Acute heart failure syndromes consist of a spectrum of clinical presentations due to an impairment of some aspect of the cardiac function. They represent a final common pathway for a vast array of pathologies and may be either a de novo presentation or, more commonly, a decompensation of pre-existing chronic heart failure. Despite being one of the most common medical presentations, there are no definitively proven prognosis-modifying treatments. The mainstay of current therapy is oxygen and intravenous diuretics. However, within this spectrum of presentations, there is a crucial dichotomy which governs the ultimate treatment approach, i.e. the presence, or absence, of cardiogenic shock. Patients without cardiogenic shock may receive vasodilators, whilst shocked patients should be considered for treatment with inotropic therapy or mechanical circulatory support, when appropriate and where available (see Chapter 53).
Non-shocked, congested, and well-perfused patients ('wet and warm') 
- Oxygen
- Diuretics and aquaretics
- Intravenous diuretics
- Vasopressin receptor antagonists

Vasodilators
- Nitroglycerin
- Sodium nitroprusside
- Nesiritide

Cardiogenic shock
- Inotropic therapy
  - Sympathomimetics
    - Dobutamine
    - Dopamine
    - Epinephrine (adrenaline)
    - Norepinephrine (noradrenaline)
    - Dopexamine
  - Phosphodiesterase inhibitors
    - Milrinone
    - Enoximone
  - Calcium sensitizers
    - Levosimendan

General considerations in patients with acute heart failure
- Pre-existing pharmacotherapy
- Thromboprophylaxis
- Pre-discharge

Emerging pharmacological therapies for acute heart failure
- Serelaxin
- Omecamtiv mecarbil
- Ularitide
- Istaroxime

Conclusion
Personal perspective
Appendix: the evidence base
Further reading

Introduction
Acute heart failure (AHF) is a common end-result of a spectrum of acute and chronic cardiovascular pathologies that impair cardiac function. Its definition continues to evolve, with the recent European Society of Cardiology (ESC) guidelines defining it as ‘the rapid onset of, or change in, symptoms and signs of heart failure’[1]. This definition encompasses all presentations, from those presenting with mild ankle swelling and breathlessness to those in fulminant cardiogenic shock (CS). Haemodynamic parameters (especially blood pressure and peripheral perfusion), the ventricular function, the respiratory function, the end-organ perfusion and function, and the underlying precipitants can vary widely across this spectrum of presentations, and treatment needs to be tailored to the individual patient.

The epidemiology of AHF is less well defined than that of chronic heart failure but is becoming better understood, following the publication of data from large contemporary registries, including ADHERE, OPTIMIZE, and the EuroHeart Survey on Heart Failure. In the developed world, AHF is predominantly due to coronary artery disease (CAD) or its sequelae, i.e. myocardial ischaemia, acute myocardial infarction (AMI), and consequent left ventricular (LV) systolic dysfunction. The majority of patients with AHF are normotensive or hypertensive [2, 3]. In the UK, patients are usually over 70 years of age, and most have a history of chronic heart failure. There is a 50–50 split between the sexes, but women are older at presentation and are more likely to have preserved left ventricular ejection fraction (LVEF). In-hospital mortality is around 15% but is much higher in patients with AHF secondary to AMI, and higher still in the presence of CS. Predictors of a poor outcome are increasing age, male sex, low systolic blood pressure, renal dysfunction, and socio-economic deprivation [4, 5].

The symptoms of AHF are predominantly driven by congestion, resulting in dyspnoea, peripheral oedema, or both, and low cardiac output. The mechanism underpinning the development of pulmonary oedema is increased intravascular pulmonary pressures, with transudation of protein-depleted plasma down a pressure gradient into the pulmonary interstitium and alveoli in severe cases. This can result in a significant impairment of gas exchange and respiratory failure. In patients with pre-existing chronic heart failure, this is compounded by the systemic hyperactivation of the sympathetic system and RAAS which promote the renal retention of Na+ and water.

No pharmacological intervention had been shown to improve survival in patients with AHF. This may be due to multiple factors. One may be the heterogeneity of patients with AHF. They comprise a diverse range of aetiologies, comorbidities, and severity at presentation. It has been postulated that the time from presentation to randomization may have been too long in earlier studies, thereby diminishing any potential benefit. Also, the sickest patients, who may have the most to gain, are often too
unwell to give fully informed consent and are therefore excluded from such trials.

The overall aims of pharmacological interventions in managing AHF are as follows:

- Immediate aims:
  - To relieve symptoms and optimize the fluid volume status
  - To restore the respiratory function, gas exchange, and systemic oxygenation
  - To improve the haemodynamics and end-organ function
  - To address any underlying cause or precipitant (e.g. myocardial ischaemia, arrhythmia, infection, anaemia, iatrogenic, etc.)

- Further aims:
  - To identify patients who may benefit from further non-pharmacological therapy in the short term (e.g. invasive ventilation, ultrafiltration, percutaneous coronary intervention (PCI), mechanical circulatory support) and medium term (e.g. cardiac resynchronization therapy, transplantation)
  - To optimize oral therapy for chronic heart failure (i.e. ACE-Is or ARNI, β-blockers, and mineralocorticoid receptor antagonists), once stable and prior to discharge

Close monitoring of the blood pressure, fluid balance, and urine output is essential during the management of AHF. Regular blood sampling, to monitor the parameters of acidosis, renal function (blood urea nitrogen, creatinine, estimated glomerular filtration rate) and electrolytes (especially K⁺), in particular, is required in the decompensated state. Figure 52.1 describes a crude and simplistic, but nonetheless useful, approach to classifying patient subtypes. This approach identifies four haemodynamic categories with which the patient may present: warm and dry, warm and wet, cold and dry, and cold and wet. Patients presenting wet and warm or wet and cold are at the highest risk of death or, in selected cases, need to be assessed for an urgent cardiac transplantation or mechanical circulatory support.
Within this spectrum of presentations exists a crucial dichotomy which governs the ultimate treatment approach—the presence, or absence, of CS

**Non-shocked, congested, and well-perfused patients (‘wet and warm’)**

**Oxygen**

Supplemental $O_2$ may be needed to treat hypoxaemia due to pulmonary congestion and/or oedema. There is no evidence base to support this approach. $O_2$ should not be used routinely in patients who are not hypoxic, as this causes vasoconstriction and a reduction in cardiac output, effects which are likely to be detrimental in AHF [6].

**Opiates**

IV morphine (2.5–10 mg IV bolus) can provide a prompt symptomatic improvement, due to several pharmacological properties. First, opiates have a mild anxiolytic effect and reduce distress associated with symptoms. They also have a mild venodilator effect which can help reduce congestion and preload. However, opiates frequently induce nausea and require the co-prescription of antiemetic drugs, some of which have undesirable actions, e.g. vasoconstriction [7]. A further unwanted side effect of opiate therapy is a potential depression of the respiratory drive which may precipitate the requirement for invasive ventilation. There is no evidence base to support the use of opiates, and indeed there are some registry data suggesting that opiate use is associated with adverse outcomes [8].

**Diuretics and aquaretics**

Intravenous diuretics
These are first-line therapy in patients with AHF and congestion (see Figure 52.2). No randomized placebo-controlled data exist for these agents, but extensive observational experience of rapid improvement in symptoms has led to these agents being endorsed by all the major international guidelines [1, 9, 10]. Generally, IV loop diuretics (e.g. furosemide or bumetanide) are used as first-line therapy and are recommended to be initiated at the earliest opportunity. Furosemide also has a venodilator action which can result in a reduction of ventricular filling pressures and a marked symptomatic improvement, prior to the onset of an augmented diuresis [11, 12]. The peak diuretic effect is typically seen between 1 and 2 hours, following IV administration, which subsides by 6 hours. Multiple daily doses may therefore be necessary to achieve the most efficient diuresis. As expected, greater responses are seen with higher doses [13]. A small randomized trial that used a patient global symptom assessment, as opposed to objective measures of fluid loss, as a primary endpoint reported that a continuous infusion of furosemide is no more effective than IV boluses [13]. Despite this, the ACC/AHA guidelines recommend switching between diuretic strategies in resistant patients [9]. A recent meta-analysis of ten trials did not demonstrate any significant difference in safety or efficacy between a bolus and a continuous diuretic infusion in patients with AHF [14].

Figure 52.2
The site of action of diuretics and aquaretics on the nephron. V2, vasopressin-2 receptor.
Reproduced from Gardner, McDonagh & Walker, OSH in Heart Failure, 2007 by permission of Oxford University Press.

In patients with resistant oedema, dual treatment with a loop and thiazide (e.g. bendroflumethiazide 2.5–5 mg) or a thiazide-like (e.g. metolozone 2.5 mg) diuretic may be needed to achieve an adequate diuresis (the so-called ‘sequential nephron blockade’) [15]. The ACC/AHA guidelines
stand alone in stipulating a level of recommendation (class 2b B) for the consideration of a low-dose dopamine infusion, in order to potentiate diuresis in certain resistant patients [9]. One relatively small trial demonstrated that the addition of dopamine to a diuretic regime is as efficacious as increasing the diuretics alone but may have a more favourable effect on renal function and plasma $K^+$ concentrations [16]. However, the recent, and much larger, ROSE-AHF trial suggested that the addition of dopamine or nesiritide (see later sections) to a diuretic regimen in patients with AHF and renal dysfunction did not improve diuresis or renal function, compared to diuretic therapy alone [17]. Interestingly, there was a trend towards both of these agents having a positive effect in the subgroup of patients with reduced LVEF. These findings serve to highlight the marked heterogeneity of the contemporary AHF population and potentially question whether the efficacy of targeted pharmacotherapy can be accurately delineated in such a diverse population. The findings from ROSE-AHF should prompt a similar study in AHF patients with reduced LVEF. Close monitoring of the blood pressure, fluid balance, renal function, and plasma electrolytes is strongly recommended in patients receiving IV diuretics [1, 9, 10].

Vasopressin receptor antagonists

Vasopressin (previously known as antidiuretic hormone) concentrations are sometimes inappropriately elevated in heart failure and may contribute to volume overload. A large multicentre randomized placebo-controlled trial of tolvaptan, a selective vasopressin-2 (V2) receptor antagonist, in addition to standard therapy, in AHF patients failed to demonstrate any mortality benefit [18]. Improvements were noted in the secondary endpoints of day 1 patient-reported dyspnoea, day 1 body weight, and day 7 oedema. There were no short to medium-term adverse outcomes, and tolvaptan is currently recommended for consideration in heart failure patients who are significantly hypervolaemic and hyponatraemic [1].

Vasodilators

In general, vasodilator treatment is recommended for patients with pulmonary congestion who are normotensive or hypertensive. These agents should be avoided in patients with concurrent obstructive valvular disease or restrictive physiology.
Nitroglycerin

Nitroglycerin is predominantly a venodilator which reduces ventricular filling pressures and helps to relieve pulmonary congestion [19, 20]. At higher doses, it also exhibits arterial dilation and is also frequently used as an effective anti-ischaemic therapy, which makes it attractive in patients with concomitant AHF and myocardial ischaemia. There are no robust data to suggest a significant improvement in either symptoms or mortality, as confirmed by a Cochrane review [21]. It can have a marked hypotensive effect, especially when the preload is also lowered by concurrent therapy, such as diuretics, so blood pressure monitoring is essential. Exposure to nitrates results in the rapid development of tolerance (particularly when given IV in high doses), limiting their effectiveness to 16–24 hours. Other AEs include resistance, headache, and abdominal bloating.

Sodium nitroprusside

Sodium nitroprusside (SNP) is a potent vasodilator that acts directly on vascular smooth muscle. It is not as widely used as nitroglycerin and has equal effects on arterial and venous tone, including the pulmonary circulation. As with nitroglycerin, SNP can improve the haemodynamic profile, but there are no robust data indicating a symptomatic or prognostic benefit from this therapy [22]. Indeed, there are some data suggesting that SNP may have a detrimental effect in patients, following an AMI [23], an effect which may be due to coronary ‘steal’. It is administered by IV infusion at 0.3–5 micrograms/kg/min, uptitrating carefully with invasive arterial monitoring. Likewise, SNP should also be downtitrated slowly to avoid rebound hypertension. SNP is rapidly metabolized and excreted entirely as metabolites, principally thiocyanate. The elimination half-life of thiocyanate is 2.7–7 days when the renal function is normal. Adverse events include hypotension and, rarely, metabolite (i.e. cyanide or thiocyanate) toxicity which is more commonly seen with concomitant hepatic or renal dysfunction. Plasma cyanide and thiocyanate levels should be monitored in such patients or those receiving a prolonged infusion. (See Table 52.1.)

<table>
<thead>
<tr>
<th>Table 52.1 Therapies as recommended by the three major guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Supplemental oxygen</td>
</tr>
<tr>
<td>Opiates</td>
</tr>
<tr>
<td>IV diuretics</td>
</tr>
</tbody>
</table>
Vasopressin receptor antagonists | - | 2b B | -
---|---|---|---
Nitroglycerin | 2a B | 2b A | 2b B
Sodium nitroprusside | 2b B | 2b A | 2b B
Nesiritide | - | 2b A | 2b B
Inotropes in cardiogenic shock | 2b C | 1 C | 2b C
Thromboprophylaxis | 1 B | 1 B | 1 B

ESC, European Society of Cardiology; ACC/AHA, American College of Cardiology/American Heart Association; HFSA, Heart Failure Society of America.

Level of recommendation: 1, is recommended; 2a, should be considered; 2b, may be considered.

Level of evidence: A, Cochrane review, large randomized trial; B, small randomized trial, meta-analysis; C, consensus expert opinion.

Nesiritide

Nesiritide is a recombinantly produced synthetic analogue of human B-type natriuretic peptide (BNP). Endogenous BNP binds to the guanylate cyclase receptor of vascular smooth muscle and endothelial cells, leading to increased intracellular concentrations of cGMP and smooth muscle cell relaxation. Thus, nesiritide causes dose-dependent reductions in pulmonary capillary wedge pressure (PCWP) and systemic arterial pressure by venous and arterial dilatation. Nesiritide has a half-life of approximately 18 min and is administered via an IV infusion at a rate of 0.01-0.03 micrograms/kg/min. Early work demonstrated the efficacy of nesiritide in reducing ventricular filling pressures, with variable effects on cardiac output [24]. It has recently been evaluated in the largest international randomized placebo-controlled trial to date in patients with AHF [25]. Nesiritide had no effect on the composite endpoint of rehospitalization for heart failure or death within 30 days. There was a trend towards an improvement in dyspnoea that did not reach the pre-specified level of statistical significance. No impact was noted on the renal function, but hypotension was more common in patients receiving nesiritide therapy. Nesiritide is currently available in North America, but in few European countries.

Cardiogenic shock
The ‘shocked’ or ‘low output’ patients, in whom the cardiac output is insufficient to maintain organ perfusion and function, represent the minority of AHF patients. Congestion, as described previously, often co-exists. An arbitrary cut-off systolic blood pressure defining CS is often quoted in the literature; however, the measured blood pressure needs to be interpreted in the context of the patient’s baseline blood pressure (if known). Other clinical signs providing information about the end-organ status, such as capillary refill time, cold skin, reduced urine output, lactate, and impaired cognition, are crucial for the diagnosis of CS.

O2 and diuretic therapy, as already discussed, should be considered in these patients; however, vasodilators described earlier are contraindicated. The aim of pharmacological therapy in these patients is to improve the cardiac function by increasing contractility and the cardiac output, with consequent optimization of tissue perfusion and end-organ function.

Certain patients with AHF are ‘wet and cold’, with ‘normal’ blood pressure, i.e. not meeting the criteria for CS. This likely represents a pre-CS compensatory phase, with peripheral vasoconstriction maintaining blood pressure. Initial therapy with diuretics should be closely monitored (with invasive monitoring, if necessary, to assess the PCWP and cardiac output). If the blood pressure subsequently falls, then these patients should be managed as CS, as outlined in the next sections.

Inotropic therapy

Inotropic agents represent ‘rescue’ therapy (see Figure 52.3). They are frequently used in patients with AHF, in an attempt to stabilize and salvage, or as a bridge to a more definitive non-pharmacological therapy such as transplantation or mechanical circulatory support. All of the major international guidelines currently recommend the use of inotropes in patients with CS. The ESC guidelines recommend this as the sole indication [1], whereas both American guidelines suggest an additional potential role in patients with end-stage heart failure receiving palliative care [9, 10]. Despite reports of beneficial haemodynamic effects, none of these agents have been shown to improve clinical outcomes, and, in some cases, their use has been shown to increase mortality. The agents of choice differ between centres, let alone countries, as no robust evidence base exists. Classes include sympathomimetics (e.g. dobutamine, adrenaline), phosphodiesterase inhibitors (e.g. milrinone, enoximone), and, more recently, calcium sensitizers (e.g. levosimendan). Agents are further categorized as to whether or not they have a vasodilating (inodilators) or vasoconstricting (inoconstrictors) effect (see Table 52.3). All of these agents improve myocardial contractility but, especially in the case of the sympathomimetics, also increase myocardial O2 consumption and can promote the development of tachyarrhythmias. Dosages/infusion rates are guided by the clinical status, blood pressure,
Acute heart failure: early pharmacological therapy

and markers of end-organ perfusion discussed earlier [26]. All patients require close monitoring of the cardiac rhythm and haemodynamic parameters during treatment with these agents.

Figure 52.3
Inotropic mechanisms and current inotropic interventions.

<table>
<thead>
<tr>
<th>Dose</th>
<th>0.5–3.0 micrograms/kg/min</th>
<th>3.0–5.0 micrograms/kg/min</th>
<th>&gt;5.0 micrograms/kg/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominant action</td>
<td>DA₁</td>
<td>β₁</td>
<td>5HT and α₁</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>↑ cardiac output</td>
<td>↑ myocardial contractility</td>
<td>↑ heart rate Vasoconstriction</td>
</tr>
<tr>
<td>Renal</td>
<td>↓ proximal tubular Na reabsorption</td>
<td>↑ renal blood flow</td>
<td>Variable effect on renal blood flow</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>↑ splanchnic blood flow</td>
<td>↑ splanchnic blood flow</td>
<td>Variable effect on splanchnic blood flow</td>
</tr>
</tbody>
</table>

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### Table 52.2 Drugs used to treat acute heart failure that are positive inotropes or vasopressors or both.

<table>
<thead>
<tr>
<th></th>
<th><strong>Bolus</strong></th>
<th><strong>Infusion rate</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine</td>
<td>No</td>
<td>2–20 μg/kg/min (β+)</td>
</tr>
<tr>
<td>Dopamine</td>
<td>No</td>
<td>&lt;3 μg/kg/min: renal effect (δ+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3–5 μg/kg/min: inotropic (β+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;5 μg/kg/min: (β+). vasopressor (α+)</td>
</tr>
<tr>
<td>Milrinone</td>
<td>25–75 μg/kg over 10–20 min</td>
<td>0.375–0.75 μg/kg/min</td>
</tr>
<tr>
<td>Enoximone</td>
<td>0.5–1.0 mg/kg over 5–10 min</td>
<td>5–20 μg/kg/min</td>
</tr>
<tr>
<td>Levosimeden(^a)</td>
<td>12 μg/kg over 10 min (optional)(^b)</td>
<td>0.1 μg/kg/min. which can be decreased to 0.05 or increased to 0.2 μg/kg/min</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>No</td>
<td>0.2–1.0 μg/kg/min</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Bolus: 1 mg can be given i.v. during resuscitation, repeated every 3–5 min</td>
<td>0.05–0.5 μg/kg/min</td>
</tr>
</tbody>
</table>

\(^a\) Also a vasodilator.

\(^b\) Bolus not recommended in hypotensive patients (systolic blood pressure, 90 mmHg).

\(^a\) ¼ alpha adrenoceptor; \(^b\) ¼ beta adrenoceptor; \(^d\) ¼ dopamine receptor.
Acute heart failure: early pharmacological therapy

McMurray et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology, European Heart Journal, 2012.

Sympathomimetics

**Dobutamine**

Dobutamine is a synthetic catecholamine, with β1-, β2-, and α1-adrenergic activity, resulting in an increased cAMP production. Its primary mode of action is via β1 activation, resulting in an increased cardiac output and a reduction in the PCWP. As such, it is one of the most widely used inotropic agents in AHF. Dobutamine has a short half-life of around 2 min, with a peak effect after 10 min. It is renally cleared and should be administered via central access. Unwanted effects of dobutamine are relatively common and include sinus tachycardia, myocardial ischaemia, arrhythmias, and hypotension at higher doses (due to β2 stimulation). At high doses, a vasoconstrictor effect can be seen, due to some α-receptor binding.

Dobutamine has not been the subject of a robust RCT with clinically meaningful endpoints; however, smaller studies [27] and meta-analyses suggest a trend towards an increasing mortality in treated patients [28, 29].

**Dopamine**

Dopamine is an endogenous precursor of norepinephrine, with a predominantly β1-receptor activity. However, at low doses, it acts on dopamine receptors (DA1), causing dilation of smooth muscles in renal arteries, which may augment diuresis, in combination with diuretics, as discussed earlier. At higher doses, it has inotropic effects through β1-receptors, and vasoconstrictor effects via α1 and 5HT receptors (see Table 52.4). It has a plasma half-life of 9 min.

**Epinephrine (adrenaline)**

Epinephrine is a direct-acting sympathomimetic agent, exerting its effect on β1-, β2-, and α1-adrenoreceptors. It is a potent inotropic, chronotropic, and vasoconstricting agent. Generally, it does not have a role in the management of AHF and should not be administered outwith the critical care setting. It is known to increase myocardial O₂ demand and is proarrhythmic, due to raised intracellular cAMP and Ca²⁺ concentrations.

**Norepinephrine (noradrenaline)**
Norepinephrine is an endogenous agonist at α1- and α2-adrenoreceptors, with only very modest effects on β1-adrenoreceptors. It is a potent vasoconstrictor and so does not generally have a role in the management of AHF, as the systemic vascular resistance is usually high in these patients. However, it can be useful in the patient with heart failure who has concurrent septic shock. It has a plasma half-life of 5–10 min. It is rapidly metabolized in the liver and tissues and excreted in the urine.

In the Sepsis Occurrence in Acutely Ill Patients II (SOAP II) trial [30], patients with shock (defined as a systolic blood pressure of <100 mmHg or MAP <70 mmHg) were randomized to receive dopamine or norepinephrine as a first-line agent. However, this was not a heart failure study, and no assessment of the cardiac function was made. It primarily included patients with septic shock (62%), and, although 16.7% were said to have ‘CS’, this group included patients with pulmonary embolism, tamponade, and valvular heart disease. Overall, there was no difference in the rate of death between patients with shock who were treated with dopamine as the first-line vasopressor agent and those who were treated with norepinephrine. A subgroup analysis showed that dopamine, compared with norepinephrine, was associated with an increased rate of death at 28 days among the 280 patients with ‘CS’, but not among the 1044 patients with septic shock or the 263 with hypovolaemic shock (P = 0.03). Dopamine was also associated with a greater number of adverse events—particularly arrhythmia (and primarily an increase in atrial fibrillation).

**Dopexamine**

Dopexamine is a synthetic analogue of dopamine, which stimulates adrenergic β2-receptors and peripheral dopamine receptors, as well as inhibiting the neuronal reuptake of noradrenaline. It leads to an increase in the cardiac output, mediated by an afterload reduction (β2, DA1), and increases the blood flow to the renal and mesenteric beds (DA1). It does not cause vasoconstriction but can lead to tachyarrhythmia and hypertension.

**Phosphodiesterase inhibitors**

Inhibitors of phosphodiesterase III are frequently used in AHF. Phosphodiesterase III catabolizes cAMP, and, as such, the inhibition of phosphodiesterase III results in increased cAMP levels, with consequent vasodilator (both pulmonary and systemic) and inotropic effects. No chronotropic effect occurs at low to medium doses. The main adverse effects seen are arrhythmias and hypotension. As before, there is no evidence suggesting that these agents improve outcomes in AHF.
Milrinone

IV milrinone has a half-life of 2.5 hours. It is renally excreted, so dose adjustment is required in renal impairment. The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study randomized patients with AHF to either IV milrinone or placebo, in addition to standard therapy. This trial demonstrated no improvements in mortality, the length of hospital stay, or readmission rates. Of note, sustained hypotension and new atrial arrhythmias were more frequent in the milrinone group [31].

Enoximone

Enoximone is approximately ten times less potent than milrinone. Enoximone is currently available for clinical use in Europe, but not in North America.

Calcium sensitizers

Levosimendan

Levosimendan is a calcium-sensitizing agent that increases the sensitivity of the myocardial contractile apparatus to Ca\(^{2+}\), supposedly without significantly affecting cAMP or intracellular Ca\(^{2+}\) concentrations. This leads to an increase in inotropy, without increasing the O\(_2\) demand. It also has a vasodilator effect, mediated by its ability to activate potassium-sensitive ATP channels, in vascular smooth muscle cells. The active metabolite of levosimendan has a half-life of approximately 80 hours. Peak effect is noted by 30 min, following the commencement of the infusion. Levosimendan reduces the wedge pressure, increases the cardiac output, and reduces the pulmonary and systemic vascular resistance, with a modest reduction in MAP. The Levosimendan Infusion versus Dobutamine (LIDO) trial randomized patients with acute HF to receive either levosimendan or dobutamine, in addition to standard therapy. Patients receiving levosimendan were more likely to reach the primary endpoint of an increase of 30% or more in the cardiac output and a decrease of 25% or more in the PCWP (\(P = 0.02\)). Mortality at 6 months was higher in the dobutamine group (\(P = 0.029\)) [32]. This comparison was investigated in the larger Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) trial [33]. There was no difference in the primary outcome of all-cause mortality between the groups. However, levosimendan appeared to exert a more profound hypotensive and tachycardic effect than dobutamine. Currently, levosimendan is available for clinical use in some European countries, but not in North America.

General considerations in patients with acute heart failure

Pre-existing pharmacotherapy
An important, and early, consideration in those patients admitted with AHF is whether or not to continue their current medication. This deserves careful consideration in the case of β-blockers. Data from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry suggest that post-discharge mortality rates were lower in patient whose β-blocker was continued on admission [34]. Post hoc analyses of the Carvedilol or Metoprolol (COMET) [35] and Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) [36] trials produced similar results. A randomized trial of β-blocker continuation vs withdrawal demonstrated that continuation of therapy does not adversely impact outcomes and is associated with a higher rate of chronic prescription of β-blocker therapy 3 months later [37]. It is therefore recommended by the ACC/AHA that the patient’s existing medications be carefully reviewed on admission, and the β-blocker withheld or stopped, only if the decompensation has occurred shortly after initiation or an increase in β-blocker therapy (i.e. the likely culprit underlying the presentation) or the patient is shocked [9]. The renine-angiotensine-aldosterone-system antagonists should be continued, unless hypoperfusion or an acute renal insufficiency precludes this. Any agent with negatively inotropic (non-dihydropyridine Ca\(^{2+}\) channel antagonists) or fluid-retaining properties (e.g. non-steroidal anti-inflammatory drugs) should be stopped.

**Thromboprophylaxis**

No randomized data exist supporting the use of thromboprophylaxis specifically in patients with AHF. However, deep vein thrombosis and pulmonary embolism are recognized causes of significant morbidity and mortality in acutely unwell medical patients [38]. Given the preponderance to higher venous pressures and a lower cardiac output in AHF patients, thromboprophylaxis should be considered for all appropriate patients requiring hospitalization [39, 40]. The Heart Failure Society of America guidelines recommend unfractionated or low molecular weight heparin or fondaparinux [10].

**Pre-discharge**

All guidelines recommend that patients with LV systolic dysfunction who stabilize with the above therapy should ideally be commenced on a low-dose ACE-I, β-blocker, and mineralocorticoid receptor antagonist, if appropriate, once euvoalaemic and prior to hospital discharge, if tolerated [1, 9, 10].

**Emerging pharmacological therapies for acute heart failure**

(See Figure 52.4.)
Serelaxin

Relaxin is a 53-amino acid endogenous peptide hormone which is a member of the insulin-like growth factor receptor family. It has an established role in pregnancy and parturition [41], and, more recently, a putative role in cardiovascular regulation and pathophysiology has been identified [42]. In humans, relaxin produces dose-dependent vasodilatation in *ex vivo* peripheral resistance arteries, but not pulmonary arteries. *In vivo*, it increases the renal blood flow and has a modest natriuretic effect in healthy humans. A large randomized placebo-controlled trial of serelaxin (recombinant relaxin-2), in addition to standard therapy, in patients with AHF revealed a significant improvement in one of the co-primary measures of dyspnoea and the safety endpoint of 180-day mortality in patients receiving serelaxin [43]. However, despite initial optimism surrounding this trial, this finding was not replicated in the adequately powered RELAX-AHF-2 trial which was presented at the ESC Heart Failure Association in May 2017 but has not yet been published.

Omecamtiv mecarbil

Omecamtiv mecarbil is a myosin-activating agent which potentiates the excitation-contraction coupling and increases the systolic ejection time, contractility, and stroke volume. In theory, it has no arrhythmogenic potential, given its lack of effect on the phosphodiesterases, intracellular Ca\(^{2+}\) concentrations, or myocardial O\(_2\) consumption. Phase II studies in stable heart failure patients have confirmed its ability to increase the stroke volume [44]. The randomized placebo-controlled Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure
(ATOMIC-AHF) study examined three doses of omecamtiv mecarbil in patients with AHF given as a 48-hour infusion. The primary endpoint of reduction in dyspnoea at 6, 24, and 48 hours was met only in the highest dose group. Tolerability and adverse events were no different to placebo but active treatment was associated with an increase in troponin concentrations [45].

**Ularitide**

Ularitide is a synthetic analogue of urodilatin, which is an endogenous natriuretic peptide (NP) expressed in the kidney. Urodilatin has an identical amino acid sequence to A-type NP but has an additional four amino acid residues at the amino terminus, rendering it more resistant to degradation by neutral endopeptidase (neprilysin) than A-type NP. Following its expression on the distal tubular cells, it is secreted luminally, and downstream it binds to the NP receptor NPR-A in the collecting duct, resulting in cGMP activation and consequent natriuresis. Phase I/II studies showed the parenteral administration of exogenous ularitide in AHF results in reductions in the right atrial pressure, PCWP, and NT-proBNP, with no adverse effect on the renal function [46, 47]. The TRial of Ularitide’s Efficacy and safety in patients with Acute Heart Failure (TRUE-AHF), was a large (>800 patients) international phase III event-driven trial of ularitide vs placebo in patients with AHF and preserved blood pressure [48]. Whist the ularitide group displayed a greater reduction in NT-proBNP concentrations, no difference was noted in the clinical course during index admission or in subsequent mortality over a follow up period of 15 months.

**Istaroxime**

Istaroxime is a novel inotropic agent with concomitant lusitropic properties. It has a dual action of increasing the cytosolic Ca\(^{2+}\) concentration through inhibition of the Na/K-ATPase, whilst also stimulating the calcium-ATPase in the sarcoplasmic reticulum, promoting prompt sequestration of Ca\(^{2+}\) in diastole and a consequent improvement in myocardial relaxation. These effects are not oxygen-dependent, meaning that the myocardial O\(_2\) demand is not increased. Infusion increases the cardiac index [49]. In AHF patients, istoroxime significantly increases the systolic blood pressure and decreases the heart rate, whilst reducing the PCWP and the LVEDD [50].

**Conclusion**

The term AHF syndromes is an oversimplification of a diverse spectrum of pathologies and presentations. Choice of initial pharmacological therapy in AHF is governed by the presence or absence of cardiogenic shock. Many of the recommendations for AHF treatments are based on lower levels of evidence and can vary between guidelines (see Table 52.1). Of note, there is not one single IA recommendation made
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by any of the three major international guidelines. No pharmacological therapy has been shown to improve prognosis in AHF.

Personal perspective

Subgroup signals from the ROSE-AHF trial suggested that dopamine may have a greater efficacy on AHF patients with reduced LVEF. Should this be confirmed by further trials, emerging AHF therapies may need to be studied separately in reduced and preserved LVEF.

Appendix: the evidence base

Nitrates

Design: Randomized controlled trial (RCT) of high-dose ISDN and low-dose furosemide vs high-dose furosemide and low-dose ISDN in AHF.

Subjects: n = 104; mean age = 74 years; 52% males; mean LVEF = 42%.

Background therapy: 87% ACE-I; 50% β-blocker.

Results: less requirement for mechanical ventilation ($P = 0.0041$) and fewer MI ($P = 0.047$) in high-dose ISDN group.


Nesiritide

VMAC (vasodilation in the management of AHF)

Design: double-blind RCT of nesiritide vs nitroglycerin vs placebo.

Subjects: n = 489; inpatients with dyspnoea at rest; mean age = 62 years; 69% males.

Results: at 24 hours: no significant difference in perceived dyspnoea; greater reduction in PCWP with nesiritide ($P = 0.04$).

ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure)

Design: double-blind RCT of nesiritide vs placebo in patients hospitalized with AHF.

Subjects: n = 7141; mean age = 67 years; 66% males; 80% with LVEF <40%.

Results: did not achieve pre-specified reduction in dyspnoea at 6 hours; no significant difference in rehospitalization/death at 30 days; no significant difference in death at 30 days; no difference in eGFR ($P = 0.11$).


Milrinone

OPTIME-CHF


Subjects: n = 951; mean age = 66 years; 93% NYHA III/IV; mean LVEF = 23%.

Follow-up: 60 days.

Results: no difference in the length of hospital stay and in-hospital or 60-day mortality; more frequent hypotension ($P <0.001$) and atrial arrhythmias ($P = 0.004$) with milrinone.


Levosimendan

LIDO study (levosimendan infusion versus dobutamine study)

Design: double-blind RCT of levosimendan vs placebo.

Subjects: n = 203; NYHA IV; LVEF ≤35%; mean age = 59 years; 87% males.

Follow-up: 6 months.
Results: 12% absolute (43% RRR) lower mortality with levosimendan, compared with dobutamine, at 6 months ($P = 0.029$); 13% (90% RRR) more patients had haemodynamic improvement at 24 hours with levosimendan, compared with dobutamine ($P = 0.022$).


**REVIVE-II (randomized multicentre evaluation of IV levosimendan efficacy vs placebo in the short-term treatment of decompensated heart failure)**

Design: double-blind RCT of levosimendan vs placebo.

Subjects: $n = 600$; heart failure admission; LVEF $\leq 35\%$; mean age = 63 years; 72% males.

Follow-up: 6 months.

Results: trend to an increase in mortality at 90 days; reduction in hospitalization by 2 days ($P = 0.001$); more reports of hypotension and AF.


**SURVIVE**

Design: double-blind RCT of levosimendan vs dobutamine.

Subjects: $n = 1327$; AHF with LVEF $\leq 30\%$; mean age = 59 years; 87% males.

Follow-up: 180 days.

Results: no significant difference in mortality at 180 days ($P = 0.40$).


**Serelaxin**

**RELAX-AHF (recombinant human relaxin-2 for the treatment of AHF)**

Design: double-blind RCT of serelaxin vs placebo.
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Subjects: n = 1161; within 16 hours of a heart failure admission; mean age = 72 years; 63% males.

Follow-up: 6 months.

Results: improvement in the visual analogue scale (P = 0.007), but not the Likert scale for dyspnoea (both primary endpoints); no change in cardiovascular death or heart failure rehospitalization (P = 0.001) (secondary endpoint); reduction in mortality at 180 days (42 deaths serelaxin, 65 placebo; HR 0.63 (0.42–0.93), P = 0.019); this was neither a primary nor a secondary endpoint.


TRUE-AHF (The TRial of Ularitide’s Efficacy and safety in patients with Acute Heart Failure)

Design: double-blind RCT of ularitide vs placebo in patients hospitalized with AHF.

Subjects: n = 2157; mean age = 68 years; 66% males; 66% with LVEF <40%.

Results: No difference in cardiovascular death during 15 month follow up (p=0.75).

Further reading


References

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