

Optimal patient management before and after hospital discharge is crucial

Acute heart failure: from pathophysiology to optimal treatment

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Summary

Acute heart failure is a life-threatening condition requiring immediate diagnosis and initiation of treatment. Systemic congestion, promoted by the activation of several pathophysiological mechanisms, is the central feature of acute heart failure, and causes the typical symptoms and leads to organ dysfunction. Cardiogenic shock is the most severe form of acute heart failure and is defined by the presence of reduced cardiac output and end-organ hypoperfusion.

Decongestive therapy is the mainstay in the initial treatment of acute heart failure with congestion. Inotropes are used in cardiogenic shock patients with reduced myocardial contractility to restore end-organ perfusion.

The first 3 months after an acute heart failure episode – the vulnerable phase – are characterised by high readmission and mortality rates. Optimal patient management before and after hospital discharge is crucial to improve patient outcome.

Key words: acute heart failure; cardiogenic shock; diagnosis; treatment



Introduction

Heart failure is a clinical syndrome induced by structural and/or functional cardiac abnormalities, resulting in reduced cardiac output and/or elevated intracardiac end-diastolic pressures and causing symptoms, often accompanied by typical physical signs [1]. The number of subjects living with heart failure has increased over recent decades because of demographic changes and, at least in part, because of the success of modern cardiology, which achieved a marked reduction in short-term mortality of several acute conditions (e.g., myocardial infarction, arrhythmia, congenital heart disease) and, by combining several drug classes and devices, improved long-term survival of patients with reduced left-ventricular ejection fraction. As a consequence, heart failure has become a major public health problem, affecting 2% of the adult population in developed countries, and the number of hospital admissions related to heart failure has tripled over the last three decades [2].

Acute heart failure (AHF) is defined as new-onset or worsening of symptoms and signs of heart failure and is the most frequent cause of unplanned hospital admission in patients aged 65 years or older. Despite major achievements in the treatment of chronic heart failure, outcomes of AHF remain poor, with high mortality and readmission rates. In this context, there is an unmet need for individualisation of AHF treatment according to the underlying pathophysiological mechanisms and for optimisation of transitions of care to, hopefully, improve patient outcome.

Congestion and the pathophysiology of acute heart failure

Heart failure was historically described with the haemodynamic model of a pump failure causing downstream hypoperfusion (forward failure) and upstream congestion (backward failure). Over recent decades, a more complex network of interactions has been added to this model for explaining the pathophysiology of heart failure. AHF may arise in patients without previous history of symptomatic heart failure (*de novo* AHF), mostly secondarily to an acute deterioration of the cardiac function (e.g., myocardial infarction, severe myocarditis, acute valve regurgitation) causing relevant haemodynamic alterations [3]. More frequently, AHF consists of acute decompensations of chronic heart failure (ADHF) and is caused by progressive congestion that may be precipitated by several factors [4].

Cardiac dysfunction induces the activation of several neuro-humoral pathways (e.g., the sympathetic nervous system, the renin-angiotensin-aldosterone system and the arginine-vasopressin system) to counter the negative haemodynamic effects of heart failure [5]. Neuro-humoral activation leads to impaired sodium excretion through the kidneys, which results in sodium and, secondarily, fluid accumulation [6]. Moreover, persistent neuro-humoral activation induces maladaptive processes resulting in detrimental ventricular remodelling and organ dysfunction.

The congestive cascade includes a subclinical stage (haemodynamic congestion), defined as increase in cardiac filling and venous pressures, followed by redistribution of fluids into the lungs and visceral organs (organ congestion), and finally to overt symptoms and signs of volume overload (clinical congestion) [7]. Although clinical and organ congestion usually follow haemodynamic congestion, the correlation between hydrostatic pressure and oedema formation is poor. Indeed, chronic sodium accumulation in heart failure impairs the function of the interstitial glycosaminoglycan network, reducing its capacity to buffer additional sodium and maintain low interstitial compliance [8]. Consequently, interstitial oedema formation may occur even in the presence of mildly elevated hydrostatic pressures.

Many AHF patients display only a minor increase in body weight before hospital admission and congestion is precipitated mainly by a sudden fluid redistribution rather than fluid accumulation. Sympathetic activation has been shown to induce transient vasoconstriction leading to rapid volume displacement from the peripheral and splanchnic venous systems to the pulmonary circulation [9]. A mismatch in the ventricular-vascular coupling relationship, with increased afterload and decreased venous capacitance (increased

preload), is the primary alteration in hypertensive AHF [10, 11]. Fluid accumulation and fluid redistribution both promote systemic congestion in AHF, but their contribution varies according to different clinical situations. Whereas fluid redistribution might be the predominant mechanism in acute *de novo* forms and in ADHF with preserved ejection fraction, fluid accumulation might be more common in ADHF with reduced ejection fraction.

Recent data suggested that venous congestion is not simply an epiphenomenon secondary to cardiac dysfunction, but rather plays an active detrimental role, inducing pro-oxidant, pro-inflammatory, and haemodynamic stimuli that contribute to the pathophysiology of AHF [12, 13].

Furthermore, systemic congestion has been recognised as a central feature in AHF, since it is the main determinant of the clinical presentation and significantly contributes to organ dysfunction in AHF. Left-sided congestion may cause dyspnoea, orthopnoea, bendopnoea (shortness of breath when leaning forward), paroxysmal nocturnal dyspnoea, cough, tachypnoea, hypoxia and pathological lung auscultation. Right-sided congestion may cause pleural effusions, jugular vein distension or positive hepatojugular reflux, ascites, hepatomegaly, icterus, abdominal pain, nausea, vomiting and decreased urine output. Peripheral oedema is not specific for right heart failure, since it can be promoted by neuro-humoral activation and fluid overload induced by left and/or right heart failure. Of note, leg oedema can be absent in the early phase of AHF. Historically, renal and hepatic dysfunctions in heart failure have been considered as the consequence of visceral hypoperfusion, but more recent data showed that central venous pressure (reflecting venous congestion) was the strongest haemodynamic determinant of renal and hepatic dysfunction in AHF [14–16]. Symptoms and signs of hypoperfusion are much less common and indicate severity. These include hypotension, tachycardia, weak pulse, mental confusion, anxiety, fatigue, dyspnoea/tachypnoea (due to cerebral hypoxemia and/or metabolic acidosis), cold sweaty extremities, decreased urine output, and angina due to myocardial ischaemia.

Diagnosis and initial treatment

The basis for the correct management of AHF patients depends on the correct diagnosis of the cardiac disease, the pathophysiology at play and comorbidities (table 1).

The treatment consists of three steps: triage, confirmation of diagnosis and initiation of treatment, and reas-

Table 1: Principles for the correct management of patients with acute heart failure.

Diagnostic challenges	Examples
Characterise the clinical syndrome	Cardiogenic shock (hypoperfusion) Acute pulmonary oedema (fluid redistribution) Congestive AHF (fluid accumulation)
Understand the pathophysiology	Impaired inotropy Excessive afterload Congestion / fluid overload
Identify triggers for decompensation	Acute myocardial ischaemia Hypertensive emergency Arrhythmia Infections Noncompliance with recommendations
Know the underlying cardiac diseases	Coronary artery disease Hypertensive heart disease Valve disorders Myocarditis
Diagnose organ dysfunctions	Encephalopathy Renal dysfunction Hepatic dysfunction
Capture comorbidities / relative contraindications to diagnostics or treatment	Severe renal failure Active bleeding / bleeding risk Arterial hypertension Diabetes mellitus COPD, smoking Allergy to contrast media Pregnancy
Consider iatrogenic harm	Hyopkalaemia after diuretics Hypotension after ACE inhibitors Bradycardia / negative inotropy after beta-blockers Hyperkalaemia after mineralocorticoid receptor antagonists

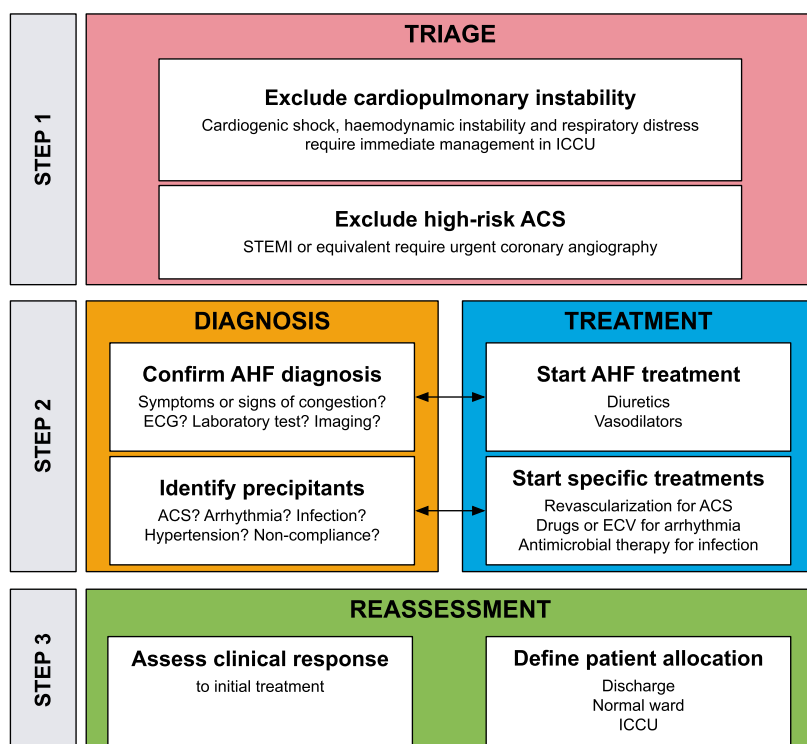


Figure 1: Initial management of acute heart failure.

ACS = acute coronary syndrome; AHF = acute heart failure; ECV = electrical cardioversion; ICCU = intensive cardiac care unit; STEMI = ST-elevation myocardial infarction. Modified from: Arrigo M, Parissis JT, Akiyama E, Mebazaa A. Understanding acute heart failure: pathophysiology and diagnosis. *Eur Heart J Suppl.* 2016;18(suppl G):G11–8, reprinted with permission of Oxford University Press.

assessment (fig. 1). Since AHF is a life-threatening condition, diagnosis and initiation of treatment go hand in hand and should be initiated within 30 to 60 minutes after hospital admission [17].

During the first step (triage), patients with cardiogenic shock, respiratory insufficiency, myocardial ischaemia and/or arrhythmia (table 2) should be identified and receive an appropriate level of monitoring and specific treatments (e.g., mechanical ventilation, pharmacological haemodynamic support). Since congestion is

the typical feature of AHF, history and physical examination should primarily focus on the presence of congestion, which would support the diagnosis of AHF. However, given the limited sensitivity and specificity of symptoms and signs of AHF, the clinical evaluation should integrate information from additional tests. According to the presence of clinical symptoms or signs of organ congestion (“wet” vs “dry”) and/or peripheral hypoperfusion (“cold” vs “warm”), patients may be classified in four groups (fig. 2). About two out of three AHF patients are classified “warm-wet” (well perfused but congested), about one in four are “cold-wet” (hypoperfused and congested) and only a minority are “cold-dry” (hypoperfused but not congested). Hypoperfusion defines cardiogenic shock, which accounts for less than 10% of AHF cases but is associated with in-hospital mortality rates of up to 50% [20]. The fourth group “warm-dry” represents the compensated (well-perfused, decongested) status. This classification may help to guide initial therapy (see below). During triage, patients with high-risk acute coronary syndrome (e.g., ST-elevation myocardial infarction or equivalent) should be recognised and rapidly transferred to the catheterisation laboratory to receive coronary angiography with percutaneous revascularisation.

The *second step* consists of confirmation of diagnosis and initiation of treatment. Natriuretic peptides, either B-type NP (BNP), amino-terminal pro-B-type NP (NT-proBNP) or mid-regional pro-atrial NP (MR-proANP) should be measured in patients with suspected AHF, since they show high accuracy and excellent negative predictive value in differentiating AHF from non-cardiac causes of acute dyspnoea. Low circulating natriuretic peptides (thresholds: BNP <100 pg/ml, NT-proBNP <300 pg/ml, MR-proANP <120 pmol/l) make the diagnosis of AHF unlikely. However, elevated concentrations of natriuretic peptides do not automatically confirm the diagnosis of AHF, as they may also be secondary to a wide variety of cardiac and non-car-

Table 2: Medical emergencies in patients with acute heart failure.

Emergency	Typical symptoms and signs	Typical physiological and laboratory variables
Shock	Anxiety, confusion Cold, mottled skin	Heart rate >100 bpm Systolic blood pressure <90 mm Hg Lactate ≥2 mmol/l SvO ₂ <60%
Respiratory insufficiency	Dyspnoea at rest, tachypnoea Use of accessory respiratory muscles Cyanosis	Respiration rate >20/min at rest SpO ₂ ≤90% paO ₂ <9 kPa paCO ₂ >5.5 kPa
Myocardial ischaemia	Chest pain	ECG with ST changes, rising troponin levels
Arrhythmia	All of the above possible	Ventricular tachycardia Atrial fibrillation and signs of AHF Bradycardia, AV block II or III

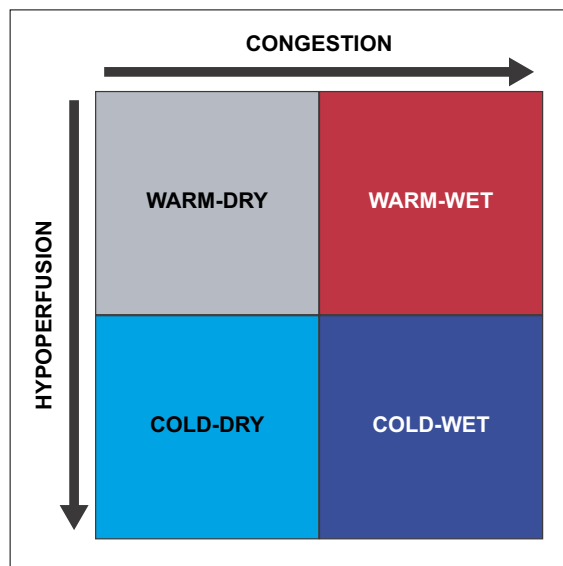


Figure 2: Haemodynamic profiles of acute heart failure according to the presence of congestion and hypoperfusion. Modified from Forrester et al. [18, 19].

diac causes (e.g., atrial fibrillation, renal failure, infections) [21]. On the other hand, circulating natriuretic peptides may be falsely low in obese patients and in those with flash pulmonary oedema. The electrocardiogram is rarely normal in AHF patients, but may be helpful for identifying potential precipitants of AHF (e.g., arrhythmia, ischaemia) and to exclude ST-elevation myocardial infarction requiring immediate revascularisation. Thoracic ultrasound and chest X-ray may both be useful to assess the presence of pulmonary congestion. Systemic congestion may be assessed by means of sonographic measurement of the inferior vena cava diameter and collapsibility. In the presence of cardiogenic shock or suspicion of acute life-threatening structural or functional cardiac abnormalities (mechanical complications, acute valve regurgitation), immediate echocardiography should be performed [22]. Early echocardiography (preferably within 24 hours from admission) should be considered in all patients with *de novo* AHF and in those with unknown cardiac function.

The initial treatment of “wet” patients with evidence of congestion frequently includes diuretics and vasodilators [23]. Whereas diuretics are mainly used in presence of fluid overload, vasodilators are administered to reduce filling pressures in the presence of fluid redistribution and preserved systolic blood pressure (>110 mm Hg, more cautiously and in experienced hands between 90 and 110 mm Hg). Decongestive therapy should be started as soon as possible, titrated according to the clinical response, and maintained until

euvolaemia is achieved [24]. In patients with severe pulmonary oedema, high-flow oxygen therapy, noninvasive ventilation or mechanical ventilation are required to ensure oxygenation. Patients with *de novo* AHF with reduced left-ventricular ejection fraction should be started with oral disease-modifying heart failure treatment (angiotensin converting-enzyme inhibitors, beta-blockers and mineralocorticoid receptor antagonists) after initial decongestion, optimally before hospital discharge (see below). Patients presenting with ADHF should be maintained on oral disease-modifying heart failure treatment whenever possible.

Notably, the use of inotropes should be restricted to “cold” patients in cardiogenic shock with impaired myocardial contractility, since their often inappropriate use is associated with increased morbidity and mortality [25]. In cases of persistent haemodynamic instability despite escalating doses of inotropes, mechanical circulatory support (e.g., venoarterial extracorporeal membrane oxygenation, va-ECMO) should be considered at an early stage to restore organ perfusion [26].

As mentioned above, AHF may be precipitated by several factors, which may coexist (e.g., myocardial ischemia, arrhythmias, infections, uncontrolled hypertension, noncompliance with medical prescriptions). The identification of precipitants during early management aims at detecting treatable causes and provides prognostic information. Indeed, according to current knowledge on the pathophysiology of AHF, the initial management should include, in addition to decongestive therapy (e.g., vasodilators and/or diuretics), specific treatments directed towards the underlying causes of AHF. In particular, early coronary angiography with revascularisation is recommended in AHF precipitated by acute coronary syndrome, antiarrhythmic treatment and/or electrical cardioversion are recommended in AHF precipitated by arrhythmia, and rapid initiation of antimicrobial therapy is recommended for AHF precipitated by infections. Sometimes percutaneous or surgical treatment of structural heart disease is required to achieve durable stabilisation. Furthermore, identification of precipitants of AHF may allow risk stratification of patients with AHF. Indeed, AHF precipitated by acute coronary syndrome or infection is associated with poorer outcomes, whereas outcomes tend to be better in AHF precipitated by atrial fibrillation or uncontrolled hypertension [4, 27, 28].

The *third step* of the initial management consists in reassessment of the clinical response to initial treatment and decision about patient allocation. The level of care (discharge, observation, ward, telemetry, and intensive or intermediate care unit) should be based on history (symptom severity, precipitating factors), physical

examination (haemodynamic and respiratory status, degree of congestion) and biomarkers (natriuretic peptides, troponin, renal function, serum lactate). Most patients require hospital admission, about half of them to intensive or intermediate care units. Low-risk patients with a good response to initial therapy may be considered for early discharge.

Hospital discharge and the vulnerable phase

The decision about the optimal time-point for hospital discharge of hospitalised patients with AHF may be challenging. Indeed, the early post-discharge period immediately following a hospitalisation for AHF is characterised by relevant short-term mortality and frequent hospital readmissions (fig. 3), causing a significant burden in healthcare expenditures [30].

The causes of this “vulnerable phase”, which usually lasts 2 to 3 months, remain controversial [29]. The combination of pathophysiological derangements (e.g., persistent congestion, insufficient neuro-humoral blockade) and healthcare system problems (e.g., lack of follow-up) seems to contribute to the poor outcome. In this context, clinicians need to balance between the risk of adverse outcome, healthcare costs and patient preferences in order to determine the optimal length of hospital stay.

Some studies suggested persistent haemodynamic congestion at hospital discharge as a critical factor in the pathophysiology underlying the high rates of death and readmission during the vulnerable phase [31]. Indeed, although most patients admitted with AHF

report improvement in symptoms during the hospital stay, circulating natriuretic peptides may still be markedly elevated at discharge. This discordance between few symptoms of congestion and high natriuretic peptide concentrations suggests persistent haemodynamic congestion at discharge. Some studies reported an association between predischARGE levels of natriuretic peptides and the risk of death or readmission during the vulnerable phase [32]. Based on these observations, the titration of the decongestive therapy based only on symptoms and signs of congestion may be insufficient and should include additional parameters (e.g., biomarkers, echocardiography) [33, 34].

Underutilisation of disease-modifying HF therapies (e.g., beta-blockers, renin-angiotensin system inhibitors [RASIs] and mineralocorticoid receptor antagonists [MRAs]) may further promote adverse events after hospital discharge. A recent meta-analysis showed detrimental effects on short-term mortality and readmission associated with beta-blocker discontinuation during AHF hospitalisation [35]. Despite lacking data on RASIs and MRAs, the current European Society for Cardiology guidelines recommend initiation or continuation of disease-modifying HF therapies during hospitalisation in all AHF patients with reduced ejection fraction, unless contraindicated [1]. Very recently, a large, propensity score-matched, cohort study showed an association between beta-blocker or RASI treatment at hospital discharge and a 40 to 50% relative risk reduction in 90-day mortality, and an additional 25 to 50% relative risk reduction associated with combined treatment with a beta-blocker and RASI at hospital discharge compared with a beta-blocker or RASI alone [36]. The early benefits were present with both reduced and preserved ejection fraction and persisted at 1-year follow-up. In the same study, no early benefit of early administration of MRAs was found. In patients intolerant to beta-blockers, early initiation of ivabradine might be considered to reduce readmissions during the vulnerable phase [37]. In light of these data, continuation or initiation of disease-modifying heart failure drugs (e.g., beta-blocker, RASI) before hospital discharge in all AHF patients, unless clearly contraindicated, seems reasonable.

A further critical point to consider before hospital discharge is whether the precipitating factors of AHF have been adequately treated and resolved. This includes revascularisation for myocardial ischaemia, antiarrhythmic therapy for arrhythmias, antimicrobial therapy for infection, antihypertensive therapy for hypertension and patient education for malcompliance. Furthermore, clinicians should take care of a delayed peak in the risk of death in AHF precipitated by infec-

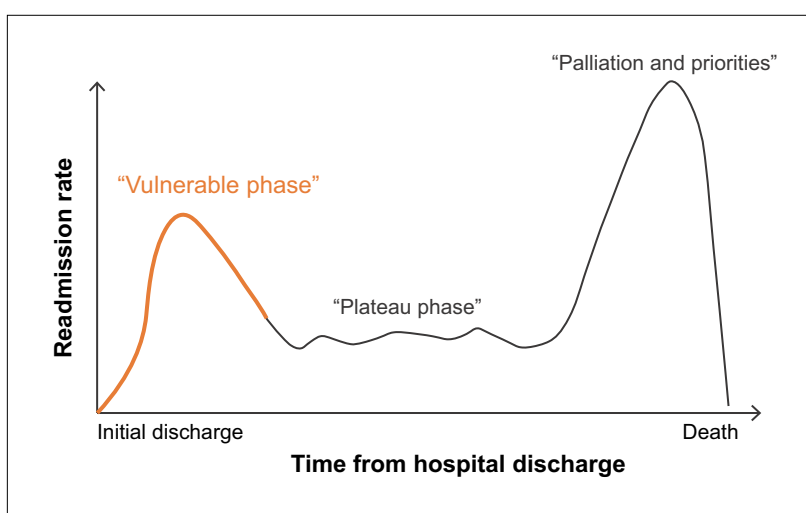


Figure 3: The “vulnerable phase” after discharge for acute heart failure. The first 3 months after hospital discharge for AHF are characterised by high rate of adverse events (death and readmission). This phase is commonly defined as “vulnerable phase”. Modified from Greene et al. [29].

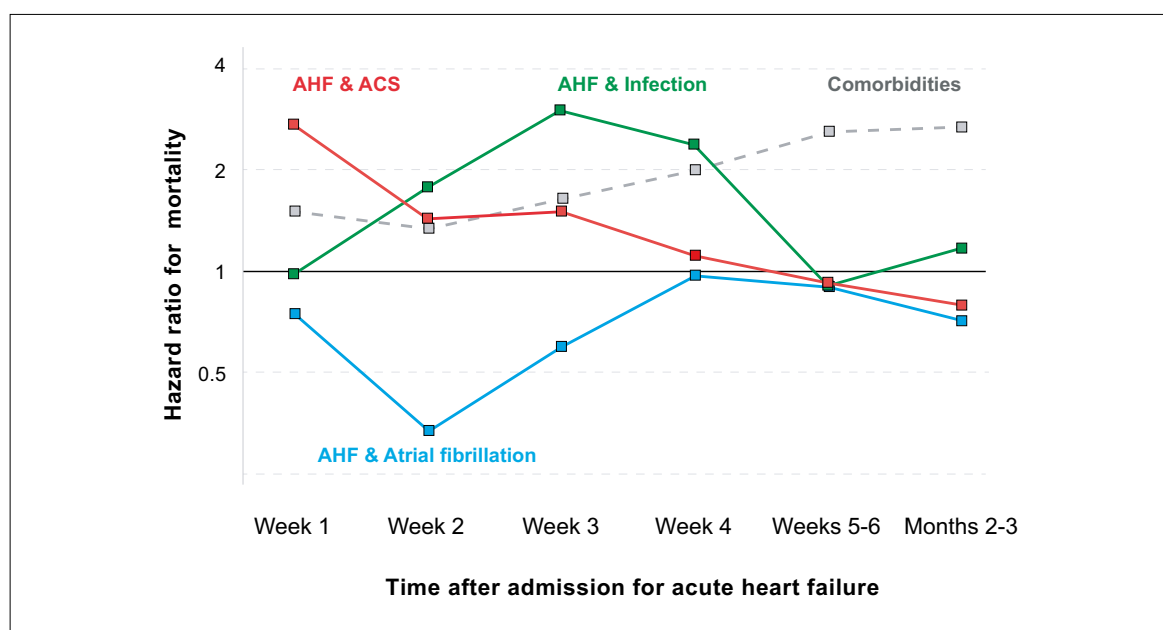


Figure 4: Time-course of risk of death according to precipitating factors and comorbidities. The weekly risk of death associated with the presence of selected precipitating factors of AHF (red, acute coronary syndrome; green, infection; blue, atrial fibrillation) compared with absence of identified precipitating factors. The weekly risk of death associated with the presence of multiple co-morbidities (AHEAD score ≥ 4 points) compared with score < 4 points is depicted in grey. Modified from Arrigo M, Gayat E, Parenica J, Ishihara S, Zhang J, Choi DJ, et al.; GREAT Network. Precipitating factors and 90-day outcome of acute heart failure: a report from the intercontinental GREAT registry. *Eur J Heart Fail.* 2017;19(2):201–8, reprint with permission. ACS = acute coronary syndrome; AHF = acute heart failure

tion, occurring at weeks 3 to 4 after admission (fig. 4) [4].

Patient education, home-based collection of subjective and objective data (symptoms, body weight, blood pressure) and early contact with healthcare providers have been proposed to reduce readmission rates, but with inconsistent results. Several strategies to achieve early detection of congestion, including intrathoracic impedance monitoring and implantable haemodynamic monitoring (e.g., the CardioMEMS HF system),

showed promising results in the trials, but their wide applicability remains questionable, mainly because of uncertainty about cost effectiveness [38, 39].

Optimally, all patients with AHF should benefit from inclusion in an early, comprehensive, post-discharge care programme. If this is not feasible because of limited resources, it should be restricted to high-risk patients (e.g., elevated natriuretic peptides, abnormal systolic blood pressure, persistent hyponatraemia, recurrent readmissions) [29]. In our centre, we recommend an early visit to the general practitioner within 1 week after discharge and we schedule a visit to the HF outpatient clinic within 2 to 3 weeks after discharge. During these early outpatient visits, assessment and optimisation of the volume status (including comparison of natriuretic peptide concentrations with pre-discharge values) and up-titration of disease-modifying HF treatment should be performed.

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References

The full list of references is included in the online version of the article at www.cardiovascmed.ch.

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Key points

- Acute heart failure is a life-threatening condition requiring immediate diagnosis and initiation of treatment.
- Systemic congestion, promoted by the activation of several pathophysiological mechanisms, is the central feature of acute heart failure and causes the typical symptoms and leads to organ dysfunction.
- Cardiogenic shock is the most severe form of acute heart failure and is defined by the presence of reduced cardiac output and end-organ hypoperfusion.
- Decongestive therapy is the mainstay in the initial treatment of acute heart failure with congestion. Inotropes are used in cardiogenic shock patients with reduced myocardial contractility to restore end-organ perfusion.
- The first 3 months after an acute heart failure episode – the vulnerable phase – are characterised by high readmission and mortality rates. Optimal patient management before and after hospital discharge is crucial to improve patient outcome.