Drugs Used in the Treatment of heart failure
TYPES OF HEART FAILURE

Right heart failure
- Congestion of peripheral tissues
  - Dependent edema and ascites
  - Liver congestion
    - Signs related to impaired liver function
      - GI tract congestion
        - Anorexia, GI distress, weight loss
  - GI tract congestion

Left heart failure
- Decreased cardiac output
  - Activity intolerance and signs of decreased tissue perfusion
- Pulmonary congestion
  - Impaired gas exchange
  - Cyanosis and signs of hypoxia
    - Cough with frothy sputum
  - Pulmonary edema
    - Orthopnea
  - Paroxysmal nocturnal dyspnea
Activation of neuro-hormonal systems in heart failure

Baroreceptor dysfunction → ↓ Afferent inhibitory signals

↑ Sympathetic nervous system activity → ↓ Limb blood flow

Vasomotor center

↑ Vasopressin secretion

↓ Renal blood flow
↑ Aldosterone secretion
↑ Sodium reabsorption
↑ Water reabsorption

Angiotensinogen → Renin → Angiotensin I → Angiotensin II

Angiotensin II receptors (AT1)

Kininogen → Kallikrein → Bradykinin

Bradykinin receptors

ACE

Aldosterone secretion

Renal vasodilatation

Arterial vasodilatation

Sympathetic activation

Hypertension

Renal sodium and fluid reabsorption

Biological actions
Activation of hormonal systems in heart failure

Activation of the renin-angiotensin-aldosterone system leads to increased Na\(^+\) and water retention through multiple mechanisms:

1) Angiotensin II directly causes Na\(^+\) retention at the proximal tubule.
2) Angiotensin II also stimulates the thirst center of the brain which further contributes to the release of vasopressin.

Increasing Na\(^+\) and water retention by the kidneys, leading to pulmonary and peripheral edema, are hallmarks of worsening heart failure.
Clinical classification of heart failure severity

**Stage A**
At high risk for HF but without structural heart disease or symptoms of HF

- Patients with:
  - Hypertension
  - Atherosclerotic disease
  - Diabetes mellitus
  - Obesity
  - Metabolic syndrome

- Or Patients:
  - Using cardiotoxic drugs
  - With family history of cardiomyopathy

**Stage B**
Structural heart disease but without signs or symptoms of HF

- Patients with:
  - Previous MI
  - LV remodeling including LV hypertrophy and low ejection fraction
  - Asymptomatic valvular disease

**Stage C**
Structural heart disease with prior or current symptoms of HF

- Patients with:
  - Known structural heart disease
  - HF signs and symptoms

**Stage D**
Refractory HF

- Patients with:
  - Marked HF symptoms at rest
  - Recurrent hospitalized despite guideline-directed medical therapy

**THERAPY**

**Goals**
- Control symptoms
- Improve HRQOL
- Reduce hospital readmissions
- Establish end-of-life goals

**Options**
- Advanced care measures
- Heart transplant
- Chronic inotropes/neseritide
- Temporary or permanent mechanical support
- Experimental surgery or drugs
- Palliative care and hospice
- ICD deactivation

**Drugs for use in patients with preserved EF**
- Diuretics
- Treat comorbidities (HTN, AF, CAD, DM)

**Drugs for routine use in patients with reduced EF**
- Diuretics
- ACEI or ARB
- ARNI
- β Blocker
- Aldosterone antagonist
- Ivabradine

**Drugs for use in selected patients with reduced EF**
- Hydralazine/ISDN
- ACEI and ARB
- Cardiac glycoside

**In selected patients**
- CRT
- ICD
- Revascularization or valvular surgery

Source: Laurence L. Brunton, Randa Hilal-Dandan, Björn C. Knollmann: Goodman & Gilman’s: The Pharmacological Basis of Therapeutics, Thirteenth Edition. Copyright © McGraw-Hill Education. All rights reserved.
2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

With the special contribution of the Heart Failure Association (HFA) of the ESC

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Sex differences in heart failure (HF) with preserved (HFpEF), reduced (HFrEF) Ejection Fraction, Coronary Artery Disease (CAD)

- Higher prevalence
- Concentric hypertrophy
  → More pronounced diastolic dysfunction
  → More fibrosis
  → More susceptible to acute events (reduced pre-load reserve)
- Post-menopausal decrease of estrogens: impaired calcium handling, reduced vasodilation, myocardial fibrosis

HFpEF

- Lower prevalence
- Different comorbidities: younger age, less likelihood of diabetes, hypertension, obesity
- Eccentric hypertrophy

HFrEF

- Higher incidence of:
  → Tako-Tsubo cardiomyopathy
- Specific types of cardiomyopathy
  → Peripartum cardiomyopathy

CAD

- Younger onset
- Higher incidence
- Classical presentation
- Earlier diagnosis and prompt treatment
- More frequently occlusive epicardial CAD

- Later onset
- Atypical symptoms and reduced sensitivity of diagnostic test (i.e. exercise test)
- Higher mortality and complications
- Higher incidence of:
  → spontaneous coronary dissection
  → non-obstructive CAD, microvascular dysfunction
- Reduced symptoms awareness and delayed seek of medical care

Fig. 3  Main sex-related differences in different cardiovascular diseases: heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), and coronary artery disease (CAD)

Heart Fail Rev (2020) 25:245–255
HFpEF – Influence of comorbidities in women

Figure 2. The influence of comorbidities on the development of HFpEF in women. Comorbidities including iron deficiency, diabetes mellitus, obesity, preeclampsia, hypertension, and autoimmune diseases contribute to HFpEF risk through cardiac structural and functional changes, and systemic inflammation. HF indicates heart failure; HFpEF, heart failure with preserved ejection fraction; and LV, left ventricle.
Acute heart failure

- Left ventricular dysfunction and increased Na\(^+\) and water retention lead to acute heart failure.

- Acute heart failure may be the first manifestation of heart failure (new onset) or, more frequently, acute heart failure is an acute decompensation of chronic heart failure.

- Peculiar clinical symptoms are mainly based on the presence of congestion and/or peripheral hypoperfusion.

- The objectives of the pharmacological treatment are the identification of precipitants, the decongestion, and in rare instances, the correction of hypoperfusion.

- Drugs administered in acute heart failure:
  1) Diuretics (loop diuretics);
  2) Inotropic agents/vasopressors (if peripheral hypoperfusion/hypotension is present).
Phenotypes of chronic heart failure

<table>
<thead>
<tr>
<th>Stade of left ventricular ejection fraction</th>
<th>Measurement of left ventricular ejection fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preserved (HFpEF)</td>
<td>40-50%</td>
</tr>
<tr>
<td>Mildly reduced (HFmrEF)</td>
<td>41-49%</td>
</tr>
<tr>
<td>Reduced (HFrEF)</td>
<td>≤ 40%</td>
</tr>
</tbody>
</table>

Right ventricular dysfunction: diagnosis by a quantitative assessment of global right ventricular function, most commonly by echocardiography.
In **HFpEF**, the main goal is the **reduction of symptoms of congestion**. Drugs administered in HFpEF: diuretics (loop diuretics are preferred, although thiazide diuretics may be useful for managing hypertension).

In **HFmrEF**, the main goals are the **relief of symptoms and signs** (loop diuretics for fluids retention) and the **reduction the risk of hospitalization and death** (β-blockers; Angiotensin converting enzyme inhibitors; Angiotensin II type 1 receptor blockers).

In **HFrEF**, the main goals are the **reduction in mortality, the prevention of recurrent hospitalizations** (due to worsening heart failure) and the **improvement in clinical status, functional capacity, and quality of life** (β-blockers; Angiotensin converting enzyme inhibitors; Angiotensin II type 1 receptor blockers; loop diuretics for fluids retention; Digoxin as a second choice).
Drugs without inotropic effects: diuretics and miscellaneous drugs for heart failure
Diuretics

- Diuretic drugs are classified according to their predominant site of action:
  1) **Loop diuretics** (furosemide, bumetanide, and torsemide) are organic anions acting in the short descending limbs of the loop of Henle.

  2) **Thiazides and thiazide-like** drugs are also organic anions that bind the thiazide-sensitive NaCl cotransporter along the distal convoluted tubule.

  3) **K⁺-sparing diuretics** include drugs that block apical Na⁺ channels (amiloride and triamterene) and those that antagonize mineralocorticoid receptors (spironolactone and eplerenone).

- Concomitant use of diuretics and natural licorice (may lead to hypokalemia) or foods containing K⁺ (banana and orange juice) should be avoided.
Loop Diuretics

Loop diuretics have the higher capacity for diuresis compared to other diuretics. Their mechanism of action is based on:

1) Inhibition of Na\(^+\) and Cl\(^-\) reabsorption at the level of the short descending limbs of the loop of Henle and collecting ducts.

2) Increase of the fractional excretion of Ca\(^{++}\) by up to 30%.

3) Increase fractional Mg\(^{++}\) excretion by more than 60%.

Loop diuretics are first-line drugs in both acute and chronic heart failure. Loop diuretics produce more intense and shorter diuresis than thiazides, which results in more gentle and prolonged diuresis and in a general improvement in the quality of life. Nevertheless, loop diuretics and thiazides may work in synergy when a sequential segmental nephron blockade is achieved.
Furosemide is a sulfonamide derivative of aminobenzoic acid.

The Food and Drug Administration (FDA) has approved furosemide to treat conditions with volume overload and edema secondary to chronic heart failure exacerbation, liver failure, or renal failure, including nephrotic syndrome.

Furosemide can predispose to excessive loss of water, resulting in dehydration with electrolyte depletion (hyponatremia, hypokalemia and hypocalcemia). The magnitude of these effects can be greater than the effects produced by thiazides because of the more prominent natriuresis produced by loop diuretics. Furosemide may also cause hyperglycemia, glycosuria, hyperuricemia, hypertriglyceridemia, increased cholesterol levels.

Furosemide interacts with antibiotics, cyclosporine, ethacrynic acid, lithium, NSAIDs, or corticosteroids (intensified electrolyte depletion). Ototoxicity can occur with the use of furosemide, but the concomitant use of ethacrynic acid, aminoglycosides, or other ototoxic drugs increases the risk.
Thiazide and thiazide-like diuretics inhibit $\text{Na}^+\text{Cl}^-$ cotransport.

Their mechanism of action is based on:

1) increase in the excretion of NaCl and reduction of extracellular fluid volume.

2) increase the reabsorption of $\text{Ca}^{++}$. This action distinguishes these compounds from loop diuretics, which promote $\text{Ca}^{++}$ excretion.

3) $\text{Mg}^{++}$ initial reabsorption is also initially increased by thiazides, but subsequently loss.
Hydrochlorothiazide is the most commonly prescribed thiazide diuretic.

The Food and drug administration (FDA) approved hydrochlorothiazide to treat hypertension as a sole agent or adjunct. Moreover, hydrochlorothiazide is recommended as adjunctive therapy to treat edema associated with congestive heart failure or renal dysfunction.

Hydrochlorothiazide can cause electrolyte imbalances, including hypokalemia, hyponatremia, hypercalcemia, and hypomagnesemia. Most prevalent among these is hypokalemia, which results from the combined effects of volume depletion–induced aldosterone release and increased delivery of Na⁺ and Cl⁻ to the collecting duct. Hyperglycemia can occur, and this drug has been known to unmask latent diabetes as well as cause an increase in cholesterol and triglycerides. There have been reports of exacerbation of systemic lupus erythematosus with the use of hydrochlorothiazide. Hydrochlorothiazide can cause acute transient myopia and acute angle-closure glaucoma, which can occur hours to weeks after beginning the drug. Risk factors for developing this reaction are a history of sulfonamide or penicillin allergy.

Hydrochlorothiazide interacts with antidiabetic drugs, corticosteroids (intensified electrolyte depletion), lithium, NSAIDs.
Hydrochlorothiazide combinations with other drugs

- K⁺-sparing diuretics.

- Another antihypertensive drug.
K⁺-sparing diuretics

- K⁺-sparing agents can be divided into those that antagonize aldosterone (spironolactone and eplerenone) and those independent of aldosterone (amiloride and triamterene).

All of the drugs in this class:

1) inhibit Na⁺ absorption in the distal tubule and the collecting duct.

2) with the block in Na⁺/K⁺ ATPase, K⁺ secretion is reduced. This effect can lead to hyperkalemia and limit their use in patients with reduced renal function and in some with heart failure.

3) reduce the excretion of Ca++ and Mg++. 

- Randomized clinical trials have shown that K⁺-sparing diuretics are able to reduce both hospitalizations and mortality in patients with chronic heart failure, although they are less useful than loop diuretics in cases of acute heart failure.
Spironolactone is structurally similar to aldosterone and functions as an aldosterone antagonist.

Spironolactone is FDA approved for the treatment of heart failure with reduced ejection fraction (HFrEF), resistant hypertension, primary hyperaldosteronism, edema secondary to cirrhosis, edema secondary to a nephrotic syndrome that is not adequately controlled using alternative therapies, and hypokalemia.

Spironolactone, because of its steroid structure, mainly induce breast complaints and hyperkalemia. Men specifically may experience gynecomastia, loss of libido, and general feminization. Menstrual irregularities have been reported for women.

Concomitant administration of ACE inhibitors with K⁺-sparing diuretics has been associated with severe hyperkalemia. Angiotensin II receptor 1 antagonists, aldosterone blockers, heparin may interact with spironolactone inducing excessive hyperkalemia.
ACE inhibitors in heart failure

- **ACE inhibitors** (Captopril) are **first-line drugs for reducing the risk of hospitalization and mortality in HFrEF and HFmrEF**, probably because they delay the long-term remodeling of the heart and vessels.
- ACE inhibitors reduce peripheral resistance, \( \text{Na}^+ \) and water retention. The reduction in tissue angiotensin levels also reduces sympathetic activity.
- Side effects: **dry cough**, skin rash, angioedema, and dysgeusia (distortion of taste). Neutropenia and agranulocytosis may appear after 3 to 12 weeks of therapy, particularly in patients with autoimmune collagen vascular diseases.
- Drug-drug interactions: drugs that may increase the level of \( \text{K}^+ \) in the blood (such as Angiotensin II type 1 receptor blockers, birth control pills containing drospirenone).

Angiotensin II receptor 1 antagonists in heart failure

- **Angiotensin II receptor 1 antagonists** (candesartan, losartan and valsartan) are **first-line drugs for reducing the risk of hospitalization and mortality in HFrEF** symptomatic patients unable to tolerate an ACE inhibitor (dry cough).
- Several guidelines recommend the use of sartans in association to an ACE inhibitor.
- Side effects: CNS (headache), cardiovascular (hypotension).
- Drug-drug interactions: interactions of sartans with other agents are mainly mediated by CYP2C9 and CYP3A4. Fluconazole impairs the conversion of losartan to its active form, and rifamycin reduces blood levels of losartan. Drugs that increase \( \text{K}^+ \) as spironolactone, may induce hyperkalemia.
Nitrates in heart failure

- **Nitrates** (nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, and sodium nitroprusside) **dilate venous and arterial vessels** leading to a reduction in venous return to the heart. At low doses, this effect occurs predominantly in the **venous circulation**, resulting in increased capacitance and a marked reduction in systemic preload, as well as venous back pressure on the kidney and other perfused organs. At higher doses (≥150–250 μg/min), nitrates dilate **arteries**, including those from the coronary vasculature.

- Intravenous nitroglycerine, isosorbide dinitrate and nitroprusside are recommended in the initial therapy of **acute heart failure** when the systolic blood pressure is >110 mm Hg, in order to improve symptoms and reduce congestion.

- The combination of hydralazine and isosorbide dinitrate provide “**balanced vasodilatation**”, since hydralazine acts predominantly on arteries, isosorbide dinitrate on veins. This combination may be considered to reduce mortality in symptomatic patients with **HFmrEF** or **HFrEF** who cannot tolerate ACE inhibitors or angiotensin II receptor I antagonists.

- Side effects: headaches, tolerance, hypotension.

- Interaction with phosphodiesterase inhibitors (sildenafil, tadalafil or vardenafil).
β-blockers in heart failure

- β-blockers (bisoprolol, carvedilol, metoprolol, nebivolol) are **first-line drugs for reducing the risk of hospitalization and mortality in HFrEF**.

- β-blockers are highly effective in the reduction of myocardial ischemia.

- β-blockers may be used **together with ACE inhibitors or diuretics**.

- Side effects: diarrhea, stomach cramps, nausea, vomiting, rash, blurred vision, disorientation, insomnia, hair loss, weakness, muscle cramps, fatigue.

- Drug-drug interaction: other cardiac drugs (antihypertensive and antianginal drugs, inotropic agents, anti-arrhythmics), NSAIDs, psychotropic drugs, anti-ulcer medications, anaesthetics, warfarin, oral hypoglycaemics and rifampicin.
Inotropic agents
Positive inotropic agents

- Inotropic agents stimulate and increase the force of contraction of the heart muscle.

- Inotropic agents currently indicated for the treatment of heart failure are:
  1) β-adrenergic agonists (dopamine, dobutamine and the catecholamines epinephrine and norepinephrine);
  2) phosphodiesterase III inhibitors (milrinone and enoximone);
  3) the Ca++ sensitizer levosimendan;
  4) digoxin.

- Inotropic agents represent a second line therapy for acute heart failure with left ventricle dysfunction, low cardiac output and low systolic blood pressure (e.g. <90 mm Hg) resulting in poor vital organ perfusion;

- Inotropic agents can be administered in patients with severe heart failure awaiting heart transplant to maintain hemodynamic stability, or as a bridge to decision (second line therapy).
Dopamine and dobutamine

- The therapeutic effects of dopamine infusion in heart failure depend on the dose:
  1) Low doses (2–5µg/kg/min) exert a vasodilatory effect;
  2) Medium doses (5–10µg/kg/min) induce a β1 inotropic effect;
  3) High doses (10–20µg/kg/min) induce vasoconstriction α1-mediated.

- Because the inotropic effects of dopamine result primarily from its effects on β1 receptors, its use in advanced heart failure is limited by the neurotransmitter depletion present in the failing heart.

- Dobutamine is a β-adrenergic agonist that is administered intravenously to stimulate β1-adrenergic, β2-adrenergic, and α1-adrenergic receptors;
- Dobutamine is approved by the Food and Drug Administration (FDA) for short-term use in patients with decreased contractility due to heart failure or cardiac surgical procedures leading to cardiac decompensation.
- Cardiac contractility is increased by its action on β1 and α1 receptors, but because the α1-adrenergic effects are generally counterbalanced by the β2 actions, there is generally little change in blood pressure.
- To ensure an adequate blood pressure it may be necessary to administer dobutamine in combination with a vasopressor (e.g. noradrenaline).

- Side effects of β adrenergic agonists: tachycardia, increase ventricular rate in patients with atrial fibrillation, arrhythmias, myocardial ischemia and increase mortality.
Phosphodiesterase III inhibitors and Levosimendan

- **Milrinone and enoximone** inhibit the phosphodiesterase III with a consequent increase in intracellular Ca$^{++}$, vasodilation and increased myocardial contractility;
- Milrinone is administered intravenously to treat patients with acute heart failure and as a bridge to transplantation;
- Despite milrinone can dramatically improve the functional status of patients with severe heart failure and improve end-organ function, the side effects limit the use of these drugs.

- **Levosimendan** is a novel inotrope that sensitizes cardiac troponin to Ca$^{++}$, thus increasing the contraction without increasing the intracellular Ca$^{++}$ concentration. It also acts on K$^+$ channels in smooth muscle to cause vasodilation. At high doses, levosimendan is also a phosphodiesterase III inhibitor.
- Levosimendan has been shown to induce protection of myocardial, renal, hepatic and neural cells from ischemia/reperfusion injury, and further anti-inflammatory and anti-oxidative effects.
- Levosimendan has been associated with a trend towards survival improvement in different meta-analyses.
- Levosimendan has a prolonged action, compared to other inotropes, that lasts several days after discontinuation of the infusion, which is provided by the long elimination half-life of the active metabolite OR-1896 of approximately 80 h.
- Levosimendan has been well tolerated in patients with acute left heart failure. Common side effects reported are hypotension, headache, and dizziness secondary to the vasodilating properties. Increased incidence of atrial fibrillation has also been associated with infusion of levosimendan compared with both dobutamine and placebo.

- Side effects of phosphodiesterase III inhibitors and levosimendan: excessive peripheral vasodilation and hypotension.
## Effect on mortality of inotropic agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Increase in Intracellular Calcium Concentration</th>
<th>Effect on Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>Na-K pump inhibitor</td>
<td>Yes</td>
<td>Neutral; increased mortality of discontinued after long-term use [1]</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>Pure adrenergic; ( \beta_1 &gt; \beta_2 &gt; \alpha ) receptor agonist</td>
<td>Yes</td>
<td>Increased [2]</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Dose related action on adrenergic and dopaminergic receptors</td>
<td>Yes</td>
<td>Increased [3]</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Endogenous catecholamine; stimulates ( \beta ) and ( \alpha ) adrenergic receptors</td>
<td>Yes</td>
<td>Increased [3]</td>
</tr>
<tr>
<td>Milrinone</td>
<td>PDE inhibitor</td>
<td>Yes</td>
<td>Increased [4]</td>
</tr>
<tr>
<td>Levosimendan</td>
<td>Calcium sensitizer</td>
<td>No</td>
<td>Not well established [5,6]</td>
</tr>
<tr>
<td>Omecamtiv</td>
<td>Enhances myosin and actin cross-bridge formation</td>
<td>No</td>
<td>Unknown [7,8]</td>
</tr>
<tr>
<td>Mecarbil</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Na = sodium; K = potassium; PDE = phosphodiesterase.
## Cardiac Glycosides

<table>
<thead>
<tr>
<th>Plants</th>
<th>Glycosides</th>
<th>Sugar</th>
<th>Aglycone/genin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Digitalis purpurea (Leaf)</td>
<td>(i) Digitoxin</td>
<td>(i) Digitoxose (3)</td>
<td>(i) Digitoxigenin</td>
</tr>
<tr>
<td></td>
<td>(ii) Gitoxin</td>
<td>(ii) ..</td>
<td>(ii) Gitoxigenin</td>
</tr>
<tr>
<td></td>
<td>(iii) Gitalin</td>
<td>(iii) ..</td>
<td>(iii) Gitoxigenin hydrate</td>
</tr>
<tr>
<td>2. Digitalis Lanata (Leaf)</td>
<td>(i) Digitoxin</td>
<td>(i) ..</td>
<td>(i) Digitoxigenin</td>
</tr>
<tr>
<td></td>
<td>(ii) Gitoxin</td>
<td>(ii) ..</td>
<td>(ii) Gitoxigenin</td>
</tr>
<tr>
<td></td>
<td>(iii) Digoxin</td>
<td>(iii) ..</td>
<td>(iii) Digoxigenin</td>
</tr>
<tr>
<td>3. Strophanthus gratus (seed)</td>
<td>(i) Ouabain</td>
<td>(i) Rhamnose</td>
<td>(i) Ouabagenin</td>
</tr>
<tr>
<td></td>
<td>(strophanthin G)</td>
<td></td>
<td>(G–Strophanthidin)</td>
</tr>
<tr>
<td>4. Strophanthus kombe (seed)</td>
<td>(i) Strophanthin–K</td>
<td>(i) Glucose and cymarose</td>
<td>(i) Strophanthidin</td>
</tr>
<tr>
<td>5. Urginia maritima (bulb)</td>
<td>Proscillaridin –A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Thevetia neriifolia (nut)</td>
<td>Thevetin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Convallaria majalis</td>
<td>Convallotoxin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Bufo vulgaris (Toad–skin)</td>
<td>Bufotoxin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Semisynthetic</td>
<td>(i) Acetyl–digoxin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(ii) Acetyl–strophanthidin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(iii) Desacetyl lanatoside</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Mechanism of action of cardiac glycosides


2. Concentration of intracellular Na⁺ increases.

3. Increased Na⁺ leads to a greater Ca⁺⁺ influx, causing stronger systolic contraction.

Ca⁺⁺ stores (Sarcoplasmic reticulum)

free Ca⁺⁺

Myofibrils
Therapeutic effects of cardiac glycosides

- Moderate but persistent positive inotropic effect;
- ↑ sensitivity of the baroreceptor reflex;
- Improved kidney function:
  - ↑ glomerular filtration rate;
  - ↑ Na+ excretion;
- ↑ vagal activity
<table>
<thead>
<tr>
<th><strong>Class</strong></th>
<th>Cardiac glycoside</th>
</tr>
</thead>
</table>
| **Pharmacodynamics (MOA)** | **CVS:** Inhibition of Na-K ATPase > accumulation of intracellular Ca2+ via Na/Ca exchanger = positive ionotropic  
**CNS:** increased vagal outflow > increased refractory period + reduced rate of conduction through AVN = negative chronotropic |
| **Clinical Uses** | Atrial fibrillation |
| **Pharmacokinetics** | T ½ 40 hours  
Narrow therapeutic index |
| **Side Effects** | New dysrhythmia, eg AV conduction block |
| **Other relevant information** | AF may cause thrombus formation in the atrium; embolus to the brain may cause a stroke  
High risk of digoxin toxicity; treated with immune Fab digibind, which “mops up” excess |
Pharmacokinetics of digoxin and digitoxin

- Digoxin and digitoxin have similar pharmacological properties, but they differ in pharmacokinetic properties and potency.

<table>
<thead>
<tr>
<th></th>
<th>Digoxin</th>
<th>Digitoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption (oral)</td>
<td>40 – 75%</td>
<td>90 – 100%</td>
</tr>
<tr>
<td>Protein binding</td>
<td>Low</td>
<td>Extensive</td>
</tr>
<tr>
<td>Half life</td>
<td>39 hours</td>
<td>168 hours</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Low</td>
<td>Extensive</td>
</tr>
<tr>
<td>Excretion</td>
<td>Predominantly renal</td>
<td>Partly renal</td>
</tr>
<tr>
<td>Vd (L/Kg)</td>
<td>6.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Therapeutic plasma Conc.</td>
<td>0.5 – 2 ng/ml</td>
<td>10 – 25 ng/ml</td>
</tr>
<tr>
<td>Toxic plasma Conc.</td>
<td>&gt; 2 ng/ml</td>
<td>&gt; 35 ng/ml</td>
</tr>
<tr>
<td>Daily dose (slow loading or maint)</td>
<td>0.125 – 0.5 mg</td>
<td>0.05 – 0.2 mg</td>
</tr>
<tr>
<td>Rapid digitalizing dose</td>
<td>0.5 – 0.75 mg</td>
<td>0.2 – 0.4 mg</td>
</tr>
<tr>
<td>Time for peak effect</td>
<td>3 – 6 hours</td>
<td>6 – 12 hours</td>
</tr>
</tbody>
</table>

- Digoxin has a narrow therapeutic index.
Side effects of digoxin

<table>
<thead>
<tr>
<th></th>
<th>Not uncommon</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardias</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Supraventricular</em></td>
<td>Ectopic beats</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td></td>
<td>Supraventricular tachycardia with 2:1 block</td>
<td></td>
</tr>
<tr>
<td><em>Ventricular</em></td>
<td>Ectopic beats (bigeminy)</td>
<td>Ventricular fibrillation</td>
</tr>
<tr>
<td></td>
<td>Ventricular tachycardia (bidirectional)</td>
<td></td>
</tr>
<tr>
<td>Bradycardias</td>
<td>Sinus bradycardia</td>
<td>Third degree AV block</td>
</tr>
<tr>
<td></td>
<td>Sinus arrhythmia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>First degree AV block</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wenckebach</td>
<td></td>
</tr>
<tr>
<td><strong>Noncardiac</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Salivation, anorexia</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td></td>
<td>Nausea, vomiting</td>
<td>Abdominal discomfort/pain</td>
</tr>
<tr>
<td>Visual</td>
<td>Haloes surrounding dark objects</td>
<td>Scotomata</td>
</tr>
<tr>
<td></td>
<td>Dark objects</td>
<td>Cortical blindness</td>
</tr>
<tr>
<td></td>
<td>Red/green colour blindness</td>
<td>Photophobia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Micropsia, macropsia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amblyopia, diplopia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Shimmering, blurring</td>
</tr>
<tr>
<td>Neurological</td>
<td>Depression, fatigue</td>
<td>Encephalopathy</td>
</tr>
<tr>
<td></td>
<td>Drowsiness</td>
<td>Vertigo</td>
</tr>
<tr>
<td></td>
<td>Difficulty in walking or raising arms</td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td>Neuralgias of arms or legs (e.g. wandering leg</td>
<td>Delirium</td>
</tr>
<tr>
<td></td>
<td>syndrome)</td>
<td>Muscle cramps</td>
</tr>
<tr>
<td></td>
<td>Nightmares, agitation</td>
<td>Trigeminal neuralgia</td>
</tr>
<tr>
<td></td>
<td>Headaches, insomnia</td>
<td></td>
</tr>
<tr>
<td>Allergic</td>
<td></td>
<td>Eosinophilia</td>
</tr>
<tr>
<td>Endocrine</td>
<td></td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gynaecomastia</td>
</tr>
</tbody>
</table>
Interactions of digoxin with other drugs

<table>
<thead>
<tr>
<th>Interacting Drug</th>
<th>Serum Digoxin Levels</th>
<th>Mechanism</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestyramine, colestipol</td>
<td>D</td>
<td>Decreased absorption</td>
<td>Wait 1 hr after digoxin administration</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>D</td>
<td>Decreased absorption due to increased GI motility</td>
<td>Monitor digoxin levels; substitute elixir for tablets</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>I (only in small percentage of patients)</td>
<td>Increased bioavailability due to decreased gut metabolism</td>
<td>Monitor digoxin levels, adjust dose</td>
</tr>
<tr>
<td>Anticancer drugs</td>
<td>D</td>
<td>Decreased absorption due to mucosal injury</td>
<td>Monitor digoxin levels; substitute elixir for tablets</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>D</td>
<td>Decreased absorption</td>
<td>Do not administer within 1 hr of digoxin</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>I</td>
<td>Decreased clearance (P-gp inhibition)</td>
<td>Decrease digoxin dose, monitor levels</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>I</td>
<td>Decreased clearance of digoxin (P-gp inhibition)</td>
<td>Monitor digoxin levels, decrease dose</td>
</tr>
<tr>
<td>Diuretics</td>
<td>I</td>
<td>Decreased renal clearance in hypovolemia; increased toxicity due to hypokalemia/ hypomagnesemia</td>
<td>Monitor serum potassium and magnesium levels; monitor digoxin levels</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>I</td>
<td>Decreased clearance (P-gp inhibition)</td>
<td>Decrease digoxin dose, monitor levels</td>
</tr>
<tr>
<td>Propafenone</td>
<td>I</td>
<td>Decreased renal clearance</td>
<td>Monitor digoxin levels, adjust dose</td>
</tr>
<tr>
<td>Quinine, quinidine</td>
<td>I</td>
<td>Decreased renal clearance (P-gp inhibition)</td>
<td>Decrease digoxin dose, monitor blood levels</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>I</td>
<td>Decreased renal clearance (P-gp inhibition)</td>
<td>Monitor levels</td>
</tr>
<tr>
<td>Verapamil</td>
<td>I</td>
<td>Decreased renal excretion (P-gp inhibition)</td>
<td>Decrease digoxin dose, monitor levels</td>
</tr>
<tr>
<td>Rifampin</td>
<td>D</td>
<td>Increased bioavailability (intestinal P-gp induction)</td>
<td>Monitor levels</td>
</tr>
</tbody>
</table>

Abbreviations: D, decrease; GI, gastrointestinal; I, increase; P-gp, P glycoprotein.
Frank-Starling curves of the ventricular function in normal heart, decompensated heart failure and decompensated heart failure treated with digoxin.
Effect of triple therapy for heart failure on mortality

- Baseline
- ACE Inhibitor Added
- Beta Blocker Added
- Aldosterone Antagonist Added

Lifespan (Years)
## Common drug-drug interactions in heart failure

<table>
<thead>
<tr>
<th>Drug 1</th>
<th>Drug 2</th>
<th>Potential outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin converting enzyme -inhibitors</td>
<td>Non-steroidal anti-inflammatory drugs</td>
<td>Hyperkalaemia, decline in renal function</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Furosemide</td>
<td>Hypokalaemia may increase risk for digitalis-intoxication</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Sildenafil</td>
<td>Increased risk of severe hypotension</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Potassium chloride</td>
<td>Hyperkalaemia</td>
</tr>
</tbody>
</table>