Drugs acting on the heart: heart failure and coronary insufficiency

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Learning objectives

After reading this article, you should be able to:

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

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; inotropes 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 when myocardial oxygen delivery is inadequate, 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 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.

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 that combines symptoms of heart failure (e.g. dyspnoea), signs of fluid retention (e.g. ankle swelling) and objective evidence of structural or functional abnormalities of the heart at rest (e.g. abnormal echocardiogram, third heart sound).¹ Heart failure can be further classified according to the clinical presentation into new onset, transient (symptoms occur over a limited time period) and chronic (including decompensated) heart failure. The cause and presentation of heart failure should be sought as they govern treatment.

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, especially dyspnoea. It 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. Decreased cardiac output leads to decreased blood flow and tissue perfusion which activates neurohormonal mechanisms leading 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 early in the course of treatment. Diuretics are indicated only if there is evidence of fluid overload. 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.

Therapeutic Goal	Drug	Mode of Action	Side-effects
Systemic congestion	Diuretics e.g. furosemide, metolazone	Diuresis and variable natriuresis	Hypotension, neurohumoral activation, electrolyte abnormalities, renal dysfunction
Vasodilation	Nitrates e.g. GTN, SNP	Venodilation, vasodilation	Profound hypotension with vasodilators, ↓coronary perfusion (SNP), headache, metabolite toxicity
Cardiac function	Inotropes: β-agonists, PDE-3 inhibitors, levosimendan	Increased force of myocardial contraction + peripheral vasodilation (inodilation)	Increased myocardial oxygen demand, hypotension, arrhythmias
Cardiac stability	Beta-blockers: emololol, metoprolol digoxin	Reduction in heart rate & sympathetic activity; anti-arrhythmic	Bradycardia, hypotension

Table: Pharmacological strategies for the emergency management of AHF (adapted from Khan et al, 2008)

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

Drugs used in AHF

Opioids

Morphine (2.5 – 5 mg) is recommended in Europe¹ as an early treatment where there is chest pain, dyspnoea or restlessness at presentation. Opioids reduce preload through venodilation, reduce afterload and lower heart rate. Dyspnoea and agitation are also improved. Opioids should however be used with caution because of their side effects of central nervous and respiratory depression.

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 $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ 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 (20 – 40 mg i.v.) and may also be administered as an infusion, with the aim of a weight reduction of approximately 1 kg per day. The maximum dose should not exceed 100 mg in the first 6 hours as adverse effects (e.g. ototoxicity, hyponatraemia, hypokalaemia and dehydration) predominate without additional benefit.

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 adverse effects. Intravenous infusions allow higher doses to be administered with a lower incidence of ototoxicity.

Vasodilators

Intravenous nitrates are recommended in patients with pulmonary oedema and a systolic pressure >110 mmHg and in the absence of significant mitral or aortic stenosis, though it is recognised that therapy with nitrates does not necessarily improve outcomes. 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. This reduces left ventricular filling pressure, making GTN effective where there is diastolic dysfunction. Predominant systolic dysfunction is effectively treated with sodium nitroprusside (SNP; starting dose 0.3µg/kg/min). SNP is a direct donor of NO and potent vasodilator.

Vasodilators may cause precipitous drops 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. SNP 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. This may result in tinnitus, nausea, abdominal pain, mental changes and ultimately coma and death. The dose and duration of treatment with SNP should be limited (10 - 200µg/min for a maximum of 3 days), particularly in the presence of impaired renal function.

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 Inotropes

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.

β₁-adrenoceptor agonists (e.g. dobutamine) increase intracellular cyclic adenylylate monophosphate (cAMP), causing the release of calcium from the sarcoplasmic reticulum, thereby increasing cardiac muscle contractile force. Their effects are both chronotropic and inotropic, though hypotension may occur due to β₂-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 levels. 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, and cause less tachycardia, fewer arrhythmias and smaller increases in myocardial oxygen demand compared with dobutamine; pulmonary and systemic vascular resistance are reduced to a similar degree. These drugs are usually administered as infusions in the acute setting. Due to their prolonged half-lives (milrinone 1 – 2 hours; enoximone 4 – 6 hours), loading doses are necessary (50 µg/kg milrinone; 90µg/kg/min enoximone). Heart failure of an ischaemic cause is a relative contraindication to their use.

Levosimendan is a newer inotrope that binds to troponin-C, sensitising myocardial microfilaments to calcium and thereby increasing cardiac output whilst reducing filling pressures. Levosimendan also facilitates adenosine triphosphate (ATP)-dependent potassium channel opening causing vasodilation which reduces preload and afterload. Following data from a large-scale RCT where there was no mortality benefit over dobutamine, there are no current plans for its marketing in the UK.

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

Vasopressin antagonists

Two vasopressin receptor antagonists, conivaptan (V_{1a} and V_2) and tolvaptan (V_2) are in clinical use. They cause vasodilation (V_1) and inhibit water-reabsorption (V_2). 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.

Adenosine-receptor antagonists

Pre-existing renal failure and deteriorating renal function are common in patients with AHF. Adenosine itself is also thought to be an important mediator of renal dysfunction and diuretic resistance (adenosine reduces the glomerular filtration rate and stimulates renin release), so A_1 -receptor antagonists (e.g. rolofylline) have been investigated as therapies for improving dyspnoea, minimising renal deterioration and reducing fluid overload. However, trials have been disappointing.

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. Digoxin may be useful in patients with HF who are in sinus rhythm³, but few definitive data are available.

Summary and future advances

Clinical trials investigating the treatment of AHF have been disappointing. RCTs of most drugs have only demonstrated improvements in haemodynamics but not long-term outcomes or survival. Furthermore, the traditional therapies of diuretics and dobutamine continue to be used despite little supportive trial evidence. 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 Ca^{2+} -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 blood vessels that are vasoconstricted. A recent study showed reduced symptoms and 180-day mortality in patients with AHF.⁴

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 function⁵ and randomized controlled trials in patients with AHF are planned.

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 $\leq 40\%$), but one in three symptomatic patients will 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 CHF or with a left ventricular ejection fraction (LVEF) $\leq 40\%$ 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. Contra-indications 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 $220\mu\text{mol/L}$. 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 β_1 -receptor blockers (e.g. bisoprolol, metoprolol) and carvedilol (β_1 , β_2 and α_1 -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 beta blocker. They are also indicated when ACEIs are not tolerated. ARBs selectively block the binding of angiotensin II to the AT_1 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 $\leq 35\%$ with severe symptoms). Addition of these drugs reduces hospital admissions and increase survival. There is probably some benefit even with mild

symptoms and one recent study found greater eplerenone had greater efficacy compared with ARBs.⁶ 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 $\leq 40\%$, symptoms, quality of life and number of hospital admissions are improved with digoxin.

Ivabradine

Ivabradine is a novel selective cardiac pacemaker current inhibitor that reduces heart rate. It has been associated with improved outcome in patients with heart failure if used either alone or in combination with dobutamine, when it limits tachycardia.

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 proven treatment for HFPEF. Minimising atrial tachyarrhythmias and minimising myocardial oxygen demand are key. 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 is due to 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, responsible for 80,568 UK deaths in 2010. The aim of therapy is to maintain coronary artery perfusion, either by

reducing myocardial oxygen demand or by maintaining or improving oxygen supply. 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 is well proven to prevent death from cardiovascular disease with an acceptably low risk of upper gastrointestinal bleeding.

The thienopyridines (e.g. clopidogrel, ticlopidine, prasugrel) are non-competitive ADP-receptor ($P2Y_{12}$) 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 $P2Y_{12}$ 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, major haemorrhage events do not appear to be significantly increased.

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- κ B has also been implicated. Platelet aggregation is also impaired via such mechanisms as reduced thromboxane and increased prostacyclin expression.

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Further Reading

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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.