Drugs act on Cardiovascular system (Heart Failure)

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Definition and Pathophysiology

- **Heart failure (HF)** is a progressive disorder in which the heart is unable to pump sufficient blood to meet the needs of the body due to an impaired ability of the heart to adequately fill with and/or eject blood.

- Chronic activation of the sympathetic nervous system and the renin-angiotensin-aldosterone axis is associated with remodeling of cardiac tissue, characterized by loss of myocytes, aterial/ventricular hypertrophy, and fibrosis.

- The geometry of the heart becomes less elliptical and more spherical, interfering with its ability to efficiently function as a pump. This prompts additional neurohumoral activation, creating a vicious cycle that, if left untreated, leads to death.
Compensatory mechanism in HF

Functional modifications
- Increased inotropy
- Increased heart rate
- Vasoconstriction
- Salt and water retention

Structural modifications
- Hypertrophy
- Increased nonmuscular tissue
- Increased expression of adult cardiac genes

Increased energy demand
- Altered loading conditions
- Altered vascular/diastolic properties
- Proarrhythmogenic effect
Clinical presentation

- If the adaptive mechanisms adequately restore cardiac output, HF is said to be compensated.
- If the adaptive mechanisms fail to maintain cardiac output, HF is decompensated and the patient develops worsening HF signs and symptoms.

Patients with HF complain of dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue, and dependent edema.
# Classification of HF

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<tr>
<th>NYHA Functional Classification</th>
<th>ACC–AHA Stages of Heart Failure</th>
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<td>Class I: No limitation of physical activity; ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea</td>
<td>Stage A: At high risk for heart failure; no identified structural or functional abnormality; no signs or symptoms</td>
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<td>Class II: Slight limitation of physical activity; comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea</td>
<td>Stage B: Developed structural heart disease that is strongly associated with the development of heart failure but without signs or symptoms</td>
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<td>Class III: Marked limitation of physical activity; comfortable at rest, but less than ordinary activity results in fatigue, palpitation, or dyspnea</td>
<td>Stage C: Symptomatic heart failure associated with underlying structural heart disease</td>
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<td>Class IV: Unable to carry on any physical activity without discomfort; symptoms present at rest; if any physical activity is undertaken, discomfort is increased</td>
<td>Stage D: Advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy</td>
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*The American College of Cardiology (ACC)–American Heart Association (AHA) classification is from Hunt et al. The New York Heart Association (NYHA) functional classification is from the Criteria Committee of the New York Heart Association.*
Goals of Pharmacological Therapy

- Relieve symptoms and signs (e.g. oedema)
- Slow disease progression
- Reduce hospital admission
- Improve survival

Beneficial effects of pharmacologic intervention

- Reduction of the load on the myocardium.
- Decreased extracellular fluid volume, improved cardiac contractility.
- Slowing the rate of cardiac remodeling.
Major sites of drug action

Heart Failure

Reduced cardiac output

Inotropic agents, Digoxin

β antagonists

Digoxin

Renin

Angiotensin I

Angiotensin II

Aldosterone

Sympathetic nervous system activation

Vasoconstriction

Elevated cardiac filling pressures

Sodium and water retention

Diuretics

ACE inhibitors

AT₁ receptor antagonists

Spironolactone

Cardiac Remodeling
Drugs used in treatment of HF

Classes of drugs that have been shown to be effective:
1- Inhibitors of the renin-angiotensin system like ACEIs (e.g. Captopril, Enalapril, Fosinopril, Lisinopril, Quinapril, Ramipril), ARBs (e.g. Candesartan, Losartan, Telmisartan, Valsartan), Direct renin inhibitors (e.g. Aliskiren, Remikiren, Enalkiren)
2- β-adrenoreceptor blockers (e.g. Carvedilol and Metoprolol)
3- Diuretics (e.g. Bumetanide, Furosemide, Hydrochlorothiazide, Metolazone)
4- Direct vasodilators (e.g. Hydralazine, Isosorbide dinitrate, Isosorbide mononitrate, Sodium nitroprusside, Relaxin)
5- Inotropic agents (e.g. Digoxin, Dobutamine, Inamrinone, Milrinone)
6- Aldosterone antagonists (e.g. Eplerenone, Spironolactone)
7- Miscellaneous novel agents (e.g. Istaroxime, omecamtiv mecarbil, Ryanodine receptor stabilizer- JTV-519, Recombinant human NRG-162, Vasopeptidase Inhibitor Omapatrilat, Carnitine palmitoyl transferase-1 inhibitor Etoxomir, Matrix Metalloproteinase (MMP) Inhibitors Batimastat, Immune modulator Celacade and Gene therapy).
**Angiotensin-converting enzyme inhibitors**

- The agents of choice in HF.
- Block the enzyme that cleaves angiotensin I to form the potent vasoconstrictor angiotensin II and diminish the rate of bradykinin inactivation.
- Decrease the secretion of aldosterone, resulting in decreased sodium and water retention.
- Decrease vascular resistance, venous tone, and blood pressure.
- Reduce preload and afterload, resulting in an increased cardiac output.
- Significantly decreased both morbidity and mortality.
Angiotensin-receptor blockers (ARBs)

- Nonpeptide, orally active compounds that are extremely potent competitive antagonists of the angiotensin type 1 receptor.

- Have the advantage of more complete blockade of angiotensin action, Why?

- Do not affect bradykinin levels.

- Use in HF is as a substitute for ACE inhibitors in those patients with severe cough or angioedema.

- Candesartan was found to be more beneficial when added to an ACE inhibitor.
Direct renin inhibitors

- **Aliskiren**: A selective renin inhibitor available for the treatment of heart failure and hypertension.

- Directly inhibits renin and, thus, acts earlier in the renin–angiotensin–aldosterone system than ACE inhibitors or ARBs.

- Metabolized by CYP 3A4 and is subject to many drug interactions.

- Can cause diarrhea, especially at higher doses, and can also cause cough and angioedema, but probably less often than ACE inhibitors.

- Contraindicated during pregnancy.
Aldosterone antagonists

- Patients with advanced heart disease have elevated levels of aldosterone due to angiotensin II stimulation and reduced hepatic clearance of the hormone causing retention of $\text{Na}^+$. 

- **Spironolactone** synthetic steroid direct antagonist of aldosterone, thereby preventing salt retention, myocardial hypertrophy, and hypokalemia.

- **Eplerenone** competitive antagonist of aldosterone at mineralocorticoid receptors. Has a lower incidence of endocrine-related side effects due to its reduced affinity for glucocorticoid, androgen, and progesterone receptors.
β-adrenoreceptor blockers

- Although it may seem counterintuitive to administer drugs with negative inotropic activity to a patient with HF, several clinical studies have clearly demonstrated improved systolic functioning and reverse cardiac remodeling in patients receiving β-blockers.

- The benefit of β-blockers is attributed, in part, to their ability to prevent the changes that occur because of the chronic activation of the sympathetic nervous system, including decreasing the heart rate and inhibiting the release of renin.

- β-blockers prevent the direct deleterious effects of norepinephrine on the cardiac muscle fibers, decreasing remodeling, hypertrophy, and cell death.

- Three β-blockers have been approved for use in chronic stable HF, carvedilol, bisoprolol and long-acting metoprolol.

- Treatment should be started at low doses and gradually titrated to effective doses based on patient tolerance.
Diuretics relieve pulmonary congestion and peripheral edema.

**Mode of Action**

- **Place of action**: Kidneys
- **Kind of action**: Forced renal excretion
  - **Effects of action**:
    - Loss of water
    - Loss of minerals
Diuretics decrease plasma volume and, subsequently, decrease venous return to the heart (preload).

This decreases the cardiac workload and the oxygen demand.

They have no direct effect on cardiac contractility.

In heart failure associated with hypertension, the reduction in blood pressure also reduces afterload.

Loop diuretics are the most commonly used diuretics in HF.

Loop diuretics are used for patients who require extensive diuresis and those with renal insufficiency.

Thiazide diuretics are relatively mild diuretics and lose efficacy if patient creatinine clearance is less than 50 mL/min.

Thiazides exhibit true synergism with loop diuretics.

Serum electrolytes and renal function should be monitored frequently.
Direct vasodilators

- Dilation of venous blood vessels leads to a decrease in cardiac preload by increasing the venous capacitance.

- Arterial dilators reduce systemic arteriolar resistance and decrease afterload.

- Nitrates are commonly used venous dilators for patients with congestive HF reduce preload.

- Hydralazine dilate arterioles and decreases afterload.

- A combination of hydralazine and isosorbide dinitrate can be used if the patient is intolerant of ACE inhibitors or β-blockers, or if additional vasodilator response is required.

- Phentolamine and nitroprusside are less commonly used.
Inotropic agents: Cardiac Glycosides

- Positive inotropic agents enhance cardiac muscle contractility and, thus, increase cardiac output.

- The cardiac glycosides are often called digitalis or digitalis glycosides, because most of the drugs come from the digitalis (foxglove) plant.

- The Na\(^+\)/K\(^+\) ATPase exchange is inhibited by glycosides (compete with potassium for the same binding site on the Na\(^+\)/K\(^+\)-ATPase pump).

- Cardiac glycosides decrease the Na\(^+\) concentration gradient and, consequently, the ability of the Na\(^+\)/Ca\(^{2+}\)-exchanger to move calcium out of the cell.

- They increase contraction of the atrial and ventricular myocardium (positive inotropic action).

- The most widely used agent is digoxin.
Mechanism of action of digoxin

- Increases the force of cardiac contraction, causing the cardiac output.
- Improved circulation leads to reduced sympathetic activity, which then reduces peripheral resistance with reduction in heart rate.
- Slows down conduction velocity through the AV node, which accounts for its use in atrial fibrillation.

1. Digoxin inhibits Na⁺/K⁺ exchange by Na⁺/K⁺-ATPase.
2. The concentration of intracellular Na⁺ increases, and the concentration gradient across the membrane decreases.
3. Increased Na⁺ decreases the driving force for the Na⁺/Ca²⁺ exchanger, so there is decreased extrusion of Ca²⁺ into the extracellular space.
Digoxin

- Increases the force of cardiac contraction, causing cardiac output to more closely resemble that of the normal heart. Vagal tone is also enhanced, so both heart rate and myocardial oxygen demand decrease. Digoxin slows conduction velocity through the AV node, making it useful for atrial fibrillation.

- Very potent, available in oral and injectable formulations with a narrow margin of safety and long half-life of around 36 hours.

- Mainly eliminated intact by the kidney, requiring dose adjustment based on creatinine clearance.

- A loading dose regimen is used when acute digitalization is needed.

- Digoxin toxicity is one of the most commonly encountered adverse drug reactions.
Digoxin adverse effects include:

a. **Cardiac effects**: The common cardiac side effect is arrhythmia, characterized by slowing of AV conduction associated with atrial arrhythmias. A decrease in intracellular potassium is the primary predisposing factor in these effects.

b. **GIT effects**: Anorexia, nausea, and vomiting (may be initial indicators of toxicity)

c. **CNS effects**: headache, fatigue, confusion, blurred vision, yellowish vision (xanthopsia), and halos on dark objects.
Digoxin Toxicity

- At low serum drug concentrations, digoxin is fairly well tolerated.

- In spite of its recognized hazards, digitalis is still heavily used and toxicity is common.

- Factors decrease incidence of digoxin toxicity include better understanding of digoxin pharmacokinetics, monitoring of serum digoxin and $K^+$ levels (Why?), and identification of important interactions between digoxin and other concomitantly administered drugs.

- Factors increase incidence of digoxin toxicity include: electrolytic disturbances, hypothyroidism, hypoxia, renal failure, myocarditis and drugs like quinidine, verapamil, and amiodarone, potassium-depleting diuretics, corticosteroids.

- Treatment should include prompt insertion of a temporary cardiac pacemaker and administration of digitalis antibodies (digoxin immune fab).
Digitoxin

- Cardiac glycoside metabolized mainly by the liver so it is safe in renal impairment.
- Its metabolism accelerated by drugs such as phenytoin and rifampin that induce hepatic metabolism.
- Has a much longer half-life than digoxin.
- Highly protein-bound.
- Given as i.v. route of administration.
Dopamine and Dobutamine

- Positive inotropic drugs with prompt onset and short durations of action.
- Dopamine has strong beta1-adrenergic, alpha-adrenergic, and dopaminergic effects are based on dosing rate. Dobutamine has a selective beta1 agonist and has no effect on dopamine receptors.
- Low dose stimulates mainly dopaminergic receptors, producing renal and mesenteric vasodilation; higher dose stimulates both beta1-adrenergic and dopaminergic receptors, producing cardiac stimulation and renal vasodilation.
- Metabolized in liver, kidney, and plasma by monoamine oxidase and catechol-O-methyl transferase.
- They are most useful in patients with failure complicated by severe hypotension.
- Must be given by intravenous infusion and is primarily used in the treatment of acute HF in a hospital setting.
Phosphodiesterase inhibitors

- **Inamrinone and milrinone** They increase the intracellular concentration of cAMP. This results in an increase of intracellular calcium and, therefore, cardiac contractility.

- These drugs are indicated for short term i.v. use in severe and refractory CHF.

- They cause balanced arterial and venous dilation with a consequent fall in systemic and pulmonary vascular resistances, and left and right heart filling pressures.

- Thrombocytopenia and arrhythmias are the major adverse effects.
Levosimendan

- A new inotopic and vasodilator agent is being used in acutely-decompensated severe congestive heart failure.

- Calcium sensitiser – it increases the sensitivity of the heart to calcium, thus increasing cardiac contractility without a rise in intracellular calcium.

- Exerts its positive inotropic effect by increasing calcium sensitivity of myocytes by binding to cardiac troponin C in a calcium-dependent manner.

- Has a vasodilatory effect, by opening ATP sensitive K⁺ channels in vascular smooth muscle to cause smooth muscle relaxation.

- Can cause hypotension and arrhythmias.
Novel agents

- **Istaroxime** investigational steroid derivative that increases contractility by inhibiting $\text{Na}^+/\text{K}^+-\text{ATPase}$ and facilitate sequestration of $\text{Ca}^{2+}$ by the SR which render the drug less arrhythmogenic than digitalis. Reduces heart rate with wider margin of safety.

- **Omecamtiv mecarbil** is an investigational parenteral agent that activates cardiac myosin and prolongs systole without increasing oxygen consumption of the heart.
Nesiritide

- Is a recombinant BNP (brain derived natriuretic peptide, normally secreted by ventricles).
- Increases cGMP and thus causes vasodilation.
- Increases the excretion of sodium through the kidney.
- It has a short half life (18 min) and has been used i.v. for acute CHF associated with dyspnoea at rest.
- Preferable to inotrophic drugs when treating refractory heart failure in patients at risk for arrhythmia.
- The primary side effect is hypotension that is reversible upon discontinuation of the drug.
Neutral Endopeptidase (NEP) Inhibitors

Natriuretic peptides are degraded by neutral endopeptidase (NEP). Inhibition of this endopeptidase results in increases in circulating levels of the natriuretic peptides, natriuresis, and diuresis.

- **Candoxatrilat** an active metabolite of candoxatril inhibits NEP and produces diuresis and natriuresis in patients with heart failure.

- **Omapatrilat** inhibits both NEP and ACE promoting diuresis, vasodilatation and reductions in preload and ventricular remodeling. Used in HF and HRT. Causes a significant incidence of angioedema in addition to cough and dizziness.

**Sampatrilat** and fasidotrilat are similar.
Endothelin-1 Receptor Antagonists

- Endothelin-1 (ET-1) is a potent vasoconstrictor peptide produced by vascular endothelium via specific cleavage by endothelium converting enzyme (ECE).
- Plasma concentration of endothelin-1 is elevated in patients with moderate to severe chronic heart failure.
- ET-1 produces its actions by acting on endothelin ETA and ETB receptors.
- ETA receptor predominates in vascular smooth muscle cells and mediates vasoconstriction in both large and small blood vessels whereas ETB receptors on endothelial cells mediate vasodilation through the production of nitric oxide and prostacyclin.
- FR 139317, a selective ETA receptor antagonist has decreased cardiac pressures and increased cardiac output, glomerular filtration rate and renal blood flow. On the other hand RES-701-1, a selective ETB receptor antagonist has increased cardiac pressures and decreased cardiac output as well as renal blood flows.

Thus, blockade of ETB receptors may not be useful in heart failure.
Dual Neutral Endopeptidase (NEP) and Endothelin Converting Enzyme (ECE) Inhibitors

- Phosphoramidon an ECE inhibitor produced vasodilation in patients with heart failure.
- **GGS 34043, GGS 34226 and GGS 26303** are dual inhibitor of ECE/NEP in development stages as future therapy for heart failure.
- They decreased preload, afterload and LV hypertrophy and increased cardiac output.

Triple Enzyme Inhibitors of ECE/NEP/ACE

- **GGS 26670** triple enzyme inhibitor improved LV function and reduced LV collagen accumulation better than either ACE alone or ECE-NEP inhibition.
Dual Dopamine D2 (D2)-α2 Adrenoceptor Agonist

- Nolomirole (CHF-1025) selective D2-α2 receptor agonistic property that inhibits catecholamine release from sympathetic nerve endings and also inhibits the release of TNF-α from cardiac tissue to improve ventricular function, significantly reduces hypertrophy and attenuates signs and symptoms of heart failure.

Dopamine β-Hydroxylation Inhibitor

- Dopamine β-hydroxylase (DBH) catalyses the conversion of dopamine (DA) to norepinephrine (NE) in sympathetic nerves.
- Nepicastat is a DBH inhibitor which has been reported to reduce NE synthesis. At low doses maintain normal plasma concentrations of NE in chronic heart failure. It attenuates ventricular remodeling and prevents systolic dysfunction.
Adenosine A1 Receptor Antagonists

- **Tonapofylline** a selective A1 receptor antagonist increased GFR, urine flow and sodium excretion in a dose-dependent manner.
- Protects renal function and exerts additive natriuretic effects without excessive potassium loss.

Partial Fatty Acid Oxidation (pFOX) inhibitor

- **Ranolazine** suppresses oxidation of fatty acids and improves mechanical efficiency and ventricular function in patients with chronic heart failure

Carnitine Palmitoyl Transferase-1 (CPT-1) Inhibitors

- **Etoxomir** reverses fetal gene expression, preserves cardiac function and prevents ventricular dilation. Improved ventricular function and reduced pulmonary pressure in patients with heart failure.
- **Oxfenicine** is another inhibitor of CPT-1 and it prevented ventricular remodeling in heart failure.
Matrix Metalloproteinase (MMP) Inhibitors

- It has been shown that enhanced expression of MMP triggers signaling cascade of cardiac remodeling and inhibition of MMP may be a potential therapeutic strategy for heart failure.
- Batimastat, ilomastat, marimastat and prinomastat are inhibitors of MMP being developed for heart failure.
- Evidence suggests that inhibition of cardiac MMP could prevent ventricular dysfunction and delay heart failure progression.

Immune modulator

- Celacade is an immune modulator which prevents chronic inflammation and apoptotic cell death by activating physiological immune system’s IL-10 mediated anti-inflammatory process. Improves quality of life in patients with heart failure and reduces the risk of death and hospitalization.