The current and future management of acute heart failure syndromes

Peter S. Pang¹,³, Michel Komajda², and Mihai Gheorghiade³*

¹Department of Emergency Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; ²Department of Cardiology, Hopital Pitie-Salpetriere and University Pierre et Marie Curie, Paris, France; and ³Center for Cardiovascular Quality and Outcomes, Department of Medicine, Northwestern University, Feinberg School of Medicine, 645 N Michigan Ave, Suite 1006, Chicago, IL 60611, USA

Received 12 January 2010; accepted 2 February 2010; online publish-ahead-of-print 5 March 2010

Hospitalization for heart failure (HF) marks a substantial crossroad for patients, as greater than one-third will be re-hospitalized or dead within 90 days post-discharge. For patients with chronic HF who present with acute heart failure syndromes (AHFS), they transition from an arena of well-established and life-saving evidence-based therapies to one where early pharmacological management has changed little over the last 40 years. Traditional therapies, such as oxygen, loop diuretics, nitrates, and morphine remain the cornerstone of early management today. Despite earlier initiation of chronic HF therapies during hospitalization, post-discharge event rates remain high. Optimizing management of known targets with proven evidence-based therapy has the potential to reduce post-discharge event rates. In this inaugural issue of the Frontiers in Cardiovascular Therapy, we briefly review current in-hospital management of AHFS, introduce the concept of cardiac reconstruction, and focus on the potential of future management strategies and therapeutics to improve outcomes in AHFS.

Keywords: Acute heart failure syndromes • Management

Introduction

Hospitalization for heart failure (HF) marks a substantial crossroad for patients, as greater than one-third will be re-hospitalized or dead within 90 days post-discharge.¹ For those patients with chronic HF, it represents a transition from an arena of well-established and life-saving evidence-based therapies to one where early pharmacological management has changed little over the last 40 years.² Traditional therapies for acute heart failure syndromes (AHFS), such as oxygen, loop diuretics, nitrates, and morphine remain the cornerstone of early management today.³ Despite earlier initiation of evidence-based chronic HF therapies during hospitalization, post-discharge re-hospitalization and mortality event rates remain high.¹³⁴ Such high post-discharge event rates represent a societal burden given the number of patients who present with AHFS and the resultant cost.

In the USA, over one million hospitalizations occur each year for HF, an increase of over 175% in the last 25 years.⁵ These hospitalizations account for the bulk of the 39 billion USD spent each year for HF care.⁶ Similar rates of hospitalization occur in the countries represented by the European Society of Cardiology (ESC), although with geographical variations in the length of stay, re-hospitalization rates, and in-hospital mortality.⁷⁸⁹ Although the incidence of first hospitalization for HF appears to be decreasing,⁹ it is projected that the overall numbers of patients who present with HF will increase, due to the ageing of the population, combined with those living longer due to advances in cardiovascular disease management.⁵¹⁰ The cost of hospitalization in terms of human life is grim: death occurs in 25–35% of patients within 1 year of hospitalization and this risk increases substantially with each subsequent hospitalization.¹¹–¹⁵

There is a clear need to improve outcomes for patients who present with AHFS. Although progress has been made in terms of characterizing the AHFS patient, there remains limited evidence linking hospital management with reduced post-discharge event rates.¹⁶ In this inaugural issue of the Frontiers of Cardiovascular Therapy, we briefly review current in-hospital management of AHFS and discuss the potential of future interventions and strategies to improve outcomes.
Definition and classification

Acute heart failure syndromes have been defined as the new onset or recurrence of gradual or rapidly worsening signs and symptoms of HF requiring urgent or emergent therapy.\(^7,^{17}\) The vast majority of patients present with congestion, however heterogeneity of underlying cardiac and non-cardiac co-morbidities and phenotypic variations in clinical presentations is a hallmark of patients with AHFS.\(^18\)

Multiple AHFS classification schemes have been previously proposed based on patients’ clinical presentation or past history.\(^17,^{19,20}\) The ESC divides patients into six clinical profiles: (i) worsening or decompensated chronic HF, (ii) pulmonary oedema, (iii) hypertensive HF, (iv) cardiogenic shock, (v) isolated right HF, (vi) ACS and HF, with the explicit acknowledgement that there is overlap between groups.\(^7\) The ACCF/AHA divides patients based on presenting clinical profile into three main groups: (i) volume overload, manifested by pulmonary and/or systemic congestion, usually due to increases in blood pressure (BP), (ii) severely reduced cardiac output often with hypotension, and (iii) combined volume overload and cardiogenic shock.\(^21\) Another schema accounts for both historical and structural features, classifying patients as follows: worsening chronic HF (75%), de novo or new onset (20%), and advanced or refractory HF (5%).\(^17,^{22}\) These patients may present with high, normal, or low BP, with reduced or preserved systolic function, and with or without coronary artery disease (CAD).\(^22\)

We propose a classification framework utilizing the ACCF/AHA stages of development of HF (Table 1)\(^21\), which outlines therapeutic goals and options based on cardiac structure and/or function. In addition, clinical profiles, as defined by the ESC guidelines, will represent further discriminating factors. Patients with de novo HF would be classified as Stage A or B ACCF/AHA class. Patients with worsening chronic HF or end-stage HF would be ACCF/AHA Stage C or D. Whether management by profile or classification or combined leads to improved outcomes requires further research.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Proposed classification for patients who present with acute heart failure syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCF/AHA stage</td>
<td>Explanation of stage</td>
</tr>
<tr>
<td>Worsening chronic HF (75%)</td>
<td>Stage C: structural heart disease with prior or current symptoms of HF</td>
</tr>
<tr>
<td>Advanced HF (5%)</td>
<td>Stage D: refractory HF requiring specialized interventions</td>
</tr>
<tr>
<td>De novo HF (20%)</td>
<td>Stage B: structural heart disease but without signs or symptoms of HF</td>
</tr>
<tr>
<td>Also neither A nor B</td>
<td>A: at high risk for HF but without structural heart disease or symptoms of HF</td>
</tr>
</tbody>
</table>

Pathophysiological concepts related to future management

The main reasons for admission and readmission in AHFS are related to pulmonary and systemic congestion, rather than a low cardiac output. Yet our current understanding of the pathophysiology of AHFS is incomplete. An analogy to acute coronary syndrome (ACS) will be used as an illustrative example.

In ACS, symptoms of chest discomfort occur with various clinical profiles (i.e. hypertensive, normotensive, or hypotensive, complicated by AHFS, etc.) with different electrocardiographic presentations [e.g. ST-elevation myocardial infarction (STEMI), ST-depressions, etc.]. The underlying pathophysiology is related to the rupture of an atherosclerotic plaque causing acute intravascular thrombosis (the ‘clot’) leading to ischaemia and myocyte necrosis.

In AHFS, patients most commonly present with dyspnoea or breathlessness with variable clinical profiles. The pathophysiology may be dominated by a single precipitating or aetiological mechanism or by multiple ‘clots,’ (e.g. hypertension, neurohormonal activation, myocardial dysfunction, arrhythmias, valvular disease, ACS, reduced systolic function, etc.) with the resulting pathophysiological process of increased pulmonary capillary wedge pressure (PCWP) and/or low cardiac output. A unifying pathophysiological construct encompassing all AHFS presentations has not yet been determined.

The apparent uncoupling of symptom improvement to outcomes not only highlights a management paradox, but suggests that altering symptoms does not appear to affect the pathophysiology which relates to outcomes. Patients with the most severe presentation, flash pulmonary oedema, appear to do well post-discharge. In contrast, those with severe chronic HF may have a less dramatic presentation (e.g. worsening fatigue) and by comparison appear less acutely sick, yet have a much worse prognosis. Current therapies make patients feel better, yet in spite of hospital use of evidence-based therapies such as angiotensin-converting enzyme inhibitors (ACE-I) or beta-blockers, the post-discharge event rate remains high.

Importantly, only a small percentage of all HF patients have advanced or end-stage HF, defined as persistent signs and symptoms despite maximal medical, surgical, and electrical therapy.\(^17\) Short of transplantation or other novel discoveries, the prognosis for these patients remains grim. For the remaining patients who comprise the vast majority of AHFS presentations, preserving or safely improving myocardial function, the concept of cardiac ‘reconstruction’ may be critical to improve outcomes in the future.

As the pathophysiology of AHFS has been extensively reviewed elsewhere,\(^7,^{23}\) we focus on specific pathophysiological concepts related to preservation and/or restoration of cardiac function, myocardial injury, the importance of CAD, viability, metabolic modulation, as well as renal function.

Myocardial injury

Acute heart failure syndromes are associated with elevated serum troponin levels, which may represent myocyte injury, even when ACS is not suspected. However, troponin release occurs in only
a small percentage of patients admitted with AHFS. Troponin release is associated with worse outcomes. Subsequently, myocardial injury has been suggested to accelerate the progression of heart failure. The mechanisms to explain troponin release have not been fully elucidated, however, preventing myocyte injury may be an important target for future management.

**Coronary artery disease**

Approximately 60% of AHFS patients have underlying CAD and have a worse prognosis. They may present with ACS complicated by AHFS or more commonly with AHFS and underlying CAD. Despite the prevalence of CAD in AHFS, whether management should change based on the presence of CAD in AHFS has not been well studied. Retrospective analysis suggests an association between revascularization and improved outcomes. Given the known effectiveness of therapies for CAD in general, CAD in AHFS may be an important target.

**Viable but dysfunctional myocardium**

In patients with systolic dysfunction, the majority of patients have viable but dysfunctional myocardium, which may be potentially salvagable. Most commonly recognized in patients with underlying CAD, described as hibernating myocardium due to chronic ischaemia, a significant number of HF patients without CAD also have viable but dysfunctional myocardium. Even in CAD patients, viable but dysfunctional myocardium may not always be related to chronic ischaemia. Although there are multiple reasons for viable but dysfunctional myocardium, such as excessive sympathetic stimulation or micronutrient deficiencies, this represents an important target for restoring contractility as well as prevention of further myocardial loss. When properly identified and measured, revascularization and beta-blocker therapy will restore function in the area of viable but non-contractile myocardium due to ischaemia or metabolic reasons, respectively. Importantly, in patients with severe systolic dysfunction hospitalized for HF, the extent and severity of viable but dysfunctional myocardium may divide patients in two groups; those with salvageable myocardium vs. those in whom myocardial function cannot be improved. However, the presence, extent, and causes of viable but dysfunctional myocardium in patients with reduced systolic function have not been well studied and remain an important area for further investigation.

**Metabolic factors contributing to left ventricular dysfunction**

The heart pumps over 7000 L of blood a day, utilizing more than 6 kg of adenosine tri-phosphate (ATP) to fuel this activity. The heart also renews its protein components every 30 days. Therefore, it is not surprising that the heart’s metabolic needs are enormous. This creates the potential for a mismatch between energy consumption and energy production. Inadequate or improper utilization of energy has been suggested to contribute to the pathophysiology of HF. Briefly, metabolism of free fatty acids and glucose allows for the generation of ATP, which is utilized by myocytes to power mechanical contraction. Lack of appropriate substrate to convert to energy, impaired metabolism of existing substrate or fuel, and/or dysfunctional utilization of released energy represent multiple pathophysiological processes. Current inotropes are a therapeutic example of misapplied energetics; short-term cardiac performance is improved, however, the mismatch between supply and demand may lead to myocardial injury. Agents that stimulate the heart without addressing cardiac metabolism may be one reason why certain haemodynamic agents have been associated with neutral or worse outcomes. Addressing cardiac metabolism, or energetics, is emerging as an important future target for intervention.

**Renal impairment**

Renal impairment at time of admission (defined as glomerular filtration rate < 60 mL/min/1.73 m²) is common in AHFS. A wealth of data have shown that baseline renal impairment as well as worsening renal function (WRF) during AHFS hospitalization are independent predictors of mortality. Pathophysiological investigations have indicated a strong interdependence between myocardial and renal function, which is at least in part mediated by neurohumoral and haemodynamic factors. The existence of a cardiorenal syndrome (CRS) has therefore been postulated to explain the abnormalities in renal function often observed in patients with AHFS. Even if progress is being made, a universally accepted definition of CRS has not yet been established, reflecting the heterogeneity of pathophysiological processes that lead to WRF. Importantly, WRF may occur despite clinical improvement. Worsening renal function may be medication related (i.e. ACE-I), reflect intravascular dehydration due to high diuretic use, due to venous congestion with decreased or preserved cardiac output, or a combination of all three. As a result, treatment may require specific targeting (e.g. venous congestion). Although renal function is a major predictor of prognosis, it is not clear whether addressing renal function alone without improving the ‘pump’ will be sufficient to substantially improve outcomes.

**The concept of cardiac reconstruction**

The traditional view of HF is as a progressive and irreversible process, despite only a small proportion of HF patients with end-stage HF. Many patients have potentially correctable causes that if treated per established guideline recommendations, such as valvular disease, obstructive CAD, and ventricular dyssynchrony, may improve or restore cardiac function. Preventing myocardial injury, optimizing metabolism, and preservation of renal function represent other possible targets. Determining the extent of viable myocardium is an objective way to delineate patients with salvageable myocardium, since its present in the majority of patients with reduced ejection fraction. Identifying potential ‘responders’ to therapy will be important to tailor future management to restore cardiac function.

**Acute heart failure syndromes management—phases of care**

There are two primary phases of AHFS care, which may be further subdivided (Table 2). Phase I is the stabilization phase, which commonly begins in the emergency department (ED). Safely improving
signs and symptoms, haemodynamics, and correction of volume overload are the primary goals. Phase II continues with stabilization during hospitalization and continues into the post-discharge period. The primary goal is to prevent progression, recover cardiac function or even reconstruct the heart through focused implementation of evidence-based guidelines.

Stabilization phase of acute heart failure syndromes

Identify and treat life-threatening conditions
Airway management, support of breathing, and circulatory support remain the cornerstone of initial resuscitative efforts and may be necessary in dramatic presentations of AHFS (e.g. flash pulmonary oedema or cardiogenic shock). Other life threatening conditions requiring timely intervention, such as ST-elevation MI, malignant arrhythmia, or hypertensive emergency should be promptly identified and treated. Treatment and diagnosis often proceed in parallel.

Diagnosis of heart failure
Diagnosis of HF is made clinically. A thorough history, assessment of symptoms, and physical exam for signs of HF (JVD, s3, rales, peripheral oedema) should be carefully performed. Radiographic evidence of pulmonary congestion may aid in diagnosis as well as rule in or rule out other diagnoses (e.g. pneumonia). However, absence of radiographic pulmonary congestion does not exclude a high filling pressure in patients with chronic HF. Measurement of natriuretic peptide levels in conjunction with the clinical impression is helpful when the diagnosis is in question.

Determine and treat the clinical profile
The clinical profile prompts initial management (Figure 1 and Table 3). Whether short- or long-term outcomes are improved as a result of initial management requires further study. In patients with elevated BP, proportional greater use of nitrate therapy with lower dose diuretic therapy vs. low-dose nitrates and high-dose diuretics has been suggested to improve outcomes. Improvement of LV filling pressures and/or cardiac output, leading to symptomatic improvement are goals of early management.

---

**Table 2** Phases of acute heart failure syndromes management

<table>
<thead>
<tr>
<th>PHASES</th>
<th>GOALS</th>
<th>Available Tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial or emergency</td>
<td>Treat life threatening conditions</td>
<td>Examples: STEMI → reperfusion therapy</td>
</tr>
<tr>
<td>department phase of</td>
<td>Establish the diagnosis</td>
<td>History, physical exam, EKG, X-ray, natriuretic peptide level</td>
</tr>
<tr>
<td>management</td>
<td>Determine the clinical profile</td>
<td>BP, HR, signs (e.g. pulmonary oedema), ECG, X-ray, laboratory analysis, echocardiography</td>
</tr>
<tr>
<td></td>
<td>Identify and treat precipitant</td>
<td>History, physical exam, X-ray, ECG, laboratory analysis</td>
</tr>
<tr>
<td></td>
<td>Disposition</td>
<td>No universally accepted risk-stratification method</td>
</tr>
<tr>
<td>In-hospital phase</td>
<td>Monitoring and reassessment</td>
<td>Signs/symptoms, HR, SBP, ECG, orthostatic changes, body weight, laboratory analysis (BUN/Cr, electrolytes), potentially BNP</td>
</tr>
<tr>
<td></td>
<td>Assess right and left ventricular pressures</td>
<td>SBP (orthostatic changes, valsalva manoeuvre), echocardiography, BNP/NT-proBNP, PA catheter</td>
</tr>
<tr>
<td></td>
<td>Assess and treat (in the right patient) other cardiac and non-cardiac conditions</td>
<td>Echo-Doppler, cardiac catheterization, electrophysiology testing</td>
</tr>
<tr>
<td></td>
<td>Assess for myocardial viability</td>
<td>MRI, stress testing, echocardiography, radionuclear studies</td>
</tr>
<tr>
<td>Discharge phase</td>
<td>Assess functional capacity</td>
<td>6 min walk test</td>
</tr>
<tr>
<td></td>
<td>Re-evaluate exacerbating factors (e.g. non-adherence, infection, anaemia, arrhythmias, hypertension) and treat accordingly</td>
<td>Examples: physical therapy, education for diet control and medication, evaluation for sleep apnoea</td>
</tr>
<tr>
<td></td>
<td>Optimize pharmacological therapy</td>
<td>ACCF/AHA and ESC guidelines</td>
</tr>
<tr>
<td></td>
<td>Establish post-discharge planning</td>
<td>Discharge instructions including body weight monitoring, smoking cessation, medication adherence, follow-up</td>
</tr>
</tbody>
</table>

Adapted and reproduced with permission from Khan et al.67
Symptom improvement, however, should not cause downstream harm, such as myocardial or renal injury, decreased coronary perfusion, increased heart rate, and/or further neurohormonal activation.\textsuperscript{50–52} Careful attention to heart rate, rhythm, and BP is essential.

Traditional medications such as loop diuretics and nitrates have not been rigorously studied. Thus, dosing and goals of such therapies remain largely empirical. Safely improving symptoms and hemodynamics during the stabilization phase of management remains an unmet therapeutic need.

**Identify and treat precipitating/contributing factors**

According to data from the Euro Heart Failure Survey II, the most common precipitants for AHFS differ between de novo and worsening chronic HF admissions.\textsuperscript{8} For those with de novo HF, ACS, valvular causes, and arrhythmias were the most common precipitants. Arrhythmias and valvular causes were also common precipitants for patients with decompensated chronic HF, but medication non-compliance was more common than ACS.\textsuperscript{8} Analysis from OPTIMIZE-HF highlight pneumonia/

**Disposition**

Evidence-based data to guide and facilitate risk-stratification/disposition after early management is lacking. Although the high-risk patient has been characterized, absence of high-risk does not necessarily equate to a low-risk patient.\textsuperscript{19,54–58} Systolic BP may represent a broadly applicable method to rapidly discriminate in-hospital mortality risk.\textsuperscript{1} Initial studies support stratification of patients to the observation unit setting (Figure 2).\textsuperscript{59} Current NHLBI funded studies are exploring risk stratification from the ED.\textsuperscript{60}

**Figure 2** In-hospital mortality rates by admission systolic blood pressure deciles ($n = 48567$). Reproduced with permission from \textit{JAMA}, \textbf{296}(18):2223. Copyright 2006. American Medical Association. All rights reserved.\textsuperscript{1}

**Table 3** Initial therapeutic management

<table>
<thead>
<tr>
<th>Target</th>
<th>Therapeutic example</th>
<th>Mechanism of action</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alleviate congestion</td>
<td>IV furosemide</td>
<td>Water and sodium excretion</td>
<td>Electrolyte abnormalities</td>
</tr>
<tr>
<td>Reduce elevated LV filling pressures</td>
<td>IV nitrates</td>
<td>Direct relaxation of vascular smooth muscle cells through various mechanisms</td>
<td>Hypotension, decreased coronary perfusion pressure</td>
</tr>
<tr>
<td>Poor cardiac performance</td>
<td>Inotropes</td>
<td>_activate camp or calcium sensitization resulting in improved contractility; also powerful vasodilators: in effect, inodilators</td>
<td>Hypotension, arrhythmias, myocardial damage, association with increased morbid events</td>
</tr>
<tr>
<td>Tachycardia and increased systemic blood pressure (i.e. in cases of excessive sympathetic tone)</td>
<td>Beta-blockers: IV esmolol may be used when HF is related to AF with RVR and/or severe hypertension</td>
<td>Blockade of beta-1 and beta-2 receptors</td>
<td>Bradycardia, hypotension, negative inotropy; however given short half-life of esmolol, these side effects should be short lived</td>
</tr>
</tbody>
</table>

Adopted and reproduced with permission from \textit{Khan et al.}\textsuperscript{67}
needed, including greater evidence regarding therapies used routinely in daily practice. Whether AHFS management and outcomes are time-sensitive is an area in need of further research.

**Therapeutic management**

As traditional AHFS therapies have been extensively reviewed elsewhere (e.g. ESC Guidelines), we refer the reader to those reviews/guidelines.

**Future management**

Future management encompasses three primary domains: (i) implementation of evidence-based therapy for HF and other cardiac and non-cardiac conditions, (ii) systems re-engineering to optimize implementation of evidence-based surgical, electrical, medical therapies as well as socio-economic and psychosocial considerations, and (iii) novel therapeutic development including novel application of existing therapies.

**Comprehensive assessment and implementation of evidence-based therapy**

The majority of patients admitted with AHFS have chronic HF, however once hospitalized, in spite of initial improvement, patients continue to have severe haemodynamic and neurohumoral abnormalities during hospitalization as well as post-discharge. These abnormalities are likely to contribute to post-discharge outcomes and should be aggressively targeted. After initial stabilization and in-hospital management, available data suggest a lack of uptake of guideline recommended therapy. Initiation of existing guideline therapy is recommended in order to treat those pathologies that are amenable to intervention. This applies not only for HF guidelines,

---

**Figure 3** Comprehensive assessment and cardiac reconstruction. Modified and reproduced with permission from Gheorghiade and Pang. AHFS, acute heart failure syndromes; JVP, jugular venous pulse; LV, left ventricle; CAD, coronary artery disease; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICD, implantable cardiac defibrillator; CRT, chronic resynchronization therapy; Hydral, hydralazine; ISDN, isosorbide dinitrate; CABG, coronary artery bypass grafting; AF, atrial fibrillation; **Select patients. #Investigational agents. **Viable but dysfunctional myocardium.
but also for all other guideline recommended therapies for co-morbid cardiac and non-cardiac conditions (i.e. diabetes, hypertension, etc.) (Figure 3). Evidence-based treatment of co-morbid conditions is especially important for HF patients with preserved ejection fraction, as evidence to treat HF in this large sub-group of patients is limited.66

Hospitalization represents a unique opportunity for comprehensive assessment, given limited time and resources available in the outpatient setting.22,67 This assessment should not increase the length of stay and should be tailored to each individual country, as there are variations in length of stay and re-hospitalization rates between countries as well as between the USA and Europe overall.68 Thorough assessment and implementation of evidence-based therapies during hospitalization or soon after and may have significant socioeconomic benefit if re-hospitalizations and/or mortality is decreased.

Quality measures

In the USA, hospital reported quality measures demonstrate differences in risk-adjusted re-hospitalization and mortality rates between hospitals.68,69 Despite similar therapeutic options, outcomes are different. Although explanations have varied, it is clear that systems re-engineering may yield improved results.70,71 This may involve improving communication between providers to ensure safe and effective transitions of care or the creation or utilization of a comprehensive disease management program, which have been shown to improve outcomes.70,71

Recent evidence suggests that in-patient HF quality measures (measurement of EF, smoking cessation, discharge instructions, ACE-I/ARB for LV systolic dysfunction, and anti-coagulation for AF) are not associated with improved 60–90 days re-hospitalization or mortality rates, with the exception of ACE-I/ARB.72,73 The high post-discharge event rate combined with the substantial cost for hospitals to achieve measures that do not improve outcomes suggests that better measures are needed.73

Novel therapeutic development

Many clinical development programs in AHFS expect that a drug will not only safely improve signs and symptoms but also positively impact long-term outcomes. While not impossible, unless a substantial pathophysiological interruption occurs or that currently used therapies cause sufficient downstream harm, it is doubtful that a drug given for hours to days will impact longer-term outcomes. Inotropic therapy may be one notable exception, given the morbidity and mortality associated with current inotropes. Rather, therapies may be divided into two general groups and should focus on specific AHFS sub-groups rather than a ‘one-size-fits-all’ approach.

(1) Short term: Typically given for hours to days, these agents target signs and symptoms, haemodynamic stabilization, potential protection/prevention of organ injury, and/or facilitate implementation of known evidence-based therapies.

(2) Long-term: Typically given for weeks to months to improve mortality and/or re-hospitalization.

Each group may be further divided into traditional (e.g. vasodilators, fluid removal) vs. non-traditional (e.g. energetics, metabolic modulators) therapeutic classes. In addition, therapies given short term might also be continued long term. The majority of novel therapies are being developed as short-term therapy (Table 4).

Table 4  Short- and long-term novel therapies for acute heart failure syndromes

<table>
<thead>
<tr>
<th>Short term</th>
<th>Long term</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cinaciguat</td>
<td>Direct renin inhibitors</td>
<td>Adenosine antagonists</td>
</tr>
<tr>
<td>CD-NP</td>
<td>Macronutrients</td>
<td>Vasopressin antagonists</td>
</tr>
<tr>
<td>Relaxin</td>
<td>Micronutrients</td>
<td>Digoxin</td>
</tr>
<tr>
<td>Adenosine regulating agents</td>
<td>CRT/AICD</td>
<td></td>
</tr>
<tr>
<td>Stresscopin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Istaroxime</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac myosin activators</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Short-term traditional type therapies

Cinaciguat

This novel vasodilator is currently in the early stages of development. From a pharmacodynamic standpoint, activation of soluble guanylate cyclase (sGC) by cinaciguat in smooth muscle cells leads to the synthesis of cyclic guanosine monophosphate (cGMP) and subsequent vasodilation.74 The same pathway is also activated by traditional nitrates; however, for nitrates to achieve their effects, the Fe/heme complex of sGC needs to be in a reduced state.75,76 During periods of increased stress, such as AHFS, a significant proportion of heme Fe may become oxidized, potentially blunting the effects of NO donors.75 In contrast, cinaciguat appears to be a heme-independent sGC activator, with more predictable vasodilator response in conditions of elevated oxidative stress. In accord with pharmacological data, preliminary studies in patients with AHFS show a beneficial haemodynamic profile of cinaciguat.74 At high doses, a substantial decrease in systolic blood pressure (SBP) was noted. However, this was not associated with adverse effects on renal function, re-hospitalization, or mortality suggesting a possible cardioprotective effect. Lower-dose trials are currently underway.

Chimeric natriuretic peptides

These molecules have been engineered to combine the beneficial aspects of different natriuretic peptides into a single molecule while minimizing potentially negative actions.77,78 CD-NP is a combination of C-type natriuretic peptide (CNP) and Dendroapsis NP (DNP).78 Although lacking natriuretic effects, CNP is a more selective venodilator than BNP, thus reducing the risk of significant hypotension. On the other side, DNP possesses significant natriuretic activity, at the expense of possible hypotensive effects.79 The chimeric peptide CD-NP combines the favourable natriuretic effects of DNP with the venodilatory profile of CNP, reducing the risk for harmful side effects.77,78 Preliminary studies in AHFS patients are ongoing.
Relaxin
First identified as a pregnancy hormone with powerful vascular effects, relaxin is currently under investigation for its systemic and renal vasodilatory actions. In AHFS patients with high SBP, data from a Phase II trial have demonstrated an improvement in dyspnoea with a single dose. A Phase III clinical trial is currently underway.

Istaroxime
A prototype of a new class of drugs, istaroxime exerts its actions on the myocyte in two ways: stimulation of membrane-bound Na-K/ATPase and by enhancing activity of sarcoendoplasmic reticulum Ca/ATPase type 2a. This mechanism results in inotropic and lusitropic benefits without adverse haemodynamic consequences. Preliminary data demonstrate that istaroxime increases SBP, while reducing HR, improves diastolic function, decreases PCWP, and improves CI, thus demonstrating significant potential for patients presenting in cardiogenic shock or low-output HF. To date, no other approved inotropic therapy has such a favourable haemodynamic profile.

Cardiac myosin activators
These new agents are cardiac-specific myosin ATPase activators designed to improve myocardial contractility by accelerating the productive phosphate-release step of the crossbridge cycle. In animal studies, these drugs have been shown to improve the indices of left ventricular systolic function by increasing the systolic ejection time. Importantly, coronary blood flow, coronary sinus oxygen content, and myocardial oxygen consumption did not change at the time of drug administration. This apparent paradox can be explained by an improved energy efficiency of the contractile apparatus induced by these drugs.

Short-term non-traditional type therapies
Adenosine regulating agents
This new class of drugs, whose prototype is represented by acadesine, has been developed to mimic the protective effects of adenosine during ischaemia. Acadesine exerts its pharmacological actions by increasing adenosine bioavailability and by activating S’adenosine monophosphate (AMP) signalling cascade via its metabolite S-aminoimidazole-4-carboxamide riboside (ZMP). The first mechanism leads to multiple anti-ischaemic effects (maintenance of endothelial function and vasodilation, inhibition of platelet aggregation and neutrophil activation), whereas the latter ameliorates glucose uptake and free fatty acid oxidation thus increasing ATP synthesis. Importantly, acadesine exerts its actions only in areas undergoing net ATP catabolism (such as ischaemic tissues) thereby avoiding potentially harmful peripheral vasodilator effects.

Urocortins
Urocortins are a recently discovered group of peptide hormones of the corticotropin releasing factor family. They bind with a strong affinity to the CRH-R2 receptor, which is highly expressed in the myocardium and in the vascular endothelium. Urocortins exhibit potent inotropic and lusitropic effects on rat and sheep hearts and activates a group of myocyte protective pathways collectively known as ‘reperfusion injury salvage kinase.’ Study in healthy humans show that brief intravenous infusions of urocortin 2 in healthy humans induce pronounced dose-related increases in cardiac output, heart rate, and left ventricular ejection fraction while decreasing systemic vascular resistance; similar effects were seen in HF patients.

Long-term traditional type therapies
Direct renin inhibitors
The mechanism of action of this class of drugs involves the inhibition of the first step in the renin–angiotensin–aldosterone system (RAS) cascade, effectively suppressing this pathway. Given the role of RAS in the neurohormonal imbalance present in patients with HF, aliskiren, an oral direct renin inhibitors (DRI) currently approved for the treatment of hypertension, is currently undergoing Phase III trials to test whether the addition of an DRI to standard therapy delays time to events, including cardiovascular death or HF re-hospitalization within 6 months in patients hospitalized for AHFS and EF <40%.

Long-term non-traditional type therapies
Macronutrients
In the last few years, numerous epidemiological and interventional studies have shown that dietary omega-3 fatty acids exert beneficial CV effects. The recent publication of the GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico) trial has expanded these observations to patients with chronic HF, showing mortality and morbidity benefits. The proposed mechanisms include anti-inflammatory and haemodynamic effects, as well as CV remodelling, neurohormonal inhibition, and arrhythmia suppression. Whether treatment with omega-3 fatty acids may benefit patients with AHFS remains undetermined and further research is warranted.

Therapies for both short and long term
Vasopressin antagonists
Vasopressin antagonists bind with various affinities to the arginine vasopressin (AVP) receptors V1a, V1b, and V2. The V1a receptor is the most widespread subtype of vasopressin receptor and is found in vascular smooth muscle and many other structures. V1b receptors have limited distribution. V2 receptors are located predominantly in principal cells of the renal collecting-duct system where they induce free water diuresis. Tolvaptan, an oral V2 antagonist has been approved for use in patients with clinically significant hypervolemic and euvoletic hyponatraemia. In the EVEREST trials, tolvaptan decreased serum sodium and body
**Table 5  Ideal properties for an acute heart failure syndromes therapy**

1. Improve signs and symptoms (e.g. dyspnoea)
2. Improve haemodynamics without adversely effecting heart rate and blood pressure
3. Improve the neurohumoral profile
4. Do not cause myocardial and/or kidney damage
5. Be effective in the context of current evidence-based therapy such as ACE-I and beta-blockers
6. Demonstrate efficacy in both the acute and chronic setting
7. Be affordable
8. Reduce both in-hospital and post-discharge morbidity and mortality.

Adenosine antagonists

Adenosine antagonists were developed for their potentially renoprotective effects derived from preservation of glomerular filtration through inhibition of adenosine-mediated tubuloglomerular feedback. Blockade of sodium re-absorption leading to mild diuresis was considered an additional benefit.\(^{100,101}\) As baseline renal function and changes in renal function during hospitalization are predictors of post-discharge outcomes in AHFS, preservation of renal function with adenosine agonists appears to be a potential target to decrease adverse outcomes. Despite the positive trends seen in a Phase II trial using rolofylline (PROTECT-Pilot), the pivotal Phase III PROTECT trial failed to reach its primary or secondary endpoints.\(^{102}\) In addition, there were non-significant, but concerning CNS safety signals. Given the relatively low proportion of patients with WRF, defined as a worsening creatinine of 0.3 mg/dL or greater at two separate time points, it is possible that the hypothesis for which PROTECT was designed has yet to be thoroughly tested.

Re-evaluating existing therapies

Currently available evidence-based therapies for chronic HF, such as ACE-I and beta-blockers, have not been well studied in AHFS. The re-evaluation of these therapies in this setting is important since the neurohumoral, haemodynamic, and renal abnormalities of AHFS are different compared to the chronic state.

Cardiac glycosides

Cardiac glycosides have been used for thousands of years, yet with the introduction of new chronic HF agents, their use has declined substantially in the last 10 years (from 70 to 15%).\(^{103,104}\) Digoxin, the most commonly used cardiac glycoside, appears to have many ideal properties for an AHFS drug, including relatively rapid onset, haemodynamic benefits, absence of negative effects on neurohormonal activation, BP, HR, or renal function.\(^{105,106}\) Unfortunately, it has not yet been tested in the AHFS setting (Table 5).\(^{107}\)

A new paradigm in clinical development—T1 translational research

Phase III trials in AHFS have, to date, largely failed. Although novel clinical development continues to be promising, repeatedly successful Phase II studies followed by unsuccessful Phase III studies raises the question that repetition of past clinical development pathways may not lead to different outcomes. In the past, Phase II was considered the stage to best understand the mechanistic properties of a drug. However, it is possible that failure was related to an incomplete understanding of the drug and/or the drug was tested in a ‘wrong’ patient population given the diverse pathophysiologic processes seen in AHFS. We propose a new paradigm and have borrowed the phrase T1 Translational Research to describe it. These would be small studies, but in multiple tightly controlled, homogenous HF patient sub-groups to limit phenotypic variability. Such an approach would maximize the signal-to-noise ratio, allowing for a more thorough understanding of the mechanistic properties of the drug. Importantly, identification of early ‘failure’ is also beneficial.

Conclusion

Improving post-discharge outcomes for patients with AHFS is a fundamental goal of therapy. Current management remains challenging, as the evidence for initial management is limited. A better understanding of existing therapies is needed. In addition, certain healthcare systems and institutions have better outcomes despite a similar therapeutic armamentarium, suggesting the benefits of optimization of therapies, including psychosocial and socioeconomic considerations. Better measures of HF quality are needed.

In spite of the commonly held belief that the high mortality and morbidity seen post-discharge is inevitable, we believe future management holds great promise as many conditions that contribute to progression of HF can be effectively treated (e.g. CAD, valvular disease, ventricular dyssynchrony). In addition, since progression of LV dysfunction contributes to the poor prognosis of HF, identifying patients with viable but dysfunctional myocardium, which is potentially salvageable, and for whom future therapies can be identified, may be the last frontier in the treatment of AHFS.

Acknowledgement

The authors would like to thank Umberto Campia MD for his editorial assistance and April York for her administrative support.
Conflict of interest: P.S.P. is or has been in the last 5 years a consultant to Astellas, Bayer, the Medicines Company, Nile Therapeutics, Otsuka, Palatin Technologies, PDL BioPharma, PeriCor Therapeutics, and Solvay Pharmaceuticals. M.K. is a consultant for Servier, a member of the steering committee for ASCEND, SHIFT-HEAAL. A speaker for GSK, sanofi-aventis, Astra Zeneca, Menarini, Bristol Meyers Squibb, Merck Sharpe Dohm, and Boehringer Ingelheim. M.G. is or has been a consultant and/or received honoraria from Astellas, Bayer, Corthera, DebioPharm, ErreKappa Terapeutici, EKR Therapeutics, GlaxoSmithKline, Medtronic, Merck, Nile Therapeutics, Novartis, Otsuka, Palatin Technologies, PDL BioPharma, Pericor Therapeutics, Scios Inc., Solvay Pharmaceuticals, and SigmaTau.

References

Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (presents as a Late Breaking Clinical Trial). Transcatheter Cardiovascular Therapies Conference, Washington, DC. Am J Cardiol 2008;102:251.


Reconstructing the failing heart

793b


77. Dec GW. Instaroxine in heart failure new hope or more hype? J Am Coll Cardiol 2008;51:2286–2288.


79. Cleland JG. The Selective Cardiac Myosin Activator CK-1827452 Increases Systolic Function in a Concentration-Dependent Manner in Patients with Stable Heart Failure (presented as a Late Breaking Clinical Trial). Heart Failure Society of America Annual Meeting, Toronto, Canada, 2008.


