ACUTE HEART FAILURE: WHAT IS NEW?

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Acute HF is a complex and often life-threatening clinical condition. Existing and new therapeutic approaches have failed to reduce the risk for recurrent hospitalizations and mortality in this condition, possibly because they treat similar patients with different clinical profiles and underlying pathophysiology. The necessary steps for the optimal evaluation and treatment of patients with acute HF include: (i) making a firm diagnosis (using biomarkers, echocardiography, thoracic ultrasound, and an invasive evaluation); (ii) classifying and evaluating the patient for specific etiologies and determining the underlying pathophysiology (CHAMP evaluation for acute de novo heart failure: four clinical scenarios based on clinical evaluation for acutely decompensated heart failure); (iii) treating the acute phase according to the underlying pathophysiology and clinical profiles; (iv) providing specific instructions for chronic disease-modifying medications after clinical stabilization; and (v) creating a discharge plan and managing significant comorbidities. This review summarizes some new aspects regarding the classification, diagnosis, and therapy of acute HF syndromes.

NEW GUIDELINE-RECOMMENDED CLINICAL CLASSIFICATION

The initial clinical evaluation aims to classify patients with acute HF into four different clinical profiles according to the presence of congestion (wet or dry patient) and/or peripheral hypoperfusion (warm or cold patient). Table I describes the new ESC HF guideline-recommended clinical classification of acute HF, clinical profile–associated in-hospital mortality, and recommended management according to each clinical scenario.

DIAGNOSTIC PROCESS AND TOOLS

Upon emergency department admission, the current diagnostic algorithm initially recommends a comprehensive investigation for the detection of severe hemodynamic instability/cardiogenic shock and/or respiratory failure requiring support with invasive or noninvasive mechanical ventilation. After excluding these severe entities, the next diagnostic step is to assess the potential specific causes of acute symptoms, such as acute coronary syndromes, hypertension emergencies, arrhythmias, mechanical factors (eg, acute valve regurgitation, septal rupture, aortic dissection), or pulmonary embolism (CHAMP diagnostic approach for acute de
novo heart failure).\textsuperscript{2} Confirmation of the diagnosis of acute HF typically requires additional diagnostic tests after the initial comprehensive clinical evaluations, which mainly consist of imaging modalities and biomarkers.

**IMAGING MODALITIES**

**Echocardiography**

In patients with hemodynamic instability or frank cardiogenic shock, immediate echocardiography is mandatory. Early echocardiography, preferably within the first 48 hours after presentation is required in cases of new-onset acute HF and in all cases with no previously documented assessment of cardiac function. Pocket-sized portable echocardiography may provide a reliable initial assessment of left ventricular systolic function and it can be used as part of the clinical evaluation of the patient in the emergency room.\textsuperscript{3}

**Thoracic ultrasound**

With appropriate expertise, bedside thoracic ultrasound can be useful for the detection of interstitial lung edema and pleural effusion. Interstitial lung edema is detected by the presence of comet-like vertical reverberation artifacts caused

<table>
<thead>
<tr>
<th>Clinical phenotype</th>
<th>Pathophysiology</th>
<th>In-hospital mortality*</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warm and dry</td>
<td>No congestion No hypoperfusion</td>
<td>1.7%</td>
<td>Dyspnea of noncardiac cause: manage accordingly</td>
</tr>
<tr>
<td>Warm and wet</td>
<td>Pulmonary and/or peripheral congestion No hypoperfusion</td>
<td>4.1%</td>
<td>CPAP IV diuretics and vasodilators Ultrafiltration</td>
</tr>
<tr>
<td></td>
<td>Acute hypertensive pulmonary edema, 2.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold and dry</td>
<td>Hypoperfusion and hypovolemia Excessive use of diuretics</td>
<td>13.6%</td>
<td>Exclude noncardiac causes Fluid administration, inotropes</td>
</tr>
<tr>
<td>Cold and wet</td>
<td>Congestion Hypoperfusion</td>
<td>16.5%</td>
<td>Inotropes IV diuretics Mechanical support Ultrafiltration</td>
</tr>
</tbody>
</table>

\textbf{Table 1. New ESC heart failure guideline-recommended clinical classification of acute heart failure, clinical profile-associated in-hospital mortality, and recommended management.}

*Mortality rates according to the ESC Long-term heart failure registry.\textsuperscript{3}
by extravascular lung water accumulation, which are called B-lines. Detection of B-lines has been shown to have 94% sensitivity and 92% specificity for the differential diagnosis of acute HF from noncardiac causes of acute dyspnea. However, the specificity of B-lines is compromised in patients with alveolar consolidations due to infectious, infiltrative, or traumatic lung diseases or in cases with fibrotic pleural abnormalities, such as in systemic sclerosis.

**BIOMARKERS**

**Natriuretic peptides**

Natriuretic peptides are useful tools in differentiating dyspnea of cardiac etiology from dyspnea of noncardiac etiology and are recommended in all patients with suspected acute HF. Their diagnostic value lies predominantly in the exclusion of acute HF in patients with normal natriuretic peptide levels, as they show a high negative predictive value of 94% to 98% (upper normal values: BNP <100 pg/mL, NT-proBNP <300 pg/mL, MR-proANP <120 pg/mL). However, increased natriuretic peptide levels do not confirm the diagnosis of acute HF, as they may become elevated in a wide variety of cardiac (eg, atrial fibrillation, pulmonary embolism, etc) and noncardiac diseases (eg, renal dysfunction, sepsis, stroke, etc).

**Procalcitonin**

The assessment of procalcitonin may be considered in patients with acute HF and suspected infection for the differential diagnosis of pneumonia and to guide antibiotic therapy in these patients. A procalcitonin level of 0.1 ng/mL excludes pneumonia in patients with acute dyspnea, while a procalcitonin level >0.21 ng/mL identifies patients with acute HF with pneumonia in need of antibiotic therapy.

**Soluble ST2**

The soluble ST2 factor is increased in acute HF vs dyspnea of noncardiac etiology, with an optimal cut-off value of 0.20 ng/mL. However, its clinical utility is best as a prognostic biomarker in acute HF. In patients with acute HF, increased ST2 levels both at admission and at discharge have been associated with an increased risk of all-cause and cardiovascular mortality, and an increased discharge ST2 is associated with an increased risk of rehospitalization.

**MANAGEMENT**

**Diuretics and vasodilators**

Diuretics are the mainstay therapy for the treatment of congestion in acute HF and they should be administered early after the diagnosis of acute HF. Dosing of intravenous diuretics should be 20 to 40 mg furosemide (or equivalent) initially in patients not previously on diuretic therapy, while patients previously treated with
Diuretics should receive an initial intravenous dose that is at least equivalent to their previously administered oral dosing.\textsuperscript{2}

Intravenous vasodilators (nitrates, nitroprusside, and nesiritide) provide symptom relief and they should be considered in patients with cardiac-type acute HF whose systolic blood pressure is >90 mm Hg in combination with diuretics. In patients with vascular-type acute HF, vasodilators should be considered as initial therapy to improve symptoms and reduce congestion.\textsuperscript{3} Newer vasodilators, including ularitide and serelaxin, have failed to show a reduction in mortality and morbidity risk in recent randomized controlled trials.\textsuperscript{2}

**Inotropes and vasopressors**

Intravenous inotropes may be considered as short-term therapy for patients with hypotension and peripheral hypoperfusion despite adequate filling status to increase cardiac output and blood pressure and maintain end-organ function. Due to an increase in myocardial oxygen consumption, inotropes may aggravate myocardial ischemia and induce tachyarrhythmias, contributing to increased medium- and long-term mortality. Levosimendan is an inodilator that was developed as an alternative to classic  β-agonists for the treatment of low cardiac output acute HF. Levosimendan may be preferred over  β-agonist inotropes in patients with acute HF previously treated with β-blockers, as its mechanism of action is independent of the  β-adrenergic receptor pathway.\textsuperscript{2}

Vasopressors may be considered in patients with cardiogenic shock, who remain hypotensive/hypoperfused despite treatment with another inotrope to increase arterial blood pressure and maintain end-organ perfusion.\textsuperscript{2} Recently published data demonstrated that epinephrine use in cardiogenic shock has been associated with increased short-term mortality (30-day mortality is up to 4.7-fold higher with epinephrine vs other vasopressors, including norepinephrine and dopamine).\textsuperscript{7} Therefore, epinephrine should be avoided and norepinephrine should be the preferred vasopressor in cardiogenic shock.\textsuperscript{2}

**Chronic life-saving medications**

In patients with previously diagnosed HFREF who are on chronic therapy with life-saving medications, it is recommended to continue these therapies during hospitalization for acute HF unless a contraindication exists, including hypotension, bradycardia, or hypoperfusion (β-blockers); worsening renal function and hyperkalemia (ACE inhibitors/ARBs/mineralocorticoid receptor antagonists).\textsuperscript{2} In this case, doses might be reduced or drugs temporarily discontinued until the patient stabilizes. Regarding sacubitril/valsartan, an ongoing study will examine the feasibility and safety of starting sacubitril/valsartan in the hospital, early after hemodynamic stabilization vs postdischarge initiation in patients with HFREF.
hospitalized for acute HF. A previous study confirmed the safety and feasibility of initiating ivabradine plus β-blockers vs β-blockers alone in hospitalized patients with HFREF. The study showed that ivabradine plus β-blockers improved heart rate during the postdischarge period.  

Existing therapies for acute HF, with the respective class of recommendation according to the most recent ESC HF guidelines, are presented in Table II.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Class of recommendation and level of evidence</th>
</tr>
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<tbody>
<tr>
<td>Diuretics</td>
<td>IC</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>IIaB</td>
</tr>
<tr>
<td>Inotropes (short-term)</td>
<td>IIbC</td>
</tr>
<tr>
<td>Vasopressors (norepinephrine)</td>
<td>IIbB</td>
</tr>
<tr>
<td>Opiates</td>
<td>IIbB</td>
</tr>
<tr>
<td>Noninvasive ventilation (CPAP/BiPAP in respiratory distress)</td>
<td>IIaB</td>
</tr>
<tr>
<td>Ultrafiltration</td>
<td>IIbB</td>
</tr>
<tr>
<td>IABP (routine use)</td>
<td>III</td>
</tr>
<tr>
<td>Short-term mechanical circulatory support</td>
<td>IIbB</td>
</tr>
<tr>
<td>Chronic HFREF medications (continuation in decompensated chronic HFREF and initiation in de novo acute HF in the absence of contraindications)</td>
<td>IC</td>
</tr>
</tbody>
</table>

**Table II. Currently available pharmacological and device therapies in acute heart failure and corresponding class of recommendation according to the ESC heart failure guidelines.**

**NEW DRUGS**

Vericiguat

Vericiguat is a direct, oral, soluble guanylate cyclase (sGC) stimulator that enhances sGC sensitivity to endogenous nitric oxide. In a phase 2 study, vericiguat reduced the natriuretic peptide levels, while being safe and tolerable in patients with chronic HFREF. Currently, an ongoing trial is testing the efficacy of vericiguat vs placebo added to standard therapy to reduce cardiovascular mortality and HF hospitalizations in patients with HFREF and a previous hospitalization due to worsening HF.
Nitroxyl donors

Nitroxyl donors are pharmacological agents that release nitroxyl (HNO), a reactive nitrogen species with unique biochemical and pharmacological actions from NO. A phase 2a trial has confirmed the positive inotropic and vasodilatory effects of a pure HNO donor (CXL-1020) in hospitalized patients with HFREF, while an ongoing phase 2b trial is testing the safety and the clinical efficacy of CXL-1020 in reducing natriuretic peptide levels and improving dyspnea in patients with acute HF.

Omecamtiv mecarbil

Omecamtiv mecarbil is a selective cardiac myosin activator that enhances cardiomyocyte contraction by promoting the transition of actin-myosin complexes from a weakly to a strongly bound state and inhibiting nonproductive degradation of ATP. The phase 2 ATOMIC-AHF trial compared intravenous infusion of omecamtiv mecarbil with placebo in patients with acute HF and reduced left ventricular ejection fraction. Although the primary efficacy end point of dyspnea relief was not met in the pooled cohort, omecamtiv mecarbil reduced dyspnea at 48 hours and through 5 days in the high-dose cohort, with concomitant increases in left ventricular systolic ejection time and decreases in end-systolic left ventricular diameter. An ongoing phase 3 trial is testing the efficacy of oral omecamtiv mecarbil in reducing cardiovascular mortality and HF hospitalizations in patients with HFREF and a recent acute decompensation.

SUMMARY

Optimal management of acute HF remains an unresolved issue in daily clinical practice. For de novo acute HF, early recognition and correction of the cause is the gold-standard practice for in-hospital management. For acutely decompensated chronic heart failure, current therapeutic strategies have failed to improve cardiovascular outcomes as patients continue to exhibit high short- and long-term morbidity and mortality. Long-term adverse cardiovascular events are more likely to be decreased by adhering to evidence-based life-saving medications for chronic heart failure as well as optimal management of comorbidities in order to prevent heart failure exacerbations. Until new effective therapies become available, individualized treatment with existing drugs and devices according to the underlying pathophysiology appears the most suitable strategy for the management of acute HF.
REFERENCES


