Abstract:

Heart failure (HF) and coronary insufficiency are common amongst surgical and critical care patients. Both are chronic conditions interrupted by acute episodes. HF activates neurohormonal mechanisms that worsen renal and cardiac function. Acute heart failure (AHF) commonly presents with dyspnoea as a consequence of systolic and / or diastolic dysfunction. Goals of treatment are symptom relief, to maintain tissue perfusion and optimise cardiac function. Diuretics and vasodilators are used early; positive inotropic drugs are reserved for when other treatment has failed.

Chronic heart failure (CHF) is treated using changes in lifestyle and drugs to manage symptoms. ACE inhibitors and beta-blockers are effective in systolic heart failure and are associated with improved mortality. HF with preserved ejection fraction (HFPEF) is less responsive to drug therapy, though outcomes are better than for systolic HF.

Coronary insufficiency occurs because of an imbalance of myocardial oxygen balance, leading to symptoms of ischaemic heart disease (IHD). Treatment goals are maintaining coronary blood flow and reducing myocardial oxygen demand. Beta-blockers and anti-platelet drugs improve outcomes; modern anti-platelets are more effective but are associated with risks of haemorrhage. Statins are effective for primary and secondary prevention of myocardial infarction; they have additional anti-inflammatory properties.

Keywords: heart failure, coronary artery disease, heart drugs, heart failure with preserved ejection fraction.
Learning objectives

After reading this article, you should be able to:

- define heart failure
- list management strategies in acute heart failure
- list drugs used in chronic heart failure
- describe the role of anti-platelet drugs and statins in coronary artery disease

Heart Failure

Heart failure (HF) is the inability of the heart to maintain sufficient blood flow to the tissues to meet physiological requirements. It is a clinical syndrome characterised by typical symptoms (breathlessness, ankle swelling, fatigue) alongside objective clinical signs (raised JVP, pulmonary congestion, peripheral oedema). It is caused by structural and/or functional abnormalities of the heart leading to reduced cardiac output or elevated filling pressures.\(^1\) Heart failure may be classified according to the acuity of clinical presentation (acute, sub-acute, chronic, decompensated), or based on the measurement of ejection fraction (heart failure with preserved ejection fraction (HFrEF) and heart failure with reduced EF (HFrEF)). Symptomatic severity of heart failure is classified according the New York Heart Association (NYHA) functional classification (Table 1). The causes and presentation of heart failure should be determined as they govern treatment.

<table>
<thead>
<tr>
<th>Table 1</th>
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<tr>
<td>The New York Heart Association (NYHA) classification of heart failure.</td>
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<td>NYHA Class</td>
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<td>Class I</td>
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Acute heart failure (AHF)

Acute heart failure (whether new onset or decompensated) is characterised by the development of a rapid onset or change in the signs and symptoms of HF. Diagnosis is based on thorough history and examination accompanied by assessment of the ECG, radiological evidence, serum biomarkers (natriuretic peptides) and early echocardiography. AHF is caused by left ventricular (LV) systolic dysfunction, diastolic dysfunction, or more commonly a combination of both. Systolic dysfunction is a consequence of impaired myocardial contractility, leading to reduced left ventricular ejection fraction (LVEF) and consequently reduced cardiac output. Diastolic dysfunction is caused by an increase in ventricular stiffness and impaired relaxation, resulting in impaired ventricular filling during diastole; LVEF may be normal. Despite decreased cardiac output, systolic blood pressure may be normal or elevated because of increased systemic vascular resistance. Patients presenting with a SBP <90 mmHg have a poor prognosis. Decreased cardiac output leads to tissue hypoperfusion, activating compensatory mechanisms that lead to renal and myocardial dysfunction (Figure 1).

The goals of treatment in AHF are to maintain adequate peripheral perfusion, improve myocardial contractility and reduce fluid overload. Supplemental oxygen should be administered to all hypoxic
patients; diuretics should be given early if there are signs of pulmonary congestion and vasodilators if there is dyspnoea at rest. However, it is important to identify the aetiology of the cardiac dysfunction and treat any precipitating factors. For example, in patients with AHF caused by diastolic dysfunction and with normal or high arterial pressure, vasodilators and continuous positive airway pressure (CPAP) or assisted non-invasive ventilation (NIV) should be used and diuretics are indicated only if fluid overload is evident. Conversely, in patients with cardiogenic shock, positive inotropic drugs should be given with intravenous fluids guided to maintain cardiac output; however in patients with isolated right ventricular failure, diuretics are the mainstay of therapy.

There has been much research aimed at developing new treatments for AHF in the last few decades and guidelines have been produced. Several newer drugs have been shown to improve symptoms of AHF, but without convincing effects on long-term outcome. In addition, it is worth noting that there are remarkably few good randomised data to support the use of traditional therapies (Table 2).

Table 2. Pharmacological strategies for the emergency management of AHF
<table>
<thead>
<tr>
<th>Therapeutic Goal</th>
<th>Drug</th>
<th>Mode of Action</th>
<th>Side-effects</th>
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<tbody>
<tr>
<td>Systemic congestion</td>
<td>Diuretics e.g. furosemide, metolazone</td>
<td>Diuresis and variable natriuresis</td>
<td>Hypotension, neurohumoral activation, electrolyte abnormalities, renal dysfunction</td>
</tr>
<tr>
<td>Vasodilation</td>
<td>Nitrates e.g. GTN, SNP</td>
<td>Venodilation, arterial vasodilation</td>
<td>Profound hypotension with vasodilators, ↓coronary perfusion (SNP), headache, metabolite toxicity</td>
</tr>
<tr>
<td>Cardiac function</td>
<td>Inotropes: β-agonists, PDE-3 inhibitors, levosimendan</td>
<td>Increased force of myocardial contraction + peripheral vasodilation (inodilation)</td>
<td>Increased myocardial oxygen demand, hypotension, arrhythmias</td>
</tr>
<tr>
<td>Cardiac stability</td>
<td>Beta-blockers: esmololol, metoprolol digoxin</td>
<td>Reduction in heart rate &amp; sympathetic activity; anti-arrhythmic</td>
<td>Bradycardia, hypotension</td>
</tr>
</tbody>
</table>

Adapted from Khan et al (further reading)

Key: AHF, acute heart failure; GTN, glyceryl trinitrate; PDE, phosphodiesterase; SNP, sodium nitroprusside.

Drugs used in AHF

**Diuretics**

Diuretics are the mainstay of treatment for acute and chronic heart failure, effectively relieving systemic or pulmonary venous congestion. Furosemide (a loop diuretic) blocks the Na⁺/K⁺/2Cl⁻ co-transporter at the loop of Henle, inhibiting sodium reabsorption and resulting in diuresis. It also acts as a venodilator to produce early relief from dyspnoea. It should be administered promptly and may also be administered as an infusion, with the aim of a weight reduction of approximately 1 kg per day. The dose should be limited to the smallest amount possible to produce clinical improvement. In those patients already taking furosemide, the i.v. bolus dose should be at least equal to the pre-existing oral dose used at home. The maximum dose should not exceed 100 mg in the first 6 hours.
as there is no additional benefit and adverse effects (e.g. otoxocity, hyponatraemia, hypokalaemia and dehydration) are more likely.

The combination of a loop diuretic and thiazides or related diuretics (e.g. metolazone) is more effective than high doses of loop diuretics alone, and also reduces the incidence of adverse effects. Intravenous infusions allow higher doses to be administered less risk of ototoxicity.

**Vasodilators**

Intravenous vasodilators are no longer recommended in the routine management of patients with acute heart failure due to very limited evidence of benefit and potential for harm. They may be indicated in specific circumstances such as in the case of concomitant myocardial ischaemia, severe hypertension or regurgitant aortic or mitral valve disease.

Glyceryl trinitrate (GTN) is used most commonly (10 – 1000µg/min, starting at lower doses). GTN indirectly produces nitric oxide (NO) which causes smooth muscle relaxation, predominately of venous capacitance vessels but also reduces arterial tone, optimising preload and reducing afterload. Sodium nitroprusside is a direct NO donor and potent vasodilator. It is metabolised to toxic products including cyanide and sodium thiocyanate. These toxins disrupt the electron transport chain through inhibition of cytochrome c oxidase, preventing aerobic ATP production resulting in a number of potential adverse effects. It is rarely used clinically and is not recommended by recent guidelines.
Vasodilators may cause precipitous decreases in blood pressure and reduce coronary blood flow.

Acute tolerance (tachyphylaxis) also occurs to GTN within 24 – 48 hours, probably caused by substrate depletion, enhanced vasoconstrictor activity and upregulation of intracellular phosphodiesterases.

In HF the secretion of natriuretic peptides A and B (ANP and BNP) by the atrial and ventricular myocardial cells is increased. These peptides act on the endothelium and vascular smooth muscle to cause vasodilation and decrease cardiac filling pressures. Additionally, they inhibit renin and aldosterone production, causing mild natriuresis, and increase both cardiac output and coronary blood flow. Nesiritide is a human recombinant B-type natriuretic peptide that mimics endogenous natriuretic peptide B (BNP) improving symptoms. Its role in the management of AHF is debatable - a large randomised controlled trial (RCT) demonstrated a significant increase in hypotension with no improvement in survival or rates of hospitalisation.²

*Positive Inotropic drugs*

Positive inotropes are reserved for patients who have either failed or displayed a limited response to vasodilator and diuretic therapy; are hypotensive (systolic pressure <90 mm Hg); or have signs of tissue hypoperfusion (cold and clammy skin, metabolic acidosis, renal failure and altered mental activity) caused by low cardiac output. The most commonly used positive inotropes are dobutamine, milrinone, or enoximone; none have been shown to improve outcome in AHF.
$\beta_1$-adrenoceptor agonists (e.g. dobutamine) increase intracellular cyclic adenylate monophosphate (cAMP), causing the release of calcium from the sarcoplasmic reticulum, thereby increasing cardiac muscle contractile force. Their effects are both positively chronotropic and inotropic, though hypotension may occur because of $\beta_2$-mediated vasodilation. Dobutamine therapy (2.5µg/kg/min – 10µg/kg/min) is limited by tachycardia, arrhythmias and myocardial ischaemia.

Inhibition of phosphodiesterase (PDE) prevents the catalysis of cAMP thereby increasing intracellular calcium. The isoenzyme PDE-3 is found in myocardial cells as well as in vasculature and platelets and is antagonised by drugs such as milrinone and enoximone. These PDE-3 inhibitors increase cardiac output and reduce filling pressures, also causing less tachycardia, fewer arrhythmias and smaller increases in myocardial oxygen demand compared to dobutamine; pulmonary and systemic vascular resistance are reduced to a similar degree. These drugs are usually administered as infusions in the acute setting. Because of their prolonged half-lives (milrinone 1 – 2 hours; enoximone 4 – 6 hours), loading doses are necessary (50 µg/kg milrinone; 90µg/kg/min enoximone) but should be given with caution because of their vasodilatory effects. Heart failure of an ischaemic cause is a relative contraindication to their use.

Levosimendan is an inodilatory drug with a novel mechanism of action. It binds to troponin-C, sensitising myocardial microfilaments to calcium and thereby increasing cardiac output whilst reducing filling pressures in an energy-independent process. It does not therefore increase myocardial oxygen demand. Levosimendan also facilitates adenosine triphosphate (ATP)-dependent
potassium channel opening causing vasodilation; this reduces both preload and afterload. It may have a role in the management of acute heart failure/cardiogenic shock in the presence of myocardial infarction.

Vasopressors (e.g. noradrenaline) may be required in AHF to increase arterial pressure where there is persistent end-organ hypoperfusion, or during treatment with inodilating drugs.

Vasopressin antagonists

Two vasopressin receptor antagonists, conivaptan (V₁a and V₂) and tolvaptan (V₂) are in clinical use. They cause vasodilation (V₁) and inhibit water-reabsorption (V₂). These drugs are indicated in the management of hyponatraemic hypervolaemia (present in over 20% of patients with AHF), but are not currently used in the UK for AHF.

Digoxin

Heart conditions have been treated with foxglove derivatives since 1785. Digoxin, a cardiac glycoside, has a relatively rapid onset and improves cardiac haemodynamics whilst avoiding many of the negative effects of hypotension, neurohormonal activation and renal failure. Although previously used in heart failure, it has now largely been superseded for this indication and is principally used in the management of supraventricular tachycardia (particularly atrial fibrillation).

Opioids
Opioids reduce preload through venodilation, reduce afterload and lower heart rate. Dyspnoea and agitation are also improved. They are not routinely recommended in the management of AHF as they have been associated with an increase in mortality. They may be cautiously used for symptom relief in patients with severe dyspnoea due to pulmonary oedema.

**Future advances**

Newer drugs under investigation include istaroxime, relaxin and omecamtiv.

**Istaroxime**

Newer drugs under investigation include istaroxime, which inhibits Na⁺/K⁺-ATPase and increases activity of Ca²⁺-ATPase at the sarcoplasmic reticulum, resulting in positive inotropy and lusitropy (myocardial relaxation) without increasing myocardial oxygen demand. Initial trials have demonstrated improvements in haemodynamics, and decreased diastolic stiffness in patients with acute heart failure but further data are needed.

**Relaxin**

Relaxin is a pregnancy hormone that antagonizes endothelin-1 by increasing the expression of endothelin-type B receptors to cause selective vasodilation in vasoconstricted blood vessels. Recent studies have produced contradictory results as to the usefulness of relaxin as a therapy in the management of AHF.
**Omecamtiv mecarbil**

Omecamtiv mecarbil is a cardiac myosin activator that increases systolic ejection time without decreasing left ventricular contractility. As a result, it increases stroke volume and cardiac output without increasing oxygen demand. In patients with stable CHF, omecamtiv was associated with dose and concentration-dependent improvements in cardiac function and randomized controlled trials in patients with AHF are planned.

**Summary**

Clinical trials investigating the treatment of AHF have been disappointing. Randomised trials of most drugs have only demonstrated improvements in haemodynamics but not in long-term outcomes or survival. Furthermore, the traditional therapies of diuretics and dobutamine continue to be used despite little supportive trial evidence.

**Drugs used in chronic heart failure**

Chronic heart failure (CHF) is a progressive disease, often interrupted by episodes of acute decompensation. Treatment is aimed at minimising these episodes and slowing the decline of myocardial function, as well treating and preventing complications associated with the failing heart. Mortality from CHF is high, with an estimated 50% of patients not surviving beyond four years.

Most therapies target systolic heart failure (LVEF ≤40%), but one in three symptomatic patients have primarily diastolic dysfunction, often termed heart failure with preserved ejection fraction (HFpEF).
Lifestyle changes (exercise, reduced salt intake, nutrition, weight loss, smoking cessation, diabetic control) and symptom management form the mainstay of treatment for both. Drugs do have a key role in reducing mortality from systolic heart failure; HFpEF treatment is less effective, although the overall prognosis with diastolic dysfunction is better.

**Angiotensin-converting enzyme inhibitors (ACEIs)**

All patients with symptomatic (or asymptomatic) heart failure with a reduced ejection fraction should be treated with ACEIs (e.g. enalapril, ramipril). Inhibiting ACE prevents the synthesis of angiotensin II, inhibits aldosterone secretion and cardiac remodelling. Successive large-scale RCTs have demonstrated improvements in ventricular function, reduced hospital admissions, and increased survival, together with an improvement in symptoms and quality of life. Contraindications to ACEI therapy are a history of angioedema, bilateral renal artery stenosis, severe aortic stenosis, hyperkalemia (K⁺ > 5.0 mmol/L) and a serum creatinine greater than 220μmol/L. ACEIs also causes cough in approximately 20% of patients as a result of reduced ACE-dependent metabolism of bradykinins.

**Beta-blockers**

Beta blockade reduces death from cardiovascular disease. Despite negative chronotropic and inotropic effects, selective β1-receptor blockers (e.g. bisoprolol, metoprolol) and carvedilol (β₁, β₂ and α₁-blocker) improve left ventricular function, symptoms and survival. Beta-blockers are anti-
arrhythmic, lower heart rate, improve diastolic function and reduce myocardial oxygen demand.

They also reduce plasma concentrations of circulating catecholamines, renin and endothelin.

Beta blockers are indicated for patients with symptomatic systolic HF, or asymptomatic systolic HF following myocardial infarction (MI). Caution is required in AHF, though evidence suggests that beta-blockers can be commenced safely. Continuing beta-blocker during acute episodes of decompensation is not harmful, and maintains adherence following hospital discharge.

**Angiotensin receptor blockers (ARBs)**

ARBs (e.g. losartan) are indicated for symptomatic systolic heart failure that has not improved with an ACEI and a beta blocker. They are also indicated when ACEIs are not tolerated. ARBs selectively block the binding of angiotensin II to the AT₁ receptor, reducing vasoconstriction, sodium retention and noradrenaline release.

**Aldosterone antagonists**

Low dose aldosterone antagonists (e.g. spironolactone, eplerenone) should be considered in patients with severe heart failure (LVEF ≤35% with severe symptoms). Addition of these drugs decreases hospital admissions and increase survival. Aldosterone antagonists reduce plasma volume and sodium retention. They also increase noradrenaline uptake, reduce myocardial oxidative stress and coronary artery inflammation, and reduce heart rate variability and ventricular remodelling.

Aldosterone antagonists can worsen renal function and induce hyperkalaemia. Serial monitoring of
electrolytes and renal function is mandatory, and as with ACEIs, aldosterone antagonists should be avoided where there is hyperkalaemia or abnormal renal function.

**Diuretics**

Diuretics provide symptomatic relief from pulmonary and systemic venous congestion, but do not improve long-term survival (except where there are anti-aldosterone effects). Diuretics activate the renin-angiotensin system so should be used in combination with ACEIs or ARBs. Loop diuretics are preferable as they are more effective at producing a diuresis and natriuresis. Electrolytes and renal function should be monitored before and during treatment.

*Hydralazine and isosorbide dinitrate*

Hydralazine and isosorbide dinitrate (H-IDN), a combination of an arterial and venodilator, has a limited role in the treatment of CHF. H-IDN may be beneficial in patients with persistent symptoms of heart failure despite maximal conventional therapy or when there is intolerance to ACEIs or ARBs.

*Digoxin*

Digoxin is mostly used in the management of tachyarrhythmias, particularly atrial fibrillation. There is some evidence that, in symptomatic patients with LVEF of ≤40%, symptoms, quality of life and number of hospital admissions are improved with digoxin.

*Ivabradine*
Ivabradine is a novel selective cardiac pacemaker current inhibitor (If-channel inhibitor) that reduces heart rate through the SA-node. It has been associated with improved outcome in patients with severe heart failure with LVEF <=35% and a heart rate of >70 bpm despite adequate beta-blockade.

**Angiotensin receptor neprilysin inhibitors (ARNI)**

ARNI is a new therapeutic class of agents acting on the RAAS and neuroendopeptidase system. The first in class is a molecule that combines valsartan and sacubitril (a neprilysin inhibitor) in a single substance. The inhibition of neprilysin slows the breakdown of natriuretic peptides, enhancing diuresis, natriuresis and myocardial relaxation. They have been shown in clinical trials to be superior to ACEIs in patients with HFrEF (<=35%) despite optimal treatment with ACEI, beta-blocker and aldosterone antagonist.

**Summary**

The main treatments for the management of CHF are ACEIs and beta-blockers; the other therapies described above may be used as second line therapies. Newer pharmacological targets (endothelin receptor antagonists, prostacyclin analogues) have not been shown to improve survival in CHF.

There is no evidence that pharmacological treatment improves outcome in patients with HFpEF. Key objectives of treatment are to minimise atrial tachyarrhythmias and myocardial oxygen demand.

Caution is required with the ACEIs, nitrates or diuretics as too great a reduction in preload may
result in decompensation. Future therapies include stem cell transplantation or targeting hormone and cytokine cell signalling.

**Coronary Insufficiency**

Coronary insufficiency occurs when myocardial oxygen demand exceeds its supply. It is caused by increases in demand (e.g. tachyarrhythmias) or reductions in supply (e.g. coronary artery disease) leading to symptoms of angina. Where reduced supply results from atherosclerotic plaque formation, plaque rupture and subsequent thrombus formation leads to complete or partial artery occlusion resulting in acute myocardial infarction (MI). The management of acute MI is outside the scope of this article.

Coronary artery disease is the commonest presentation of coronary insufficiency. The aim of therapy is to maintain coronary artery perfusion, either by reducing myocardial oxygen demand or by maintaining or improving oxygen supply. From a pharmacological perspective, nitrates and beta-blockers are key to management. Beta-blockers are effective at treating symptoms (i.e. angina) and improving mortality in cardiovascular disease; nitrates provide only symptomatic relief.

*Anti-thrombotic agents*

These drugs stabilise atherosclerotic plaques, preventing thrombus formation. Inhibiting platelet activation impairs aggregation and thrombosis. Aspirin irreversibly inhibits the platelet enzyme
cyclo-oxygenase 1 and hence prevents the production of thromboxane, a key component of platelet aggregation. At doses between 75 – 150 mg per day, aspirin prevents death from cardiovascular disease with an acceptably low risk of upper gastrointestinal bleeding.

The thienopyridines (e.g. clopidogrel, ticlodipine, prasugrel) are non-competitive ADP-receptor (P2Y₁₂) antagonists that block activation of the glycoprotein IIb/IIIa complex, so inhibiting platelet aggregation. They are used in combination with aspirin primarily to prevent stent-occlusion following coronary artery stent insertion. The metabolism of clopidogrel to its active metabolite is highly variable - clopidogrel may have a minimal therapeutic effect in poor metabolisers. Prasugrel is less affected by differences in metabolism, and is better than clopidogrel at preventing stent thrombosis and reducing non-fatal MI occurrence. However, the risk of major (including life-threatening) bleeding is significantly increased.

Ticagrelor is a new class of drug that is a direct-acting, reversible P2Y₁₂ inhibitor. It has more rapid and potent inhibitory effects on platelets compared to high-loading-dose clopidogrel, and also has a very quick offset, with rapid recovery of platelet function. Studies suggest that ticagrelor is more effective than clopidogrel at reducing cardiovascular death after ACS and preventing stent thrombosis. Unlike prasugrel, the occurrence of major haemorrhage does not appear to be increased significantly.
Other anti-thrombotic drugs that inhibit glycoprotein IIb/IIIa include specific antibodies (e.g. abciximab), cyclic peptides (e.g. eptifibatide) and non-peptide antagonists (e.g. tirofiban). These are all used in the management of acute coronary syndromes and in preventing thrombus formation after cardiac stent insertion.

**Statins**

Statins (e.g. simvastatin, atorvastatin) are HMG-Co-A reductase inhibitors, used for primary and secondary prevention of MI. Statins lower serum lipids, but also have anti-inflammatory properties related and unrelated to their lipid-lowering ability. Statins are associated with impaired endothelial-leukocyte adhesion, inhibition of T-cell activation, impaired chemokine expression, as well as impaired synthesis of cell-signalling components. Modulation of the pro-inflammatory transcription factor NF-κB has also been implicated. Platelet aggregation is also impaired via such mechanisms as reduced thromboxane and increased prostacyclin expression.
Further Reading


References


Legend to Figure 1: Reduced ejection fraction (EF) varies, depending on the degree of diastolic and systolic dysfunction (EDV, end diastolic volume; ESV, end systolic volume), both tend to co-exist. Heart failure activates compensatory neurohumoral mechanisms within the vasculature and kidneys.
Left unchecked, these mechanisms worsen cardiac function, with increased fluid retention increasing venous return (preload), and peripheral vasoconstriction increasing afterload. Pharmacological targets are indicated.