Acute Heart Failure: the Heart Failure Patient’s Journey—the Vulnerable Phase

Editorial

Acute heart failure: the heart failure patient’s journey—the vulnerable phase
R. Ferrari, K. Fox, M. Metra

Lead Article

Acute heart failure - M. Metra, C. Lombardi, V. Carubelli

Expert Answers to Three Key Questions

What is the epidemiology of acute heart failure? - A. P. Maggioni
Diagnosis of acute heart failure: what’s new? - A. Caillard, A. Cescau, A. Mebazaa
Management of acute heart failure: what are the options? - P. Ponikowski, E. A. Jankowska

Fascinom a Cardiologica

Trails of Discovery: The discovery of the phosphodiesterase-5 inhibitor sildenafil (Viagra)
J. D. Fitzgerald

Summaries of Ten Seminal Papers - V. Carubelli

Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) database – C. W. Yancy and others

Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure
M. Gheorghie and others

Worsening renal function and prognosis in heart failure: systematic review and meta-analysis – K. Daneman and others

Hemodynamic, echocardiographic, and neurohormonal effects of istaroxime, a novel intravenous inotropic and lusitropic agent: a randomized controlled trial in patients hospitalized with heart failure – M. Gheorghie and others

Diuretic strategies in patients with acute decompensated heart failure – C. M. Felker and others

Impact of serial troponin release on outcomes in patients with acute heart failure: analysis from the PROTECT pilot study
C. M. O’Connor and others

Effect of nesiritide in patients with acute decompensated heart failure – C. M. O’Connor and others

Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial – J. R. Teerlink and others

Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure – M. Packer and others

Liver function abnormalities, clinical profile, and outcome in acute decompensated heart failure – M. Nikolaou and others

Bibliography of One Hundred Key Papers 73
Editorial

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ACUTE HEART FAILURE: THE HEART FAILURE PATIENT’S JOURNEY—THE VULNERABLE PHASE

The heart failure patient’s journey? “Journey” conjures up the idea of traveling from one place to another, in other words, a usually somewhat agreeable occupation. Not quite fitting here. “Journey” can also be taken to refer to a person’s experience of evolving from one state of mind to another. That’s more like it, but only inasmuch as it concerns the cardiologist, because, in the case of acute heart failure, so much still needs to be done, our ideas, our very concepts need to evolve: the road is still very long. To use an image: a “Long March” is still ahead, with all the difficulties this implies. To return to the patient, the better term would be “Via Crucis,” with “acute heart failure,” “acute decompensated heart failure,” “worsening chronic heart failure,” “hospitalization for heart failure,” “acute heart failure syndromes” being so many possible “Stations.” Marco Metra, in his Lead Article, quite rightly reminds us that acute heart failure is a major health care issue and the leading cause of hospitalization worldwide. The figures are actually staggering: acute heart failure is associated with a risk of major events that carry a 10% to 15% mortality rate, a 25% to 35% rehospitalization rate within a mere 6 months of the initial event.

To date, over 20 billion dollars have spent on research, and what do we have to show for it? Unfortunately not all that much!

One of the problems is that everybody has his or her own definition, perception, or concept of acute heart failure. However, there are some aspects on which everyone agrees. The typical patient is elderly and usually has comorbidities. A reduced ejection fraction, which is the preferred heart failure index for cardiologists, is actually not as helpful as it would seem, because 40% to 50% of patients have a preserved ejection fraction with normal or even elevated blood pressure. This is probably the most difficult pathophysiological issue. But that is not all. The typical patient is elderly as we just mentioned. But is a 60-year-old male patient with a long history of post–myocardial infarction, 3 weeks of gradually worsening symptoms, and a blood pressure of 85/40 mm Hg comparable to an 80-year-old woman with a long history of hypertension, 1 hour of...
sudden symptom onset, and a blood pressure of 185/120 mm Hg? Obviously not! However, if we look at current therapeutic options, these tend to be rather standardized and fail to take such differences into account. This explains why the findings of many clinical trials are so disappointing, since they enroll so many heterogeneous groups, with uncertain diagnoses, with so many heterogeneous clinical profiles, etiologies, and precipitating factors, and the presumption that drugs with the same mechanism of action will be equally effective in spite of all.

So much is clear today: acute heart failure is an unmet need, which begs evidence-based solutions, as is apparent from the many existing registries that show that all-cause mortality is significantly higher than that of chronic heart failure, ranging from 20% to 30% per year.

These are just some of the reasons why this issue of *Dialogues in Cardiovascular Medicine* is important. We need to set rules for future research. These rules should involve: (i) less heterogeneous populations; (ii) documented diagnoses; (iii) a better understanding of the mechanisms of action of the drugs; (iv) enrolling populations likely to benefit from a certain drug; (v) short time to treatment—the sooner the better; (vi) setting of treatment: should cardiologists continue to be the main protagonists of research in this field?; and (vii) end points.

**Marco Metra** is currently conducting, along with John Teerlink, from the University of San Francisco, US, a promising new biological and therapeutic approach with serelaxin in the RELAX-AHF-2 trial (RELAXin for the Treatment of Patients with Acute Heart Failure 2). **Aldo P. Maggioni** is the ideal person to address the issue of epidemiology, as he has been involved in both the Italian and European registries on heart failure. **Anaïs Caillard** and **Alexandre Mebazaa** look at recent developments in the diagnosis of acute heart failure and **Piotr Ponikowski** and **Ewa A. Jankowska** discuss the contemporary management of the condition.
Acute heart failure

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Cardiology - Department of Medical and Surgical Specialties - Radiological Sciences, and Public Health University and Civil Hospital of Brescia - Brescia - ITALY

Acute heart failure is a major health care problem and is the leading cause of hospitalizations worldwide. Acute heart failure is associated with a high risk of major events with a 10% to 15% mortality rate and a 25% to 35% rehospitalization rate in the 6 months after the initial event. The main cause of acute heart failure is congestion due to fluid overload and/or fluid redistribution to the lungs. The detection of congestion can be challenging if it is based only on clinical signs. Therefore, a comprehensive approach, combining clinical findings, laboratory tests, and imaging techniques, may be needed. Currently available therapies, mainly diuretics, vasodilators, and inotropes, are effective in improving signs and symptoms during hospitalization, but patients still have high mortality and rehospitalization rates in the early postdischarge period. Several new drugs have been tested, but they have mostly produced neutral or negative results on patient outcomes. Identification of novel therapies and therapeutic targets, through a better knowledge of the pathophysiology of acute heart failure, is a major unmet need of current cardiovascular research.

A cute heart failure (HF) is the leading cause of hospitalizations worldwide, and is associated with a high risk of major events with a 10% to 15% mortality rate and a 25% to 35% rehospitalization rate in the 6 months after the initial event. Despite intensive research, no new agent has been shown to be beneficial for acute HF; therefore, treatment and prognosis have remained almost unchanged in the last decades. This article summarizes the state of the art for acute HF, including recent advances in its pathophysiology and treatment.

EPIDEMIOLOGY

HF affects approximately 1% to 2% of adults in developed countries and its prevalence increases with age. In the US, it is estimated that 3% of the adult population (8.5 million people) will have HF by 2030. Generally, one in five individuals will develop HF at some point. Most people with HF experience acute episodes over the course of the disease, which will result in emergency department visits and hospitalizations. In the UK, HF accounts for 5% of all emergency hospital admissions. Between 1992 and 2001, in the US, acute HF accounted for 10.5 million visits or 2.9% of all emergency department visits by patients ≥40 years of age. Almost 75% of these visits resulted in hospitalizations. Health care service data showed that hospitalizations for HF generally account for >1% to 2% of all hospital admissions in many European countries and about 3% in the US.

The increasing prevalence of HF with age means that the elderly population represents a high proportion of patients hospitalized for HF. Data from several European countries showed that patients ≥65 years of age represent >70% of HF admissions and patients ≥85 years of age accounted for 25% of HF admissions.

The average length of hospitalization for HF is between 5 and 10 days, with longer stays reported in European countries than in the US. The average length of the hospital stay has decreased by 1 to 2 days in European countries during the last decade. However, the aver-
age length of the stay tends to increase with the patient’s age, and in the UK, it was 5 and 9 days for 65- and 85-year-old patients, respectively.6,8

Due to aging of the general population and better treatment of acute cardiac conditions, hospitalizations due to HF have increased over the past decade in many European countries. A particularly large increase in admissions has been observed in Germany (40% increase between 2000 and 2007), making HF the most common cause for hospitalization. In the US, Medicare data revealed a general reduction in hospitalizations in the patients with HF from 1998 to 2008, which may reflect improvements in the overall management of HF risk factors, but the persistently high 1-year mortality rates suggest that postdischarge practices for patients with HF have not been as effective.3

Although the overall prevalence of HF is increasing, once patients have a diagnosis of heart failure, their prognosis has slightly improved in the last years, mainly because of better treatments. However, the prognosis of the patients hospitalized for HF remains poor. Despite continuing improvements, mortality remains high with many patients dying in or soon after leaving the hospital, and most die within 5 years. In-hospital mortality rates are age related and range between 4% and 10%.6 Some improvements in short-term and in-hospital mortality rates have been observed in recent years, but these changes are much less than in the overall patients with HF. A Medicare analysis reported a decreased in-hospital mortality rate from 5.1% in 2001 to 4.2% in 2005; however, 3-month and 1-year mortality rates remained constant at approximately 26% and 37%, respectively. Rehospitalization rates after admission for HF have slightly decreased in the last years.9 The majority of readmissions are related to cardiovascular reasons, with worsening HF being the most common single reason.6,10-14 In European studies, reported readmission rates ranged from 24% to 44% at 30 days to 1 year after discharge.6,10 In the US, the reported 30-day readmission rate was about 20% to 25%, with a readmission rate between 60% and 67% being reported during a longer follow-up.

In conclusion, the prevalence of acute HF is increasing due to aging of the general population and better treatment of acute cardiac conditions. The outcomes (deaths and rehospitalizations) have slightly improved...
in the last decades because of a better treatment of HF, but they remain exceedingly poor for the patients with acute HF. This is largely caused by the lack of new effective therapies and the lack of knowledge of the exact mechanisms that cause the high mortality and morbidity of the patients who have an acute decompensation.

**PATHOPHYSIOLOGY**

Acute HF is an extremely heterogeneous condition with respect to its clinical presentation and its prognosis.\(^\text{15,16}\) Congestion is the mechanism causing symptoms in virtually all patients with acute HF. It can be limited to the lungs with pulmonary edema, or it can be systemic with peripheral edema, increased jugular venous pressure (JVP), and hepatic dysfunction.\(^\text{16,17}\) The main mechanisms leading to congestion and HF decompensation are summarized in Figure 1. Cardiac dysfunction is always, by definition, the leading cause of HF; however, precipitant factors, such as infections, tachyarrhythmias, myocardial ischemia, and concomitant therapies (eg, nonsteroidal anti-inflammatory agents), may contribute. The neurohormonal and inflammatory activation is another leading cause of HF, which has been indirectly shown from the beneficial effects of neurohormonal antagonists in HF.\(^\text{18,19}\) Decompensation may then develop abruptly, often with concomitant hypertension and sympathetically driven fluid redistribution from the peripheral venous circulation to the lungs. Generally, these patients are more likely to be elderly females with a normal left ventricular ejection fraction (LVEF) and normal to high blood pressure. In other cases, patients develop fluid accumulation gradually, over days or weeks, with an increase in body weight and whole body fluid overload with peripheral edema. These patients generally have severe left ventricular systolic dysfunction, a tendency to have low blood pressure, and a history of chronic HF and ischemic heart disease.\(^\text{17,20}\)

**CLINICAL ASSESSMENT**

Congestion is the hallmark of acute HF and represents the main reason for hospital admissions.\(^\text{15}\) Although the clinical exam plays a major role, it has little sensitivity or specificity for the diagnosis of acute HF.\(^\text{21}\) Clinical congestion may occur several days after the development of hemodynamic overload and may persist until the time of discharge, despite resolution of the clinical signs. A comprehensive assessment of congestion remains a major challenge for the physician. A summary of the signs and measurements related to congestion is shown in Table 1 (page 8).\(^\text{21}\)

Dyspnea is the leading symptom of acute HF and frequently represents the reason for hospital admission. However, it may be caused by many other diseases, even in the case where the patient suffers from HF; therefore, both noncardiac (eg, anemia or lung disease) and cardiac (eg, atrial fibrillation and acute coronary syndrome) diseases may make the diagnosis difficult. Orthopnea is typically associated with HF and may help in the differential diagnosis when there is a bronchial or pulmonary cause of dyspnea.

Among the signs of acute HF, one of the most important is jugular venous distension (IVD), which reflects the right atrial pressure and indicates that the patient has increased intracardiac pressure. Its assessment may be strongly limited due to the difficulty in obtaining accurate and reproducible JVP measurements in obese subjects. Hepatojugular reflux has the same limitations as the IVD evaluation. Peripheral edema is another sign with a high positive predictive value in patients with acute HF; however, it occurs relatively late and may not be present, especially in patients with rapid onset acute HF. An increase in body weight is generally a clinical sign of fluid retention in patients with
An increase in body weight after hospitalization is a predictor of rehospitalization; however, a reduction in body weight may not necessarily be associated with a better outcome.

Instrumental exams, such as chest x-rays and echocardiography, can help the clinician diagnose acute HF and monitor the response to the treatment. A chest x-ray is performed in the majority of patients at the time of admission; however, its accuracy for the diagnosis of lung congestion is low and patients may have high pulmonary capillary wedge pressure (PCWP) with a normal chest x-ray. Echocardiography is more accurate than chest x-rays, and new portable instruments allow the use of this technique at the patient’s bedside.

Estimation of right atrial pressure can be done using 2-dimensional echocardiography to measure the diameter of the inferior vena cava (IVC) and the dynamic variation of the IVC during deep breathing. Left ventricular filling pressure can be estimated using Doppler echocardiography, whereby, the E/e’ ratio (ie, the relation of peak early transmitral ventricular filling velocity to early diastolic tissue Doppler velocity measured at the level of mitral annulus) provides a reasonable estimate of PCWP. Other standard measurements by Doppler echocardiography, such as the pattern of left ventricular filling by the transmitral flow, assessment of valve structure and function, and cardiac chamber volumes and kinetics, are also useful. Finally, the presence of “lung comets” at lung ultrasound allows an estimate of increased PCWP and pulmonary congestion.

Measuring natriuretic peptides (NPs), namely brain natriuretic peptide (BNP) and the N-terminal pro-BNP (NT-proBNP), is a standard clinical practice for the diagnosis of acute HF. Although several factors may influence the concentration of NPs (eg, age, gender, obesity, renal dysfunction), these biomarkers remain a useful tool for the diagnosis of acute HF, with the notable exception of obese patients, where low plasma BNP or NT-proBNP levels in an untreated patient virtually excludes significant cardiac disease, making further examinations, including an echocardiographic exam, unnecessary. Many conditions (eg, elderly age, concomitant atrial fibrillation, previous cardiac dysfunction, and renal insufficiency) may, on the other hand, increase NP levels even in the absence of an acute decompensation.

Measurement

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Dyspnea at rest</th>
<th>Dyspnea on exertion</th>
<th>Orthopnea</th>
<th>Fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs</td>
<td>Jugular venous pressure</td>
<td>Hepatomegaly</td>
<td>Peripheral edema</td>
<td>Third heart sound</td>
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<td></td>
<td>Hepatogenous reflux</td>
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<td></td>
<td>Increase in body weight</td>
<td>Orthostatic testing</td>
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<td>Valsalva maneuver</td>
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<tr>
<td>Chest x-ray</td>
<td>Lung congestion</td>
<td>Pleural effusion</td>
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<tr>
<td>Echocardiography/portable echocardiography</td>
<td>IVC diameter and dynamics</td>
<td>LV filling pattern and E/e’ ratio</td>
<td>Lung ultrasound</td>
<td></td>
</tr>
<tr>
<td>Laboratory exams</td>
<td>BNP, NT-proBNP, MR proANP, etc</td>
<td></td>
<td></td>
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</tr>
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</table>

Table 1. Methods to assess congestion in patients with acute heart failure.

Abbreviations: BNP, brain natriuretic peptide; E/e’, relation of peak early transmitral ventricular filling velocity to early diastolic tissue Doppler velocity as an echocardiographic estimate of filling pressure; HF, heart failure; IVC, inferior vena cava; LV, left ventricle; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-BNP.

HF. An increase in body weight after hospitalization is a predictor of rehospitalization; however, a reduction in body weight may not necessarily be associated with a better outcome.

PROGNOSIS

As pointed out in the introduction, improvement in the poor prognosis of these patients with exceedingly high rehospitalization and mortality rates is the main unmet need in the treatment of acute HF. Patients hospitalized for HF have a 10% to 15% mortality rate and a 25% to 35% rehospitalization rate within the first 6 months after discharge. Unlike acute coronary syndromes or chronic HF with reduced ejection fraction (HFREF), no new treatment has demonstrated evidence of efficacy in patients hospitalized for HF; therefore, no change in either treatment or prognosis has occurred in the last decades.
talization rate of 31.9%. These rates increased to 17.4% and 43.9%, respectively, in patients hospitalized for acute HF. Similarly, the annual mortality rates for the patients in the IN-HF Outcome study (Italian Network Heart Failure Outcome study) were 5.9% in chronic HF outpatients, and 19.2% and 27.7% in patients hospitalized for either new onset or chronic decompensated acute HF, respectively. Longitudinal prospective clinical trials have shown similar results.

Compared with patients who remain in stable clinical conditions, there is a dramatic increase in mortality risk in patients hospitalized for HF, which is independent from the baseline ejection fraction (EF), with no difference between patients with HREF and patients hospitalized for HF with preserved ejection fraction (HFPEF). This mortality risk decreases exponentially in the months following discharge, but remains 3- to 4-fold higher even 12 to 18 months after the initial hospitalization. Therefore, hospitalizations for HF are also associated with an increased risk of long-term mortality, and this effect on patient prognosis is similar to that described for acute coronary syndromes.

Consequently, improving postdischarge outcomes in HF patients remains a major unmet need in current clinical practice. A better understanding of the mechanisms underlying the poor prognosis of patients hospitalized for HF may also assist in providing better care and improving postdischarge readmission and mortality.

**WHICH OUTCOMES? THE WEAK RELATIONSHIP BETWEEN EARLY REHOSPITALIZATION AND DEATH**

Rehospitalization and mortality are the most important outcomes in acute HF trials. However, they are not necessarily related. Early rehospitalizations, 30 days postdischarge, are an important performance measurement for US hospitals. However, early rehospitalizations are poorly related to postdischarge mortality, and an inverse relationship between 30-day rehospitalizations and mortality has even been shown in the RELAX-AHF trial (RELAXin for treatment of Acute HF), serelaxin was associated with a numerically lower incidence of 60-day mortality and a higher 60-day rehospitalization rate. Whereas, hospitalizations in patients with chronic HF are an index of HF severity and precede death, early postdischarge rehospital-

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**Figure 2. Diagnosis of acute heart failure based on the current European guidelines.**

Abbreviations: BNP, brain natriuretic peptide; HF, heart failure; MR-proANP, mid-regional pro–atrial natriuretic peptide; NP, natriuretic peptide; NT-proBNP, N-terminal pro-BNP.

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**PATIENT SUPPORT AND COMPLIANCE AND THE ROLE OF THE INITIAL HOSPITALIZATION**

Social support plays a major role in a patient’s compliance with treatment. In the OPTIMIZE-HF registry (Organized Program To Initiate lifesaving treatMent In hospitaliZed patiEnts with Heart Failure), noncompliance with the medications and diet were frequent causes of HF hospitalization. This is particularly important in the early postdischarge period, which is characterized by the introduction of new therapies and dosages. Socioeconomic status and level of education
may affect both compliance and availability of treatment. Studies in hypertensive patients have shown a worse prognosis for patients who live in low-income countries. 38

Other factors influencing the early postdischarge rehospitalization rate are related to the initial hospitalization. The length of the initial hospitalization has shown an inverse relationship in some, but not all, studies reporting the rate of rehospitalization. The amount of HF patients in the emergency department also has an inverse relationship with the rate of rehospitalization. These factors may also explain why postdischarge rehospitalization may have different determinants compared with mortality, as they are less likely to affect disease progression.

**COMORBIDITES**

In addition to factors related to the hospitalization itself (Table II), three major mechanisms seem to affect the postdischarge outcomes of HF patients: comorbidities, congestion, and end-organ damage, whereby the latter two are likely related.

Both cardiovascular and noncardiovascular comorbidities play a major role in the postdischarge event rates of patients with HF, and considering that they are less likely, or seem to be less likely, to be influenced by HF treatment, they are often overlooked. Cardiovascular comorbidities, which may precipitate rehospitalizations, include myocardial ischemia, arrhythmias (namely atrial fibrillation), and uncontrolled hypertension. They are all tightly related to the clinical course of HF and may be potentially treated by targeted treatment at the time of the first hospitalization.

The role of noncardiovascular comorbidities is extremely important, especially for rehospitalizations. In an analysis of the causes of rehospitalizations in US hospitals, the proportion of patients readmitted for the same condition was 35.2% after the first hospitalization for HF. Thus, although to a lower extent than with other causes of hospitalization, the majority of readmissions after a first HF hospitalization may not be due to HF itself.

Among the 4133 patients randomized in the EVEREST trial (Efficacy of Vasopressin antagonism in heart failure: outcome Study with Tolvaptan), there were 5239 rehospitalizations and 1080 deaths during a median of 9.9 months. Of all the rehospitalizations, 39.2% were due to noncardiovascular causes, 46.3% to HF, and a minority to stroke, myocardial infarction (MI), arrhythmia, or other cardiovascular causes. Of all deaths, 13.2% were due to noncardiovascular causes, 41.0% to HF, 26.0% to sudden cardiac death (SCD), and the rest to MI or stroke. Similar data were obtained in the RELAX-AHF trial, with 18% of deaths due to noncardiovascular causes, 35% to HF, 23% to SCD, 14% to other cardiovascular causes, and 10% were classified as unknown.

Patients enrolled in controlled trials generally have a lower prevalence of comorbidities compared with those in the “real world.” Therefore, the impact of noncardiovascular causes of hospitalizations and death is larger in observational studies. In the ESC-HF pilot survey, diabetes, chronic kidney disease, and anemia were independently associated with a higher risk of mortality and/or HF hospitalizations. Other noncardiovascular comorbidities that may cause rehospitalizations include infections, chronic kidney dysfunction, and chronic pulmonary disease. Elevated blood glucose levels on admission and iron deficiency have also been shown to be independent prognostic factors in patients hospitalized for HF. In an analysis from the Cardiovascular Health Study on the risk factors for all-cause

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**Table II. Variables that are potentially related to an increased risk of postdischarge events in patients with acute heart failure.**

**Abbreviations:** HF, heart failure.
hospitalizations among elderly patients with a new diagnosis of HF, the only two cardiovascular variables related to outcomes were LVEF and the New York Heart Association (NYHA) class, whereas many noncardiovascular factors (namely, diabetes mellitus, chronic kidney disease, weak grip strength, slow gait speed, and depression) had prognostic value. As pointed out before, many other noncardiovascular factors, related to the patient’s characteristics, may affect early rehospitalizations. These include lack of adherence to treatment, dietary indiscretion, drug and alcohol abuse, family and social support, and access to care.

**Congestion**

Congestion is the main cause of hospitalizations for HF. Most of the hospitalizations for HF are heralded by a gain in body weight. When this does not occur due to prevailing fluid redistribution, other markers of congestion, such as pulmonary artery pressure or BNP levels, are increased. Congestion is also a major cause of postdischarge deaths and rehospitalizations.

Lack of, or slower, resolution of signs and symptoms of congestion during the first days of hospitalization for HF is associated with more adverse outcomes. In its most extreme form, lack of decongestion manifests as in-hospital worsening HF, which is an independent predictor of increased mortality. Clinical signs are poor surrogates of the hemodynamic status; therefore, measuring BNP levels may identify persistent congestion even in the presence of a seeming resolution of clinical signs. Failure of BNP levels to decrease during hospitalization is associated with a poor prognosis. In the RELAX-AHF study, both worsening HF during hospitalization and a failure of NT-proBNP levels to decrease during hospitalization were associated with an increase in 180-day all-cause mortality.

Assessment of signs of congestion (eg, pulmonary rales, JVD, peripheral edema, and weight gain) is also important at the time of or soon after discharge. Similar to that observed during hospitalization, the prognostic assessment can be improved by obtaining other measurements, such as pulmonary artery pressure monitoring, or more simply, by measuring BNP or NT-proBNP levels.

**Organ damage**

There are reasons to hypothesize that congestion is not the only determinant of the increase in cardiovascular events after discharge (Figure 3). First, studies have shown that measurements related to congestion, such as weight gain or poor diuretic response, are associated with rehospitalizations and short-term outcomes, but not long-term mortality. Second, the risk of death after hospitalization for HF remains elevated, even up to 12 to 18 months after the event. This is consistent with persistent organ damage associated with hospitalization, similar to what occurs after acute MI, rather than to a mechanism, such as congestion, which is more likely to cause symptoms. Third, in addition to the levels of BNP, other markers related to organ damage and/or function are independently related to outcomes, especially mortality, after hospitalization for HF. The RELAX-AHF trial was particularly important in this respect because biomarker measurements were taken at baseline and during hospitalization, and unlike other trials, the study drug was not associated with untoward effects on outcomes.

Changes in markers for myocardial damage (serum troponins), renal function (cystatin C), and liver function (transaminases) were shown to have an independent relation with 180-day mortality, which persisted after adjustment for their baseline values.
Multiple mechanisms may cause myocardial damage during acute HF. An increase in plasma troponin levels is very common in patients hospitalized for HF and are independent predictors of subsequent outcomes. In addition to baseline values, the serum troponin levels increased during hospitalization, which is an index of an event related to myocardial necrosis and a powerful predictor of outcomes. The relationship between chronic renal dysfunction and/or worsening renal function and poor outcomes in patients with HF has been well established. However, there are important exceptions, because an increase in serum creatinine may have a neutral, or even a favorable, significance when it occurs after intensive diuretic treatment or after the initiation of renin angiotensin inhibitors. Acute HF may cause kidney dysfunction through multiple mechanisms, and more recently, a role of acute HF in hepatic dysfunction has been shown. The increase in the inferior vena cava pressure, caused by congestion, is transmitted backward causing cholestasis and hepatocyte death. This is shown by an increase in serum transaminases and has an independent prognostic value. Hepatic cytolysis is related to hypoperfusion and/or hypoxogenesis of the liver cells of the centrilobular region, which are distant from the dual circulatory supply of the hepatic artery and portal veins. In the acute care setting, hepatocyte necrosis has been the most frequently described histological finding associated with alterations in liver function tests (LFTs). In a post hoc analysis of the SURVIVE trial (SURVival of Patients with acute heart failure in need of intravenous inotropic support), increases in LFTs, especially alkaline phosphatase (AP), were associated with a higher 6-month mortality rate (34.9% vs 23.5% in patients with normal AP levels, \( P=0.001 \)), while increased transaminases were associated with both 1-month and 6-month mortality (17.6% vs 8.4% and 31.6% vs 22.4%, \( P<0.001 \)).

**TREATMENT**

Treatment of acute HF is still based on diuretics, vasodilators, and inotropes. Currently available therapies for acute HF are summarized in Table III.

### Diuretics

Loop diuretics are the cornerstone of treatment for acute HF because they improve congestion, which relieves the signs and symptoms of acute HF. However, several studies have shown a correlation between higher diuretic doses and a poorer prognosis. Although this may be influenced by the fact that more severe patients receive higher diuretic doses, the relationship between the diuretic dose and mortality has persisted by multivariable analyses after adjustment for baseline variables related to HF severity. High doses of diuretics have also been associated with worsening renal function and the development of diuretic resistance.

### Medication

| Medication | Relief of congestion and fluid overload<br>Associated with poorer outcomes at high doses<br>No evidence of benefit from large, randomized clinical trials<br>Mild improvement in symptoms during clinical trials<br>No effect on outcomes<br>Not associated with clinical improvement and better outcomes in clinical trials and meta-analyses<br>Increased mortality in retrospective analyses of clinical studies<br>High rate of side effects<br>Increased mortality, above all, in patients with ischemic heart disease<br>Side effects<br>Possible untoward effects on outcomes when administered with bolus and high doses to hypotensive patients<br>No differences in outcomes, possible increased rate of side effects compared with diuretic treatment in the large CARRESS trial<br>No differences compared with standard treatment in the largest randomized trial (3CPO) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Diuretics | Vasodilators | Nitrates | Nesiritide* | Inotropes | Dopamine | Dobutamine | PDE-3 inhibitors | Levosimendan | Mechanical support | Ultrafiltration | NIMV |

*Approved for clinical use only in US.

**Abbreviations:** 3C PO, Three interventions in Cardiogenic Pulmonary Oedema; CARRESS, CardioRenal REScue Study in acute decompensated heart failure; HF, heart failure; NIMV, noninvasive mechanical ventilation; PDE-3, phosphodiesterase-3.
Few data are available regarding the proper diuretic strategy to treat patients with acute HF. Recently, the DOSE trial (Diuretic Optimization Strategies Evaluation) evaluated the clinical effects of different diuretic regimens (low vs high dose and bolus vs continuous infusion) in acute HF and observed no differences between treatment regimens. 71

**Vasodilators**

Although nitrates are widely used in clinical practice, there is little evidence of their efficacy. Few studies, based on a small number of patients, have shown greater efficacy of a nitrate-based treatment compared with a treatment based on high doses of furosemide. 76, 77 However, a recent meta-analysis, including 4 studies with a total of 634 subjects hospitalized for acute HF showed no benefit of nitrates compared with alternative treatments on multiple variables, including the need for mechanical ventilation, changes in blood pressure and PCWP, and progression to MI. 78 As with all vasodilators, their use is limited by side effects, namely hypotension and headaches, and they may be associated with the development of tolerance and increased oxidative stress after prolonged administration, unlike other drugs. 79

Nesiritide is a recombinant human BNP with both arterial and venous vasodilating properties. In the VMAC trial (Vasodilation in the Management of Acute Chronic Heart Failure), nesiritide improved hemodynamic parameters with a reduction in PCWP that was larger than with nitrates and was maintained during the infusion. 79 In the subsequent ASCEND-HF study (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure), which enrolled 7141 patients with acute HF, nesiritide treatment was associated only with a mild improvement in dyspnea and no differences in 30-day all-cause mortality or HF readmission rates compared with placebo. 80

**Inotropes**

Dopamine stimulates the dopaminergic D1 and D2 receptors causing splanchnic and renal vasodilation and an increase in renal blood flow when administered at low doses (0.5 to 3 μg/kg per minute). The recent ROSE trial (Renal Optimization Strategies Evaluation), a randomized open study, failed to demonstrate any improvement in renal function and clinical outcomes when comparing low doses of dopamine or nesiritide with placebo. 81 Dobutamine is the prototype of inotropic agents and acts via β-adrenergic receptor stimulation to provide beneficial short-term hemodynamic effects, including increased cardiac output and decreased PCWP in patients with acute HF. Dobutamine administration has been associated with an increased risk of death in several studies and meta-analyses. 82-84 Despite its limitations, it is still widely used in clinical practice in patients with low cardiac output; however, this is also due to the relative lack of alternatives.

Phosphodiesterase-3 (PDE-3) inhibitors block the breakdown of cyclic adenosine monophosphate (cAMP) and have inotropic and vasodilator properties. Unlike dobutamine, acting independently from the β-adrenergic receptors, PDE-3 inhibitors may maintain their effects in patients on β-blocker treatment. 85 In a prospective randomized, double-blind, placebo-controlled trial, milrinone did not improve outcomes and was associated with an increased likelihood of hypotension and arrhythmias. 86

Levosimendan is a calcium sensitizer with an associated vasodilating activity. Compared with placebo, levosimendan administration improved clinical status, reduced BNP levels, and reduced episodes of worsening HF; however, the episodes of hypotension and cardiac arrhythmias were more frequent, with a numerically higher risk of death. 87 Compared with dobutamine, levosimendan did not decrease mortality and/or any secondary events, even with a significantly larger decrease in BNP levels. 88

**Other supports**

Compared with furosemide, ultrafiltration has had beneficial effects on readmission in some studies. 89-91 However, in a recent and larger trial, ultrafiltration was associated with more side effects and an increase in serum creatinine with no difference in outcomes compared with standard care. 92 Similarly, in a prospective, randomized controlled trial, no benefit has been proven with noninvasive mechanical ventilation. 93 Despite this lack of evidence from controlled trials, ultrafiltration continues to be necessary in patients who do not respond to diuretic treatment, and noninvasive mechanical ventilation is largely used to improve symptoms.

**INVESTIGATIONAL DRUGS**

Many novel compounds are under investigation and may provide favorable results in the coming years. A summary of the drugs under investigation in acute HF is provided in Table IV (page 14).
Vasopressin-receptor antagonists

In the EVEREST trial, the vasopressin V2-receptor antagonist Tolvaptan, in addition to standard therapy, improved signs and symptoms of congestion in patients with acute decompenated HF. The drug was well tolerated with no untoward effects on renal function. Unfortunately, it had no effect on outcomes when compared with placebo.94,95 Other vasopressin antagonists are currently being studied.96

Cenderitide (CD-NP)

Cenderitide, also known as CD-NP, is derived from both the C-type natriuretic peptide (CNP) and the dendroaspis natriuretic peptide (DNP). It is a chimeric compound that acts as an agonist of natriuretic peptide receptor B (NPR-B) and a partial agonist of NPR-A. In experimental models, CD-NP exhibited natriuretic and diuretic effects, improved the glomerular filtration rate, and inhibited renin release. It also had fewer hypotensive properties when compared with BNP, and inhibited cardiac fibroblast proliferation.97

Ularitide

Ularitide is the synthetic analogue of urodilatin, a hormone produced by differential processing of pro-atrial natriuretic peptide (pro-ANP) in the cells of the renal distal tubule and collector ducts. It has vasodilating, and natriuretic and diuretic effects. The SIRIUS I and II trials (Safety and efficacy of an Intravenous placebo-controlled Randomized Infusion of Ularitide in a prospective double-blind study in patients with Symptomatic decompenated chronic heart failure) demonstrated an improvement in congestion and hemodynamic parameters, with a decrease in PCWP, an increase in cardiac output, and no worsening renal function with ularitide administration at 15 ng/kg/min.98,99 The TRUE-AHF trial (TRial of Ularitide’s Efficacy and safety in patients with Acute Heart Failure) is a large, phase 3, placebo-controlled, randomized trial, designed to evaluate the effects of a 48-hour infusion of ularitide (15 ng/kg/min) on long-term rehospitalizations and mortality.100

Guanylate cyclase activators

Cinaciguat is a potent nitric oxide (NO)-independent and heme-independent activator of the soluble guanylate cyclase (sGC), which is an enzyme that converts guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). Activation of sGC leads to vasodilation and promotes a long-lasting reduction in blood pressure. The phase 2b COMPOSE program showed favorable hemodynamic responses with a decrease in right atrial pressure and PCWP, an increase in cardiac output, and an increase in episodes of nonfatal hypotension in the active group.101

Serelaxin

Serelaxin is the synthetic analogue of the peptide that modulates cardiovascular and renal responses during pregnancy, leading to vasodilation and an increase in the glomerular filtration rate. In the phase 2b clinical trial Pre-RELAX-AHF (Relaxin for the Treatment of Patients with Acute Heart Failure), a dose-ranging pilot study, 234 patients with an SBP >125 mm Hg were randomized to receive a 48-hr intravenous infusion of serelaxin (at the dose of 10, 30, 100, or 250 μg/kg) or placebo. Serelaxin administration was associated with improved dyspnea, fewer episodes of worsening heart failure, shorter length of hospital stay, and fewer deaths and rehospitalizations. The 30 μg/kg dose of serelaxin showed the greatest efficacy on multiple points.102 In the phase 3 RELAX-AHF trial, 1161 patients were randomized 1:1 to receive a 48-hour infusion of serelaxin (30 μg/kg) or placebo. The trial demonstrated a reduction in dyspnea with serelaxin vs placebo (P=0.007) when assessed by the visual analog scale, but not by the Likert scale (coprimary end points). The secondary end point of cardiovascular deaths or rehospitalizations for HF or renal failure at day 60 was not affected by the study drug because it was associated with a reduction in the number of cardiovascular deaths, 19 with serelaxin and 27 with placebo, and a concomitant increase in rehospitalizations at 60 days, 60 with serelaxin vs 50 with placebo. Other variables, such as signs of congestion at day 2, episodes of worsening HF, and length of the hospital stay, were all favorably affected by serelaxin. Cardiovascular and all-cause mortality at

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Table IV. Investigational therapies for acute heart failure.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Vasopressin-receptor antagonists</th>
<th>CD-NP</th>
<th>Ularitide</th>
<th>Serelaxin</th>
<th>TRV120027</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasodilators</td>
<td></td>
<td>CD-NP</td>
<td>Ularitide</td>
<td>Serelaxin</td>
<td></td>
</tr>
<tr>
<td>Inotropes</td>
<td></td>
<td>Omecamtiv mecarbil</td>
<td>Istaroxime</td>
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</tbody>
</table>
day 180 were both reduced by 37% by serelaxin administration. In order to confirm the survival results of the RELAX-AHF trials, another large, randomized trial (RELAX-AHF-2) has been designed and is currently ongoing. Primary end points of the trial are time to cardiovascular death at day 180 and time to worsening HF at day 5. The inclusion and exclusion criteria are similar to RELAX-AHF and the trial is projected to enroll 6800 patients.

TRV120027

TRV120027 is a novel β-arrestin biased ligand of the angiotensin II type 1 receptor. It inhibits angiotensin II-mediated vasoconstriction while, via β-arrestin coupling, it increases cardiomyocyte contractility. Its administration has been associated with favorable hemodynamic effects in experimental models and a phase 2 trial is ongoing in patients with acute HF.

Cardiac myosin activators

Cardiac myosin activators are a novel class of inotropic drugs that bind to myosin and increase systolic contraction. In a first study, omecamtiv mecarbnil was associated with an increased ejection time, left ventricular ejection fraction, and stroke volume in patients with acute HF. Although promising, these results need to be confirmed by larger trials.

Istaroxime

Istaroxime is an investigational inotrope with lusitropic properties. It associates digoxin-like activity with sarcoplasmic reticulum Ca2+-ATPase (SERCA) stimulation. Istaroxime favors the reuptake of calcium in the sarcoplasmic reticulum during the diastolic phase, thus, improving relaxation and increasing the availability and release of calcium during systole. In the HORIZON-HF trial (Hemodynamic, echocardiographic and neurohormonal effects of Istaroxime, a novel intravenous inotropic and lusitropic agent: a randomized controlled trial in patients hospitalized with Heart Failure), istaroxime improved several hemodynamic parameters, increased blood pressure, and reduced heart rate. In addition, it also improved left ventricular filling pressure, which was evaluated by the E/e’ ratio.

CONCLUSIONS

Acute HF represents a major health care problem with a steady increase in incidence and prevalence. Though the clinical presentation of patients admitted for acute HF can vary widely, the most important clinical manifestation is congestion, which is common to all types of HF and is the cause of the signs and symptoms of this disease. The prognosis of acute HF remains unsatisfactory with high rates of morbidity and mortality, especially in the early postdischarge period. The reasons for worse outcomes are multiple and linked to patient management, patient characteristics, and disease-related factors. The treatment for acute HF represents an important limitation since it still consists of drugs that have not been proven to be effective with randomized, controlled, clinical trials. Unfortunately, many new drugs have failed to achieve satisfactory results in phase 3 clinical trials. Therefore, the identification of novel therapeutic targets, through a better knowledge of the pathophysiology of this disease, is a necessary goal for future research.


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Acute Heart Failure: the Heart Failure Patient’s Journey— the Vulnerable Phase

Expert Answers to Three Key Questions

1. What is the epidemiology of acute heart failure?
   A. P. Maggioni

2. Diagnosis of acute heart failure: what’s new?
   A. Caillard, A. Cescau, A. Mebazaa

3. Management of acute heart failure: what are the options?
   P. Ponikowski, E. A. Jankowska
Acute heart failure (HF) is a major public health problem, and current epidemiological data confirm the severe clinical characteristics of these patients, the high in-hospital mortality rate, and the prolonged length of stay with, as a consequence, a strong socioeconomic impact. Despite the relevant burden of acute HF, therapeutic developments have been scarce in the last decades. For this reason, current guidelines are not including recommendations based on solid evidence from randomized clinical trials. Prospective studies are necessary, should focus on different acute HF phenotypes with measurements of biomarkers to improve understanding and identify new treatment strategies, and be combined with observational research, which are still important to confirm the results of trials in the real-world setting, to collect periodical reports, and to assess the quality of care indicators.

Acute heart failure (HF) is a complex, heterogeneous, clinical syndrome that is often life threatening and requires urgent therapy.\(^{1-3}\) Despite the relevant burden of this clinical condition, therapeutic developments have been scarce in the last couple of decades; consequently, current guidelines cannot include recommendations based on solid evidence from controlled trials.\(^{3,4}\)

For this reason, patients with acute HF remain at substantial risk for recurrent acute exacerbations and death \(^{5-7}\) in the last 10 years, registries and surveys have been conducted in patients with acute HF to improve knowledge of the “real world”,\(^{8-11}\) considering that clinical trials mainly enrolled patients younger, less severely compromised, and generally, with fewer comorbidities than those commonly seen in clinical practice. However, local conditions leading to hospitalization of patients with acute HF, as well as their in-hospital care, may be vastly different in various countries and can change over time.\(^{12}\)

This paper aims to describe the clinical profile and the in-hospital outcomes of patients admitted to the hospital for an acute HF episode. More specifically, it will focus on the following: (i) the demographic, clinical, and biological characteristics of patients with acute HF; (ii) the in-hospital outcome of these patients; and finally (iii) the prognostic predictors of in-hospital all-cause mortality.

**Keywords:** cardiogenic shock; congestion; epidemiology; heart failure; prognosis; pulmonary edema

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(e-mail: maggioni@anmco.it)

**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AF</td>
<td>atrial fibrillation</td>
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<tr>
<td>BNP</td>
<td>brain natriuretic peptide</td>
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<tr>
<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
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<tr>
<td>CRT</td>
<td>cardiac resynchronization therapy</td>
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<tr>
<td>eGFR</td>
<td>estimated glomerular filtration rate</td>
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<tr>
<td>ESC-HF</td>
<td>Heart Failure Registry of the European Society of Cardiology</td>
</tr>
<tr>
<td>HF</td>
<td>heart failure</td>
</tr>
<tr>
<td>ICCU</td>
<td>intensive coronary care unit</td>
</tr>
<tr>
<td>ICD</td>
<td>implantable cardioverter defibrillator</td>
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<tr>
<td>IN-HF Outcome</td>
<td>Italian Network on Heart Failure Outcome</td>
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<tr>
<td>IQR</td>
<td>interquartile range</td>
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<tr>
<td>LVEF</td>
<td>left ventricular ejection fraction</td>
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<tr>
<td>MDRD</td>
<td>Modification of Diet in Renal Disease method</td>
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<tr>
<td>NT-proBNP</td>
<td>N-terminal pro–brain natriuretic peptide</td>
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<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
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</table>
WHAT ARE THE CHARACTERISTICS OF PATIENTS WITH ACUTE HEART FAILURE?

Two recent observational studies have provided reliable answers to this question: the Italian Network on Heart Failure Outcome (IN-HF Outcome) and the Heart Failure Registry of the European Society of Cardiology (ESC-HF).

IN-HF Outcome findings

The IN-HF Outcome registry included 5610 HF patients: 1855 patients were admitted for acute HF and were classified as either new de novo HF in 797 (43.0%) patients or worsening HF in 1058 (57.0%) patients.

According to the ESC Guidelines utilized at the time of data collection, the acute HF profiles at entry were classified as acute pulmonary edema in 27.0% of patients, cardiogenic shock in 2.3%, decompenated HF in 43.9%, right failure in 8.8%, and HF in the context of acute coronary syndrome in 12.9%, hypertension was interpreted as the cause of decompensation in 51% of the patients. This classification does not seem to be really useful to guide diagnostic and therapeutic procedures, consequently more recent ESC guidelines do not mention it anymore. Demographics, clinical history, and clinical data on admission of patients included in the IN-HF Outcome are reported in Table I. The mean age was 72±12 years (range, 21 to 98 years) and 40% were women. Ischemic etiology was significantly higher in the worsening HF group. Comorbidities such as chronic obstructive pulmonary disease (COPD), diabetes, and history of renal failure or atrial fibrilation (AF) were more frequent in worsening HF; in contrast, entry systolic blood pressure (SBP), heart rate, and left ventricular ejection fraction (LVEF) were significantly higher in the de novo HF patients. An implantable cardioverter defibrillator (ICD) and/or cardiac resynchronization therapy (CRT) were present in 13.3% of cases (21.1% in worsening HF compared with 2.9% in de novo HF, P<0.0001). The large majority of patients had signs of peripheral and/or pulmonary congestion.

<table>
<thead>
<tr>
<th>Total (n=1855)</th>
<th>WHF (n=1058)</th>
<th>DN-HF (n=797)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Age (y, mean±SD)</td>
<td>72±11</td>
<td>72±11</td>
<td>72±13</td>
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<tr>
<td>Age ≥70 y (%)</td>
<td>64.4</td>
<td>65.8</td>
<td>62.6</td>
</tr>
<tr>
<td>Females (%)</td>
<td>39.8</td>
<td>37.2</td>
<td>43.2</td>
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<tr>
<td>Ischemic etiology (%)</td>
<td>42.3</td>
<td>45.3</td>
<td>38.4</td>
</tr>
<tr>
<td>BMI (kg/m², mean±SD)</td>
<td>28±5</td>
<td>28±6</td>
<td>28±5</td>
</tr>
<tr>
<td>SBP (mm Hg, mean±SD)</td>
<td>134±33</td>
<td>129±30</td>
<td>141±34</td>
</tr>
<tr>
<td>Heart rate (bpm, median [IQR])</td>
<td>90 [73-110]</td>
<td>82 [70-100]</td>
<td>95 [80-116]</td>
</tr>
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</table>

Clinical history

| Treated hypertension (%) | 57.8 | 55.7 | 60.7 | 0.03 |
| Diabetes mellitus (%) | 40.4 | 43.0 | 36.9 | 0.008 |
| COPD (%) | 30.1 | 32.9 | 26.5 | 0.003 |
| Renal dysfunction (%) | 32.5 | 39.1 | 23.6 | <0.0001 |
| History of atrial fibrillation (%) | 37.7 | 43.3 | 30.4 | <0.0001 |
| Previous stroke (%) | 5.2 | 5.3 | 5.1 | 0.89 |
| Peripheral artery disease (%) | 19.8 | 21.8 | 17.1 | 0.01 |
| ICD in situ (%) | 9.5 | 14.8 | 2.4 | <0.0001 |
| CRT-D in situ (%) | 3.8 | 6.2 | 0.5 | <0.0001 |
| CRT-P in situ (%) | 1.6 | 2.3 | 0.6 | 0.005 |

Signs/symptoms at presentation

| Pulmonary congestion (%) | 78.2 | 75.8 | 81.4 | 0.004 |
| Peripheral congestion (%) | 56.1 | 61.3 | 49.1 | <0.0001 |
| Pulmonary and/or peripheral congestion (%) | 88.4 | 87.8 | 89.1 | 0.40 |
| Peripheral hypoperfusion (%) | 12.0 | 12.4 | 11.4 | 0.53 |
| Cold (%) | 10.8 | 11.1 | 10.4 | 0.66 |
| Somnolent, confused, sedated (%) | 11.5 | 9.6 | 14.1 | 0.003 |
The biohumoral data are reported in Table II. Anemia was observed in 38.7% of the patients. Almost 55% showed an estimated glomerular filtration rate (eGFR). Modification of Diet in Renal Disease (MDRD) method <60 mL/min/1.73 m² and 13.1% of the patients had severe renal dysfunction (eGFR <30 mL/min/1.73 m²), mainly in the worsening HF group. When measured, the median values of N-terminal pro–brain natriuretic peptide (NT-proBNP) or brain natriuretic peptide (BNP) were elevated, and they were similar in the worsening and de novo HF groups. In the de novo group, high-sensitivity C-reactive protein (hsCRP), as a possible index of inflammation, was higher than in the chronic patients. During hospitalization, a large proportion of acute HF subjects underwent echocardiography (90.8%) and standard chest x-ray (75.6%). Coronary angiography was performed in 19.3% of the patients, and more frequently, in the de novo HF group (28.2%), but only in 44.4% of the patients who had coronary acute syndrome at entry. Procedures such as ultrafiltration and noninvasive ventilation were rarely utilized (1.8% and 0.9%, respectively).

An ECG was available for 1779 patients (95.9%), showing AF in one-third of the subjects (31.5%). Left bundle branch block was represented to a greater extent in the worsening HF patients (11.0% vs 6.9%, respectively; P=0.004). ECG was defined as normal in only 2.3% of the entire population. When considering echocardiographic parameters (Table II), worsening HF patients showed a significantly lower LVEF (<30%), and more frequently, severe mitral regurgitation.

**ESC-HF Pilot Survey**

From October 2009 to May 2010, 5118 patients were included in the ESC-HF Pilot Survey.14 Table III (page 28) shows the characteristics of in-hospital acute HF patients that were compared with those of ambulatory patients with chronic HF. In-hospital patients were generally older than patients with chronic HF and more often female. As expected, comorbidities were more frequent in patients admitted for acute HF, whereas the rate of implanted devices was more common in patients with chronic HF. More than half of the patients with acute HF had an ischemic etiology, which was confirmed by coronary angiography in 64% of the cases. At hospital entry, clinical signs of pulmonary congestion were detected in 62% of the cases, peripheral congestion was detected in 65%, and either pulmonary or peripheral congestion was detected in 82% of the cases. Clinical signs of peripheral hypoperfusion were reported in 8.6% of the patients; 10.5% of admitted patients were described as somnolent or confused. From the ECG performed at hospital entry, AF was diagnosed in 35% of the cases and a large QRS (≥120 ms) was detected in 35.5% of the patients. Left ventricular hypertrophy was reported in 16.1% of the cases. An echocardiographic examination was performed in 75% of the patients. The median ejection fraction was 38% (interquartile range [IQR], 27-52); 39.1% of the patients had a preserved
Anemia, defined as a hemoglobin level inferior to 12 g/dL, was detected in 31.4% of the patients; an eGFR <50 and <30 mL/min/1.73 m² was reported in 32.9% and 9.8% of the patients, respectively. NT-proBNP and BNP were only measured at entry in 489 and 204 patients, respectively. The median values were 4007 pg/mL (IQR, 2043-9487) and 870 pg/mL (IQR, 423-1950), documenting the severity of the clinical conditions at hospital admission. Troponin (I or T) was measured in 987 patients with a median value of 0.04 ng/mL (IQR, 0.01-0.29).

Figure 1 shows the stratification of in-hospital patients according to the clinical profiles of the ESC guidelines.16 Decompensated HF (75% of the cases) was most frequent, while pulmonary edema and cardiogenic shock were reported in 13.3% and 2.3% of the patients, respectively. The clinical profile at entry in this registry differs from the data of the IN-HF Outcome13 since patients admitted for decompensated HF were 43.9% vs 75% and those with pulmonary edema were 27.0% vs 13.3%. These differences are largely due to the different definition adopted in the two observational studies.

The percentage of patients admitted with cardiogenic shock and hypertension was similar. It is important to stress that in the ESC-HF Pilot Survey, acute coronary syndrome as a cause of acute HF was not reported separately, while it is largely described as a frequent precipitating factor in ischemic HF patients.17,18

**ESC-HF Long-Term Registry**

From May 2011 to April 2013, 12,440 of the 12,785 patients screened for the ESC-HF Long-Term Registry15 gave their informed consent, and therefore, are part of this analysis. Of these patients, 5039 (40.5%) were patients hospitalized for acute HF, while 7401 (59.5%) were ambulatory patients with chronic HF. Table IV reports the characteristics of the patients included in the registry. Patients included in the ESC-HF Long-Term Registry present with baseline characteristics, clinical history, and comorbidities that largely overlap with the observations of other European or US registries.9,12,19-23 Patients hospitalized for acute HF show a more severe clinical profile, as well as a higher rate of comorbidities than patients with chronic HF. The substantial similarity of this population of patients with respect to previous reports allows the findings of this registry to be considered largely applicable in other clinical contexts.
WHAT ARE THE COMES OF PATIENTS WITH ACUTE HEART FAILURE?

To answer this question, the IN-HF Outcome and the ESC-HF Pilot Survey will be considered again.

IN-HF Outcome findings

In this registry, the median time spent in the hospital was 10 days (IQR, 7-15), 51.9% of patients (46.5% and 59.1% of those with worsening and de novo HF, respectively, \(P<0.0001\)), were admitted to the intensive coronary care unit (ICCU) for a median time of 4 days (IQR, 3-7). Despite (or as consequence of) a greater number of admissions to the ICU, de novo HF patients spent less time in the hospital (9 days [IQR, 6-14] vs 10 days [IQR, 7-16], \(P=0.0011\)). The all-cause in-hospital death rate was 6.4% (almost 90% cardiac), and was not different in worsening or de novo HF groups (6.0 vs 6.9, respectively; \(P=0.41\)). As reported in Figure 2, patients with cardiogenic shock had the highest mortality rate (23.8%), followed by those with acute coronary syndrome (13.0%), while patients with hypertensive HF had the lowest death rate (3.2%). Further, a significant trend between all-cause

### Table IV. ESC-HF Long-Term Registry: baseline characteristics.

| Abbreviations: BMI, body mass index; bpm, beats per minute; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; EF, ejection fraction; ESC-HF Long-Term Registry, European Society of Cardiology Heart Failure Long-Term Registry; HF, heart failure; HHF, hospitalized heart failure; HR, heart rate; ICD, implantable cardioverter defibrillator; IQR, interquartile range; NYHA, New York Heart Association; PAD, peripheral artery disease; PM, pacemaker; SBP, systolic blood pressure; TIA, transient ischemic attack. From reference 15: Maggioni et al. Eur J Heart Fail. 2013;15(10):1173-1184. © 2013, The Authors. |
|---|---|---|
| **H HF** | **CHF** | **P value** |
| Age (y, median [IQR]) | 71 [61-79] | 66 [57-75] | <0.0001 |
| Age ≥75 y (%) | 39.5 | 26.0 | <0.0001 |
| Females (%) | 37.3 | 28.8 | <0.0001 |
| BMI (kg/m², median [IQR]) | 28 [25-31] | 28 [25-31] | 0.0002 |
| SBP (mm Hg, median [IQR]) | 130 [110-150] | 120 [110-136] | <0.0001 |
| SBP ≥110 mm Hg (%) | 27 | 31 | <0.0001 |
| HR (bpm, median [IQR]) | 88 [73-104] | 70 [62-80] | <0.0001 |
| HR ≥70 bpm (%) | 83.0 | 55.6 | <0.0001 |
| EF (%) (median [IQR]) | 38 [30-51] | 35 [28-45] | <0.0001 |

#### Figure 2. IN-HF Outcome Registry: all-cause in-hospital mortality according to the acute HF profile at entry.

in-hospital mortality and age, SBP, and eGFR was observed (Figure 3A-3C). No significant differences in mortality were observed between worsening and de novo HF groups.

Patients admitted with HF and acute coronary syndrome were not mentioned in previous registries, but their risk of in-hospital death appears severe (13.0%), confirming the need for a more intensive assessment and treatment.

**ESC-HF Pilot Survey**

Figure 4 shows the overall rates of in-hospital mortality that were stratified by clinical profiles in the ESC-HF Pilot Survey. Overall, 71 patients died during the hospital stay; the highest mortality rate being observed in patients with cardiogenic shock and the lowest in those with hypertensive HF. The cause of death was cardiovascular in 90.1% of the cases.

To summarize the findings presented so far, Table V reports some selected clinical characteristics of the IN-HF Outcome and the ESC-HF Pilot Survey patients compared with subjects enrolled in the other four main US and European registries.

The in-hospital all-cause mortality rate of the IN-HF Outcome registry was slightly lower than reported in a previous Italian survey (6.4% vs 7.3%), but still higher when compared with the ESC-HF Pilot Survey and the US registries (4%) reported in Table V. However, considering the differences in length of stay and the rapid discharge home in US hospitals, some deaths may have occurred several days later; this is supported by the analysis of the 3-month mortality, which seems similar in European and US registries (about 13%). In-hospital mortality was higher in patients with...
### Patient characteristics in previous AHF registries and IN-HF Outcome.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>ADHERE5 (n=105,388)</th>
<th>EHFS II (n=3,580)</th>
<th>Italian S (n=2,807)</th>
<th>OPTIMIZE-HF6 (n=48,612)</th>
<th>ESC-HF Pilot14 (n=1892)</th>
<th>IN-HF Outcome13 (n=18,559)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y, mean±SD)</strong></td>
<td>72.4±14</td>
<td>69.9±12</td>
<td>73±11</td>
<td>73±14</td>
<td>70±13</td>
<td>72±12</td>
</tr>
<tr>
<td><strong>Females (%)</strong></td>
<td>52</td>
<td>38.7</td>
<td>39.5</td>
<td>51.6</td>
<td>37.3</td>
<td>39.8</td>
</tr>
<tr>
<td><strong>Ischemic etiology (%)</strong></td>
<td>65</td>
<td>53.6</td>
<td>46</td>
<td>45.7</td>
<td>50.7</td>
<td>42.3</td>
</tr>
</tbody>
</table>

### Medical history

| **Hypertension (%)** | 73 | 62.5 | 65.6 | 70.9 | 61.8 | 57.8 |
| **Diabetes Mellitus (%)** | 44 | 32.8 | 38.4 | 41.5 | 35.1 | 40.4 |
| **Renal insufficiency (%)** | 30 | 16.8 | 24.7 | 19.6 | 26 | 32.5 |
| **Atrial fibrillation (%)** | 31 | 38.7 | 28.4 | 30.8 | 43.7 | 37.7 |

### Baseline medications

| **ACE inhibitors/ARBs (%)** | 53 | 63 | 72.5 | 51.3 | 60 | 59 |
| **Diuretics (%)** | 70 | 71 | 81 | 65.7 | 68 | 64 |
| **Β-blockers (%)** | 48 | 43 | 32 | 53.1 | 62 | 41 |
| **Digoxin (%)** | 28 | 27 | NA | 23.4 | 21 | 16 |

| **de novo HF (%)** | 35 | 37.1 | 44 | 11.7 | NA | 43 |

### Cardiogenic shock at entry (%)

| **Hypertensive AHF at entry (%)** | NA | 3.9 | 7.7 | NA | 2.3 | 2.3 |

### Physical and laboratory findings

| **SBP (mm Hg, mean±SD)** | 144±33 | 135±NA | 141±37 | 143±33 | 133±29 | 134±33 |
| **HR (bpm, mean±SD)** | NA | 95±NA | 97±22 | 87±21 | 88±24 | 93±26 |
| **Creatinine (mg/mL, mean±SD)** | 1.8±1.6 | NA | 1.7±1 | 1.8±1.6 | NA | 1.5±1.0 |
| **LVEF (%, mean±SD)** | 34.4±16 | 38.0±15 | 37±13 | 39±18 | 38±NA | 38±14 |
| **HFPEF (% LVEF cut-off)** | 46 (>40%) | 34.3 (>45%) | 34 (>40%) | 51.2 (>40%) | 36.1 (>40%) | 35.0 (>40%) |

### IV therapy and intervention

| **Diuretic (%)** | NA | 84.4 | 95.3 | NA | 84.6 | 99.0 |
| **Vasodilators (%)** | 21 | 38.7 | 51.3 | 14.3 | 18.5 | 29.9 |
| **Inotropes (%)** | 15 | 29.8 | 24.6 | 10.9 | 10.5 | 19.4 |

### Outcome

| **ICU admission (%)** | 18.7 | 50 | 69 | NA | 48 | 51.9 |
| **Length of stay (days)** | 4.3 | 9.0 | 9.0 | 5.7 | NA | 10 |
| **In-hospital mortality (%)** | 4.0 | 9.0 | 7.3 | 3.8 | 3.8 | 6.4 |

---

**Table V. Patient characteristics in previous AHF registries and in IN-HF Outcome.**

**Abbreviations:** ACE inhibitor, angiotensin-converting enzyme inhibitor; ADHERE, Acute Decompensated Heart Failure National Registry; AHF, acute heart failure; ARB, angiotensin receptor blocker; bpm, beats per minute; EHFS II, EuroHeart Failure Survey II; ESC-HF pilot, European Society of Cardiology Heart Failure Pilot study; HPPEF, heart failure with preserved ejection fraction; HR, heart rate; ICU, intensive care unit; IN-HF Outcome registry, Italian Network on Heart Failure Outcome; Italian S, Italian survey on acute heart failure; HR, heart rate; LVEF, left ventricular ejection fraction; OPTIMIZE-HF, Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure; SBP, systolic blood pressure; SD, standard deviation.

Cardiogenic shock, as previously described, but it was lower than reported in the EuroHeart Failure Survey II.11

**IS IT POSSIBLE TO IDENTIFY THE PROGNOSTIC PREDICTORS OF OUTCOME?**

Independent predictors of in-hospital all-cause mortality of the IN-HF Outcome registry are reported in Table VI. Even on multivariable analysis, shock remained the strongest independent predictor of in-hospital all-cause mortality. Older age, low SBP, hyponatremia, and increased creatinine levels were the other important markers of a poor in-hospital outcome. A strong correlation was also noted between neurological symptoms and outcome, probably because this is related to a more severe low output state.

As far as the ESC-HF Pilot Survey is concerned, owing to the nature of this pilot experience, only a relatively small number of deaths were observed. For this reason, an adjusted model to identify the independent predictors of death was not performed. However, when the three major well-known independent determinants of death (SBP, older age, and reduced renal function) were considered, 93% of deaths could be explained by the presence of at least one of these factors (Figure 5). These three variables (age, SBP, and renal function) emerged in all databases as being independently associated with patients’ outcomes.

**CONCLUSIONS**

Acute HF is a major public health problem, and the data reported here confirm a high in-hospital mortality rate and a prolonged length of stay, with a strong socioeconomic impact. In the last decades, there has been a small improvement in this field, and probably the most important issue to consider is that acute HF is not a single entity with a unique cause, but a spectrum of complex multisystem pathologies. The treatments are still largely empiric, and for many years, have remained practically unchanged; the recommendations of guidelines are largely based on observational data or expert consensus.

Undoubtedly, it is time to dedicate more resources to this field; prospective studies focused on a careful description of acute HF phenotypes, with measurements of multiple biomarkers during and after hospitalization to improve understanding and identify new treatment strategies, are needed. The role of observational research remains important to confirm the results of the trials in the real world, to collect periodical reports, and to assess the quality of care indicators.
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Diagnosis of acute heart failure: what’s new?

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The diagnosis of acute heart failure (HF) could be difficult at the early stages due to nonspecific symptoms. Reducing the delay between admission and the onset of appropriate treatment implies that the diagnosis should be performed as rapidly as possible in patients presenting at the hospital with suspected acute HF. Natriuretic peptides, such as the brain natriuretic peptide (BNP) and N-terminal pro–brain natriuretic peptide (NT-proBNP), are the gold standard biomarkers for the diagnosis and prognosis of patients with acute HF. Hence, they should be measured immediately at admission of patients with acute dyspnea. The main reason for hospitalization for worsening HF is related to the symptoms of congestion, rather than low cardiac output. Therefore, we will describe how to assess lung, kidney, and liver congestion.

**Keywords:** cardiohepatic syndrome; cardio-renal syndrome; congestion; natriuretic peptide; ultrasound lung comets

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Acute heart failure (HF) is defined as a rapid onset or a deterioration of the signs and symptoms of HF with an abnormal cardiac structure or function, which requires urgent treatment. It may present as a first event of HF (also called de novo acute HF) or as worsening HF in unstable chronic HF patients. This definition, already described repeatedly in various European Society of Cardiology (ESC) guidelines, is still valid. \(^1\) Recently, two critical features have emerged in the management of acute HF. First, increasing evidence shows that the delay between admission and onset of an appropriate treatment in acute HF markedly affects the short- and mid-term outcomes of the patients. Second, organ congestion is the main pathophysiological mechanism of acute HF, and most importantly, of the organ dysfunction associated with acute HF.

- Reducing the delay between hospital admission and administration of the appropriate treatment in acute HF

Several clinical trials showed that the earlier the tested drug was administered, the better. The early administration of the tested drug in the emergency department (ED) was associated with shorter hospital stays and lower in-hospital mortality rates. \(^2,3\) The ADHERE registry (Acute Decompensated HEart failure national registry) data indicated that the administration of nesiritide to acute HF patients was instituted a median of 7.8 hours after presentation at the ED (25th percentile, 3.3; 75th percentile, 28.1). \(^4\) Post hoc analysis of ADHERE showed that early initiation of nesiritide, while the patient is in the ED (median of 2.8 hours vs 15.5 hours after presentation at the ED), was associated with improved clinical outcomes. \(^5\) Efforts have, therefore, been made in acute HF trials to start the administration of the studied drugs as early as possible. In the RELAX-AHF trial (RELAXin in Acute Heart Failure), serelaxin (the recombinant human relaxin-2) was administered 7.8 hours (SD, 4.6 hours) after hospital admission. \(^6\) In the PRONTO trial (study of blood PReSSure cONTrol in acute heart failure—a pilot study), which assessed the effects of clevidipine in acute HF patients with high blood pressure, the tested drugs were administered 3.2 hours after hospital admission. \(^7\) The ongoing TRUE-AHF trial (TRial of Ularitide’s Efficacy and safety in patients with Acute Heart Failure) was designed to administer ularitide as early as possible after the initial presentation at the ED. \(^8\)

It is important to note that despite efforts to administer the tested drugs as soon as possible after admission, this delay is still greater in trials than in “real-life” settings as depicted by surveys. Indeed, in the ALARM-HF registry (Acute HF Global Survey of Standard Treatment), the delay between ED admission and
onset of IV diuretics and/or vasodilators was, on average, 30 minutes after admission.\textsuperscript{9}

Reducing the delay between admission and the onset of appropriate treatment implies that the diagnosis of acute HF should be performed as rapidly as possible after admission. However, physicians in charge of acute HF are not necessarily experts in this field. To overcome this problem, plasma biomarkers, especially plasma natriuretic peptides (NPs), are highly beneficial, particularly when clinical signs are nonspecific. In the future, the early measurement of NPs, to ascertain the diagnosis of acute HF, should be applied to any dyspneic patient to facilitate triage.

• The diagnosis of acute HF is mostly an evaluation of the degree of organ congestion

Organ congestion appears to be a main pathophysiological mechanism of acute HF. Available studies suggest that the main reason for hospitalization for worsening HF is related to the symptoms of congestion rather than low cardiac output.\textsuperscript{10} To date, there are no clear methods to quantify the degree of organ congestion at admission. Below, we will describe how to assess lung, kidney, and liver congestion.

**CLINICAL ASSESSMENT OF CONGESTION: SYMPTOMS AND SIGNS**

At early stages of the disease, the diagnosis of acute HF, based on physical examination, is not easy due to nonspecific symptoms, particularly in elderly and obese patients.\textsuperscript{11,12} Most of the symptoms of acute HF are linked with organ congestion. Dyspnea is a frequent symptom, but it is nonspecific, particularly in patients with pulmonary disease. Moreover, the severity of these symptoms correlates poorly with ventricular function, while severity does correlate with survival.\textsuperscript{13} Hence, it is critical to evaluate the signs of organ congestion. An acute change in body weight is a reasonable marker of fluid balance. Signs of congestion and findings related to pulmonary rales, third heart sound (S\textsubscript{3}), jugular venous distention, right hypochondrial pain (liver distension), and abdominal swelling (ascites) are known to have diagnostic importance in acute HF patients. Other symptoms, however, are more specific to acute HF, such as orthopnea or paroxysmal nocturnal dyspnea, but they are less frequent, and therefore, have little predictive value.\textsuperscript{13} Signs resulting from sodium and water retention, such as peripheral edema, resolve quickly with diuretic therapy. Elevated jugular venous pressure and S\textsubscript{3} are associated with adverse outcomes.\textsuperscript{14} A systematic approach to grading congestion would be helpful in initiating therapy, as well as following the response to therapy, although no score for congestion is used in practice yet.\textsuperscript{15}

As described above, there are signs and symptoms that help when suspecting acute HF. Clinical examination should also rapidly assess the existence of signs of gravity, such as respiratory distress or hypoperfusion. Therefore, the initial evaluation must determine signs of respiratory distress based on respiratory rate, intolerance to the supine position,
effort of breathing, and degree of hypoxia; and signs of hemodynamic instability, such as cold extremities, narrow pulse pressure, hypotension, and delayed capillary refill.

Regarding cardiac function, ECG is recommended at admission to determine the appropriate treatment (eg, β-blocker, anticoagulant) and etiology of acute HF, such as arrhythmia or acute coronary syndrome. In the AHEAD registry (Acute HEArt failure Database), patients admitted for acute HF showed that the important ECG parameters to look for were ST-segment elevation, presence of atrial fibrillation, and a prolonged QRS, which independently predicts a poor outcome.16

**BIOMARKERS FOR DIAGNOSIS OF ACUTE HF**

**Natriuretic peptides for an early diagnosis of acute HF**

Nonspecific symptoms make the diagnosis of acute HF difficult. NPs are great indicators to rule out (low circulating levels) or rule in (high circulating levels) acute HF. Increased filling pressures induce myocardial stretch and overproduction of NPs, which are released by the cardiomyocytes into the plasma. NPs include atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and N-terminal pro–brain natriuretic peptide (NT-proBNP).

Measurement of NPs (BNP, NT-proBNP, and midregional proANP [MR-proANP]) added significant independent predictive power to other clinical variables in models predicting which patients had congestive acute HF.17 Therefore, NPs are equally effective for diagnosis.17,18 BNP and NT-proBNP concentrations are known to increase with age, female sex, and renal dysfunction.19 To analyze the optimal cut points for NPs, Hill et al tested, in a recent meta-analysis, the performance characteristics of BNP and NT-proBNP for the diagnosis of acute HF in the ED.20 For BNP, the study confirmed that 100 pg/mL appears to be a consensus cut point with 83.4% sensitivity.21 However, as body mass index influences the selection of cut points for BNP in diagnosing acute HF, a lower cut point (BNP ≥54 pg/mL) should be used in severely obese patients to preserve sensitivity.21 The negative predictive value of BNP at levels lower than 50 pg/mL was 96%. However, no clear consensus has emerged for NT-proBNP. The age-adjusted cut points of 450 pg/mL, 900 pg/mL, and 1800 pg/mL for persons <50 years, 50 to 75 years, and >75 years, respectively, appear promising and merit greater scrutiny and validation. Post hoc analysis of the ADHERE registry showed that a delay in obtaining BNP levels was associated with a prolonged time to treatment.22 The delayed measurement of BNP levels and the delay in treatment for acute HF were associated with a modest increase in the in-hospital mortality rates, independently of other prognostic variables. Altogether, these results prompt for early and systematic measurements of NPs at admission of dyspneic patients.

Of note, NPs may also improve risk prediction regarding short- and long-term prognosis.23-25 and when measured at admission or discharge, NPs may help risk stratify acute HF patients.

**Novel biomarkers for the diagnosis of acute HF: specificity for cardiac remodeling**

In patients with a history of chronic heart failure, pneumonia, heart ischemia, and/or renal failure, NPs lack specificity. This is mostly seen when circulating plasma levels are in the “gray zone.”26 The “gray zone” for BNP27 is defined as being in the 100 to 400 pg/mL range, and for NT-proBNP,28 300 to 450 pg/mL, 300 to 900 pg/mL, and 300 to 1800 pg/mL in patients <50 years, 50 to 75 years, and ≥75 years, respectively.

Efforts have been made by our group and others to identify new biomarkers for the diagnosis of acute HF to discriminate acute from nonacute HF in patients with NP values in the “gray zone.” Using an unbiased proteomics discovery strategy, we discovered Quiescin Q6 (OSOX1), which exhibited a particular value for the clinical evaluation of dyspnea. Increased plasma OXSO1 is specific for acute HF and seems to be unaffected by many of the factors that weaken the value of BNP. The combination of OXSO1 with BNP provided the best sensitivity and specificity for the diagnosis of acute HF among patients with acute dyspnea.29

Assessing the severity of acute HF is often needed at admission in order to triage the patient between the ED, cardiac care unit, and intensive care unit (ICU). Severity is mostly assessed by clinical signs of respiratory distress or hemodynamic instability. We suggest using circulating cardiovascular biomarkers to complement clinical signs. Indeed, high levels of NPs are associated with poor outcomes.18 Markers of cardiac remodeling (eg, ST2 or galectin-3) have also been shown to be associated with poor prognosis in patients with acute HF30,31 and rehospitalization.32 Lassus et al showed that biomarkers, such as midregional proadrenomedullin (MR-proADM) and ST2, provided an incremental value for risk stratification of 30-day and 1-year mortality in acute HF33.
Thus, early evaluation of the prognosis and risk stratification could lead to optimized early management in acute HF. A multibiomarker strategy may provide superior risk stratification compared with single biomarker measurements, particularly when biomarkers from distinct pathophysiological pathways are combined.34

LABORATORY TESTS AT PRESENTATION FOR THE ASSESSMENT OF ORGAN CONGESTION

Assessment of cardiorenal syndrome

In acute HF patients, elevated right atrial pressure may contribute, in part, to the cardiorenal syndrome through reduction in the perfusion gradient across the kidney.35 A high prevalence of elevated intra-abdominal pressure was shown in patients with acute HF despite the absence of overt abdominal symptoms, and was associated with a greater impairment in renal function. Acute renal dysfunction occurs as a consequence of de novo kidney injury or the acute deterioration of existing chronic kidney disease. Compared with de novo kidney injury, the acute deterioration of existing chronic kidney disease was associated with a higher risk of in-hospital mortality, longer hospital stay, and failure to recover a normal renal function.36 Serum creatinine is broadly used to derive the glomerular filtration rate (GFR) as an indicator of kidney function. However, in ICU patients, GFR is frequently overestimated due to edema and volume overload, which are typical in acute HF.37

Several new biomarkers of the early stage of kidney damage, such as serum cystatin C (sCyC) and neutrophil gelatinase-associated lipocalin (NGAL), have been identified to diagnosis acute kidney injury (AKI) early, before a significant increase in serum creatinine levels, and these biomarkers can lead to earlier specific therapies to repair or prevent the progression of kidney dysfunction.38 sCyC appeared to be a good biomarker of AKI with a sensitivity and specificity of 86% and 82%, respectively.39 In acute HF patients, sCyC was a stronger predictor of the length of hospitalization or death.40,41 Plasma NGAL levels appear to be a sensible tool for determining the worsening of renal function during hospitalization with a sensitivity and specificity of 92% and 71%, respectively, and prognosis.42,43 However, these results are still debated.44 Indeed, variations between studies could be attributed to different definitions of AKI, as the definition of a disease is critical in the field of biomarker research. Nevertheless, these biomarkers cannot be recommended yet because of a lack of evidence for cost effectiveness. Creatinine is still the preferred biomarker for serial monitoring of renal function in individuals.45

Assessment of cardiohepatic syndrome

Abnormal liver function tests (LFTs) in HF patients can originate from different pathophysiological mechanisms: lack of hepatic perfusion and congestion. A decrease in cardiac output, which leads to impaired organ perfusion, is associated with acute centrilobular hepatocellular damage, hepatic ischemia, then necrosis, and is mainly related to aspartate transaminase (AST), alanine transaminase (ALT), and bilirubin. In contrast, elevated right atrial filling pressures with increased central venous pressure and systemic congestion lead to congestive hepatic injury and are related to all LFTs, especially γ-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), and bilirubin.46 The prevalence of abnormal LFTs in acute HF patients was between 46% and 76% at admission.48-50 Abnormal ALP levels were associated with marked signs of systemic congestion, elevated right-side filling pressure, and an increased 180-day mortality.48 Abnormal transaminase profiles were associated with clinical signs of hypoperfusion and greater 30-day and 180-day mortality compared with normal transaminase profiles.48 LFT abnormalities were strongly associated with acute HF severity (left ventricular ejection fraction [LVEF] and New York Heart Association [NYHA] functional class) and clinical manifestation.49 Other studies showed the prognostic value of measuring total bilirubin levels.51 Low albumin levels have also been found to have prognostic value in patients with acute decompensated HF.52

After elimination of potential biliary tract obstruction and/or primary hepatic pathology, abnormal LFTs are indicative of cardiohepatic syndromes, and provide information on the mechanism of liver injury and heart dysfunction: liver congestion in case of elevated ALPs and/or liver ischemia in case of elevated transaminases. More studies are necessary to evaluate the kinetics of the abnormal LFTs, but abnormal LFTs could be considered as a guide to manage acute HF patients. Alterations in liver functioning also lead to changes in liver drug metabolism and reductions in the synthesis of plasma protein with an impact on drug effects (like anticoagulant agents).

Other laboratory assessments for the etiology of acute HF

Water homeostasis and renal and liver functions have to be evaluated at admission to assess the level of
hydration and organ congestion, and to adjust drug dosage with respect to kidney function. Measurement of thyroid-stimulating hormone eliminates thyroid disease as a potential diagnosis, which can mimic or aggravate acute HF. D-dimer is indicated in patients with suspicion of acute pulmonary embolism. Arterial blood gases are not routinely indicated and should be restricted in case of persistent respiratory distress, despite initial therapy to detect respiratory or metabolic acidosis.

The majority of patients with acute HF have elevated troponin levels and an acute coronary syndrome cannot be excluded. FINN-AKVA (FINNish Acute Heart Failure study) is a prospective, multicentric study of 364 acute HF patients. 51.1% had troponin I, cardiac form (cTnI) and 29.7% troponin T, cardiac form (cTnT) levels above the cutoff value. Both cTnI and cTnT elevations were associated with an increase in mortality that was proportional to the elevation, but they were not independent risk markers. Patients with elevated levels of troponin had lower systolic blood pressure, lower LVEF, and higher in-hospital mortality.

In addition, Mebazaa et al showed, in a large cohort of patients with acute HF, that blood glucose concentration at presentation was a powerful prognostic marker for 30-day mortality, independently of a diagnosis of diabetes mellitus or other clinical variables.

Chest radiography is one of the most widely used modalities for the evaluation of acute HF. A chest radiograph is positive when congestion has already been established. Wang et al showed that the presence of edema and cardiomegaly was the most useful radiographic finding for the diagnosis of heart failure. However, in the ADHERE registry, approximately one acute HF patient out of five had no signs of congestion on chest x-ray. Chest x-rays are also useful to rule out alternative causes of dyspnea (like pneumonia).

Early thoracic ultrasounds can provide important information by enabling direct visualization of accumulated lung water. This phenomenon is due to the different echogenicity between air-filled and water-rich structures. In the lung, which is normally air-filled and nonchogenous, the accumulation of water generates linear artifacts.

Figure 1. Echocardiographic diagnostic flowchart for patients with suspected heart failure in the ED.

 Abbreviations: ED, emergency department; HF, heart failure.

**ROLE OF ECHOCOGRAPHY IN ACUTE HF**

Early thoracic ultrasounds can provide important information to assess lung edema by trained emergency departments.

Figure 2. Lung ultrasound to visualize accumulation of lung water.

Panel A. Normal lung ultrasound: the chest wall is visualized as multiple layers of echogenicity representing muscles and fascia. The visceral and parietal pleura (arrows) appear as echogenic bright lines that glide during respiration. Reverberation echo artifacts beneath the pleural lines imply an underlying air-filled lung. Panel B. Lung ultrasound showing ultrasound lung comets (arrows), also known as multiple B-lines, from a case of cardiogenic pulmonary edema.
known as B-lines or ultrasound lung comets (ULCs) (Figure 2, page 39). An early pulmonary ultrasound should be systematically performed on the entire chest including: (i) anterior, lateral, and posterior faces; (ii) right and left sides of the chest; and (iii) from the second to the fifth intercostal space. ULCs are a sign of distress of the alveolar-capillary membrane even if the mechanism producing ULCs is debated.57 In patients admitted for dyspnea and/or chest pain syndrome, ULCs were showed to be a more powerful predictor than other echocardiographic variables of recognized prognostic value, including ejection fraction and wall motion score index.58,59 A correlation between ULCs and NT-proBNP values has been shown.60

Early thoracic ultrasounds are simple (with a learning curve of <10 examinations) and quick to perform (requiring <3 minutes). ULCs have high accuracy in predicting the cardiac origin of dyspnea.60

Immediate echocardiography is not needed during the initial evaluation in most cases except when hemodynamic instability is present

In the case of hemodynamic instability, at least “fast echocardiography” should be performed as early as possible to look for tamponade, severe left ventricular (LV) and right ventricular (RV) dysfunction, and severe valvular involvement.61 Most often, echocardiography is only needed after stabilization of acute HF, especially if the disease is de novo.62 It must be performed by experienced and competent personnel. Echocardiography examinations must be complete63 and should include 2D/3D echocardiography, continuous- and pulsed-wave Doppler, color-flow Doppler, and tissue Doppler imaging. The examination provides information on both structure (eg, volume, mass, geometry of chambers) and cardiac function (eg, LV diastolic and systolic function and wall motion, valvular function,65 RV function, pulmonary artery pressure, and pericardium).

Left ventricular systolic dysfunction
LVEF is usually used to assess LV systolic function. The recommended echographic method for its measurement is the apical biplane method of discs64 (modified Simpson’s rule); a contrast agent should be used when image quality is suboptimal (eg, difficulty identifying the endocardial border). Teicholtz and visual assessment are not recommended. It is important to note that LVEF is not an index of contractility because it varies with volume, preload/afterload, heart rate, and valvular function, and LVEF is not the same

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**Figure 3. Diagnostic flowchart for patients with suspected heart failure showing natriuretic peptide measurements as a first approach.**

Respiratory distress signs include tachypnea, intolerance of the supine position, effort of breathing, and degree of hypoxia. Hemodynamic instability signs include cool extremities, narrow pulse pressure, hypotension, and delayed capillary refill.

**Abbreviations:** BNP, brain natriuretic peptide; CCU, cardiac care unit; HF, heart failure; ICU, intensive care unit; NT-proBNP, N-terminal pro–brain natriuretic peptide.
as stroke volume. LVEF can be normal, while stroke volume is reduced, in patients with significant mitral regurgitation or in patients with HF with preserved ejection fraction and concentric hypertrophy; stroke volume can be maintained by LV dilatation in patients with HF with reduced ejection fraction.

**Left ventricular diastolic dysfunction**
Assessment of LV diastolic function is important, considering that more than half of patients admitted with acute HF have preserved LVEF. As there is no single echographic parameter that is specific or reproducible enough, its evaluation must include a combination of Doppler parameters, including Doppler on mitral inflow (morphology, ratio of peak E to peak A velocities [E/A] at rest and after a Valsalva maneuver), and on pulmonary vein inflow (A pulm-A mitral duration); tissue Doppler imaging (measurement of e', the early diastolic myocardial velocity at mitral annulus: a normal value [ie, >8 cm/s septal or >10 cm/s lateral] is really uncommon in HF). Structural parameters should not be overlooked: LV hypertrophy and left auricular dilatation, which is known as the “glycated hemoglobin A1c (HbA1c) of chronic HF.” Of note, values for assessment of diastolic function depend on age, heart rate, arrhythmia, and body size.

**ALGORITHM FOR THE DIAGNOSIS OF HEART FAILURE**
Reducing the delay between admission and the onset of appropriate treatment implies that the diagnosis of acute HF should be performed as rapidly as possible by the physicians in charge, who may not be specialized in the field of HF (Figure 3). NPs should be measured immediately, concomitant with the clinical examination. The optimal exclusion cutoff point is 300 pg/mL for NT-proBNP and 100 pg/mL for BNP. The following laboratory assessments should be performed at admission from the blood of all acute HF patients: troponin, creatinine, electrolytes, LFTs, glucose, and a complete blood count. Chest x-ray and ECG are also recommended at admission. Patients with a high pretest likelihood of HF, such as those with a history of myocardial infarction, and symptom severity may be referred directly for echocardiography (Figure 1).

**CONCLUSION**
Early appropriate treatment implies that the diagnosis of acute HF should be performed as rapidly as possible in patients presenting at the hospital with suspected acute HF. NPs, such as BNP and NT-proBNP, are the gold standard biomarkers for the diagnosis and prognosis of patients with acute HF, and should be measured immediately at admission of patients suffering from acute dyspnea.

In addition, organ congestion appears to be the main pathophysiological mechanism of acute HF. Available studies suggest that the main reason for hospitalization for worsening HF is related to the symptoms of congestion, rather than low cardiac output. Assessment of lung, kidney, and liver congestion at admission will allow for an early and appropriate management of the patient.

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Management of acute heart failure: what are the options?

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Heart failure hospitalization should always be considered as a life-threatening condition that requires intensive and immediate medical attention. This paper presents the currently recommended strategy on the management of patients with acute heart failure. Due to the complexity of the acute heart failure syndrome, a uniform and simple diagnostic and therapeutic algorithm does not exist. The management depends on initial presentation, clinical severity, and dynamic changes in the clinical status particularly during the initial phase. This paper also discusses evidence on novel promising therapies in acute heart failure.

THE LANDSCAPE AT THE BEGINNING OF THE 21ST CENTURY

Hospital admission due to either deterioration of an existing chronic heart failure (HF) or de novo rapid development of HF signs and symptoms should be considered as a life-threatening condition that requires intensive and immediate medical attention.1-3 In recent years, a lot of effort was spent developing optimal treatment strategies for these patients in order to stabilize them and improve clinical conditions, relieve symptoms during admission, reduce the risk of in-hospital complications, and improve outcomes after hospital discharge.1-4 However, these tasks remain very complex and challenging in clinical practice due to: (i) unacceptably high percentages of patients remaining symptomatic during the initial phase of treatment; (ii) worsening clinical courses in 20% to 30% of patients, complicating hospital stays; and (iii) in-hospital mortality ranging from 4% to 10%.2,5,6 The longer-term outcomes are even more alarming: the recent data from the EURObservational Research Programme, which was conducted in 12 European countries in 2009-2010, show that the 1-year all-cause mortality rate was 17% and the 1-year hospitalization rate reached 44% among patients admitted to the hospital for acute HF.7 This mainly reflects the complexity of acute HF syndromes, which in fact:
• May be triggered by different, often nonidentified causes,
• Comprise a wide spectrum of clinical conditions with heterogeneous, and often uncertain, pathophysiology, as well as different risks for subsequent complications, and
• Its natural course can be affected by cardiovascular and noncardiovascular comorbidities, with subsequent consequences on the therapeutic strategies.

Selected Abbreviations and Acronyms

<table>
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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
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<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
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<tr>
<td>HF</td>
<td>heart failure</td>
</tr>
<tr>
<td>RELAX-AHF</td>
<td>RELAXin in Acute Heart Failure [trial]</td>
</tr>
<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
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<tr>
<td>TRUE-AHF</td>
<td>Trial of Ulartidie’s Efficacy and safety in patients with Acute Heart Failure</td>
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Therefore, a uniform and simple diagnostic and therapeutic algorithm does not exist, and the management depends on the initial presentation, clinical severity, and dynamic character of the clinical conditions, particularly in the initial phase. A plethora of controlled clinical trials in acute HF settings has been designed and executed, often however, addressing different clinical endpoints ranging from symptomatic relief during initial hours to the long-term effects on morbidity and mortality. Sadly, most, if not all, of these novel therapeutic approaches demonstrated a dissociation between early symptomatic improvement, clinical stabilization, and favorable long-term outcomes. Thus, the statement made by Felker et al. that “broadly speaking, the pharmacological armamentarium for AHFS [acute HF syndromes]—loop diuretics, vasodilators, and inotropes—is largely unchanged from the 1970s” still holds true.

**CURRENT ESC GUIDELINE RECOMMENDATIONS VS EVERYDAY CLINICAL PRACTICE**

Current European Society of Cardiology (ESC) guidelines on HF management recommend prompt initiation of the management for all patients with acute HF. Diagnostic work-up and treatment need to be initiated in parallel immediately after hospital admission. A clear description of the initial clinical profile is fundamental for decision making at the initial stage in order to identify and effectively treat life-threatening conditions (Figure 1). The following questions should be addressed on admission (Figure 1):

- Is the ventilation and peripheral oxygenation adequate? If not, oxygen should be administered; in more severe cases, there may be a need for endotracheal intubation and invasive ventilation.

![Figure 1. Initial phase in ED/ICU/CCU profiling and strategic care.](image)

**Suspected acute HF**

- Ventilation/systemic oxygenation inadequate
  - Oxygen
  - NIV
  - ETT and invasive ventilation

- Life-threatening arrhythmia/bradycardia
  - Electrical cardioversion
  - Pacing

- Blood pressure <85 mm Hg or shock
  - Inotrope/vasopressor
  - Mechanical circulatory support (eg, IABP)

- Acute coronary syndrome
  - Coronary reperfusion
  - Antithrombotic therapy

- Acute mechanical cause/severe valvular disease
  - Echocardiography
  - Surgical percutaneous intervention

### Abbreviations:
- CCU, coronary care unit; ECG, electrocardiogram; ED, emergency department; ETT, endotracheal tube; HF, heart failure; IABP, intra-aortic balloon pump; ICU, intensive care unit; NIV, noninvasive ventilation; NP, natriuretic peptide; PaO₂, partial pressure of oxygen; SpO₂, saturation of peripheral oxygen.

Are life-threatening tachyarrhythmias or bradyarrhythmias present? If so, there is a need to consider either electrical cardioversion or temporary pacing.

Is the patient in cardiogenic shock, with symptomatic hypotension? If so, pharmacological support with inotropic agents and vasopressors should be considered, and in select cases, mechanical circulatory support may be needed.

Is the acute coronary syndrome the underlying cause of acute HF? If so, urgent transfer to a catheterization laboratory with subsequent coronary reperfusion should be considered.

Is there any acute mechanical cause as a potential factor leading to hemodynamic deterioration? After echocardiographic verification in selected cases, either surgical or percutaneous intervention may be considered.

From the very beginning, monitoring the patient's vital functions is essential and many patients should be managed in an intensive or coronary care unit at least during the first hours. At the initial phase (which typically starts in the emergency department), treatment needs to target the following goals (Figure 2):

- Fast and effective relief of symptoms (most typically dyspnea).
- Restoration of peripheral oxygenation.
- Improvement in organ perfusion and hemodynamics.
- Limitation of end-organ damage.
- Prevention of thromboembolic complications.
- Minimizing length of stay in the intensive/coronary care unit.

Acute HF comprises a wide spectrum of clinical conditions ranging from gradual worsening of chronic conditions (ie, peripheral edema and dyspnea) to life-threatening pulmonary edema or cardiogenic shock. This explains why profiling patients on admission helps to select optimal management strategies for different clinical presentations. In practice, profiling based on the evaluation of congestion and perfusion is often used, which allows differentiation into four different “hemodynamic” profiles (Figure 3, page 48):

- “Warm and wet”—most commonly present with a patient demonstrating congestion and still adequate peripheral perfusion.
- “Cold and wet”—with congestion and low peripheral perfusion.
- “Cold and dry”—with impaired perfusion and lack of congestion.
- “Warm and dry.”

The profiles are associated with the outcome, but more importantly, also have certain therapeutic implications, which are discussed below.

Congestion due to volume overload is the cardinal abnormality in acute HF. Signs and symptoms of fluid overload are present in the majority of patients hospitalized due to HF decompensation, whereas only a minority demonstrate significantly
impaired peripheral perfusion and hypotension.\textsuperscript{10-12} This explains why a “warm and wet” profile is most commonly observed, and effective relief of congestion is considered a key therapeutic target in these clinical settings. However, a “warm and wet” profile may comprise two entirely different groups\textsuperscript{13,15}.

- Patients with rather slow deterioration, gradual (over several days) fluid accumulation with concomitant weight gain and peripheral edema, and typically a history of chronic HF with impaired left ventricular ejection fraction.
- Patients with rapid deterioration, no (or minimal) weight gain, evidence of pulmonary congestion (sometimes in the form of pulmonary edema), where fluid redistribution to the lungs is essential for symptoms.

In the former group, the treatment strategy should be based on appropriate use of diuretics to remove fluid overload, whereas in the latter, a combination of vasodilators and diuretics should be considered\textsuperscript{13-15}.

Diuretics are most commonly used in patients hospitalized with acute HF. The recent ESC Heart Failure Long-Term Registry, which recruited $>12,000$ acute HF patients from 21 ESC countries, regardless of systolic blood pressure (SBP), showed that more than 80% of patients received a diuretic.\textsuperscript{16} The ESC guidelines recommend an intravenous loop diuretic to improve breathlessness and relieve congestion (class I, level of evidence B).\textsuperscript{9} Symptoms, urine output, renal function, and electrolytes should be carefully monitored to avoid hypovolemia, renal dysfunction, and hypokalemia.\textsuperscript{9} Still, the optimal dose and route of administration (bolus or continuous infusion) is uncertain, but in general, high doses may be deleterious. In patients admitted with pulmonary edema/congestion who are already taking a diuretic, the initial dose should be 2.5 times the existing oral dose. In patients who develop insufficient response or diuretic resistance, a switch from furosemide to bumetanide, torasemide, or a combination of a loop and thiazide diuretic (eg, bendroflumethiazide) may be considered after carefully checking fluid intake. In selected cases, isolated venovenous ultrafiltration can be used to remove fluid overload. A recent study evaluated ultrafiltration in decompensated HF patients with cardiorenal syndrome and demonstrated that the use of a standard, stepped pharmacologic-therapy algorithm was superior to a strategy of ultrafiltration for the preservation of renal function, with a similar effect on weight loss with the two approaches.\textsuperscript{17} Importantly, use of ultrafiltration was associated with a higher rate of adverse events.

For patients with clinical evidence of volume redistribution, combining a vasodilator (nitrates, nitroprusside, and nesiritide) with a diuretic to relieve congestion and symptoms is a logical therapeutic option.\textsuperscript{15} Vasodilators, given as an intravenous infusion, are recommended for the treatment of patients with pulmonary edema/congestion, as well as preserved SBP (ie, above 110 mm Hg). They affect hemodynamics by reducing preload and pulmonary capillary wedge pressure, reducing afterload, and potentially increasing cardiac output. In clinical practice, nitrates are most commonly used, however, with their use, tolerance may develop relatively quickly, and more importantly, they may cause significant hypotension once administered without careful blood pressure monitoring. This should be avoided because excessive hypotension is associated with deleterious consequences and higher mortality in patients hospitalized with acute HF.\textsuperscript{18} Additionally, nitrates should be used with caution in patients with concomitant, clinically relevant aortic or mitral stenosis. In a recent study, nesiritide (a recombinant human brain natriuretic peptide, which mainly acts as a vasodilator), given in the early phase of acute HF, demonstrated only modest symptomatic improvement compared with standard therapy and it had no effect on patient outcomes.\textsuperscript{19}
Some patients appear with low blood pressure, signs and symptoms of peripheral hypoperfusion, and low cardiac output (“cold and wet” profile). This clinical situation is relatively rare (in less than 10% of all acute HF patients), but is always associated with a poor outcome either during the hospital stay or after discharge. In such cases, there is an indication to initiate inotropic support in order to stabilize patients’ compromised hemodynamics and improve peripheral perfusion.9 In clinical practice, therapy usually starts with dobutamine infusion (acting through stimulation of β1-adrenergic receptors to produce dose-dependent positive inotropic and chronotropic effects), but phosphodiesterase-3 inhibitors (milrinone and enoximone) and levosimendan (calcium sensitizer that improves cardiac contractility by binding to troponin C in cardiomyocytes) are also available. The ESC guidelines recommend levosimendan or phosphodiesterase-3 inhibitors to reverse the effects of β-blockade, if the β-blockade contributes to hypotension and hypoperfusion.9 Inotropic drugs are inevitably associated with clinically relevant adverse effects, such as myocardial ischemia (due to increased myocardial oxygen consumption and coronary hypoperfusion) and life-threatening tachyarrhythmias; therefore, continuous ECG monitoring is recommended. Dopamine is another, often-used inotropic agent, which acts via stimulation of β-adrenergic receptors when used in moderate doses. However, larger doses (>5 µg/kg/min) also demonstrated an α-adrenergic receptor stimulatory effect with subsequent vasoconstriction. For a long time, it was believed that dopamine, at low doses (<3 µg/kg/min), stimulated dopaminergic receptors and had diuretic and natriuretic effects. Recently, this view has been challenged because in a double-blind, placebo-controlled study neither low-dose nesiritide nor low-dose dopamine was shown to significantly enhance decongestion or improve renal function when added to standard therapy in patients with acute HF and renal dysfunction.20

If combining inotropic support with a diuretic does not lead to clinical stabilization, adding a vasopressor (most often dopamine or norepinephrine) may be considered. Again, ECG monitoring is recommended as these agents can cause myocardial ischemia and arrhythmias. In such cases of cardiogenic shock, intra-arterial blood pressure monitoring should also be considered, and in some centers, pulmonary artery catheterization is applied in order to optimally treat severely compromised hemodynamics, which becomes the main goal of therapy. Another option, which may be considered, is temporary mechanical support with either an intra-aortic balloon pump or ventricular assist device, particularly when there are potentially reversible causes of acute deterioration (either as a bridge to the final decision or treatment response).

The algorithm for management of acute pulmonary edema/congestion proposed by the recent ESC Guidelines is based on the blood pressure evaluation with subsequent therapeutic decisions (Figure 4, page 50). Briefly, after an initial administration of an intravenous loop diuretic (either as a bolus or an infusion), oxygen for patients with hypoxemia (saturation of peripheral oxygen [SpO2] <90%), and opiates for patients with severe anxiety or distress, further modification of pharmacological intervention should be based on the SBP level. In normotensive patients (SBP >110 mm Hg), adding a vasodilator is often a reasonable choice to intensify treatment effects. In patients with borderline blood pressure and no signs of hypoperfusion (SBP between 85 and 110 mm Hg), continuation of the diuretic therapy with adequate dose modification depending on the clinical response, is recommended. In patients with hypotension (SBP <85 mm Hg), particularly with peripheral hypoperfusion, inotropic support should always be considered. Patients should be kept under careful observation for assessment of clinical status. In addition to symptom evaluation, regular monitoring of SBP, saturation (with pulse oximetry), and urine output is mandatory. In the case of stabilization and further improvement, transfer to a normal ward is typically planned (Figure 4). However, 15% to 30% of patients, despite initial therapy, either do not improve or deteriorate after initial stabilization, and therapy needs to be intensified and individualized with several other available options (Figure 4). Only recently, such cases of HF worsening21 have generated interest as they represent a meaningful change in clinical status leading to intensification/change of therapy and are associated with markers of end-organ damage and unfavorable short- and long-term prognoses.22

After stabilization and improvement, patients are transferred to a normal ward where the next phases of in-hospital management are initiated: the intermediate phase and predischarge/long-term planning phase.9,23–24 These periods should always be viewed as an integral part of the management of acute HF patients with relevant implications in the long-term outcomes due to patients’ receptivity to accept health care recommendations and the opportunity to implement long-term intervention strategies. Treatment goals should include (Figure 2):
Management of acute heart failure - Ponikowski and Jankowska

Figure 4. Algorithm for management of acute pulmonary edema/congestion.

- **Cold skin, low pulse volume, poor urine output, confusion, myocardial ischemia.** For example, start an iv infusion of dobutamine 2.5 μg/kg/min, doubling the dose every 15 min according to response or tolerability (dose titration is usually limited by excessive tachycardia, arrhythmias, or ischemia). A dose >20 μg/kg/min is rarely needed. Even dobutamine may have mild vasodilator activity as a result of β₂-adrenergic receptor stimulation. *Patient should be kept under regular observation (symptoms, heart rate/rhythm, SpO₂, SBP, urine output) until stabilized and recovered.*

- **An increase in oxygen saturation (if hypoxemic), and usually, reduction in the heart and respiratory rate (which should occur in 1 to 2 hours).**

- **Peripheral blood flow may also increase as indicated by a reduction in skin vasoconstriction, increase in skin temperature, and improvement in skin color.** There may also be a decrease in lung crackles.

- **An intra-aortic balloon pump or other mechanical circulatory support should be considered in patients without contraindications.** Usually start with 40% to 60% oxygen, titrating to an SpO₂ >90%; caution is required in patients at risk of CO₂ retention.

- **CPAP or NIPPV should be considered in patients without contraindications.** Consider endotracheal intubation and invasive ventilation in the event of worsening hypoxemia, failing respiratory effort, increasing confusion, etc.

- **Double the dose of the loop diuretic, up to the equivalent of furosemide 500 mg (doses of 250 mg and above should be given by infusion over 4 hours).**

- **If there is no response to doubling the diuretic dose despite adequate left ventricular filling pressure (either inferred or measured directly), start iv infusion of dopamine 2.5 μg/kg/min. Higher doses are not recommended to enhance diuresis.**

- **An adequate response includes reduction in dyspnea and adequate diuresis (>100 mL/h urine production in the first 2 hours), accompanied by an increase in oxygen saturation (if hypoxemic), and usually, reduction in the heart and respiratory rate (which should occur in 1 to 2 hours).**

- **Peripheral blood flow may also increase as indicated by a reduction in skin vasoconstriction, increase in skin temperature, and improvement in skin color.** There may also be a decrease in lung crackles.

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Abbreviations: CPAP, continuous positive airway pressure; ETT, endotracheal tube; HF, heart failure; iv, intravenous; NIPPV, noninvasive positive pressure ventilation; NIV, noninvasive ventilation; NTG, nitroglycerine; SBP, systolic blood pressure; SpO₂, saturation of peripheral oxygen.

• Maintaining patient stabilization with optimized treatment.
• Initiation, up titration, and optimization of disease-modifying pharmacological therapy. For patients with HF with reduced ejection fraction, it comprises: angiotensin-converting enzyme inhibitor (ACE inhibitor) or angiotensin receptor blocker if ACE inhibitors are not tolerated, β-blocker, and mineralocorticoid receptor antagonist; optimally, combination therapy with these agents needs to be initiated in the hospital (clinical conditions, blood pressure, and renal function permitting) and optimized during the postdischarge period. For patients with elevated heart rate, ESC Guidelines recommend using ivabradine.
• Identification of the underlying etiology and relevant comorbidities.
• Consideration of device therapy for appropriate patients.
• Identification of high-risk patients and evaluation of fluid status. Proper risk stratification is fundamental for identifying patients at a particularly high risk for postdischarge complications. Recently, Metra et al\textsuperscript{26} proposed that the predischARGE assessment should be based on a comprehensive, but simple, evaluation of the following elements: (i) clinical variables (e.g., signs of congestion, blood pressure, heart rate, and orthostatic test); (ii) ECG (e.g., duration of the QRS complex, presence of atrial fibrillation); and (iii) selected laboratory examinations (e.g., natriuretic peptides, renal function, electrolytes, anemia, iron deficiency, and myocardial viability). Among them, elevated heart rate seems to be of particular interest as growing evidence suggests that, in patients discharged after HF decompensation, elevated heart rate predicts an unfavorable outcome, similar to chronic HF.\textsuperscript{26,27}
• Enrollment in a disease management program, education, and initiation of appropriate lifestyle adjustments.
• There is no doubt that guidelines must be implemented in everyday practice. However, for a more efficient use, remember that identification of the consecutive phases of in-hospital treatment with different goals (Figure 2) and clinical profiling of patients is mandatory.

**OUTLOOK FOR THE FUTURE**

Unsatisfactory results in a vast majority of recently completed large clinical trials in patients with acute HF\textsuperscript{2,4} raise the question of whether we need to consider changing the traditional paradigm of treatment. It would be difficult, or virtually impossible, to list all the changes necessary to achieve better outcomes with novel therapies. We believe the following elements are important for proper planning of future studies:

• Targeted approach directed toward well-characterized patient populations, which can be based on clinical profiling, biomarker profiling, etc. Previously, we applied the rule “one size fits all,” frequently trying to test different pathophysiological processes. It is prudent to expect to change this rule to “different therapies for different profiles” when testing new therapies in very broad, unselected patient populations.

• It is broadly accepted that, in addition to clinically meaningful symptomatic improvement, new drugs/interventions need to improve the neurohumoral and proinflammatory profile. Recently, the concept of “end-organ” protection has been raised\textsuperscript{22} and this should be prospectively tested.

• The recommendation of an appropriate timing for each therapy is obvious, but in the context of acute HF, early initiation of comprehensive diagnostic and therapeutic management and early administration of tested therapies needs to be considered in the future. In contrast to ischemia-related clinical syndromes where the rule “the earlier, the better” is widely accepted and applied, for many patients admitted with acute HF, particularly those with chronic and gradually deteriorating HF, there is no belief that early initiation of therapies may be beneficial. In fact, “the earlier, the better” approach may lead to prevention of end-organ damage, early clinical stabilization, and the chance of introducing disease-modifying therapies.

At this stage, these are only suggestions, among many others, that need to be verified with clinical studies. In the recent RELAX-AHF trial (RELAXin in Acute Heart Failure), some of these elements were applied in the study design\textsuperscript{28,29}: serelaxin, a drug with potential multiple beneficial properties for acute HF patents,\textsuperscript{30} was given in the patient population with an SBP >125 mm Hg (reflecting a certain clinical profile) and the therapy was initiated early (ie, within the first 16 hours of hospital admission). In comparison with placebo, 48-hour serelaxin infusion resulted in clinical stabilization, symptomatic improvement, and significant reduction in all-cause and cardiovascular mortality during the 180-day follow-up.\textsuperscript{29} Currently, there are two ongoing, large, phase 3 clinical trials investigating whether short-term intervention in the early phase of acute HF (RELAX-AHF-2 [with serelaxin] and TRUE-AHF [TRial of Ulartide’s Efficacy and safety in patients with Acute Heart Failure, with ulartide]) would impact long-term mortality. The results of these studies may change the statement made by Felker et al, presented earlier in the article, that “broadly speaking, the pharmacological armamentarium for AHFS
[acute HF syndromes]. — loop diuretics, vasodilators, and inotropes—is largely unchanged from the 1970s. " The results will be available in a few years, and in the meantime, we need to use this limited armamentarium optimally by applying the guidelines in everyday clinical practice.

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This essay describes the scientific advances and human factors that led to the discovery and clinical development of the cardiovascular drug sildenafil (Viagra). The series of events leading to this successful outcome provides another example of the recurring theme in the “Trails of Discovery” that success depends on a combination of a dedicated drug hunter, concomitant advances in basic science, and our old friend serendipity.

**DRUG HUNTER**

In this example, the committed drug hunter was Dr David Brown, an experienced medicinal chemist who, as a young scientist, worked at ICI Pharmaceuticals between 1974 and 1985. In 1985, he left ICI Pharmaceuticals in order to manage a group of medicinal chemists at Pfizer UK. At the beginning of his career at Pfizer UK, his remit included oversight of the medicinal chemistry of two related programs, one of which eventually led to the invention of Viagra. The original biological target was modification of the function of atrial natriuretic peptide (ANP), a recently discovered cardiac peptide. The objective for Pfizer’s two cardiovascular projects in 1985 was to either inhibit the breakdown of endogenous ANP (36 amino acids) or enhance its effect on second messenger systems, both of which should reduce elevated blood pressure. While there was already a range of antihypertensive agents on the market, the mode of action of ANP was such that vasodilation could be achieved without affecting electrolyte homeostasis.

The priority target, at that time, was to find inhibitors of the endopeptidase enzyme 24.11, which would prevent the breakdown of ANP, and thus, prolong vasodilation and natriuretic actions. Two specific inhibitors were identified—UK79300 and UK69578. Both compounds were taken forward for clinical evaluation in hypertension and heart failure. Despite a promising profile in both experimental models and clinical trials, the overall effects on blood pressure reduction and heart failure were not sufficient to warrant further development.

The other medicinal chemistry approach in Dr David Brown’s department, involved the potentiation of ANP-mediated vasodilation by inhibiting the breakdown of cyclic guanosine monophosphate (cGMP), an ANP intracellular messenger, targeting the cGMP phosphodiesterase enzyme (PDE). Inhibition of this enzyme would boost the second messenger system and promote cGMP-mediated vasodilation. This approach eventually led to the discovery of sildenafil (Viagra).

**NITRIC OXIDE AND cGMP**

In order to fully explain the rationale for inhibiting the PDE enzyme, it is perhaps helpful to summarize the biological mechanisms involved in relaxation of vascular tissues. An impressive array of scientific research on the mechanisms involved in the control of vascular smooth muscle tone identified nitric oxide (NO) as a key, locally released mediator causing arterial relaxation. In the early 1980s, there were intense scientific advances and human factors that led to the discovery and clinical development of the cardiovascular drug sildenafil (Viagra). The series of events leading to this successful outcome provides another example of the recurring theme in the “Trails of Discovery” that success depends on a combination of a dedicated drug hunter, concomitant advances in basic science, and our old friend serendipity.

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Dr David Brown’s small team of three chemists (headed by Dr Nicholas Terrett), one biologist (Dr Peter Ellis), and one biochemist (Dr Paul Barclay) set about finding orally active specific inhibitors of PDE that would boost levels of cGMP. A major hurdle was determining which of the six known forms of PDE was the appropriate target. The enzymes had yet to be isolated and fully characterized, leaving uncertainty about whether PDE-1, PDE-2, or PDE-5 was the required target. Without the necessary biochemical knowledge, a pharmacological approach was the only way forward—seeking selective inhibitors that might clarify the target.

Initially, the chemical synthesis strategy was based on the known PDE-5 inhibitor zaprinast, which had been developed by the May & Baker pharmaceutical company to treat allergies. This compound was shown to inhibit PDE-5 activity, but it was weakly potent and relatively nonselective for PDE-5 inhibition. However, the compound did provide a useful chemical template to enable chemistry modeling studies. Progress was slow over the following 2 to 3 years. The project had weak support from management and was underresourced compared with the parallel project seeking endopeptidase inhibitors, which at the time, ironically, was seen as the ‘crown jewel’ project at the Pfizer UK site.

Then, a very fortunate external scientific breakthrough occurred with the invention of fast protein liquid chromatography (FPLC). The team recognized that this new technology had the potential to provide purer fractions of the PDE isoforms. A collaboration was forged with Prof Miles Houslay (University of Glasgow) who had the equipment required. This proved to be a critical juncture, as access to a purified form of PDE-5 provided a major boost to the program. Until this time, the team had been using crude whole tissue assays, such as relaxation using aortic rings. With purified fractions of each PDE in hand, the slow progress made in the initial years of the project was replaced by very rapid progress. Importantly, several of the lead series pursued during 1985-1988 had poor PDE inhibitory activity, but one chemical series demonstrated potent and selective inhibition of PDE-5, which proved to have good activity in vivo.

The chemical synthesis program became focused on analogs within the pyrazolopyrimidinone series that eventually formed the patent containing sildenafil (Figure 1). In addition to the in vitro enzyme assays, the pharmacological effects of analogs were assessed for inhibition of platelet aggregation and alterations in blood pressure in cannulated spontaneously hypertensive rats, which were given the compound parenterally and orally. Thus, the initial chemical targets included angina pectoris, hypertension, congestive heart failure, and possibly stroke, based on the above preclinical profiles.

**Figure 2. Biochemical mechanisms that relax vascular smooth muscle.**

Abbreviations: cGMP, cyclic guanosine monophosphate; NO, nitric oxide; NOS, nitric oxide synthase; PDE, phosphodiesterase enzyme; VSM, vascular smooth muscle.

Dr Robert F. Furchgott, Dr Louis Ignarro, and Dr Ferid Murad “for their discoveries concerning nitric oxide as a signaling molecule in the cardiovascular system.”
The cardiovascular profile observed prompted a change in the therapeutic target to angina pectoris, instead of hypertension, because the hemodynamic profile observed in rodents resembled that of the classic drug glyceryl trinitrate. The latter is administered sublingually, whereas the new target would be an orally active agent that could reduce or prevent anginal pain. The company considered that a drug, which was essentially a "long-acting oral nitrate," would be an attractive commercial proposition.

Thus, in 1989, after the team had optimized potency, selectivity, and pharmacokinetic properties, an orally active specific inhibitor of PDE-5 was found and given the codename UK92480. Preclinical studies showed that the drug could cause arterial dilation and inhibit thrombus formation, and therefore, potentially be effective for treating angina pectoris. UK92480 relaxed isolated strips of arteries from two species of animal, and in vivo, it caused coronary artery dilation in dogs, rabbits, and spontaneously hypertensive rats. In 1990, after 5 years of work, coming so close to failure, UK92480 was selected to undergo clinical trials in order to assess its efficacy on angina. The named inventors on the patent (containing sildenafil/Viagra) were Mr Andrew Bell, Dr David Brown, and Dr Nicholas Terrett. Dr David Brown continued to lead the team over the next 3 years through the early clinical phase, until the discovery of UK92480's effectiveness in male erectile dysfunction.

**SERENDIPITY**

At the same time, additional phase 1 volunteer studies were being carried out in order to fully characterize the profile of UK92480. One trial, in Wales, involved keeping the subjects in the clinical research unit overnight. Each volunteer had to complete a form describing specific and potentially unwanted effects. The questioning included an "open" question: have you noticed anything else following treatment with this compound? Several of the (male) volunteers commented that they had developed sustained penile erections during the night.

This unanticipated clinical target could so easily have been ignored. As it happened, there had been recent publications indicating that NO could dilate blood vessels and the lead Pfizer biologist Dr Peter Ellis was aware of this information. In addition, a few years earlier, Dr David Brown had jointly proposed, with colleague Dr Michael Wiley, to work on the male impotence indication, based on finding a centrally acting aphrodisiac-based mechanism of action. In preparing the research proposal, they had become familiar with the details of the prevalence and management of the indication. Dr David Brown and Dr Michael Wiley had also been involved in an initial market analysis, and as such, were aware of the unmet medical need and potential for very large sales of an effective oral treatment. That research proposal was rejected by senior management. However, Dr David Brown’s prior knowledge of the field was a significant factor in influencing his clinical colleagues and senior management to take the first observation of erections in human volunteer trials seriously.

As a consequence, the clinical research project was not suspended, but was changed in direction after an intensive discussion between Dr David Brown and clinical head Dr David McGibney.
Initially, Dr David McGibney was reluctant to fund any more trials on a molecule out of favor with senior management, but upon hearing the scientific evidence, he made the critical decision to fund a study in patients with erectile dysfunction. A proof-of-concept study was designed by Dr Mike Allen and Dr Mitra Booel of Pfizer's clinical sector and performed under the guidance of Dr Clive Gingell in the South Meadow Hospital, Bristol, in twelve male patients with impotence. They received the drug 3 times a day for a week. Active treatment improved erectile function in ten out of twelve subjects, compared with two out of twelve on placebo. A second pilot study, in 1994, showed that a single dose was capable of enabling erections. Under the leadership of Dr Ian Osterloh, the clinical trials' program was markedly expanded to European countries, and the outcome showed >80% efficacy in the phase 2 and phase 3 trials. Between 1994 and 1997, 21 clinical trials in 13 countries were conducted in nearly 4500 men with erectile dysfunction. The entire program took nearly 4 years.

In 1997, Pfizer filed a New Drug Application (NDA) with the USA Food and Drug Administration (FDA). The agency gave Viagra priority review status, which is reserved for drugs that represent major advances in treatment or fulfill a significant medical need. In parallel, on the same day, Pfizer filed for approval with the European Medicines Agency (EMA)—the first time the company had simultaneously submitted NDAs with two large agencies.

In 1998, the USA FDA, the UK, and other countries approved marketing authorization for the first oral medication for erectile dysfunction, which became known as sildenafil citrate (generic name) or Viagra (trade name).

Following its launch in the USA in April 1998, more than 300 000 prescriptions were written for sildenafil citrate in a single week of May that year. Total sales for Viagra are currently greater than $25 billion.

The other vascular bed of clinical relevance is the pulmonary artery, which, like the corpus cavernosum in the penis, also contains a high concentration of the PDE-5 isoenzyme. Sildenafil citrate was evaluated in patients with pulmonary arterial hypertension, which is a serious condition that leads to failure in the functioning of the right ventricle. Sildenafil citrate was approved in this clinically important indication, and marketed under the trade name Revatio.

Another speculative association with raised pulmonary arterial hypertension is altitude sickness. Sildenafil citrate is valuable for the prevention and treatment of high altitude pulmonary edema. Now (2014), a number of other clinical indications are currently being explored in most countries of the world following expiry of the patent covering Viagra, including its use in the original indication of angina pectoris.

CONCLUSION

The serendipitous discovery of the actions of sildenafil has led to important improvements in the quality of life in males with erectile dysfunction. It has proven to be a remarkably effective and safe drug. There are now similar competitive compounds, eg, tadalafil and vardenafil. The efficacy and tolerability of this class of drugs is impressive. Equally impressive is the quality of the drug discovery team, which demonstrated persistence in the face of repeated scientific and clinical disappointments, as well as the ability to swiftly move on in the face of serendipitous off-target properties.

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Acute Heart Failure: the Heart Failure Patient’s Journey—the Vulnerable Phase

Summaries of Ten Seminal Papers

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Dialogues Cardiovasc Med. 2015;20:61-71

1. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function…
   C. W. Yaney and others. J Am Coll Cardiol. 2006

2. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure
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3. Worsening renal function and prognosis in heart failure: systematic review and meta-analysis
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4. Hemodynamic, echocardiographic, and neurohormonal effects of istaroxime, a novel intravenous inotropic and lusitropic agent…
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5. Diuretic strategies in patients with acute decompensated heart failure

6. Impact of serial troponin release on outcomes in patients with acute heart failure: analysis from the PROTECT pilot study
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   J. R. Teerlink and others. Lancet. 2013

9. Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure
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10. Liver function abnormalities, clinical profile, and outcome in acute decompensated heart failure
    M. Nikolaou and others. Eur Heart J. 2013

Selection of seminal papers by Valentina Carubelli, MD
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Highlights of the years by Sherri Smith, PhD
Publications office
Patients with heart failure have a high rate of rehospitalization for worsening signs and symptoms due to fluid overload, which accounts for nearly 1 million admissions every year in the US. Nearly half of these are for patients with a preserved or mildly reduced ejection fraction. However, few data are available in this population since many clinical trials excluded patients without left ventricular dysfunction. The ADHERE database (Acute Decompensated Heart Failure National Registry) recorded data from more than 100,000 hospitalizations for acute heart failure (HF) in the US and 50.4% were patients with heart failure with preserved ejection fraction (HFPEF). Compared with patients having systolic dysfunction (heart failure with reduced ejection fraction [HFREF]), HFPEF patients were more likely to be female, older, and have a higher rate of comorbidities, namely hypertension, diabetes, and chronic obstructive pulmonary disease (COPD). The percentage of patients with renal dysfunction was 26% in both groups. Regarding clinical presentation, HFPEF patients frequently had more hypertensive heart failure (patients with systolic blood pressure >140 mm Hg, 61% vs 44%; P < 0.001) and atrial fibrillation (21% vs 17%; P < 0.001) at admission. In-hospital mortality was significantly lower for HFPEF compared with HFREF (2.8% vs 3.9%; odds ratio [OR], 0.86; P = 0.005), but other in-hospital measures, such as length of stay or length of intensive care unit stay, were similar. Among the prognostic factors, serum creatinine (>2 mg/dL) was a predictor of in-hospital mortality in both groups. The independent predictors of in-hospital mortality, listed according to their power, were systolic blood pressure, blood urea nitrogen, sodium, age, dyspnea at rest, serum creatinine, no therapy with β-blockers, and heart rate.

The ADHERE database defined the profile of hospitalized patients with HFPEF, and the current knowledge about this topic is still based on these data. Patients with HFPEF account for half of the overall acute HF hospitalizations and have distinct characteristics, such as older age, female sex, and a high prevalence of comorbidities. The role of comorbidities is particularly important in these patients, because frequently, worsening of a concomitant clinical condition represents the precipitant factor of the acute HF episode. Indeed, patients with HFPEF were more likely to have a history of hypertension, which is consistent with the greater proportion of patients with higher systolic blood pressure at admission.

Atrial fibrillation is another common cause of acute decompensation in HFPEF patients, especially when it is associated with a high ventricular response rate. Interestingly, the in-hospital outcome of patients with HFPEF is better than it is in patients with HFREF. This can have several explanations. First, in HFPEF patients, the cause of decompensation is frequently not the heart itself, but rather a concomitant disease, and thus, the treatment must be targeted to resolve the precipitant cause. Moreover, recent data showed that HFPEF is frequently associated with an increased rate of noncardiovascular hospitalizations, and therefore, these events may not have been captured in several studies. Although the risk of events is different between HFPEF and HFREF, the prognostic factors for in-hospital mortality are similar with a predominant role of renal function and systolic blood pressure at admission.

Patients with preserved ejection fraction represent half of the total acute HF hospitalizations and are more frequently elderly women with a high rate of comorbidities. In-hospital prognosis of HFPEF is better than it is with HFREF, but the most important prognostic factors are similar.
Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure

M. Gheorghiade, W. T. Abraham, N. M. Albert, B. H. Greenberg, C. M. O’Connor, L. She, W. G. Stough, C. W. Yaney, J. B. Young, G. C. Fonarow; OPTIMIZE-HF Investigators and Coordinators

JAMA. 2006;296:2217-2226

The term acute heart failure syndrome (AHFS) has been recently introduced to more effectively explain the wide heterogeneity of these diseases and is characterized by several different clinical profiles at admission. In fact, the patient’s clinical presentation at admission is one of the most important prognostic predictors and affects patient management in the emergency department, during the in-hospital phase, and eventually, in the postdischarge period. Although many classifications have been proposed in recent years, the major determinant of the clinical profile is represented by systolic blood pressure (SBP), which is strongly associated with patient outcomes.

The OPTIMIZE-HF registry (Organized Program To Initiate lifesaving treatment in hospitalized patients with Heart Failure), a US registry that enrolled 48,612 patients hospitalized for AHFS, evaluated the relationship between SBP at admission and outcomes. One of the main findings of this study was that 50% of the patients had a high SBP at admission (SBP ≥140 mm Hg). Patients with a lower SBP were more likely to be males with left ventricular systolic dysfunction, and more frequently, have received therapy with inotropes. In-hospital mortality decreased across SBP subgroups, with higher mortality rates in patients with a lower SBP (7.2% vs 1.7% in patients with an SBP <120 mm Hg vs ≥160 mm Hg). The overall odds risk of in-hospital death was estimated to have a 21% increase for each 10 mm Hg decrease in SBP below 160 mm Hg. Postdischarge mortality followed the same trend, ranging from 14% in the lower SBP group to 5.4% in the higher SBP group. Interestingly, while SBP at admission showed a strong influence on patient mortality, it had no effect on the rehospitalization rate, which was similar in both groups (30.6% in the lower SBP group vs 27.6% in the higher SBP group).

The OPTIMIZE-HF registry has provided important clinical and prognostic information about patients hospitalized for AHFS. This analysis demonstrated that SBP at admission is the most important predictor of in-hospital and post-discharge outcomes in both patients with reduced or preserved left ventricular ejection fraction, independently from the patient’s treatment. From a clinical point of view, this is an important finding since SBP at admission can immediately stratify patients into different risk groups, and therefore, affects the clinical management of patients during the in-hospital course and postdischarge.

The assessment of the end points in clinical trials on AHFS has always taken into account mortality and rehospitalization as two similar measures, with a parallel trend. However, one of the most interesting insights of this study is that high SBP values were associated with lower in-hospital and postdischarge mortality, but were associated with similar rehospitalization rates compared with patients with a lower SBP. This establishes that despite having a high SBP, patients are at a lower risk of mortality during hospitalization. However, in this subgroup, morbidity remains high, demonstrating the necessity for a close follow-up during the postdischarge phase. The characteristics of patients hospitalized for AHFS vary widely according to the SBP at presentation. Although the majority of patients have a high SBP at admission, the presence of a low SBP is associated with worse in-hospital and postdischarge mortality and is the major determinant of clinical outcomes, irrespective of comorbidities and treatment.

Former Beatle Paul McCartney turns 64 after writing “When I’m Sixty-Four” at age 16; the Qinghai-Tibet Railway launches a trial operation, making Tibet the last province-level entity of China to have a conventional railway; and Kirby Puckett, the all-time leader for the Minnesota Twins’ baseball team in career hits, runs, doubles, and total bases, dies at age 46 from a cerebral hemorrhage due to hypertension.
Chronic kidney disease is a frequent comorbidity in patients with heart failure (HF), and several clinical trials have demonstrated a strong correlation with poor outcomes. In recent years, the decrease in renal function during hospitalization for acute heart failure (HF), the so-called worsening renal function (WRF), has also been recognized as an important prognostic marker in these patients.

In this article, the authors performed a systematic review and meta-analysis of the studies about WRF in patients hospitalized for acute HF in order to clarify its prognostic significance. Eight studies were included in the analysis for an overall population of 18,634 patients. Worsening renal function was defined as an increase in serum creatinine (≥0.2 mg/dL) or a corresponding decrease in the estimated glomerular filtration rate (≥5 mL/min/1.73 m²). The mean age of the study population was 67 years. WRF events were recorded in 4734 (25%) patients. The all-cause mortality rates after 6 months of follow-up were 43% and 36% for patients with or without WRF, respectively, and the odds ratio (OR) for WRF patients was 1.62 (95% confidence interval [95% CI], 1.45-1.82, P<0.001). In addition, the authors developed a meta-regression model, and the factors that increased the risk of mortality associated with WRF were the severity of the event, male sex, age, and history of myocardial infarction. Similar data have been observed regarding the secondary end point of all-cause hospitalizations, which were also increased in patients with a WRF event during index hospitalization (OR, 1.30; 95% CI, 1.04-1.62, P=0.022).

This was the first systematic review to investigate the relationship between WRF and outcomes in patients hospitalized for acute HF. The main finding of this study was that WRF is a common event during acute HF hospitalizations with a 25% average frequency. There are several causes of WRF in acute HF patients. In fact, during acute HF, decreased renal perfusion, increased venous congestion, and treatment with diuretics all contribute to the deterioration of renal function. In the majority of cases, these alterations are transitory and resolve after treatment of the acute HF episode, however, they determine organ damage to the kidney, which leads to a worse long-term prognosis. In addition, renal dysfunction is a common comorbidity in HF patients with a prevalence of ~30%, and these patients are at a higher risk of developing a WRF event. This meta-analysis has several clinical implications as it highlighted the importance of monitoring renal function and the role of organ damage during hospitalization for acute HF. Furthermore, this study showed the importance of kidney function as a therapeutic target to guide the development of new drugs.

In conclusion, WRF is a common complication during hospitalization for acute HF, especially in patients with renal dysfunction, and has been associated with unfavorable outcomes during follow-up. Organ damage during acute HF contributes to a poor long-term prognosis, and thus, novel treatments to protect kidney function should be developed.

Steve Jobs, CEO and founder of Apple Inc, announces the first generation iPhone; Rambhadracharya, a Hindu religious leader, releases the first Braille version of Bhagavad Gita, with the original Sanskrit text and a Hindi commentary, at New Delhi, India; and Russian cellist and conductor Mstislav Rostropovich, one of greatest cellists of the 20th century, dies at age 80 from intestinal cancer.
Istaroxime is a novel intravenous drug with both inotropic and lusitropic properties. It inhibits the Na+/K+ adenosine triphosphatase in a digoxin-like fashion and stimulates the sarcoplasmic reticulum Ca²⁺ adenosine triphosphatase isofor 2a. This results in greater calcium sequestration during diastole, which favors ventricular relaxation, and increases the availability of calcium during the subsequent systole, enhancing inotropism. In animal models, istaroxime improved left ventricular contraction and relaxation, without increasing myocardial oxygen demand.

The HORIZON-HF trial (Hemodynamic, echocardiographic, and neurohormonal effects of istaroxime, a novel intravenous inotropic and lusitropic agent: a randomized controlled trial in patients hospitalized with heart failure) was a double-blind, placebo-controlled study that included 120 patients hospitalized for acute heart failure (HF) with a left ventricular ejection fraction (LVEF) ≤ 35%. All patients underwent pulmonary artery catheterization (PAC) for the evaluation of hemodynamic parameters, particularly pulmonary capillary wedge pressure (PCWP). Patients enrolled were randomized, in a 3:1 ratio, to receive 6 hours of continuous infusion with istaroxime at doses of 0.5, 1.0, or 1.5 μg/kg/min or placebo. Istaroxime infusion lowered PCWP in all dose regimens (3.2±6.8 mm Hg, 3.3±5.5 mm Hg, and -4.7±5.9 mm Hg from baseline, respectively; P<0.05 for all) and increased systolic blood pressure at the 1.0 and 1.5 μg/kg/min dose. Cardiac output and the left ventricular filling pattern improved significantly at the higher doses. Regarding safety, no increase in cardiac troponins or worsening renal function were reported. All the main adverse events, namely nausea, vomiting, and injection site pain and inflammation, were dose related.

Istaroxime represents a novel class of drugs with inotropic and lusitropic properties. In this study, a 6-hour istaroxime infusion improved hemodynamics without causing hypotension or an increase in cardiac troponins. Moreover, the treatment was safe with few adverse events in the low-dose groups. The use of inotropic agents has decreased in the last decade because the guidelines have progressively limited their indication to patients with hypotension and signs of hypoperfusion. Indeed, treatment with inotropic drugs was associated with an increase in the mortality rate in several studies. Even new inotropes have failed to reach satisfactory results in clinical trials. Milrinone, a phosphodiesterase-3 inhibitor, was associated with a 30% mortality increase in patients with ischemic heart disease in the OPTIME-CHF trial (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure). Levosimendan-treated patients showed only a mild improvement in HF symptoms, but an unacceptably high rate of adverse events, such as tachyarrhythmia and hypotension.

These data clearly demonstrate the unmet need of novel treatments that can improve cardiac function with a good safety profile. Although data regarding safety, efficacy, and prognostic outcomes of a longer istaroxime infusion are still lacking, the effect of this drug on diastolic function and blood pressure seems promising. In conclusion, istaroxime treatment was effective in improving hemodynamic parameters in patients hospitalized for acute HF. In addition, at lower doses, it was associated with few adverse events. Further studies are currently ongoing to assess the efficacy of this new therapy in the acute HF setting.

Kosovo formally declares independence from Serbia; Albert Hofmann, a Swiss chemist best known for being the first person to synthesize lysergic acid diethylamide (LSD), dies at age 102; and the remains of a Viking-era stave church are uncovered near the cemetery of the Lännäs church in Odensbacken outside Örebro in central Sweden.

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**Hemodynamic, echocardiographic, and neurohormonal effects of istaroxime, a novel intravenous inotropic and lusitropic agent: a randomized controlled trial in patients hospitalized with heart failure**


*J Am Coll Cardiol.* 2008;51:2276-2285
Diuretic strategies in patients with acute decompensated heart failure


*NEJM*. 2011;364:797-805

Furosemide remains the cornerstone therapy for acute heart failure (HF). However, the dosing and optimal mode of administration of loop diuretics in acute HF are still a matter of debate, with several questions still unanswered. High doses of furosemide have been associated with worse outcomes and an untoward impact on renal function. In addition, it is unclear whether different modes of administration of loop diuretics may affect the response to therapy.

In the DOSE study (Diuretic Optimization Strategies Evaluation), a double-blind, randomized study that enrolled 308 patients, the authors investigated different diuretic strategies in patients admitted for acute decompensated heart failure. They compared low or high doses of furosemide administered as either a continuous infusion or an intravenous intermittent bolus. After 48 hours, the physician was allowed to increase or maintain the diuretic dose or switch to an open oral diuretic. The two coprimary end points were changes in serum creatinine and a global assessment of the patient’s symptoms. There were no significant differences with regard to the prespecified end points for intravenous versus bolus administration, although patients treated with a bolus were more likely to receive a dose increase at 48 hours. At 48 hours, patients assigned to the low-dose strategy were more likely to receive a dose increase, while patients assigned the high-dose strategy were more likely to be switched to an oral diuretic. No significant differences were found in the primary end points for these two groups. However, the high-dose group showed greater fluid and weight loss, relief from dyspnea, and fewer adverse events. On the other hand, a significantly greater proportion of the high-dose group showed a worsening renal function. No differences were found in survival end points among the groups.

The novelty of this study was the attempt to concretely answer several questions regarding diuretic strategies in patients hospitalized for acute HF. The first important conclusion is that no significant difference was found in the efficacy and safety between bolus and continuous infusion. Secondary, but important, findings were that high doses of furosemide may be more effective with regard to decongestion. Patients on high-dose regimens had more worsening renal function events. Although worsening renal function has been associated with increased cardiovascular events in several studies and meta-analyses, in this study, there were no significant differences in outcomes. This may be explained by the fact that, in this case, the increase in serum creatinine was due to the so-called “underfilling state” secondary to the diuretic response and not kidney injury. These data confirm the recent literature showing that a transient worsening renal function may not be detrimental when associated with effective decongestion. Further studies are needed to clarify the relationship between diuretic responses and worsening renal function, novel renal biomarkers may be useful in this setting.

In conclusion, this trial showed no significant differences when comparing different diuretic strategies in patients with acute HF. However, a trend toward an improved decongestion was observed in patients who received high-dose diuretics.
Impact of serial troponin release on outcomes in patients with acute heart failure: analysis from the PROTECT pilot study


Circ Heart Fail. 2011;4:724-732

Acute heart failure (HF) is characterized by several pathophysiological mechanisms, including abnormal hemodynamics, fluid overload, neurohormonal activation, and inflammatory activation. One of the consequences of these alterations is organ damage to the heart, kidney, and liver, which has a significant long-term impact on outcomes. Direct injury to the cardiac muscle can be clinically evaluated by troponin release. During acute HF, the increased hemodynamic burden and the reduction in coronary blood flow, especially in patients with ischemic heart disease, led to a greater stress on the cardiac myocytes, and thus, favored troponin release. However, several studies have previously demonstrated that cardiac troponins are also increased in patients with acute HF, but without significant coronary artery disease, due to the increase in cardiac workload, arrhythmias, and treatment with some classes of drugs, namely inotropes. In addition, the increase in troponin levels during hospitalization for acute HF has been associated with a worse prognosis.

The PROTECT trial (Placebo-controlled, Randomized study of the selective A1-adenosine receptor antagonist rololfylline for patients hospitalized with acute heart failure and volume Overload to assess Treatment Effect on Congestion and renal function) investigated the safety and efficacy of rololfylline, a selective A1-adenosine receptor antagonist in patients with acute HF. The main results were negative and rololfylline was associated with an increased risk of adverse events. In this subanalysis, the authors focused on the role of cardiac troponin T (cTnT) release. A total of 288 patients were included. 172 (60%) patients had detectable cTnT (>0.01 ng/mL) and 97 (34%) patients had positive cTnT (>0.03 ng/mL). In addition, 21% of patients with negative cTnT at baseline developed an increase at day 7. Patients with positive cTnT at baseline showed a worse clinical outcome, evaluated as HF or renal hospitalization and mortality at 60 days (hazard ratio [HR], 1.84; 95% confidence interval [95% CI], 1.04-3.26, P=0.036). Moreover, patients who had a conversion to detectable cardiac troponin during hospitalization had a lower rate of treatment success and a prognosis similar to those with positive cTnT at baseline.

Troponin T elevation is a common finding in patients hospitalized for acute HF. The release of cardiac troponin is one of the markers for organ damage that can occur during decompensation and fluid overload. This clinical trial confirmed that positive cTnT at admission is associated with worse short- and long-term outcomes. Moreover, this trial enrolled patients with renal dysfunction, and thus, the prognostic significance of cTnT has been demonstrated in this setting. However, the most interesting result was the prognostic significance of a cTnT increase during hospitalization, which has clinical implications, highlighting the importance of serial cTnT sampling in acute HF patients. In this view, cardiac troponins may be an important marker to evaluate treatment safety. Indeed, inotropes, which may favor even a slight release of cTnT, have been associated with increased mortality. Hence, cTnT levels can represent a new end point to monitor investigational drug safety.

In conclusion, cardiac troponin elevation at admission is common in patients hospitalized for acute HF, and in addition, serial measurements of cTnT allow subjects to be identified who may develop cTnT elevations during hospitalization. Patients with positive cTnT or an increase after admission are at a high risk of cardiovascular events during hospitalization, with a similar increased rate of cardiovascular events during follow-up.

The passenger ferry MV Spice Islander I sinks off the coast of Zanzibar, killing over 1500 people; the European Union Council extends the copyright on sound recordings from 50 years to 70 years; and researchers at Monash University, Melbourne, Australia have identified a previously unknown species of bottlenose dolphin living in and around southeastern Australia.
Effect of nesiritide in patients with acute decompensated heart failure


Nesiritide is the recombinant form of the human brain natriuretic peptide (BNP). BNP has vasodilatory and natriuretic properties. Nesiritide was approved in the US in 2001 for use in patients hospitalized for acute heart failure (HF) following the publication of the VMAC trial results (Vasodilation in the Management of Acute Congestive heart failure). The VMAC trial demonstrated an improvement in hemodynamic parameters in treated patients. After this study, a pooled analysis of previous clinical trials raised some concerns about safety because they demonstrated an increase in worsening renal function in patients treated with nesiritide.

The ASCEND-HF study (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) was designed to confirm the results of previous studies and to investigate the effects of nesiritide on renal function. This double-blind, placebo-controlled clinical trial included patients hospitalized for acute HF who could be randomized within the 24 hours before treatment. Eligible patients were randomized to receive, in a 1:1 ratio, either intravenous nesiritide for 24 hours up to 7 days or placebo. Overall, 7141 patients were included. Nesiritide treatment was associated with a slight relief of symptoms compared with placebo at 6 hours (44.5% vs 42.1%, P=0.03) and at 24 hours (68.2% vs 66.1%, P=0.007), but did not reach the prespecified level of significance. No significant differences were found in the composite end point of all-cause death or HF hospitalizations. Worsening renal function, defined as a >25% decrease in estimated glomerular filtration rate (eGFR), was similar in both groups (31.4% vs 29.5%, P=0.11). The most common adverse event during treatment was hypotension, either symptomatic or asymptomatic, which was significantly higher in the nesiritide group (26.6% vs 15.3%, P<0.001).

Vasodilators represent a cornerstone in the treatment of acute HF, reducing both preload and afterload and improving congestion. Among vasodilators, nitrates are still widely used in clinical practice. However, few randomized and blinded studies have investigated the efficacy of these drugs, and thus, their results are frequently uncertain and should be interpreted with caution. Although limited by the poor data quality, a recent meta-analysis showed that adding nitrates to standard therapy in patients hospitalized for acute HF was not associated with any significant improvement in several end points. Thus, the development of new drugs with vasodilating properties is mandatory in acute HF. Nesiritide seemed promising in the relatively small VMAC trial, but did not reach satisfactory results in the ASCEND-HF trial and was associated with a high rate of adverse events, namely symptomatic hypotension. Since many investigational drugs for acute HF have failed to move from phase 2 to phase 3 studies, some concerns about clinical trial design have been raised. The ASCEND-HF trial was primarily addressed to investigate the nesiritide safety profile; therefore, the study population included a broad spectrum of patients with acute HF. Beyond these results, the ASCEND-HF trial confirms that a careful selection of eligibility criteria and end points are extremely important and further studies are needed to clarify how to design successful clinical trials.

In conclusion, the ASCEND-HF trial showed that nesiritide can mildly improve HF symptoms, but did not affect 30-day all-cause mortality and HF rehospitalization rates. Regarding the safety profile, the drug was not associated with worsening renal function, but hypotensive episodes were more common in the treatment group.

King Abdullah of Saudi Arabia announces reforms to give women the right to vote and run in municipal elections; Kathryn Gray, a 10-year-old Canadian, becomes the youngest person ever to discover a supernova; and Asif Ali Zardari, the President of Pakistan, launches an emergency polio immunization program targeting 32 million children under the age of 5.
Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial


Serelaxin is the recombinant form of human relaxin-2, a vasoactive peptide hormone, which is physiologically released during pregnancy. Endogenous relaxin-2 is produced by multiple tissues in both males and females, but its levels rise steeply during pregnancy when it is released by the corpus luteum. It is predominantly secreted during the first trimester when remarkable maternal systemic and renal hemodynamic adjustments occur. Serelaxin acts as a vasodilator with several hemodynamic effects, increasing global arterial compliance with a concomitant decrease in arterial stiffness of renal arterioles. Due to the improvement in kidney hemodynamics, serelaxin also showed a modest natriuretic effect. Serelaxin has pleiotropic actions with antioxidative, anti-inflammatory, and connective tissue–regulating properties that are still under investigation. Due to its unique pharmacological properties, serelaxin was tested in patients hospitalized for acute heart failure in the pre-RELAX trial (efficacy and safety of RELAXin), a pilot dose-finding phase 2 study, where serelaxin improved dyspnea and cardiovascular events at 60 and 180 days.

The subsequent RELAX-AHF trial (efficacy and safety of RELAXin for the treatment of Acute Heart Failure) was designed to confirm data from the early phase trials. In this study, 1138 patients hospitalized for acute heart failure were enrolled and randomized to receive, in a 1:1 ratio, either serelaxin or placebo. The study showed that serelaxin significantly reduced dyspnea from baseline to day 5. While serelaxin did not affect 60-day readmission or mortality, largely due to a lack of an effect on readmissions, it significantly reduced 180-day all-cause mortality. This result remained significant after adjustment for baseline characteristics associated with 180-day all-cause mortality by multivariate analysis in the placebo group.

This trial is the first in recent decades that demonstrated a significant benefit of a new treatment for acute heart failure (HF). In fact, the postdischarge prognosis remains unsatisfactory with high mortality and rehospitalization rates. This can be explained by the following two reasons: (i) persistence of congestion at the time of discharge, leading to early readmission during follow-up; and (ii) cardiac, renal, and hepatic damage caused by congestion, neurohormonal activation, and inflammatory activation. Serelaxin was demonstrated to attenuate organ injury during hospitalization, preventing the damage that leads to a progressive worsening of organ function. In fact, an increase in serum troponin T (an index of myocardial injury), serum cystatin C (for worsening renal function), and serum transaminases (for hepatic injury) had an independent prognostic value for 180-day mortality in the RELAX-AHF trials; serelaxin administration was associated with lower levels of these biomarkers. This suggests that protection from acute HF-associated organ damage may be a mechanism for improved survival in these patients. However, since the trial was underpowered for the mortality end point, this result needs to be confirmed and the RELAX-AHF-2 trial, a larger randomized, placebo-controlled trial, with cardiovascular mortality as the primary end point, is currently ongoing.

In conclusion, serelaxin is a novel vasodilator with unique properties, allowing organ protection in patients with acute HF. Serelaxin improved 180-day mortality in the RELAX-AHF trial and this result is currently under investigation in the RELAX-AHF-2 trial.

2013

American author Tom Clancy, best known for his military thriller novels, dies at the age of 66;
Divers in Russia recover a 570 kg portion of the Chelyabinsk meteor; and the complete nuclear genome of a Siberian boy who died 24,000 years ago suggests that approximately one-third of the ancestry of today’s US Native Americans can be traced to Western Eurasia
Levosimendan is a drug with inotropic and vasodilating properties, which has been approved in recent years for clinical use in Europe. Levosimendan is a calcium sensitizer that acts on cardiac contractile proteins to improve contractility and block vascular smooth muscle potassium channels, which results in peripheral vasodilation. In addition, it has long-lasting effects due to the production, after hepatic enzymatic transformation, of an active metabolite. In clinical trials, in patients admitted for acute heart failure (HF), levosimendan improved symptoms and cardiac performance.

The REVIVE study program (Randomized Evaluation of Intravenous LeVosimendan Efficacy) has been developed in order to confirm the results of previous studies. The REVIVE studies I and II enrolled patients hospitalized for acute HF with severe left ventricular dysfunction who remained symptomatic despite treatment with intravenous diuretics. The study had a double-blind, placebo-controlled design and included 700 patients overall. A total of 100 patients were enrolled in the REVIVE I study, which was developed to assess new efficacy end points, and 600 patients were enrolled in the REVIVE II study to confirm the value of these novel end points. In the REVIVE II study, the treatment with levosimendan was associated with clinical improvement in all prespecified time points (ie, 6 hours, 24 hours, and 5 days). Clinical worsening, a new composite variable that included death, unresponsive symptoms of heart failure, and worsening heart failure (need of rescue therapy), was reduced in the levosimendan group compared with placebo (58 vs 82 patients, \( P=0.015 \)). In addition, patients in the treatment group had lower BNP levels (\( P<0.001 \)) and a shorter length of stay (\( P=0.009 \)). Regarding safety, more patients in the levosimendan group had hypotension (50% vs 36%, \( P<0.05 \)), ventricular tachycardia (25% vs 17%, \( P<0.05 \)), and atrial fibrillation (9% vs 2%, \( P<0.05 \)). Although not statistically significant, levosimendan was associated with an increased rate of death at 90 days (49 vs 40, \( P=0.29 \)).

The REVIVE studies showed a significant clinical improvement in levosimendan-treated patients, however, there was a very high rate of adverse events and a numerical increase in mortality. The risk of death in this study has been associated with hypotension. Indeed, patients with lower systolic blood pressure at admission had worse outcomes. Recently, several studies, especially a subanalysis of clinical trials with vasodilators, confirmed that hypotensive events during acute HF hospitalizations are associated with higher rates of cardiovascular events during follow-up. In the REVIVE II study, a significant hazard for mortality was observed in the levosimendan group when the baseline systolic blood pressure was <100 mm Hg. Moreover, the trial design allowed for the use of concomitant inotropes and vasodilators, which may have led to confounding effects. On the other hand, a pooled analysis of trials with levosimendan reported a significant decrease in mortality in the intervention group. Hence, these data should be interpreted with caution. Another consideration is related to the high dose of levosimendan administered in clinical trials. Indeed, a loading dose is no longer used in clinical practice, and generally, patients start treatment with a very low-dose infusion to assess tolerability. This could be another contributing factor to the unfavorable results of this study.

In conclusion, levosimendan was associated with clinical improvement in this trial; however, there was a high rate of adverse events, namely hypotension and tachyarrhythmia. Further studies are needed to ascertain the numerical increase in mortality that was observed in this trial.

The Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure


JACC Heart Fail. 2013;1:103-111

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Scott Carpenter, a Mercury 7 astronaut and the second American to orbit the earth, dies at 88 following complications from a stroke; the Boston Red Sox win the 2013 Major League Baseball World Series, which is their first series victory since 1918; and Turkey opens a sea tunnel connecting Europe and Asia across the Bosphorus Strait in Istanbul
Liver function abnormalities, clinical profile, and outcome in acute decompensated heart failure


Eur Heart J. 2013;34:742-749

Acute heart failure (HF) is a systemic syndrome that also involves other organs, such as the kidney and liver. Although several studies have investigated the role of renal dysfunction, few data are available about liver function in this setting. Indeed, venous congestion has a strong impact on hepatic structures since it favors liver cell necrosis. Therefore, liver function tests (LFTs) may represent important biomarkers of organ injury.

This article is a subanalysis of the SURVIVE trial (SURVival of patients with acute heart failure in need of intravenous inotropic support), which investigated the effectiveness and safety of levosimendan in patients admitted with acute HF. Data regarding LFTs were available for 1134 patients enrolled in the main study. Any LFT abnormalities were recorded in 46% of patients and most of them were classified with a moderate degree. The majority of patients had an isolated increase in liver transaminases (26%), an increase in alkaline phosphatase ([AP]; 11%), and a combination of these alterations (9%). The pattern of hepatic dysfunction was associated with specific clinical profiles. Patients with AP abnormalities frequently had more signs of peripheral venous congestion and right ventricular involvement, and patients with high transaminases had more signs of hypoperfusion. Regarding prognosis, patients with high AP values had an increase in mortality at 6 months (33.8% vs 23.5%, P=0.001), whereas patients with high transaminases had greater mortality at both 31 days (17.6% vs 8.4%, P<0.001) and 6 months (31.6% vs 22.4%, P<0.001) compared with subjects with normal transaminase levels. No differences in terms of outcome were seen in patients with the combined increase in LFTs.

The liver has been recently recognized as a target of organ damage in acute HF patients; however, few data are available and little is known about the underlying pathophysiological mechanisms. In patients with chronic heart failure, congestion of hepatic sinusoids favors cell necrosis and enhances fibrosis, which leads to the development of cardiac cirrhosis. In acute HF patients, especially with a long-standing history of heart failure, increases in venous pressure are associated with further hepatic injury. This paper also offers interesting insights about the different patterns of LFT alterations in relation to the patient’s clinical profile. In fact, patients with low-output signs tended to have a predominant increase in transaminases, and thus, a functional hepatic injury. Patients with a cholestatic pattern have the typical phenotype of worsening chronic HF, namely with signs of right ventricular dysfunction and systemic venous congestion. In this case, hepatic damage is more related to the compression of the biliary system due to congestion. In any case, this analysis clearly demonstrated the prognostic significance of LFTs for acute HF; therefore, LFTs should be recommended during the early evaluation to identify high-risk subjects. Data regarding the significance of LFT changes during hospitalization and in response to treatment are still lacking and may represent an aim for further research.

In conclusion, LFTs are abnormal in nearly one-half of the patients hospitalized for acute HF, and specific patterns, such as an increase in APs or transaminases, are associated with the patients’ clinical profiles. This study confirmed the role of LFTs in predicting long-term prognosis in patients with acute HF.

Researchers at Washington University in St. Louis, MO show that a toxin from bee venom is able to destroy the HIV virus; Kenyan protestors release dozens of pigs in front of parliament to protest perceived greed; and a new study finds that the white blood cell levels in men decrease faster during aging than in women, possibly providing one clue as to why women have longer average lifespans.

Liver function abnormalities, clinical profile, and outcome in acute decompensated heart failure
Acute Heart Failure: the Heart Failure Patient’s Journey—the Vulnerable Phase

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