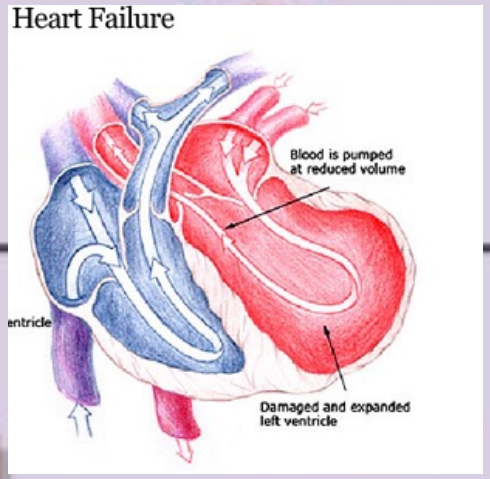
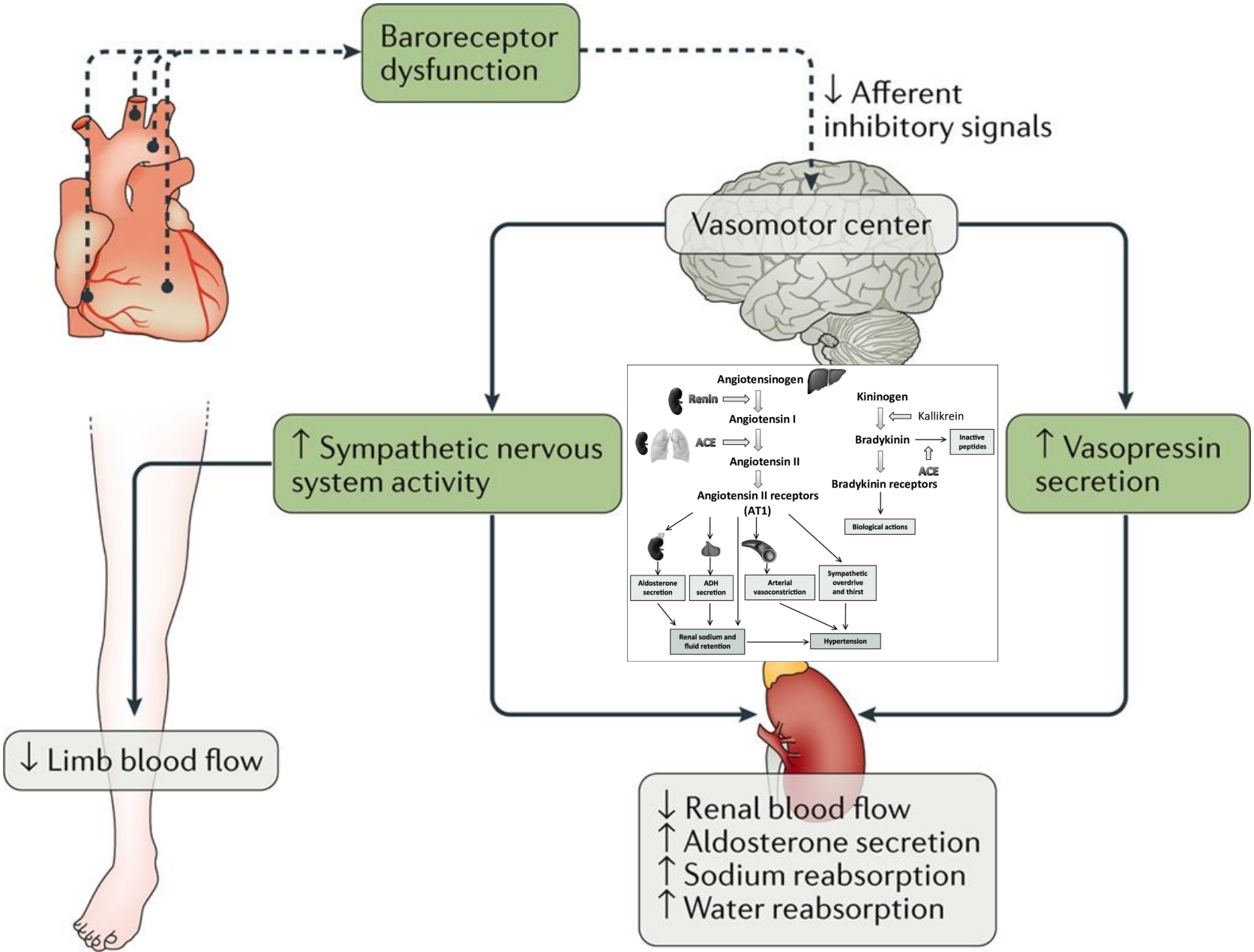
Drugs Used in the Treatment of heart failure

TYPES OF HEART FAILURE



- Right heart failure
  - Congestion of peripheral tissues
    - Dependent edema and ascites
    - GI tract congestion
      - Anorexia, GI distress, weight loss
    - Liver congestion
      - Signs related to impaired liver function
- Left heart failure
  - Decreased cardiac output
    - Activity intolerance and signs of decreased tissue perfusion
  - Pulmonary congestion
    - Impaired gas exchange
      - Cyanosis and signs of hypoxia
    - Pulmonary edema
      - Orthopnea
      - Cough with frothy sputum
      - Paroxysmal nocturnal dyspnea

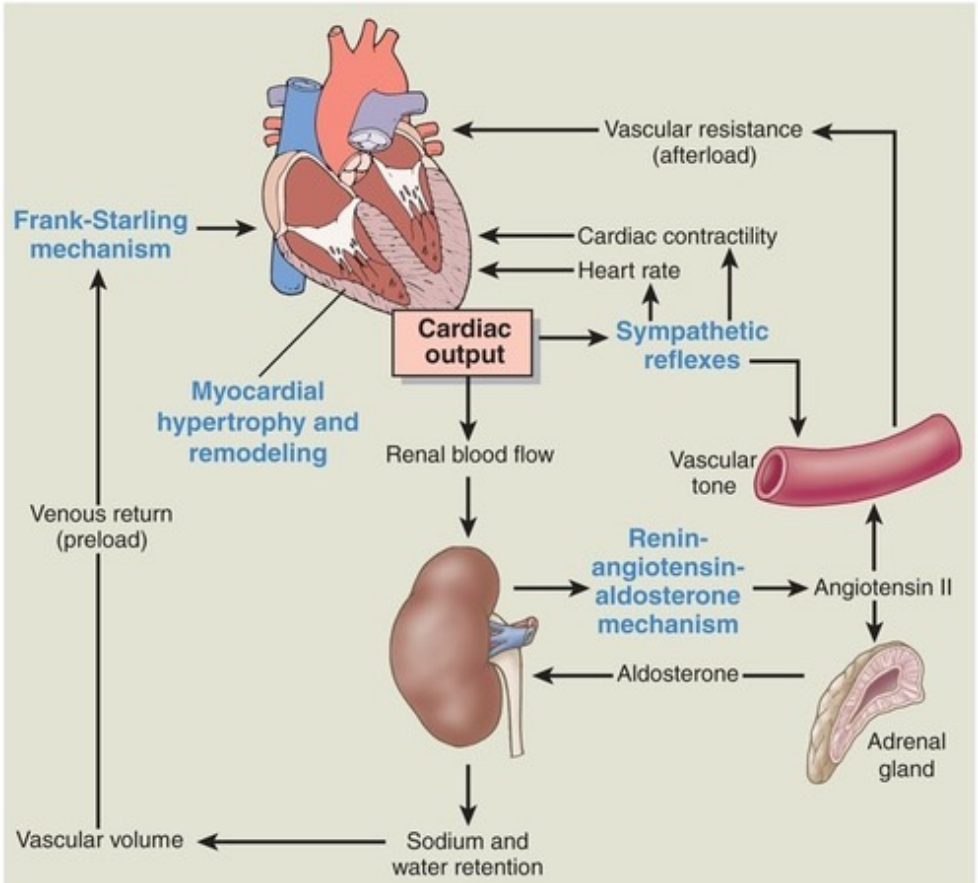
Activation of neuro-hormonal systems in heart failure



Activation of hormonal systems in heart failure

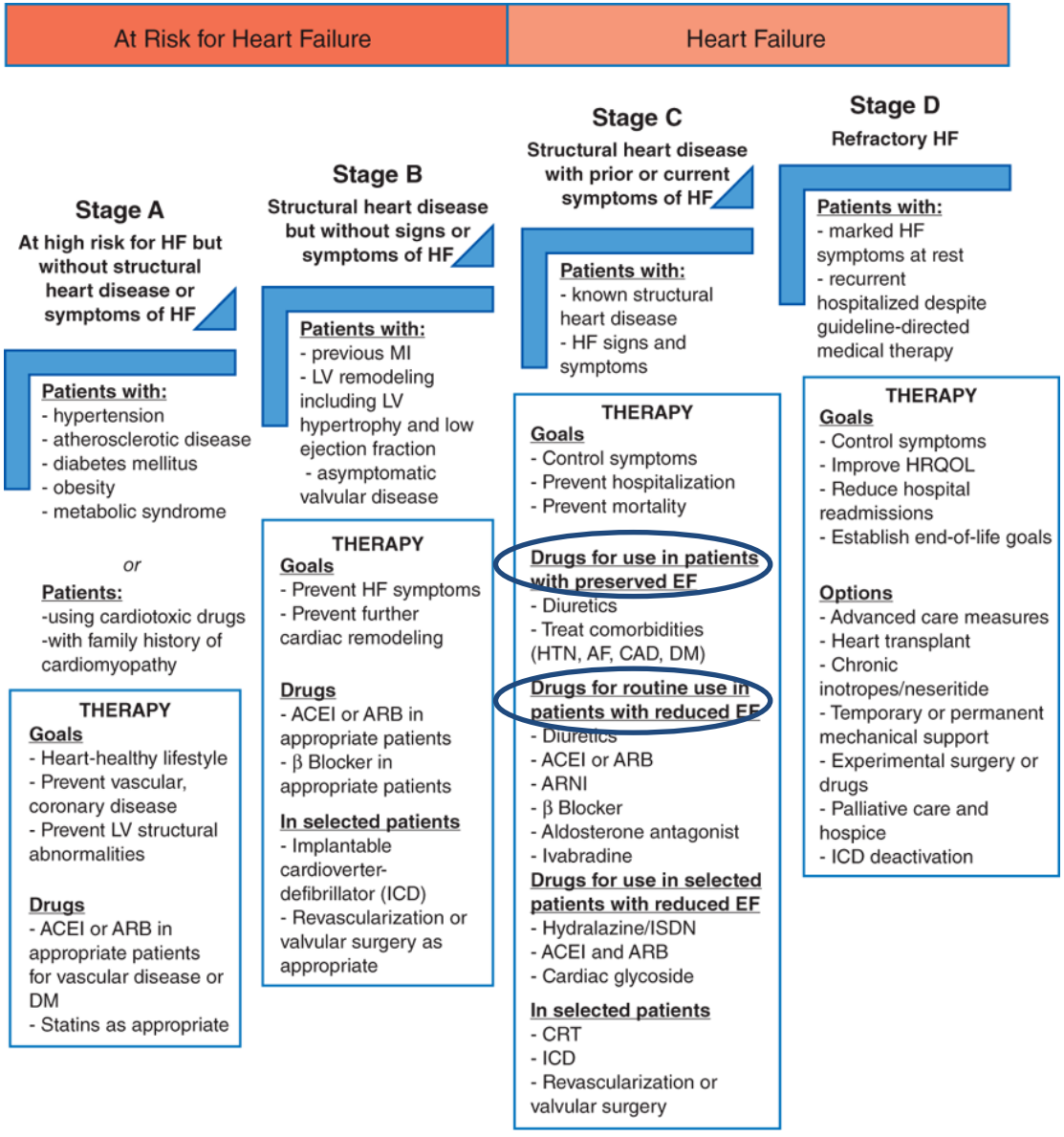
Activation of the renin-angiotensin-aldosterone system leads to increased Na^+ and water retention through multiple mechanisms:

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



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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)

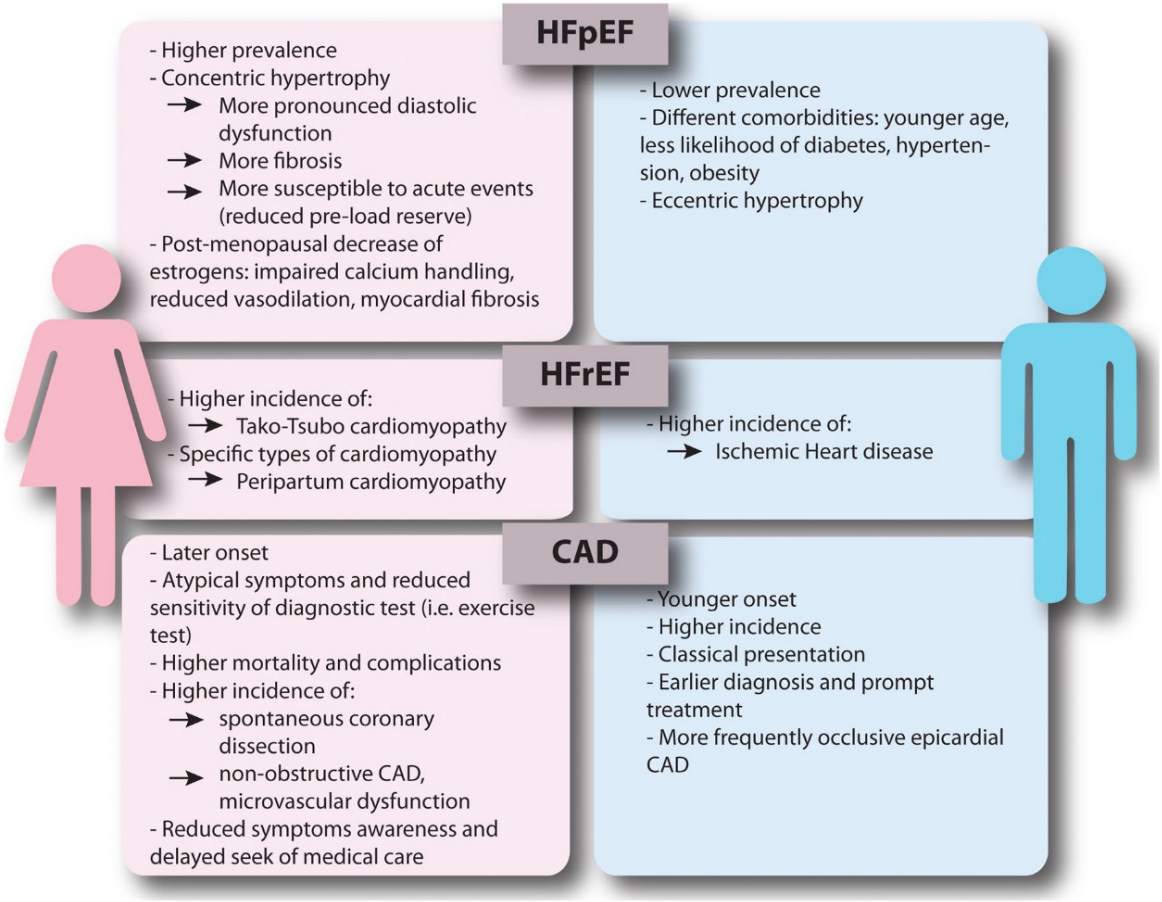

Fig. 3 Main sex-related differences in different cardiovascular diseases: heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), and coronary artery disease (CAD)

Heart Fail Rev (2020) 25:245–255

HFpEF – Influence of comorbidities in women

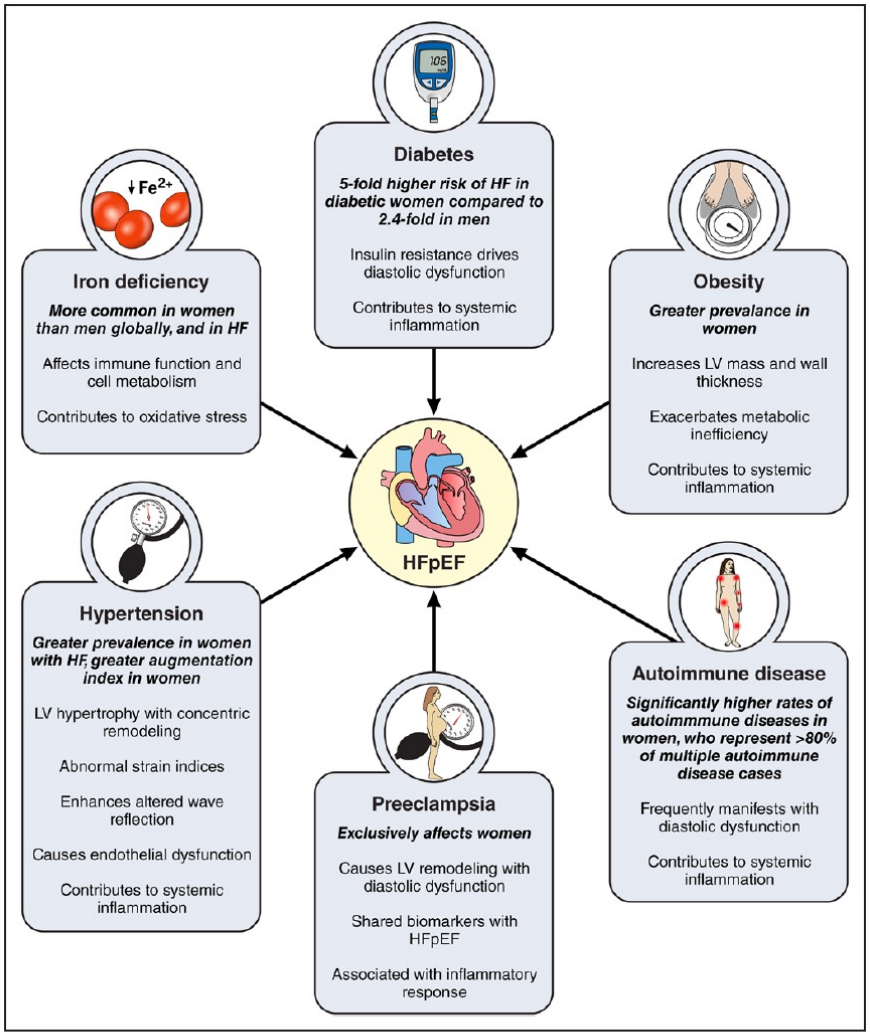

Figure 2. The influence of comorbidities on the development of HFpEF in women.
Comorbidities including iron deficiency, diabetes mellitus, obesity, preeclampsia, hypertension, and autoimmune diseases contribute to HFpEF risk through cardiac structural and functional changes, and systemic inflammation.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

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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:

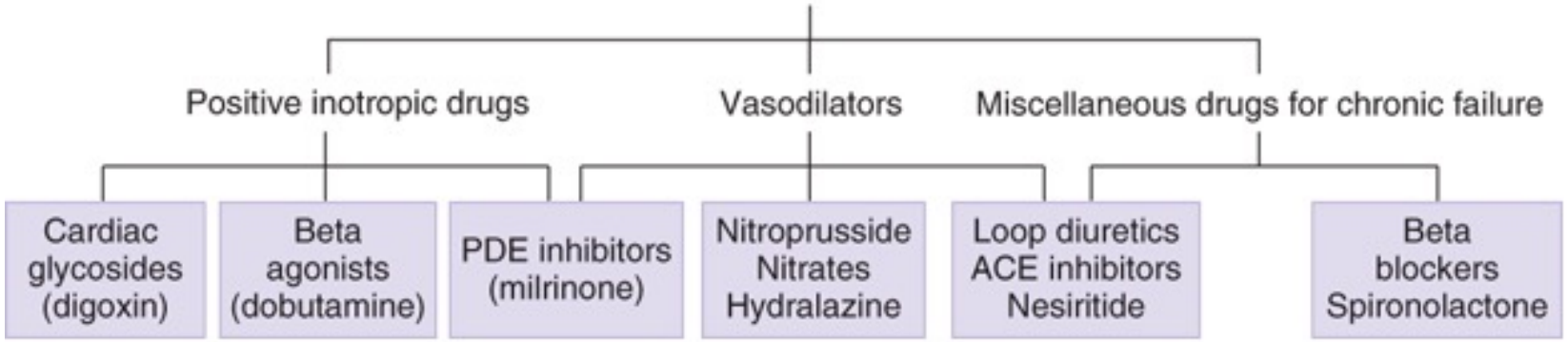
1) Diuretics (loop diuretics);
2) Inotropic agents/vasopressors (if peripheral hypoperfusion/hypotension is present).

Phenotypes of chronic heart failure

Stade of left ventricular ejection fraction	Measurement of left ventricular ejection fraction
Preserved (HFpEF)	40-50%
Mildly reduced (HFmrEF)	41-49%
Reduced (HFrEF)	≤ 40%

Right ventricular dysfunction: diagnosis by a quantitative assessment of global right ventricular function, most commonly by echocardiography.

Drugs administered in heart failure



- 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

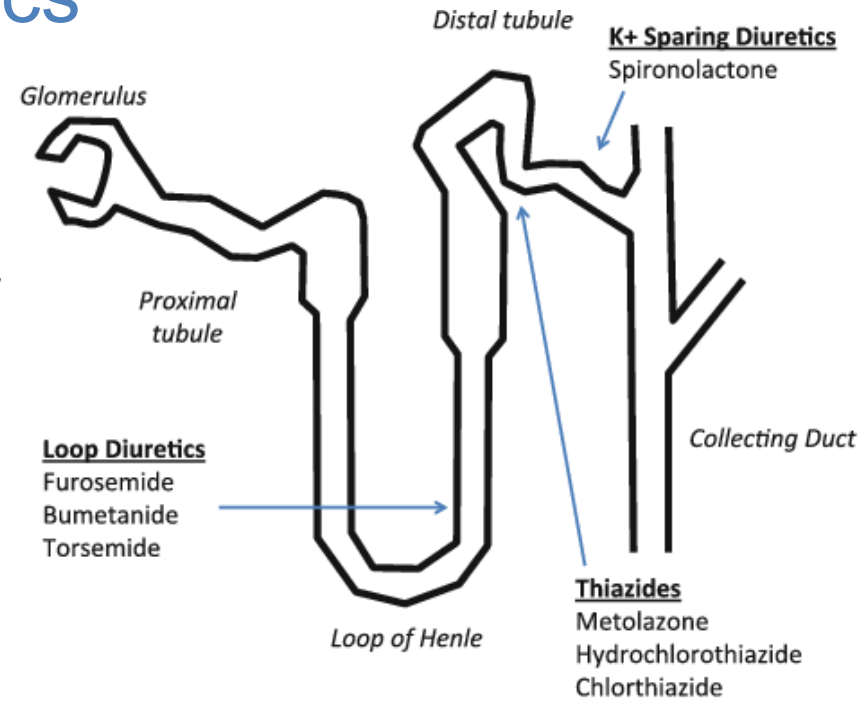
Diuretics

❑ 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.**

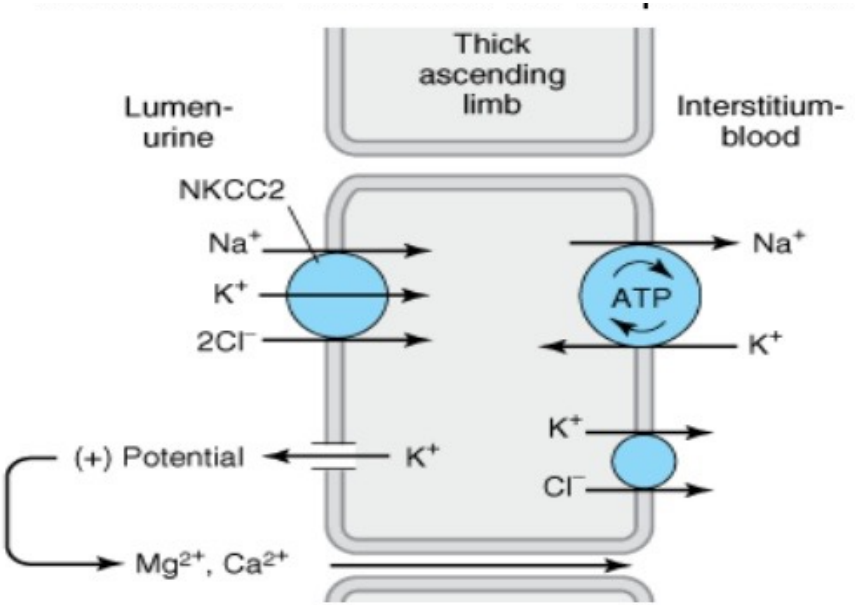
Loop Diuretics

❑ 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%.

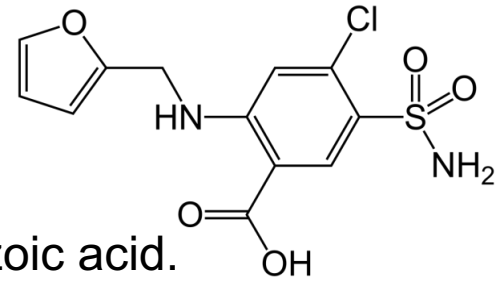
3) increase fractional Mg^{++} excretion by more than 60%.



❑ **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



❑ 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

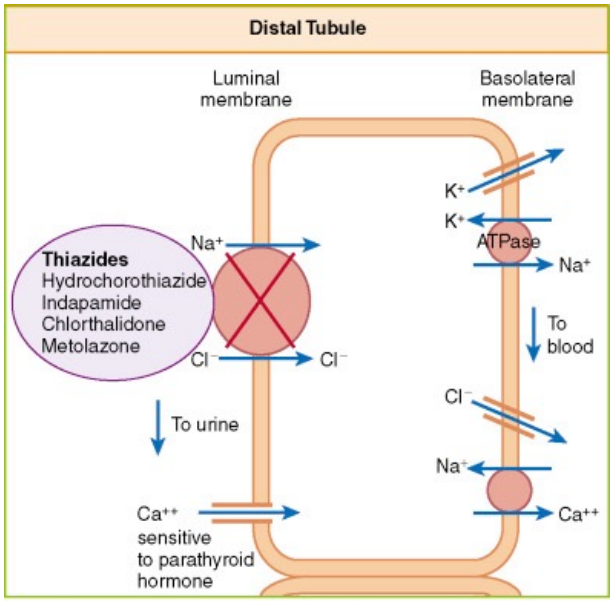
❑ Thiazide and thiazide-like diuretics inhibit Na^+Cl^- cotransport.

Their mechanism of action is based on:

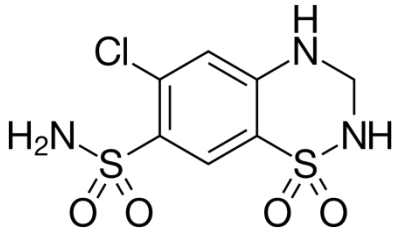
1) increase in the excretion of NaCl and reduction of extracellular fluid volume.

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

3) Mg^{++} initial reabsorption is also initially increased by thiazides, but subsequently loss.



Hydrochlorothiazide



❑ Hydrochlorothiazide is the most commonly prescribed thiazide diuretic.

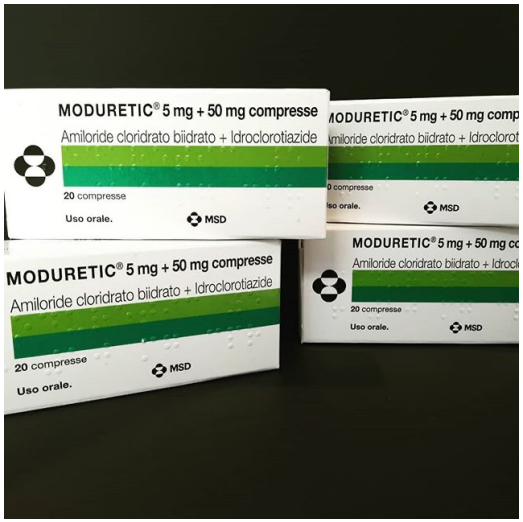
❑ The Food and drug administration (FDA) approved hydrochlorothiazide **to treat hypertension** as a sole agent or adjunct. Moreover, hydrochlorothiazide is recommended as adjunctive therapy to treat **edema associated with congestive heart failure or renal dysfunction**.

❑ 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.

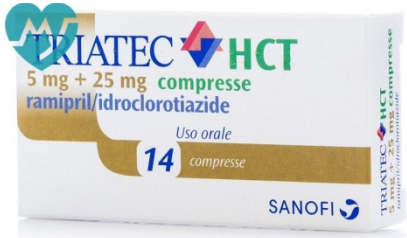
❑ Hydrochlorothiazide interacts with antidiabetic drugs, corticosteroids (intensified electrolyte depletion), lithium, NSAIDs.

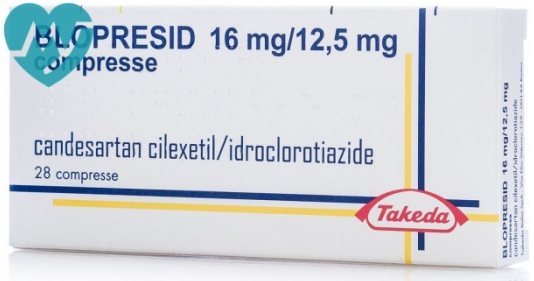
Hydrochlorothiazide combinations with other drugs

- K^+ -sparing diuretics.



- Another antihypertensive drug.





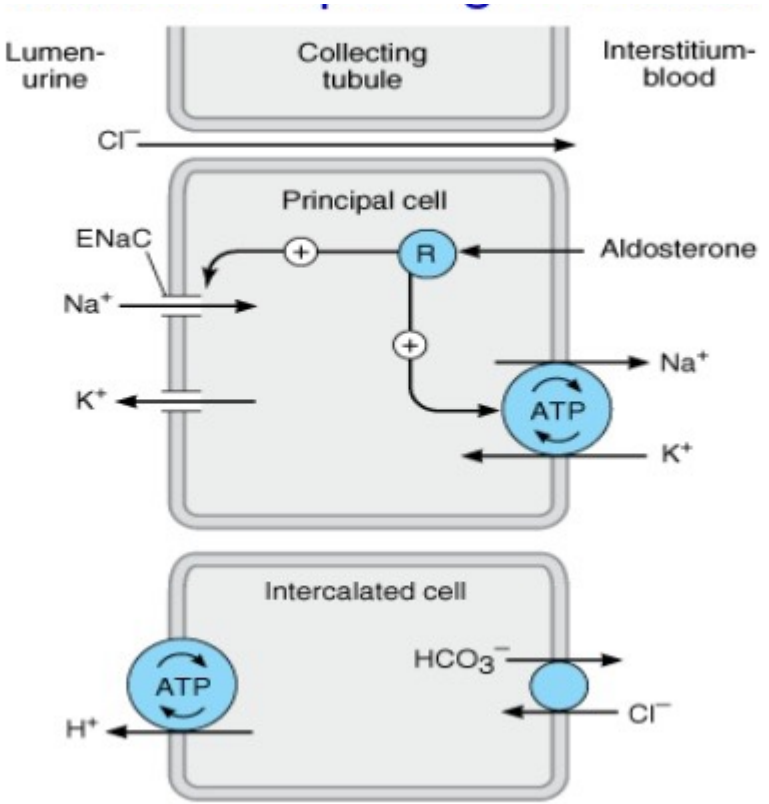
K^+-sparing diuretics

❑ 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.

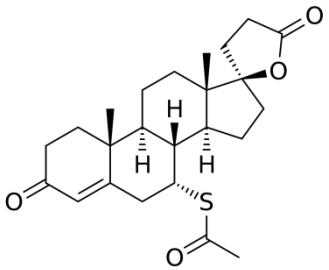
2) with the block in Na^+/K^+ ATPase, K^+ secretion is reduced. This effect can lead to **hyperkalemia** and limit their use in patients with reduced renal function and in some with heart failure.

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



❑ 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, 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 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 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

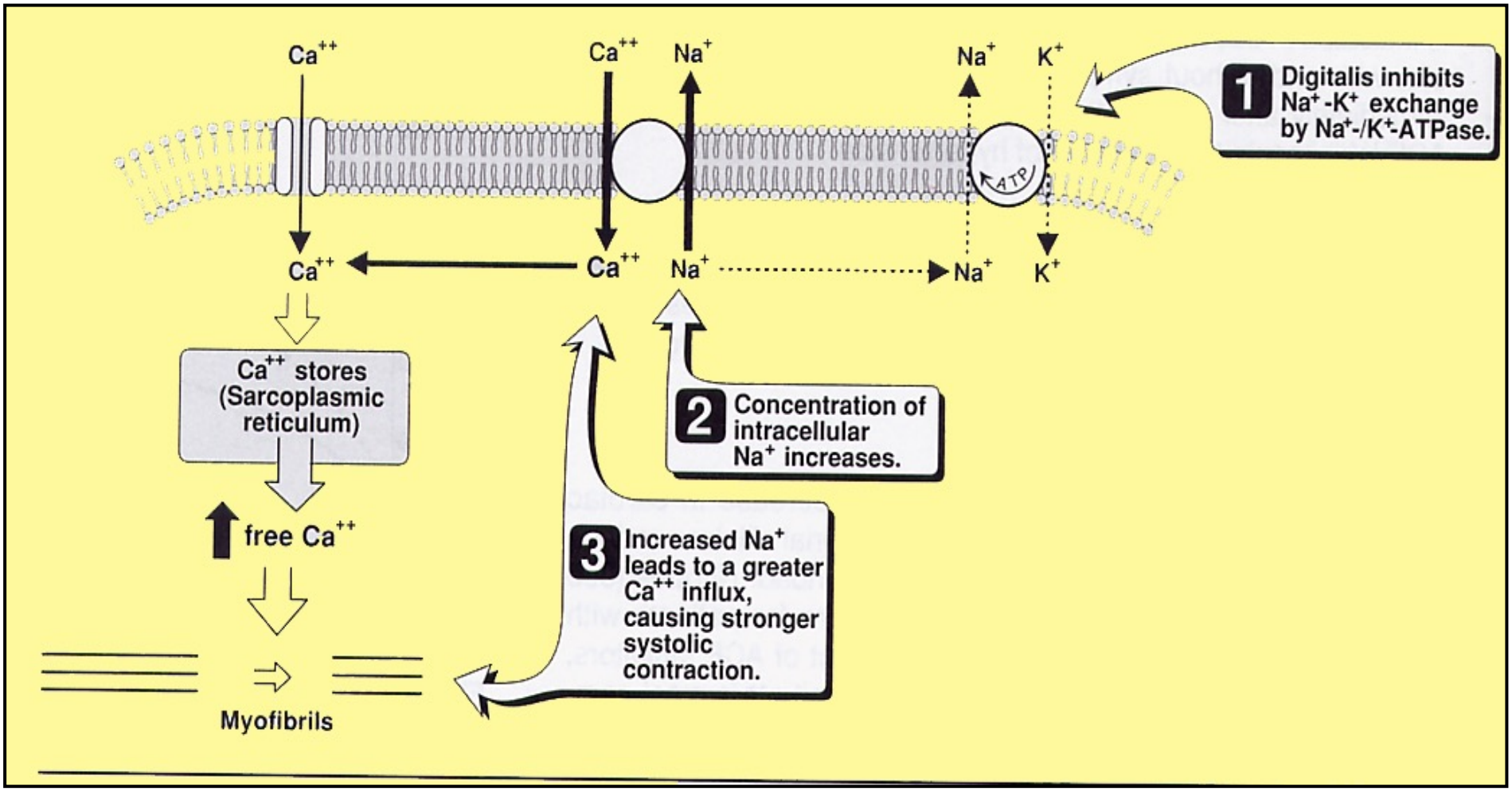
Drug	Mechanism	Increase in Intracellular Calcium Concentration	Effect on Mortality
Digoxin	Na-K pump inhibitor	Yes	Neutral; increased mortality of discontinued after long-term use [1]
Dobutamine	Pure adrenergic; β1 > β2 > α receptor agonist	Yes	Increased [2]
Dopamine	Dose related action on adrenergic and dopaminergic receptors	Yes	Increased [3]
Norepinephrine	Endogenous catecholamine; stimulates β and α adrenergic receptors	Yes	Increased [3]
Milrinone	PDE inhibitor	Yes	Increased [4]
Levosimendan	Calcium sensitizer	No	Not well established [5,6]
Omecamtiv Mecarbil	Enhances myosin and actin cross-bridge formation	No	Unknown [7,8]

Na = sodium; K = potassium; PDE = phosphodiesterase.

Cardiac Glycosides

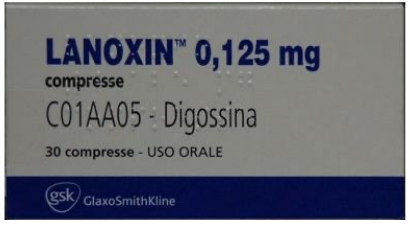
Plants	Glycosides	Sugar	Aglycone/genin
1. Digitalis purpurea (Leaf)	(*i*) Digitoxin. (*ii*) Gitoxin (*iii*) Gitalin	(*i*) Digitoxose (3) (*ii*) ,, (*iii*) ,,	(*i*) Digitoxigenin (*ii*) Gitoxigenin (*iii*) Gitoxigenin hydrate
2. Digitalis Lanata (Leaf)	(*i*) Digitoxin (*ii*) Gitoxin (*iii*) Digoxin	(*i*)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

Mechanism of action of cardiac glycosides

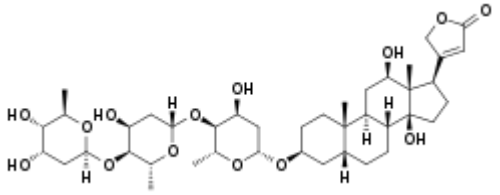


Therapeutic effects of cardiac glycosides

- ❑ Moderate but persistent positive inotropic effect;
- ❑ ↑ sensitivity of the baroreceptor reflex;
- ❑ improved kidney function:
  ↑ glomerular filtration rate;
  ↑ Na+ excretion;
- ❑ ↑ vagal activity



Digoxin



Class	Cardiac glycoside
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 differs in pharmacokinetic properties and potency.

	DIGOXIN	DIGITOXIN
ABSORPTION (ORAL)	40 – 75%	90 –100%
PROTEIN BINDING	LOW	EXTENSIVE
HALF LIFE	39 HOURS	168 HOURS
METABOLISM	LOW	EXTENSIVE
EXCRETION	PREDOMINANTL RENAL	PARTLY RENAL
Vd (L/Kg)	6.3	0.6
THERAPEUTIC PLASMA CONCENTRATION	0.5 – 2 ng/ml	10 – 25ng/ml
TOXIC PLASMA CONC.	> 2ng/ml	> 35 ng/ml
DAILY DOSE (SLOW LOADING OR MAINT)	0.125 – 0.5mg	0.05 – 0.2mg
RAPID DIGITALIZING DOSE	0.5 – 0.75mg 8 HRLY X 3 DOSES	0.2 - .4mg 12 HRLY X 3 DOSES
TIME FOR PEAK EFFECT	3 – 6 HOURS	6 – 12 HOURS

❑ Digoxin has a narrow therapeutical index.

Side effects of digoxin

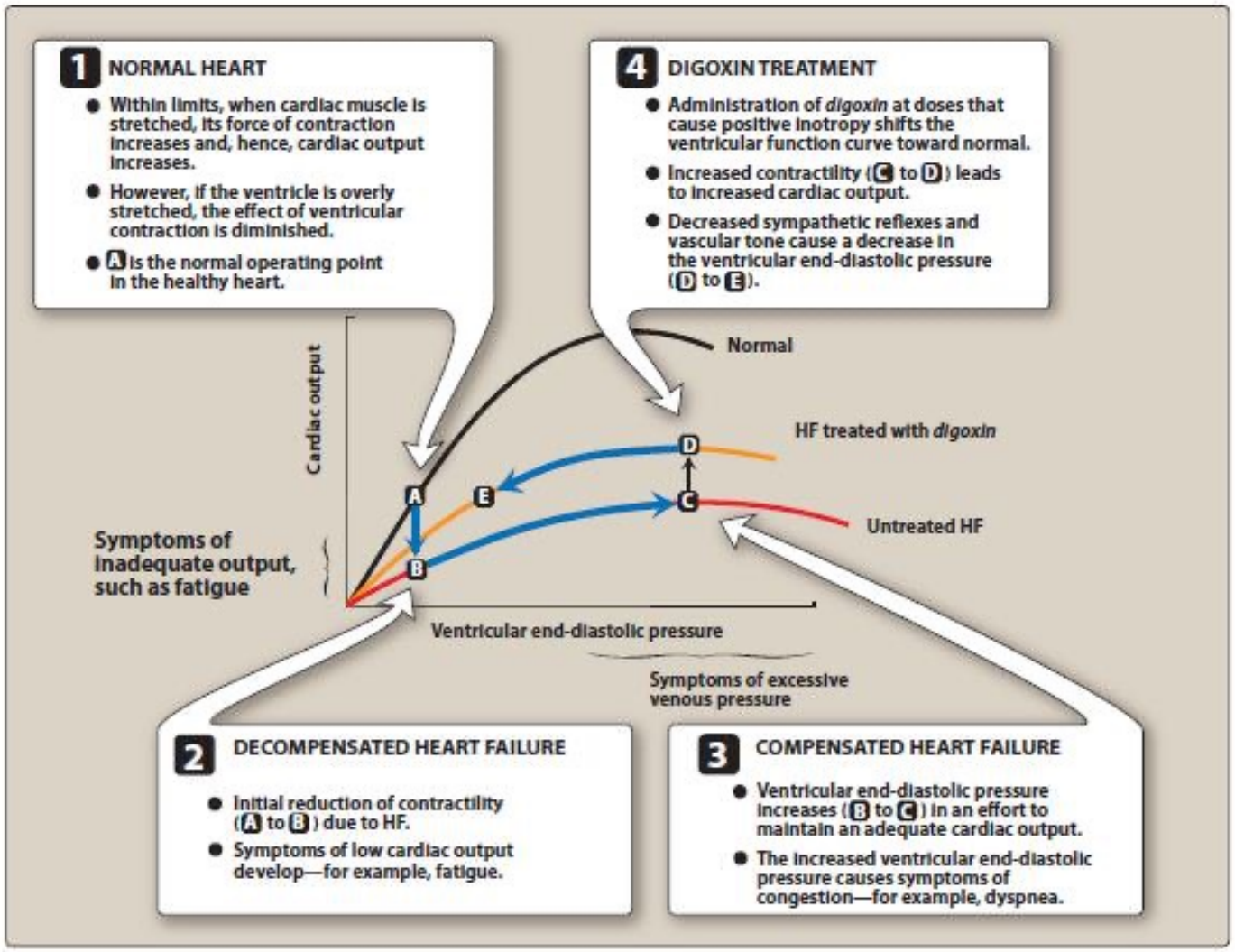
	Not uncommon	*Uncommon*
Cardiac		
Tachycardias		
Supraventricular	Ectopic beats Supraventricular tachycardia with 2:1 block	Atrial fibrillation
Ventricular	Ectopic beats (bigeminy) Ventricular tachycardia (bidirectional)	Ventricular fibrillation
Bradycardias	Sinus bradycardia Sinus arrhythmia First degree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

Interactions of digoxin with other drugs

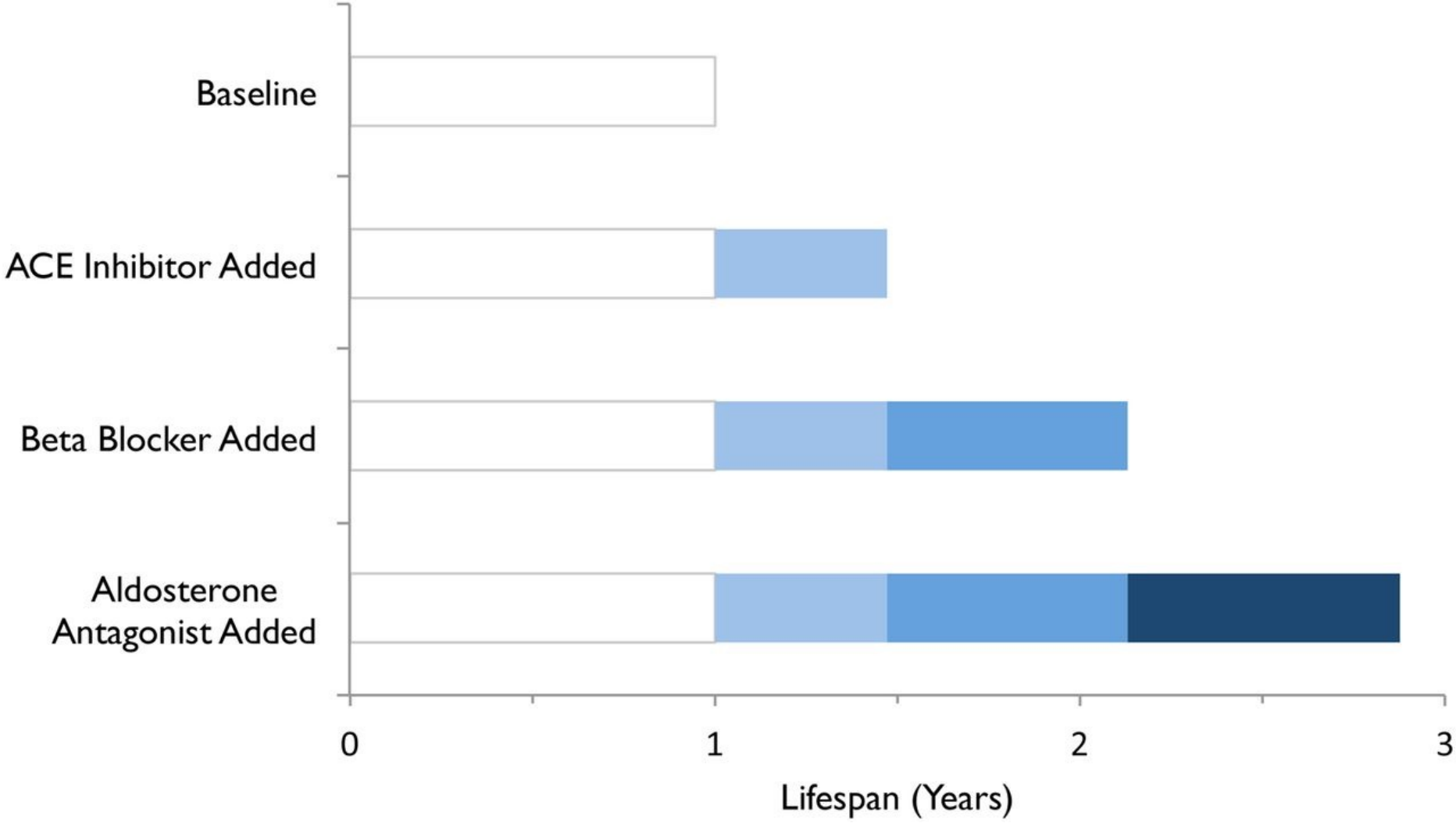
Interacting Drug	Serum Digoxin Levels	Mechanism	Comments
Cholestyramine, colestipol	D	Decreased absorption	Wait 1 hr after digoxin administration
Metoclopramide	D	Decreased absorption due to increased GI motility	Monitor digoxin levels; substitute elixir for tablets
Erythromycin	I (only in small percentage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

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



Common drug-drug interactions in heart failure

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