of intravenous furosemide as well as a high-dose vs. low-dose approach in patients with acutely decompensated HF requiring hospital admission. The trial showed no significant difference in the primary efficacy endpoint of a global assessment of patient-reported symptoms or the primary safety endpoint of the incidence of acute kidney injury in either the continuous vs. bolus dosing or the high-dose vs. low-dose cohort. Patients receiving high dose of intravenous furosemide, however, did report greater dyspnoea relief, fluid loss, and weight loss, though a higher proportion met a pre-specified secondary safety endpoint of increased serum creatinine. At 60 days, any difference in serum creatinine or cystatin C in the high- and low-dose cohort resolved, and clinical outcomes were comparable between treatment arms.[29] Given the short duration of action of furosemide and bumetanide, optimal dosing of these loop diuretics should be twice a day to avoid rebound sodium reabsorption. In patients requiring high doses of diuretics to maintain an appropriate response, the addition of a thiazide diuretic such as metolazone may augment diuresis through sequential nephron blockade, decreasing sodium reabsorption in the distal convoluted tubule.

Recent research has focused on the utility of using natriuretic doses of mineralocorticoid receptor antagonists (MRAs) such as a spironolactone at a dose of 50 mg or greater to augment diuresis, counteract neurohormonal and sympathetic activation seen with loop diuretics, and offset electrolyte disturbances such as hypokalaemia.[30–32] Accordingly, ATHENA-HF studied if high-dose MRA therapy could improve clinical and haemodynamic congestion compared to standard of care in patients hospitalized for HF, but was neutral in the primary endpoint of a reduction in NT-proBNP level as well as in all secondary endpoints.[33,34] Key questions remain and further research is required to clarify the role of high-dose MRA therapy in key subgroups, including patients with renal insufficiency as well as those with demonstrated diuretic resistance.

Tolvaptan, an oral vasopressin-2 receptor antagonist, has been studied extensively in addition to standard diuretic therapy to relieve congestion specifically in the setting of hyponatraemia. Although it was successful in reducing hyponatraemia and inducing weight and fluid loss, it has not been shown to improve clinical outcomes, including reducing signs

or symptoms of HF beyond standard therapy. This suggests that hyponatraemia is a marker but not a target for drug therapy and that tolvaptan is unable to specifically reduce intravascular volume as opposed to total body volume.[35–39]

The role of ultrafiltration has been evaluated in treating congestion in those with acute HF. In UNLOAD, patients hospitalized for HF with signs of hypervolaemia were randomized to ultrafiltration vs. fixed-dose intravenous diuretic therapy. The trial showed increased weight loss and fluid removal in the ultrafiltration cohort.[40] In CARESS-HF, patients hospitalized for HF who remained persistently congested in the setting of cardiorenal syndrome were randomized to a stepped pharmacologic approach vs. ultrafiltration. The pharmacologic approach was superior in maintaining kidney function at 96 h and equivalent in relieving congestion, with less adverse side effects related to initiating and maintaining ultrafiltration such as vascular access complications and catheter-related line infections.[41] UNLOAD and CARESS-HF varied in both patient population, with CARESS-HF enrolling patients with persistent congestion and cardiorenal syndrome, as well in pharmacologic therapy as UNLOAD encouraged fixed-dose diuretics whereas CARESS-HF allowed investigators to titrate medications as they determined necessary including inotropes and vasodilators. AVOID-HF further investigated aquapheresis vs. intravenous diuretics, and although it showed a trend towards longer time to first HF event in the aquapheresis group, the trial was terminated early by the sponsor.[42] Stepped pharmacologic therapy in the hands of an experienced provider is the preferred management strategy and ultrafiltration should remain reserved for patients with persistent congestion and cardiorenal syndrome despite aggressive decongestion therapy.

Vasodilators have been investigated in the treatment of congestion in acute HF in several studies but have been unable to significantly improve dyspnoea, rehospitalization rates, and/or mortality. VMAC suggested nesiritide and nitroglycerine may be superior to placebo in this cohort at reducing pulmonary capillary wedge pressure and/or dyspnoea in acute HF over a short time period.[43] Nesiritide, however, was subsequently studied in ASCEND-HF and did not significantly decrease dyspnoea or achieve a composite endpoint of reduction in rehospitalization for HF or death at 30 days.[44] In RELAX-AHF-2, the follow-up trial of RELAX-AHF, serelaxin was unable to significantly reduce cardiovascular death through 180 days or worsening HF through 5 days in patients hospitalized with acute HF who received a 48 h infusion of the drug within 16 h of hospitalization.[45,46] Similarly, ularitide in addition to standard therapy was unable to improve cardiovascular mortality or a composite endpoint that evaluated early effects of the drug.[47] The results of this trial call into question the ‘injury hypothesis’, specifically that short-term infusion of a vasoactive agent aimed at improving central haemodynamics in acute HF can prevent or reverse cardiac injury and end-organ damage translating into benefits in short-term clinical status or long-term improvement in clinical outcomes.

Digoxin has been used for a number of years in patients with HF, and the DIG trial showed a reduction in all-cause and HF-specific hospitalizations.[48] Although post-hoc analyses of the DIG database have raised the hypothesis that digoxin might increase mortality in subsets of patients at high risk for digoxin toxicity (i.e. women, the elderly, patients with renal insufficiency, etc.), detrimental effects on survival were attenuated after adjusting for serum

digoxin concentration.[49–52] Digoxin improves haemodynamics both at rest and with exercise and does not adversely affect heart rate, blood pressure, or renal function.[53] Further investigation is needed to clarify the role of digoxin at the lower serum concentration typically targeted in the modern era, as well as in the setting of contemporary background HF therapies. Moreover, no data are available regarding the use of digoxin in acute HF.

Additionally, patients with hospitalization for HF may require early non-invasive ventilation for respiratory support while undergoing decongestive therapies, and current guidelines provide recommendations for such an approach.[54] Non-invasive ventilation in patients with acute HF requiring hospitalization and sleep apnoea was recently studied in the CAT-HF trial. In the early stages of the trial, no reduction in safety was seen, there was a moderate improvement in quality of life, and a trend towards improvement in the composite endpoint of death, cardiovascular hospitalization, and 6-minute walk test distance in those with HF and preserved EF was observed.[55] The trial was stopped early as increased cardiovascular morbidity and mortality was seen in the separate but related SERVE-HF study, investigating chronic, ambulatory, symptomatic HFrEF patients with predominantly central sleep apnoea.[56] ADVENT-HF is an ongoing trial investigating sleep-disordered breathing in HFrEF patients, both with central and obstructive sleep apnoea, and will hopefully provide instruction on if adaptive servo-ventilation can improve morbidity and mortality.[57] Invasive ventilation and circulatory support were needed in ~4% and ~2% of patients in ADHERE and OPTIMIZE-HF, respectively, and as such the related management is beyond the scope of this review.[12,58]

In summary, we manage in-hospital congestion with an aggressive approach that utilizes diuretic therapy with a loop diuretic as : bolus dosing at least twice daily, with the addition of a thiazide-type diuretic in refractory patients. We prescribe a neurohormonal dose of MRA in patients with creatinine <2.5 mg/dL and potassium <5.5mEq/L. For those with normal to high systolic blood pressures, intravenous vasodilators such as nitrates and nitroprusside may be considered as an adjunct to diuretics. In those with persistent signs and symptoms of congestion, digoxin may be considered. Ultrafiltration or renal replacement therapy should be reserved for the minority of patients in whom aggressive titration of pharmacotherapy does not achieve adequate clinical decongestion, and respiratory support should be provided on an as needed basis.

Pre-discharge

In OPTIMIZE-HF, patients were discharged without adequate weight loss or resolution of clinical congestion as assessed by common signs and symptoms of HF, and in EVEREST and ASTRONAUT patients often had high NPs, concerning for persistent haemodynamic congestion.[19,20,59,60] This may play a role in high readmission rates and early post-discharge mortality. Thus, we recommend aggressive decongestive therapy until intravascular volume is sufficiently decreased. Physical exam findings should support relief of intravascular congestion, specifically a reduction in dyspnoea on exertion, orthopnoea, jugular venous pressure, body weight, and pitting edema.

Serum creatinine may be used to assess congestion and decongestive therapy. Although there may be concern regarding irreversible kidney damage and the precipitation of the

cardiorenal syndrome in response to aggressive diuresis, in-hospital worsening renal function is short-lived and reversed in the vast majority of patients by the first post-discharge follow-up visit.[18,61] This may be because in-hospital worsening renal function is often a transient phenomenon due to arterial under-filling, a passive bystander to successful decongestion therapy. It may be associated with favourable prognostic findings including weight loss, haemoconcentration, and decreased natriuretic peptide levels.[62] Further, some recent studies have suggested, paradoxically, that patients with improving renal function during hospitalization may actually have a significantly higher rate of post-discharge events.[63]

A reduction in NPs by 30% during hospital stay has been shown to decrease mortality and may suggest adequate reduction in congestion. An extensive discussion of this topic, including NP-guided therapy, is beyond the scope of this article and has been previously completed, and we point readers towards several high-quality reviews.[64,65] Haemoconcentration, or relative concentration of cellular elements within blood such as haematocrit or albumin, has been associated with improved post-discharge mortality and rehospitalization rate in several studies, and as such can be used to help determine the appropriate duration and intensity of decongestion therapy.[66]

Additionally, imaging can provide additional tools to assess congestion and progress with decongestive therapy, including bedside cardiopulmonary ultrasound and chest X-ray, topics that have been reviewed previously.[67,68] Overall, we emphasize an ongoing, thorough assessment of congestion with the goal of adequately reducing intravascular volume in all patients with acute HF prior to consideration for discharge.

Vulnerable phase

The vulnerable phase starts immediately after discharge, with a sharp rise in the risk of death and rehospitalization in the days to weeks immediately after admission ends and a gradual decline thereafter. Therefore, follow-up within 1 to 2weeks is recommended.[69] At that follow-up visit, a comprehensive examination assessing congestion and titrating medications as well as risk stratification should take priority.[70] A recent analysis from EVEREST showed that those who are diuretic responsive and demonstrate haemoconcentration are at lower risk for adverse early post-discharge outcomes, while an analysis from DOSE-AHF showed those with adequate loss of weight, fluid removal, and NP reduction after treatment during a hospitalization for HF had improved clinical outcomes at 60 days.[71,72] However, there is currently no validated well-performing risk score accepted for accurately identifying patients at high risk for mortality and early readmission, an area in need of active research. There is also a need for a prospective study to evaluate the role of early post-discharge follow-up as well as the utility of comprehensive disease management programmes focused on transitions in care, which have had an inconsistent effect on preventing readmissions.

Altering the natural history of heart failure with reduced ejection fraction

While an adequate assessment of congestion and appropriate therapy to reduce intravascular volume is key in acute HF, the time during and surrounding hospitalization is also an opportunity to implement guideline-directed medical therapy recommended by European

and US professional societies for HFrEF as well as to manage cardiac and non-cardiac co-morbidities.

Guideline-directed medical therapy

We invite readers to review guidelines by major professional societies in the US and Europe for a discussion on well-established medications for chronic HFrEF patients that reduce mortality and readmissions.[73–75] Additionally, recent clinical trials have provided new, outcome improving therapies and are detailed below.

In PARADIGM-HF, sacubitril/valsartan was found to be superior to angiotensin-converting enzyme inhibitor (ACEI) alone in reducing cardiovascular death and HF hospitalization in chronic, ambulatory HFrEF patients otherwise on guideline-directed medical therapies.[76] In an analysis of patients in PARADIGM-HF who were hospitalized with HF, sacubitril/valsartan reduced 30-day all-cause readmission by 26% and 30-day HF readmission by 38% compared to enalapril.[77] Consequently, sacubitril/valsartan has been added to the US and European guidelines for HF with a class I recommendation for patients with New York Heart Association (NYHA) class II or III disease with chronic HFrEF as a replacement for ACEI or angiotensin receptor blocker to decrease mortality.[74] Pre-discharge switching to sacubitril/valsartan therapy in eligible patients may facilitate implementation and improve outcomes, and as such PIONEER-HF will evaluate the safety, tolerability, and efficacy of pre-discharge initiation of sacubitril/valsartan vs. enalapril in patients hospitalized with HFrEF (ClinicalTrials.gov NCT02554890).

Ivabradine was evaluated in the SHIFT trial. Its mechanism of action occurs reducing the diastolic depolarization rate of sinoatrial node pacemaker cells through the inhibition of hyperpolarization-activated cyclin-nucleotide gated-channel mediated current, the so-called ‘funny’ current.[78,79] It was shown to reduce HF hospitalizations in chronic, ambulatory HFrEF patients otherwise on guideline-directed medical therapies including a BB at maximally tolerated dose in normal sinus rhythm with a heart rate > 70 b.p.m. at rest and is now recommended in the population studied.[74,75,80,81] Though the BB dosage used in the SHIFT was lower than target dose for other HF trials, it reflects real-world usage where fewer patients actually reach target doses.[82] PRIME-HF is an ongoing strategy trial evaluating whether ivabradine initiation prior to discharge is effective at increasing the proportion of patients using ivabradine at 180 days as the primary endpoint as well as secondary endpoints investigating the effect of the drug on heart rate and patient-reported outcomes (ClinicalTrials.gov NCT02827500).

Despite effective treatments for HFrEF, patients are still discharged from the hospital without the initiation or titration of guideline-directed medical therapies to target dosing.[14] This is particularly the case for MRA, with only 60% of eligible patients receiving this therapy in Europe and <35% in the US.[83] Pre-discharge implementation of carvedilol in the IMPACT-HF study was shown to be safe, well-tolerated, and to improve short-term compliance, while discharge use of carvedilol in OPTIMIZE-HF was associated with improved medication adherence and survival.[84–86] It is imperative clinicians use hospitalization as a time to assess medical regimens, add appropriate therapies, and increase doses to target.

Cardiac contributors to heart failure

Pathology in the coronary arteries, myocardium, valves, and conduction system can all lead to the progression of HF or death and each should be considered in those in acute HF.

Although CAD is highly prevalent amongst those with HF and is often the underlying cause of acute HF, less than 10% of patients undergo an ischaemia evaluation during hospitalization for HF.[5,12,13] Patients with CAD and HF have higher mortality compared with HF patients without CAD (9.2% vs. 6.9%, hazard ratio 1.37, 95% confidence interval 1.03–1.81), but revascularization in such patients may result in a decrease in the mortality rate back to that of patients without CAD.[87] STICHES investigated patients with CAD with an EF of ≤35% undergoing coronary artery bypass graft surgery and showed a mortality benefit at 10 years as well as a decrease in the rate of death from cardiovascular causes and/or hospitalization for cardiovascular causes.[88,89] Assessing for viability may provide insight into those that would benefit from revascularization, but this needs further study, as does the role of percutaneous coronary intervention as a mode of revascularization in the population described.[90]

Patients with valvular dysfunction including mitral regurgitation, supraventricular tachyarrhythmias including atrial fibrillation, and pulmonary hypertension should be managed according to established guidelines.[91–97] Significant data exist that support the role of QRS duration and morphology in all-cause mortality in patients with HFrEF, suggesting a role for cardiac resynchronization therapy (CRT) for ventricular dyssynchrony.[98–100] Those particularly with a left bundle branch block morphology in addition to a prolonged QRS may benefit from early intervention with CRT as shown in MADIT-CRT.[101] As such CRT is a class I, level of evidence A indication for patients in normal sinus rhythm with a left bundle branch block, QRS duration ≥150 ms, and NYHA functional class II–IV HF with left ventricular EF <35%.[73,75] Risk of sudden cardiac death should be assessed and patients who are candidates for primary prevention should be identified and referred for implantable cardioverter-defibrillator (ICD) placement. Although the optimal timing of ICD placement is yet to be determined, referrals made for follow-up appointments after hospitalization can aid patients receiving the appropriate device.[102]

Non-cardiac contributors to heart failure

Two-thirds of readmissions within 30 days of a hospitalization for HF are for non-HF primary issues, regardless of EF. Co-morbidities are highly prevalent in this population, and not only do they precipitate rehospitalization; uncontrolled co-morbidities worsen HF over time.[12]

Treatment of type 2 diabetes warrants mention, as new data on empagliflozin from the EMPA-REG OUTCOME trial showed a decrease in the primary composite endpoint of death from cardiovascular cause, non-fatal myocardial infarction, or non-fatal stroke in patients with type 2 diabetes and high cardiovascular risk, as well also a decreased risk of hospitalization for HF in the treatment group.[103] Empagliflozin is being further investigated in EMPEROR-Reduced and EMPEROR-Preserved, and DEFINE-HF is further studying the

effects of dapagliflozin on outcomes in patients with type 2 diabetes and HFrEF (ClinicalTrials.gov NCT03057977, NCT03057951, and NCT02653482).

Several studies now support improved outcomes in HF with iron repletion including FAIR-HF and CONFIRM-HF.[104–106] Recent data, however, offer different results depending on mode of iron administration. EFFECT-HF showed an improvement at 6 months in peak exercise capacity in those with iron deficiency and chronic HF treated with aggressive intravenous iron replacement.[107] To the contrary, IRONOUT did not show increased oxygen consumption at peak activity and had no effect on secondary outcomes in chronic HFrEF patients receiving high-dose iron orally. This despite patients receiving over 15 times the cumulative iron dose given in a typical one-time intravenous infusion of iron, suggesting decreased oral absorption in HF patients.[108] HEART-FID, FAIR-HF2, and AFFIRM-AHF are ongoing trials investigating iron repletion in HF patients (ClinicalTrials.gov NCT03037931, NCT03036462, and NCT02937454).

Skeletal abnormalities may be considered as a co-morbidity of HF, and accordingly cardiac rehabilitation should be prescribed to those eligible. HF-ACTION showed that cardiac rehabilitation was safe and led to a modest improvement in health-related quality of life as measured by the KCCQ and EQ-5D, however only 10% of eligible patients in the Get With the Guidelines database received a referral at the time of hospital discharge.[109–111] Further, investigation in REHAB-HF will study whether a structured rehabilitation programme in patients over the age of 60 recently hospitalized for HF can improve function and reduce subsequent hospitalizations (ClinicalTrials.gov NCT02196038).

Conclusion

Outcomes for patients hospitalized for HF continue to be poor, and several recent clinical trials have failed to produce novel therapies to alleviate progression of the disease. Simply relying on positive clinical trials, however, ignores considerable data already accumulated that can improve how we treat this complex patient population. The first step in a HF admission remains a focused clinical assessment of fluid status to guide effective, thorough decongestive therapy, keeping in mind the concept of haemodynamic congestion and using appropriate therapies. As data suggest those hospitalized for HF have a grim prognosis, it is crucial to utilize hospitalization as an opportunity to initiate and optimize guideline-directed, life-prolonging HF therapies, assess the individual components of the cardiac substrate, identify and treat co-morbidities, and risk stratify patients for follow-up. While we may not have answered every question a patient hospitalized for HF poses, we have enough information at our fingertips to improve quality of care and perhaps alter the natural history of this condition and the unacceptably high morbidity and mortality experienced by this high-risk patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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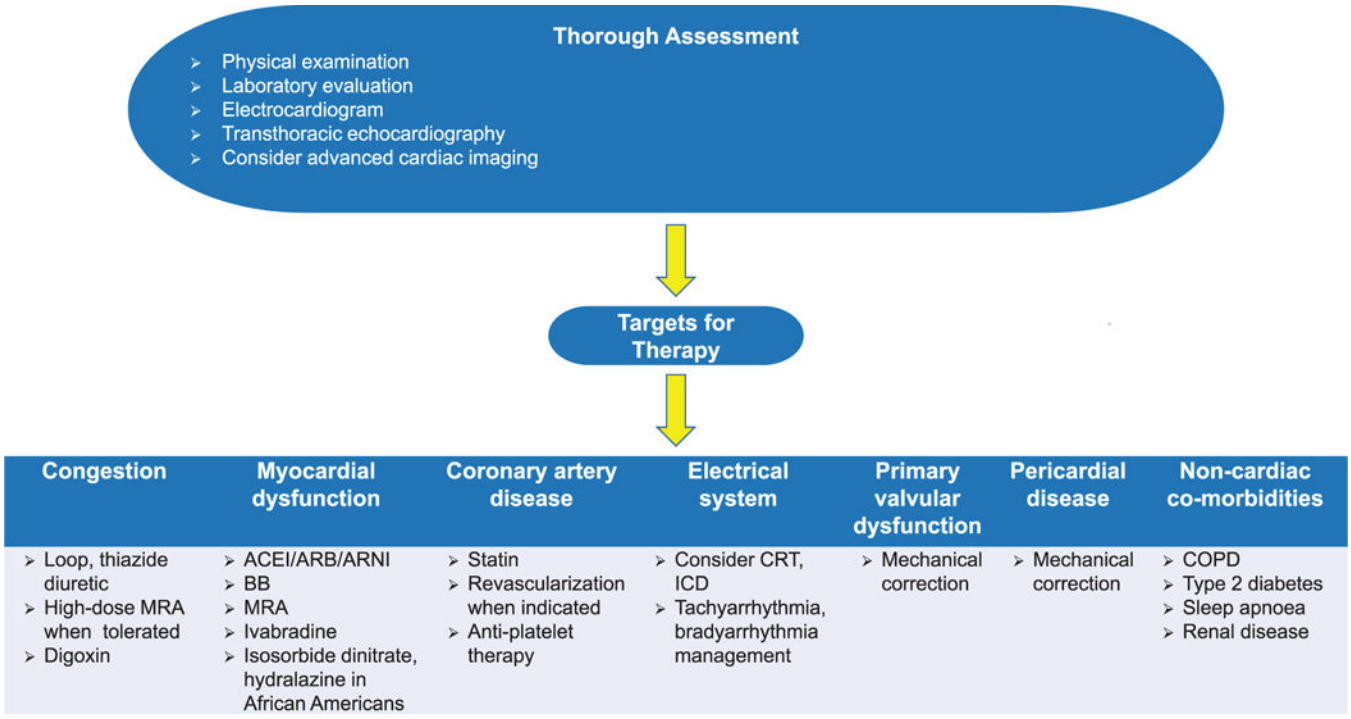

Figure 1.

Mechanistic approach to heart failure in the vulnerable phase and thereafter. Our recommendation is in addition to the established guidelines by European and US professional societies for heart failure.[73–75] We additionally recommend following established guidelines for coronary artery disease, arrhythmias, valvular heart disease, and non-cardiac co-morbidities

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; BB, beta-blocker; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist.

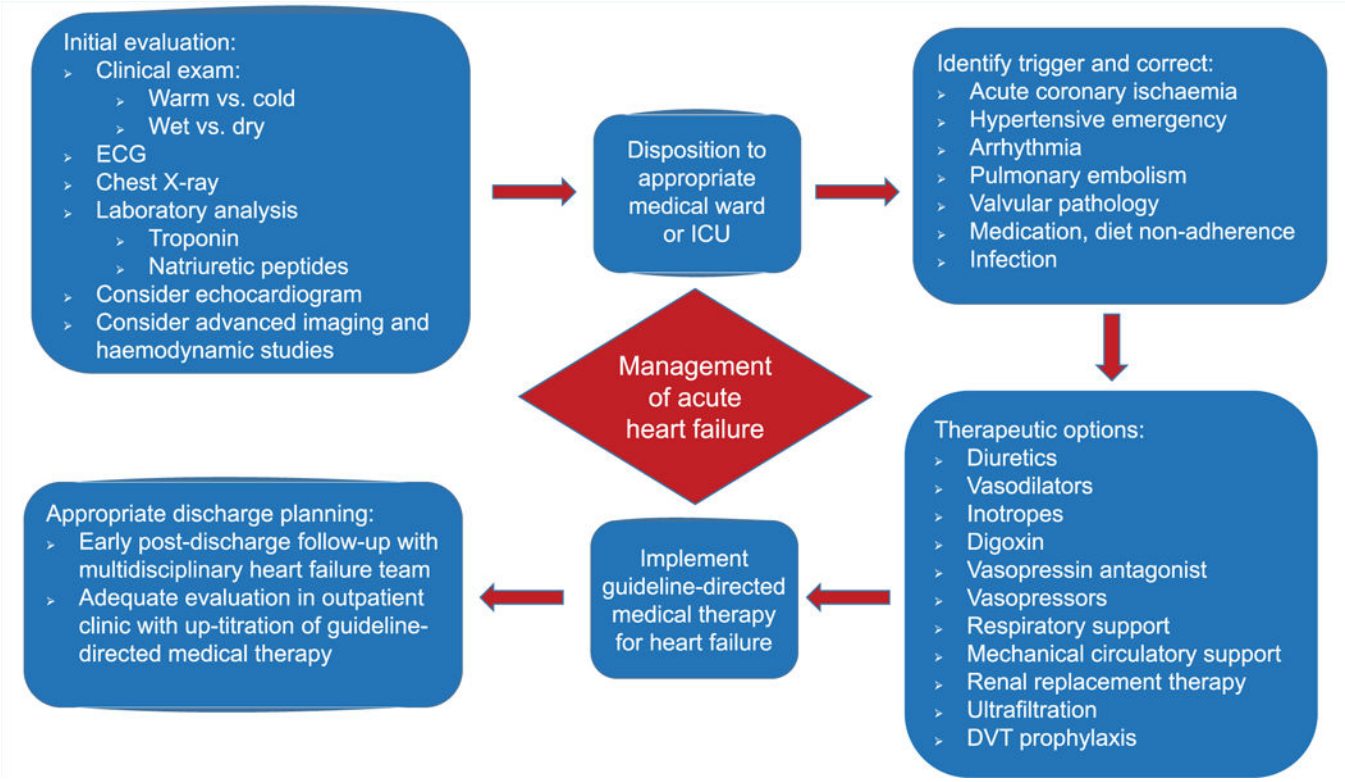

Figure 2.

A visual summary of the US and European guidelines' recommendations for the management of acute heart failure[73–75]

DVT, deep vein thrombosis; ECG, electrocardiogram; ICU, intensive care unit.

Table 1

Critical insights from years of heart failure trials and registries

• The main reason for hospitalization for HF is congestion, manifested by patient-reported dyspnoea.[12,19,20]
• Haemodynamic congestion, as evidenced by elevated cardiac filling pressures, is present in the days and weeks leading up to overt clinical congestion and may persist following the resolution of resting signs and symptoms.[21,22]
• Up to 80% of patients with hospitalization for HF have a history of HF. Coronary artery disease, hypertension, atrial fibrillation, diabetes mellitus, chronic lung disease, sleep disorders, depression, and chronic kidney disease are common co-morbidities.[12,13]
• Most patients admitted for HF are normotensive or hypertensive, not hypotensive, and they respond readily to intravenous diuretic therapy, suggesting the presence of viable but dysfunctional myocardium and significant underlying cardiac reserve.[12,112,113]
• Half of HF readmissions are non-cardiovascular in aetiology.[12]
• Half of all HF patients have a preserved EF, their post-discharge outcomes are as poor as those with reduced EF, and there are currently no available disease-modifying therapies.[12]
• Hospitalization may be associated with cardiac injury, as evidenced by elevated circulating cardiac troponins and other signs of end-organ damage secondary to haemodynamic fluctuations, ultimately leading to progression of HF.[8–10]
• In-hospital worsening renal function is often a transient phenomenon due to arterial under-filling and not venous congestion and/or hypoperfusion, a passive bystander to decongestion therapy is associated with /favourable prognostic findings including weight loss, haemoconcentration, and decreased NF levels.[61,63,66]
• Mineralocorticoid receptor antagonists and hydralazine/isosorbide dinitrate therapy in eligible patients are substantially underutilized.[14]
• Patients hospitalized for HF with wide QRS complex may benefit from cardiac resynchronization therapy. QRS duration does not change during hospitalization.[98]
• There are several important markers of poor prognosis such as low blood pressure, low serum sodium, high NFs, and worsening renal function. It is important to distinguish between markers and targets for therapy.
• Most patients have no symptoms of congestion at rest prior to discharge but have exertional symptoms that can be elicited by provocative manoeuvres as well as high NFs, suggesting persistent haemodynamic congestion.[27]
• Although most patients do not have advanced HF, the early post-discharge vulnerable phase is characterized by a deterioration in clinical status and associated with an unacceptably high rate of morbidity and mortality.[8–11]
• Evidence-based therapy for cardiac co-morbidities such as coronary artery disease, atrial fibrillation, valvular heart disease, and hypertension should be implemented.[73,75,110]
• Many patients do not receive sufficient education, optimal transition of care planning, early post-discharge follow-up, adequate secondary prevention, and implementation of exercise training programmes, potentially contributing to high readmission rates.[110]

EF, ejection fraction; HF, heart failure; NF, natriuretic peptide.

Table 2

A summary of advantages and limitations of commonly available methods of measuring congestion

Measurement	Advantages	Limitations
Resting dyspnoea and orthopnoea	Rapid assessment	May be non-cardiac in origin
Dyspnoea on exertion	Provides functional information	May be non-cardiac in origin
Rales	Rapid assessment	Not sensitive or specific for congestion
Jugular venous pressure	Good sensitivity and specificity	Difficult to assess in obesity; intraobserver variation
Edema	Simple measurement	May not represent congestion; must correlate with jugular venous pressure
Body weight	Simple measurement	Fluctuations may not represent changes in intravascular volume
Serum sodium	Predicts outcomes	
Urea nitrogen	Predicts outcomes	
Natriuretic peptides	Predicts outcomes	Do not change acutely (B-type peptides); elevations found in other conditions such as renal disease or cirrhosis
Radiographic congestion		Not sensitive or specific
Orthostatic testing	Important guide for therapy	Complex measurement
Valsalva manoeuvre		Dependent on patient effort; can require specialized equipment
Sublingual nitroglycerine		Impractical in most patients
Portable ultrasound	Evolving technology	Requires training and specialized equipment

Modified from Gheorghiade *et al.*[24]

Table 3

Grading congestion

Variable	Score				
	−1	**0**	**1**	**2**	**3**
Bedside assessment					
Orthopnoea [a]		None	Mild	Moderate	Severe/worst
JVP (cm)	<8 and no hepatojugular reflux		8–10 or hepatojugular reflux	11–15	>16
Hepatomegaly	Absent in the setting of normal JVP	Absent	Liver edge	Moderate pulsatile enlargement	Massive tender enlargement extending to midline
Oedema [b]		None	1+	2+	3+/4+
Laboratory					
Natriuretic peptides (one)					
BNP		<100	100–299	300–500	>500
NT-proBNP		<400	400–1500	1500–3000	>3000
Dynamic manoeuvres					
Orthostatic testing	Significant decrease in SBP or increase in HR	No change in SBP or HR			
6-minute walk test	>400 m	No difficulty 300–400m	Mild 200–300m	Moderate 100–200m	Severe/worst <100 m
Valsalva manoeuvre	Normal response		Absent overshoot pattern	Square wave pattern	

BNP, B-type natriuretic peptide; HR, heart rate; JVP, jugular venous pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP systolic blood pressure. Congestion grade: <1, none; 1–7, mild; 8–14, moderate, 15–20, severe.

[a]Orthopnoea: 0, absent; mild (use of one pillow); moderate (use of more than one pillow); severe, sleeps in an armchair or in a seated position.

[b]Oedema, in the absence of other cause of oedema.

Modified from Gheorghiade *et al.*[24]