- The treatment of heart failure (HF)
- Antiarrhythmic drugs

Lecture 9

College of Pharmacy

By:

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➢ The treatment of heart failure (HF)

- Heart failure (HF) **is a complex, progressive disorder in which the heart is unable to pump sufficient blood to meet the needs of the body.**
- Its cardinal symptoms are **dyspnea, fatigue, and fluid retention.**
- It is **often accompanied by abnormal increases in blood volume and interstitial fluid.**
- Underlying causes of HF include, **but are not limited to, atherosclerotic heart disease, hypertensive heart disease, valvular heart disease, and congenital heart disease.**
- **Chronic activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS)** is **associated with remodeling of cardiac tissue, loss of myocytes, hypertrophy, and fibrosis.** This prompts additional **neurohormonal activation**, creating a vicious cycle that, if **left untreated, leads to death**.

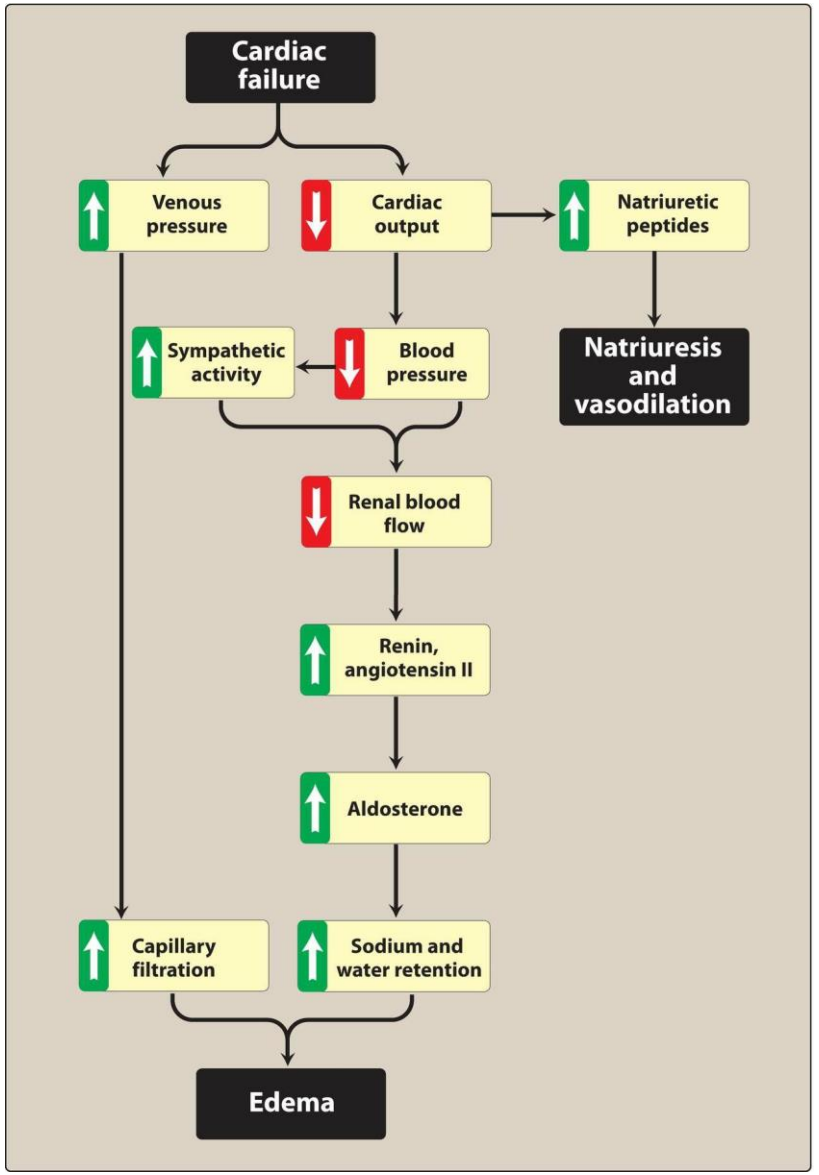


Figure 1: Cardiovascular consequences of HF.

Compensatory physiological responses in HF

The failing heart evokes four major compensatory mechanisms to enhance cardiac output (Figure 1).

Goals of pharmacologic intervention in HF

Goals of treatment are to alleviate symptoms, slow disease progression, and improve survival. The following classes of drugs have been shown to be effective (figure 2). Pharmacologic intervention provides the following benefits in HF:

- reduced myocardial work load
- decreased extracellular fluid volume
- improved cardiac contractility
- reduced rate of cardiac remodeling

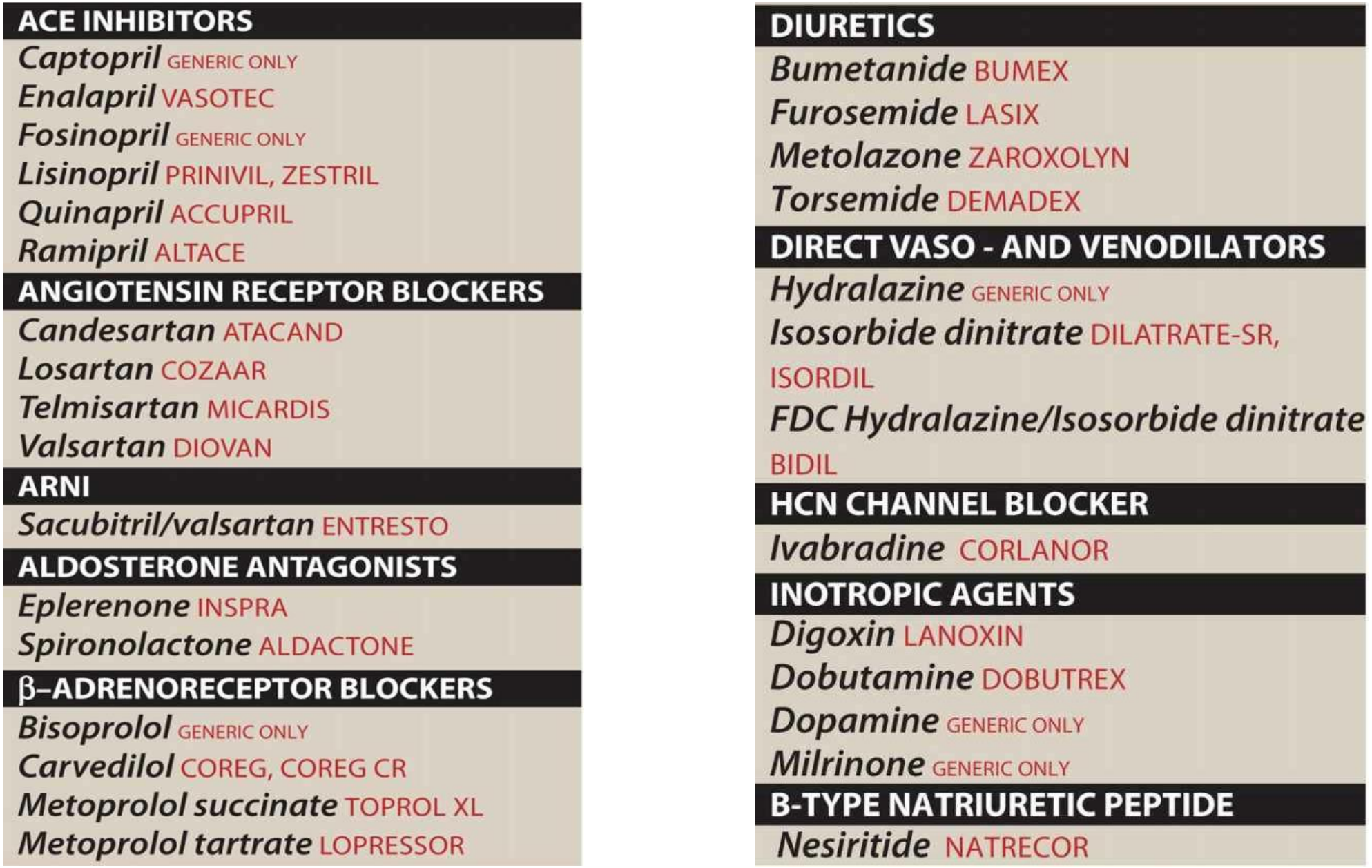


Figure 2: Summary of drugs used to treat HF. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; FDC = fixed-dose combination; HCN = hyperpolarization-activated cyclic nucleotidegated.

Therapeutic strategies in HF

- Chronic HF is typically managed by fluid limitations (less than 1.5 to 2 L daily); low dietary intake of sodium (less than 2000 mg/d); treatment of comorbid conditions; and judicious use of diuretics.
- Specifically for HFrEF, inhibitors of the RAAS, inhibitors of the sympathetic nervous system, and drugs that enhance activity of natriuretic peptides have been shown to improve survival and reduce symptoms.
- Inotropic agents are reserved for acute signs and symptoms of HF and are used mostly in the inpatient setting.
- Drugs that may precipitate or exacerbate HF, such as nonsteroidal anti-inflammatory drugs (NSAIDs), alcohol, nondihydropyridine calcium channel blockers, and some antiarrhythmic drugs, should be avoided if possible.

❖ Inhibitors of the Renin–Angiotensin–Aldosterone System

The compensatory activation of the RAAS in HF leads to increased workload on the heart and a resultant decline in cardiac function. Therefore, inhibition of the RAAS is an important pharmacological target in the management of HF.

A. Angiotensin-converting enzyme inhibitors

ACE inhibitors decrease vascular resistance (afterload) and venous tone (preload), resulting in increased cardiac output. ACE inhibitors also blunt the usual angiotensin II–mediated increase in epinephrine and aldosterone seen in HF. ACE inhibitors improve clinical signs and symptoms of HF and have been shown to significantly improve patient survival in HF.

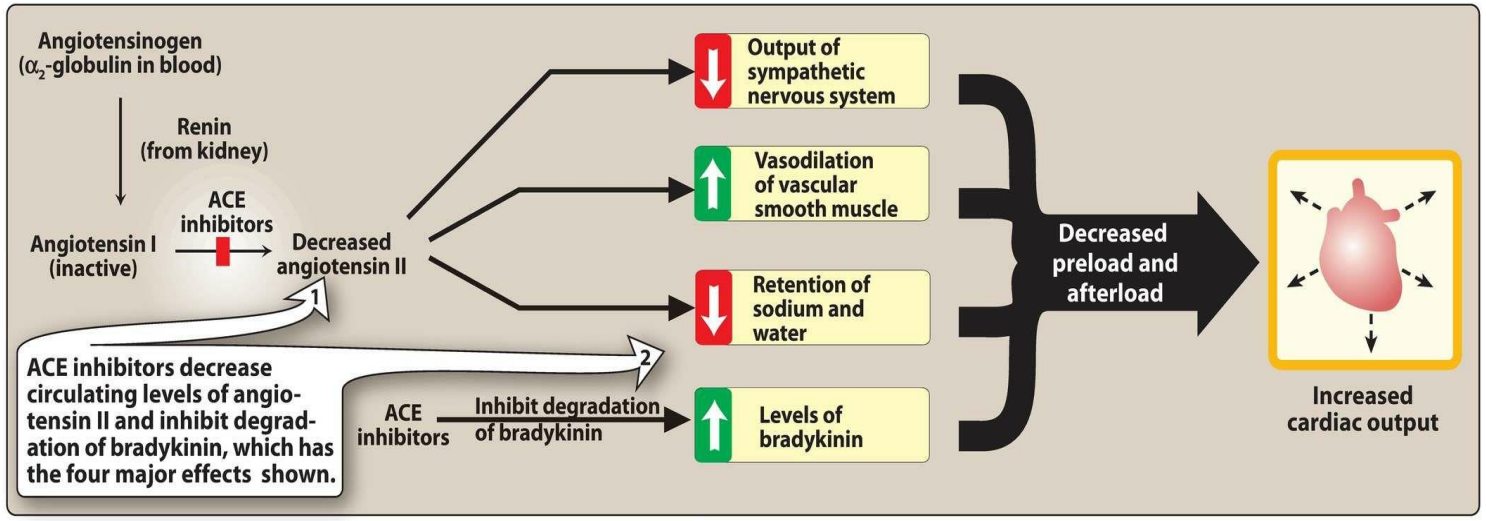


Figure 3: Effects of ACE inhibitors. [Note: The reduced retention of sodium and water results from two causes: decreased production of angiotensin II and aldosterone.

Therapeutic use

- ACE inhibitors may be considered for patients with asymptomatic and symptomatic HFrEF. Importantly, ACE inhibitors are indicated for patients with all stages of left ventricular failure.
- These agents should be started at low doses and titrated to target or maximally tolerated doses in the management of HFrEF.
- ACE inhibitors are also used in the treatment of hypertension.
- Patients who have had a recent myocardial infarction or are at high risk for a cardiovascular event also benefit from long-term ACE inhibitor therapy. (for more information such as pharmacokinetics and adverse events; see drugs for heart failure and drugs used for treating hypertension).

B. Angiotensin receptor blockers

- ARBs are a substitute for **patients who cannot tolerate ACE inhibitors due to cough or angioedema**.
- Although ARBs have a different mechanism of action than ACE inhibitors, their actions on preload and afterload are similar. (for more information such as therapeutic use, pharmacokinetics and adverse events; see drugs for heart failure and drugs used for treating hypertension).

C. Aldosterone receptor antagonists

- Patients with HF have elevated levels of aldosterone due to angiotensin II stimulation and reduced hepatic clearance of the hormone.
- **Spironolactone and eplerenone** are antagonists of aldosterone at the mineralocorticoid receptor, thereby preventing salt retention, myocardial hypertrophy, and hypokalemia.
- **Spironolactone** also has affinity for androgen and progesterone receptors, and is associated with endocrine-related adverse effects such as gynecomastia and dysmenorrhea.
- Aldosterone antagonists are indicated in patients with symptomatic HFrEF or HFrEF and recent myocardial infarction.

❖ β-Blockers

- Although it may seem counterintuitive to administer drugs with negative inotropic activity in HF, **evidence clearly demonstrates improved systolic function and reverse cardiac remodeling in patients receiving β-blockers.** These benefits arise in spite of an occasional, initial exacerbation of symptoms. The benefit of β-blockers is attributed, in part, to their ability to prevent the changes that occur because of chronic activation of the sympathetic nervous system.

- These agents decrease heart rate and inhibit release of renin in the kidneys.
- In addition, β-blockers prevent the deleterious effects of norepinephrine on the cardiac muscle fibers, decreasing remodeling, hypertrophy, and cell death.
- β-Blockade is recommended for all patients with chronic, stable HFrEF.
- Treatment should be started at low doses and gradually titrated to target doses based on patient tolerance and vital signs.
- β-Blockers should also be used with caution with other drugs that slow AV conduction, such as **amiodarone, verapamil, and diltiazem**.(for more information such as therapeutic use, pharmacokinetics and adverse events; see drugs for heart failure and drugs used for treating hypertension).

❖ Diuretics

- Diuretics **reduce signs and symptoms of volume overload**, such as **dyspnea on exertion, orthopnea, and peripheral edema.**
- They decrease plasma volume and, subsequently, decrease venous return to the heart (preload). This decreases cardiac workload and oxygen demand.
- They may also decrease afterload by reducing plasma volume, thereby decreasing blood pressure.
- Loop diuretics are the most commonly used diuretics in HF.
- These agents are used for patients who require extensive diuresis and those with renal insufficiency.
- Since diuretics have not been shown to improve survival in HF, they should only be used to treat signs and symptoms of volume excess.

❖ Angiotensin Receptor–Neprilysin Inhibitor (ARNI)

Inhibition of neprilysin augments the activity of the vasoactive peptides. To maximize the effect of natriuretic peptides, stimulation of the RAAS must be offset without further increase in bradykinin. Therefore an ARB, instead of an ACE inhibitor, is combined with a neprilysin inhibitor to reduce the incidence of angioedema.

A. Sacubitril/valsartan

Sacubitril /valsartan is the **first available angiotensin receptor–neprilysin inhibitor (ARNI).**

1. Actions

Sacubitril/valsartan combines the actions of an ARB with neprilysin inhibition. Inhibition of neprilysin results in increased concentration of vasoactive peptides, leading to natriuresis, diuresis, vasodilation, and inhibition of fibrosis. Together, the combination decreases afterload, preload, and myocardial fibrosis. An ARNI improves survival and clinical signs and symptoms of HF, as compared to therapy with an ACE inhibitor.

2. Therapeutic use

An ARNI should replace an ACE inhibitor or ARB in patients with HFrEF who remain symptomatic on optimal doses of a β-blocker and an ACE inhibitor or ARB.

3. Pharmacokinetics

Sacubitril/valsartan is orally active, administered with or without food, and quickly breaks down into the separate components. Sacubitril is transformed to active drug by plasma esterases. Both drugs have a high volume of distribution and are highly bound to plasma proteins. Sacubitril is mainly excreted in the urine. The half-life of approximately 10 hours for both components allows for twice-daily dosing.

4. Adverse effects

- The adverse effect profile is similar to that of an ACE inhibitor or ARB.
- Because of the added reduction of afterload, hypotension is more common with an ARNI.
- Due to inhibition of neprilysin with sacubitril, bradykinin levels may increase and angioedema may occur. Therefore, the combination is contraindicated in patients with a history of hereditary angioedema or angioedema associated with an ACE inhibitor or ARB.
- To minimize risk of angioedema, an ACE inhibitor must be stopped at least 36 hours prior to starting sacubitril/valsartan.

➢ Hyperpolarization-Activated Cyclic Nucleotide–Gated Channel Blocker (HCN)

HCN channel is **responsible for the I_f and setting the pace within the sinoatrial (SA) node. Inhibition of the HCN channel results in slowing of depolarization and a lower heart rate.**

Ivabradine

1. Actions

By selectively slowing the I_f current in the SA node, reduction of heart rate occurs without a reduction in contractility, atrioventricular (AV) conduction, ventricular repolarization, or blood pressure.

2. Therapeutic use

Ivabradine is utilized in HFrEF to improve symptoms in patients who are in sinus rhythm with a heart rate above 70 beats per minute and are on optimized HF pharmacotherapy.

3. Pharmacokinetics

Ivabradine should be administered with meals to increase absorption. It undergoes extensive first-pass metabolism by cytochrome P450 3A4 to an active metabolite. It has a high volume of distribution and is 70% protein bound. The half-life is 6 hours, which allows for twice-daily dosing.

4. Adverse effects

- Bradycardia, which may improve with dose reduction.
- Increase the risk of atrial fibrillation.
- Ivabradine inhibits similar channels in the eye, and luminous phenomena may occur early in therapy.
- Ivabradine should not be used in pregnancy or breast-feeding, with more advanced heart block, or with potent 3A4 inhibitors.

➢ Vaso- and Venodilators

- Dilation of venous blood vessels leads to a decrease in cardiac preload by increasing venous capacitance.
- **Nitrates** are commonly used venous dilators to reduce preload for patients with chronic HF.
- Arterial dilators, such as **hydralazine**, reduce systemic arteriolar resistance and decrease afterload.
- If the patient is intolerant of ACE inhibitors or ARBs, or if additional vasodilator response is required, a combination of hydralazine and isosorbide dinitrate may be used.
- Headache, dizziness, and hypotension are common adverse effects with this combination. Rarely, hydralazine has been associated with drug-induced lupus.

➢ Inotropic Drugs

- **Positive inotropic agents enhance cardiac contractility and, thus, increase cardiac output.** The inotropic action is the result of an increased cytoplasmic calcium concentration that enhances the contractility of cardiac muscle.
- All positive inotropes in HFrEF that increase intracellular calcium concentration have been associated with reduced survival. For this reason, these agents, with the exception of digoxin, are only used for a short period mainly in the inpatient setting.

A. Digitalis glycosides

They are a group of chemically similar compounds that can increase the contractility of the heart muscle and, therefore, are used in treating HF. The digitalis glycosides have a low therapeutic index. The only available agent is **digoxin**.

1. Mechanism of action

a. Regulation of cytosolic calcium concentration

See Figure 4

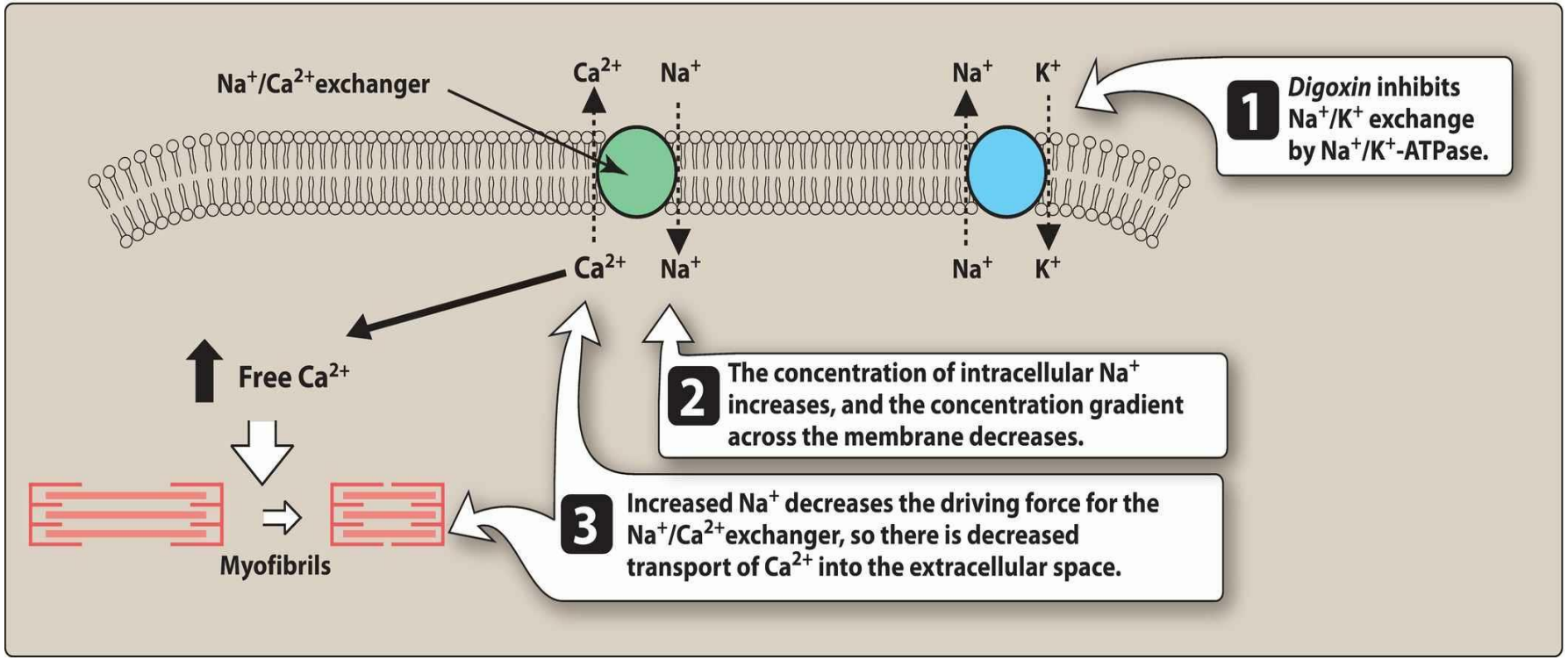


Figure 4: Mechanism of action of digoxin. ATPase = adenosine triphosphatase.

b. Increased contractility of the cardiac muscle

See Figure 5.

c. Neurohormonal inhibition

low-dose digoxin inhibits sympathetic activation with minimal effects on contractility. This effect is the reason a lower serum drug concentration is targeted in HFrEF.

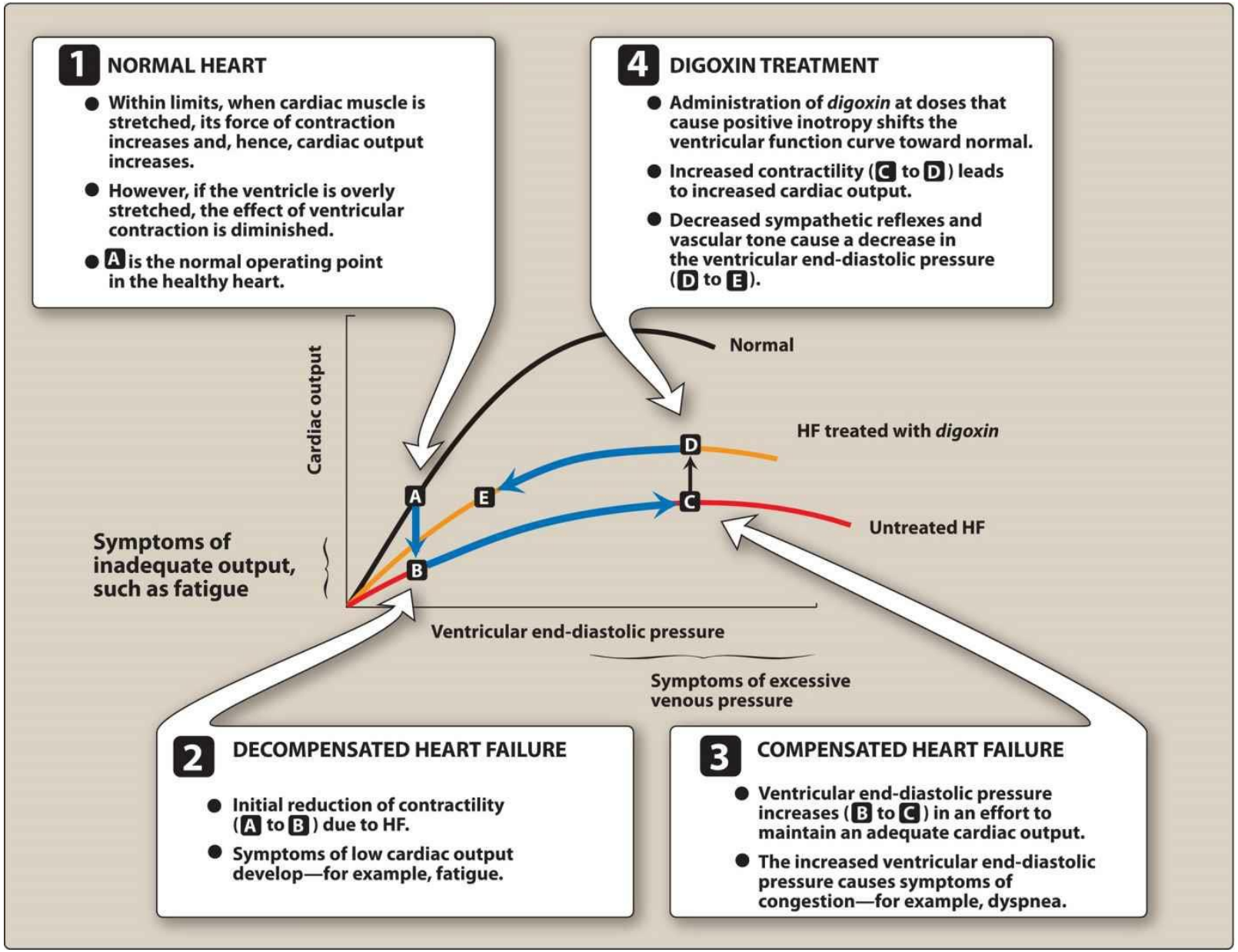


Figure 5: Ventricular function curves in the normal heart, in heart failure (HF), and in HF treated with digoxin.

2. Therapeutic use

Digoxin therapy is indicated in patients with HFrEF who are symptomatic on optimal HF pharmacotherapy. A low serum drug concentration of digoxin (0.5 to 0.8 ng/mL) is beneficial in HFrEF.

3. Pharmacokinetics

Digoxin is available in oral and injectable formulations. It has a large volume of distribution, because it accumulates in muscle. Digoxin has a long half-life of 30 to 40 hours. It is mainly eliminated intact by the kidney, requiring dose adjustment in renal dysfunction.

4. Adverse effects

- Anorexia, nausea, vomiting, blurred vision, or yellowish vision may be initial indicators of toxicity.
- When Na^+/K^+-ATPase is markedly inhibited by digoxin, the resting membrane potential may increase, which makes the membrane more excitable, increasing the risk of arrhythmias.
- Decreased levels of serum potassium (hypokalemia) predispose a patient to digoxin toxicity, because digoxin normally competes with potassium for the same binding site on the Na^+/K^+-ATPase pump.
- Drugs like clarithromycin, verapamil, and amiodarone, can significantly increase digoxin levels, necessitating a reduced dose of digoxin.
- Digoxin should also be used with caution with other drugs that slow AV conduction, such as β-blockers, verapamil, and diltiazem.

B. β-Adrenergic agonists

β-Adrenergic agonists, such as **dobutamine and dopamine**, **improve cardiac performance by causing positive inotropic effects and vasodilation**. β-Adrenergic agonists ultimately lead to increased entry of calcium ions into myocardial cells and enhanced contraction (Figure 6). Both drugs must be given by intravenous infusion and are primarily used in the short-term treatment of acute HF in the hospital setting.

C. Phosphodiesterase inhibitors

Milrinone is a **phosphodiesterase inhibitor** that **increases the intracellular concentration of cAMP** (Figure 6). Like β-adrenergic agonists, this results in an increase of intracellular calcium and, therefore, cardiac contractility. Milrinone is usually given by intravenous infusion for short-term treatment of acute HF. However, dobutamine and milrinone may also be considered for intermediate-term treatment in the outpatient setting for palliative care.

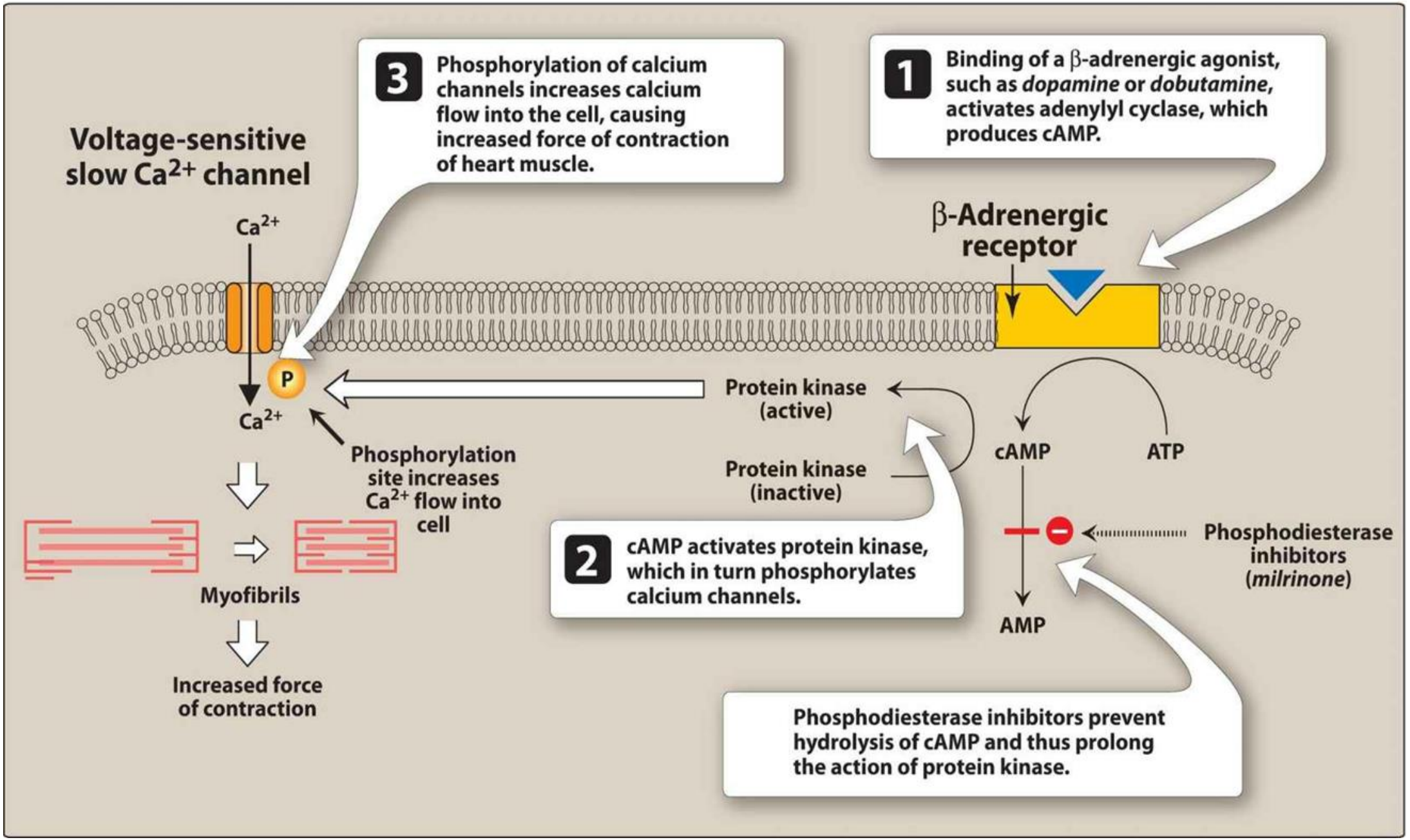


Figure 6: Sites of action by β-adrenergic agonists on heart muscle. AMP = adenosine monophosphate; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; P = phosphate.

➢ Recombinant B-type Natriuretic Peptide (BNP)

- When IV diuretics are minimally effective, a recombinant B-type natriuretic peptide (BNP), or nesiritide can be used as an alternative. **Through binding to natriuretic peptide receptors, nesiritide stimulates natriuresis and diuresis and reduces preload and afterload.**
- Nesiritide is administered intravenously as a bolus (most often) and continuous infusion.
- Like endogenous BNP, nesiritide has a short half-life of 20 minutes and is cleared by renal filtration, cleavage by endopeptidases and through internalization after binding to natriuretic peptide receptors.
- The most common adverse effects are hypotension and dizziness, and like diuretics, nesiritide can worsen renal function.

Order of Therapy

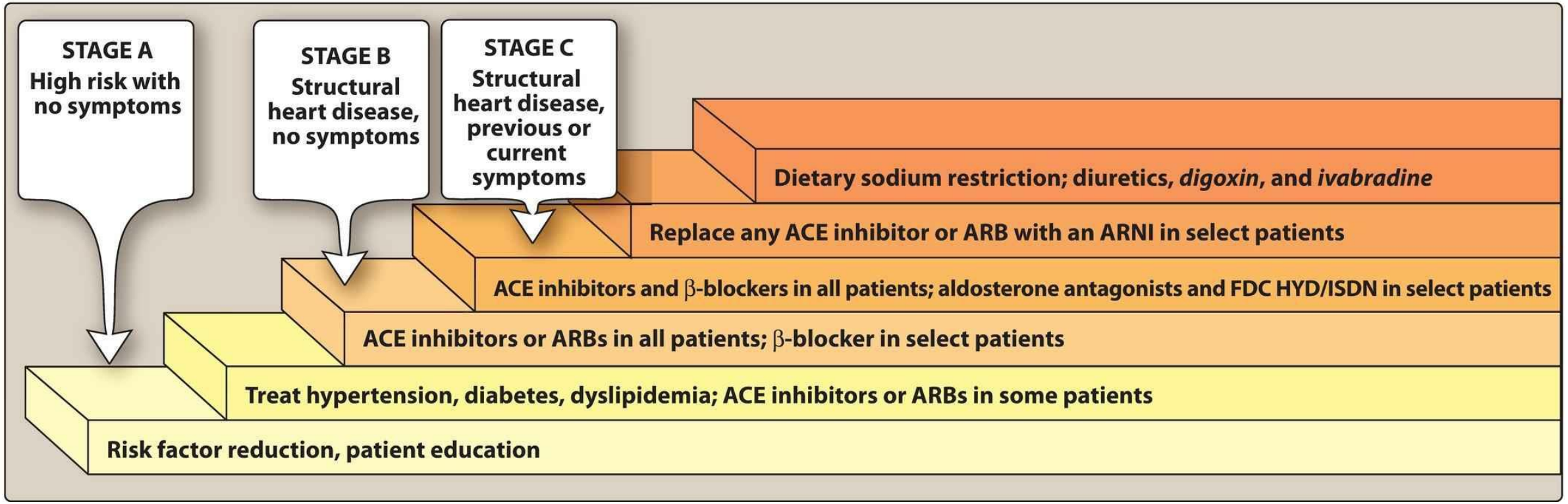
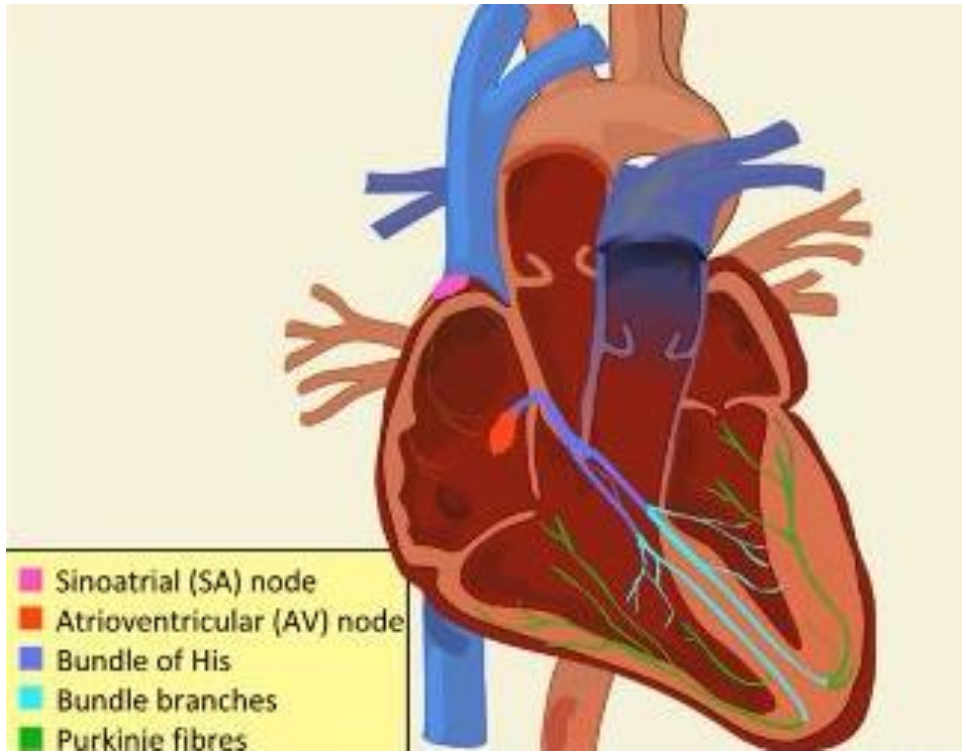


Figure 7: Treatment options for various stages of HF. ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers; FDC = fixed-dose combination; HYD = hydralazine; ISDN = isosorbide dinitrate. Stage D (refractory symptoms requiring special interventions) is not shown.

Antiarrhythmic drugs



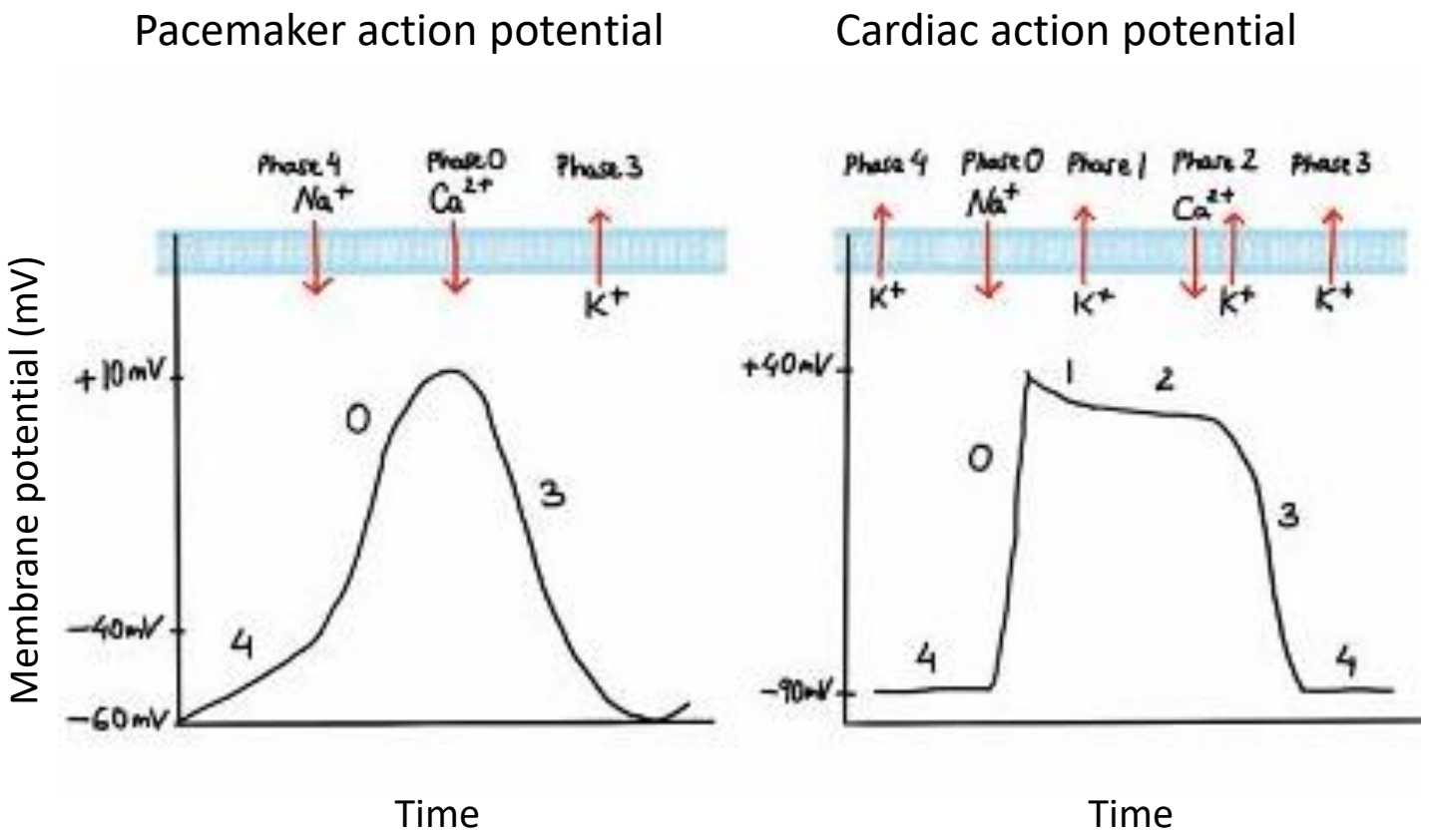


Figure 8: Pacemaker and cardiac action potential

Causes of arrhythmias

1- Abnormal automaticity
2- Abnormalities in impulse conduction

Antiarrhythmic drugs

- Antiarrhythmic drugs **can modify impulse generation and conduction to prevent arrhythmias** or **to reduce symptoms associated with arrhythmias.**
- Antiarrhythmic drugs can be classified (Vaughan-Williams classification) **according to their predominant effects on the action potential** (Figure 9).

CLASSIFICATION OF DRUG	MECHANISM OF ACTION	COMMENT
IA	Na^+ channel blocker	Slows Phase 0 depolarization in ventricular muscle fibers
IB	Na^+ channel blocker	Shortens Phase 3 repolarization in ventricular muscle fibers
IC	Na^+ channel blocker	Markedly slows Phase 0 depolarization in ventricular muscle fibers
II	β-Adrenoreceptor blocker	Inhibits Phase 4 depolarization in SA and AV nodes
III	K^+ channel blocker	Prolongs Phase 3 repolarization in ventricular muscle fibers
IV	Ca^{2+} channel blocker	Inhibits action potential in SA and AV nodes

Figure 9: Actions of antiarrhythmic drugs. SA = sinoatrial; AV = atrioventricular.

➢ Class I Antiarrhythmic Drugs

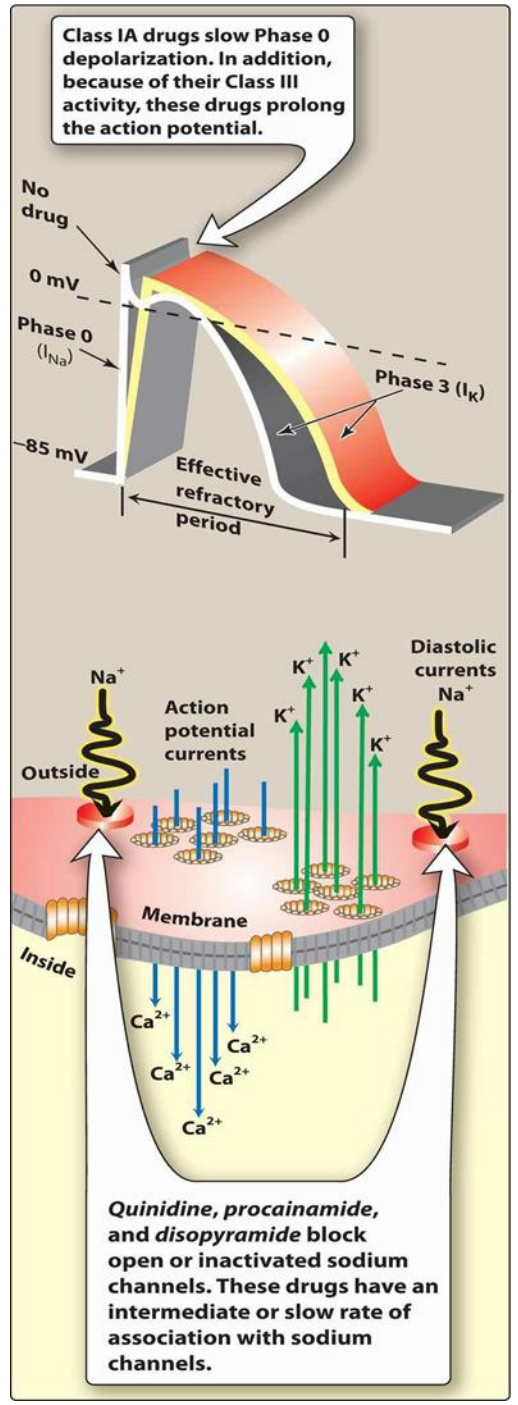
- These drugs act by **blocking voltage-sensitive Na^+ channels**. They bind more rapidly to open or inactivated Na^+ channels than to channels that are fully repolarized.
- The use has been declining continuously due to their possible proarrhythmic effects, particularly in patients with reduced left ventricular function and ischemic heart disease.

A. Class IA antiarrhythmic drugs: Quinidine, procainamide, and disopyramide

Quinidine is the **prototype class IA drug**. Other agents in this class include **procainamide and disopyramide**. Because of their concomitant class III activity, they can precipitate arrhythmias that can progress to ventricular fibrillation.

1. Mechanism of action

- Quinidine binds to open and inactivated Na^+ channels and prevents Na^+ influx, thus slowing the rapid upstroke during phase 0.
- It decreases the slope of phase 4 spontaneous depolarization, inhibits K^+ channels and blocks Ca^{2+} channels. Because of these actions, it slows conduction velocity and increases refractoriness.
- Quinidine also has mild α-adrenergic blocking and anticholinergic actions.



- There is less anticholinergic activity with procainamide and more with disopyramide.
- Neither procainamide nor disopyramide has α-blocking activity.
- Disopyramide produces a greater negative inotropic effect, and unlike the other drugs, it causes peripheral vasoconstriction.

2. Therapeutic uses

- Quinidine is used in the treatment of a wide variety of arrhythmias, including atrial, AV junctional, and ventricular tachyarrhythmias.
- Procainamide is only available in an intravenous formulation and may be used to treat acute atrial and ventricular arrhythmias.
- Disopyramide can be used as an alternative treatment of ventricular arrhythmias and may also be used for rhythm control in atrial fibrillation or flutter.

3. Pharmacokinetics

- Quinidine sulfate or gluconate is rapidly and well absorbed after oral administration.
- It undergoes extensive metabolism primarily by the hepatic cytochrome P450 3A4 (CYP3A4) isoenzyme, forming active metabolites.

- A portion of procainamide is acetylated in the liver to N-acetylprocainamide (NAPA), which has the properties and adverse effects of a class III drug. NAPA is eliminated via the kidney; therefore, dosages of procainamide should be adjusted in patients with renal dysfunction.
- Disopyramide is well absorbed after oral administration and is metabolized in the liver by CYP3A4 to a less active metabolite and several inactive metabolites. About half of the drug is excreted unchanged by the kidneys.

4. Adverse effects

- Class IA drugs should not be used in patients with atherosclerotic heart disease or systolic heart failure.
- Large doses of quinidine may induce the symptoms of cinchonism (for example, blurred vision, tinnitus, headache, disorientation, and psychosis).
- Drug interactions are common with quinidine since it is an inhibitor of both CYP2D6 and P-glycoprotein.
- Intravenous administration of procainamide may cause hypotension.
- Disopyramide has the most anticholinergic adverse effects of the class IA drugs (for example, dry mouth, urinary retention, blurred vision, and constipation).
- Both quinidine and disopyramide should be used with caution with potent inhibitors of CYP3A4.

B. Class IB antiarrhythmic drugs: Lidocaine and mexiletine

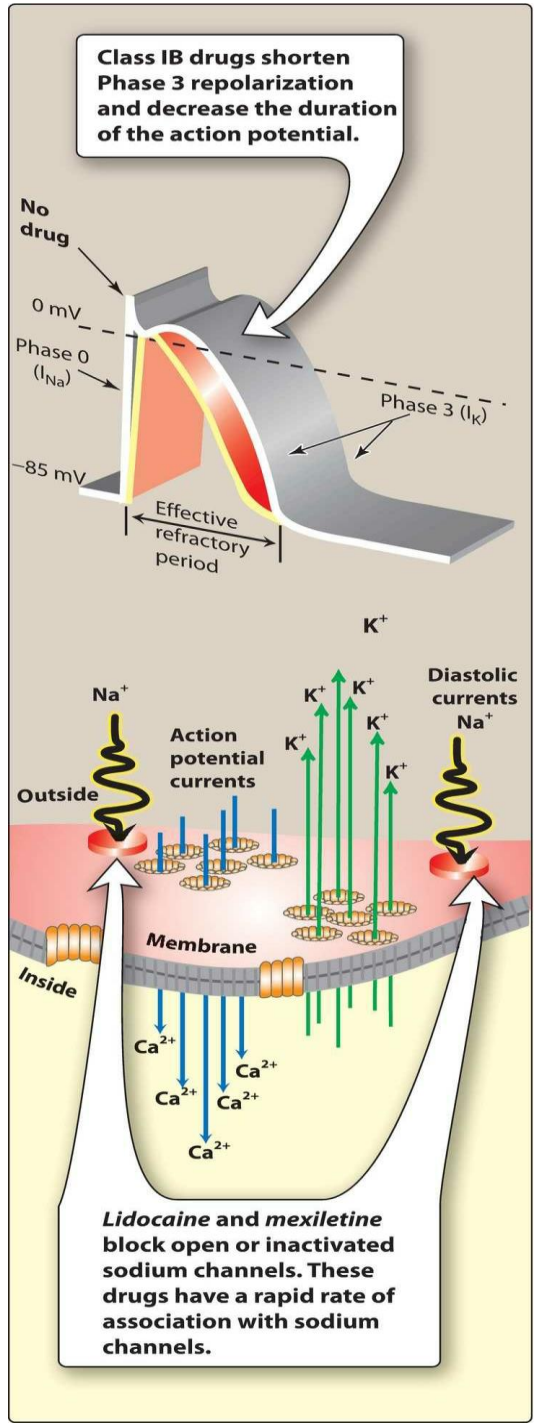
The class IB agents rapidly associate and dissociate from Na^+ channels. Thus, the actions are greater when the cardiac cell is depolarized or firing rapidly. The class IB drugs **lidocaine and mexiletine** are useful in treating ventricular arrhythmias.

1. Mechanism of action

In addition to Na^+ channel blockade, lidocaine and mexiletine shorten phase 3 repolarization and decrease the duration of the action potential. Neither drug contributes to negative inotropy.

2. Therapeutic uses

- Although amiodarone is the drug of choice for ventricular fibrillation or ventricular tachycardia (VT), lidocaine may be used as an alternative.
- Lidocaine may also be used in combination with amiodarone for VT storm.
- Mexiletine is used for chronic treatment of ventricular arrhythmias, often in combination with amiodarone.



3. Pharmacokinetics

- Lidocaine is given intravenously because of extensive first-pass transformation by the liver.
- The drug is dealkylated to two active metabolites.
- Mexiletine is well absorbed after oral administration. It is metabolized in the liver primarily by CYP2D6 to inactive metabolites and excreted mainly via the biliary route.

4. Adverse effects

- Lidocaine has a fairly wide therapeutic index. Central nervous system (CNS) effects include nystagmus (early indicator of toxicity), drowsiness, slurred speech, paresthesia, agitation, confusion, and convulsions, which often limit the duration of continuous infusions.
- Mexiletine has a narrow therapeutic index and caution should be used when administering the drug with inhibitors of CYP2D6. Nausea, vomiting, and dyspepsia are the most common adverse effects.

C. Class IC antiarrhythmic drugs: Flecainide and propafenone

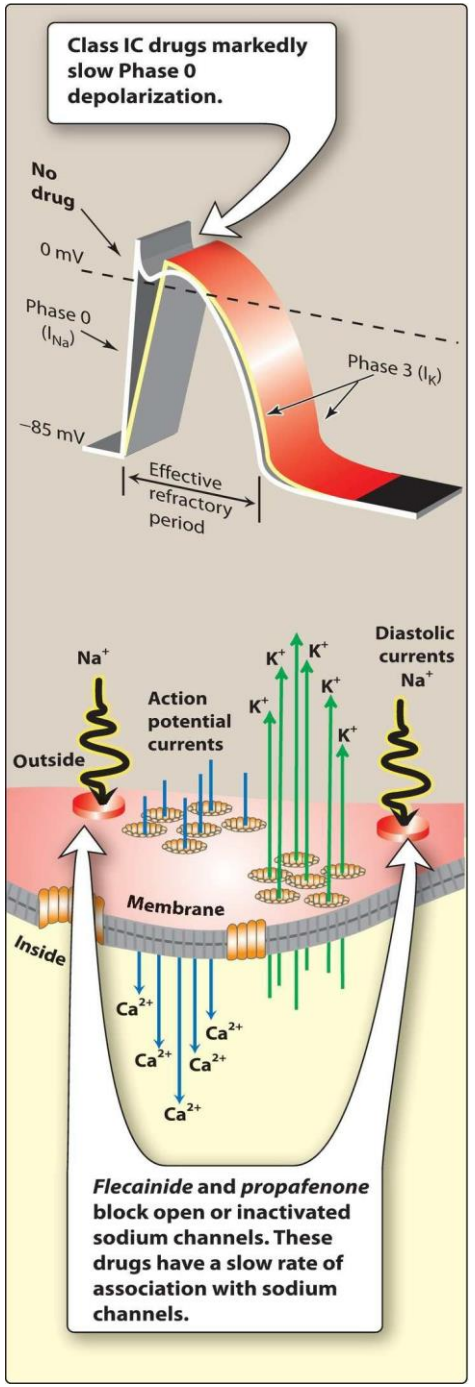
These drugs slowly dissociate from resting Na^+ channels and show prominent effects even at normal heart rates. Due to their negative inotropic and proarrhythmic effects, use of these agents is avoided in patients with structural heart disease (left ventricular hypertrophy, heart failure, atherosclerotic heart disease).

1. Mechanism of action

- **Flecainide** suppresses phase 0 upstroke in Purkinje and myocardial fibers. This causes marked slowing of conduction in all cardiac tissue, with a minor effect on the duration of the action potential and refractoriness. Automaticity is reduced by an increase in the threshold potential, rather than a decrease in slope of phase 4 depolarization.
- Flecainide also blocks K^+ channels, leading to increased duration of the action potential.
- **Propafenone**, like flecainide, slows conduction in all cardiac tissues but does not block K^+ channels.

2. Therapeutic uses

- Flecainide is useful in the maintenance of sinus rhythm in atrial flutter or fibrillation in patients without structural heart disease and in treating refractory ventricular arrhythmias.
- Use of propafenone is restricted mostly to atrial arrhythmias.



3. Pharmacokinetics

- Flecainide is well absorbed after oral administration and is metabolized by CYP2D6 to multiple metabolites. The parent drug and metabolites are mostly eliminated renally.
- Propafenone is metabolized to active metabolites primarily via CYP2D6, and also by CYP1A2 and CYP3A4. The metabolites are excreted in the urine and the feces.

4. Adverse effects

- Flecainide is generally well tolerated, with blurred vision, dizziness, and nausea occurring most frequently.
- Propafenone has a similar side effect profile, but may cause bronchospasm and should be avoided in patients with asthma.
- Propafenone is also an inhibitor of P-glycoprotein.
- Both drugs should be used with caution with potent inhibitors of CYP2D6.

➢ Class II Antiarrhythmic Drugs

- These agents **are β-adrenergic antagonists**, **or β-blockers**; they diminish phase 4 depolarization and, thus, depress automaticity, prolong AV conduction, and decrease heart rate and contractility.
- Class II agents are useful in treating tachyarrhythmias caused by increased sympathetic activity, they are also used for atrial flutter and fibrillation and for AV nodal reentrant tachycardia.
- In addition, β-blockers prevent life-threatening ventricular arrhythmias following a myocardial infarction.
- **Metoprolol** is the most widely used β-blocker for the treatment of cardiac arrhythmias. Compared to nonselective β-blockers, such as propranolol, it reduces the risk of bronchospasm.
- It is extensively metabolized by CYP2D6 and has CNS penetration.
- **Esmolol** is a very short and fast-acting β-blocker used for intravenous administration in acute arrhythmias that occur during surgery or emergency situations.
- Esmolol is rapidly metabolized by esterases in red blood cells.
- Common adverse effects with β-blockers include bradycardia, hypotension, and fatigue.

➢ Class III Antiarrhythmic Drugs

- Class III **agents block K^+ current during repolarization of cardiac cells**.
- These agents prolong the duration of the action potential without altering phase 0 of depolarization or the resting membrane potential. Instead, they prolong the effective refractory period, increasing refractoriness.
- All class III drugs have the potential to induce arrhythmias.

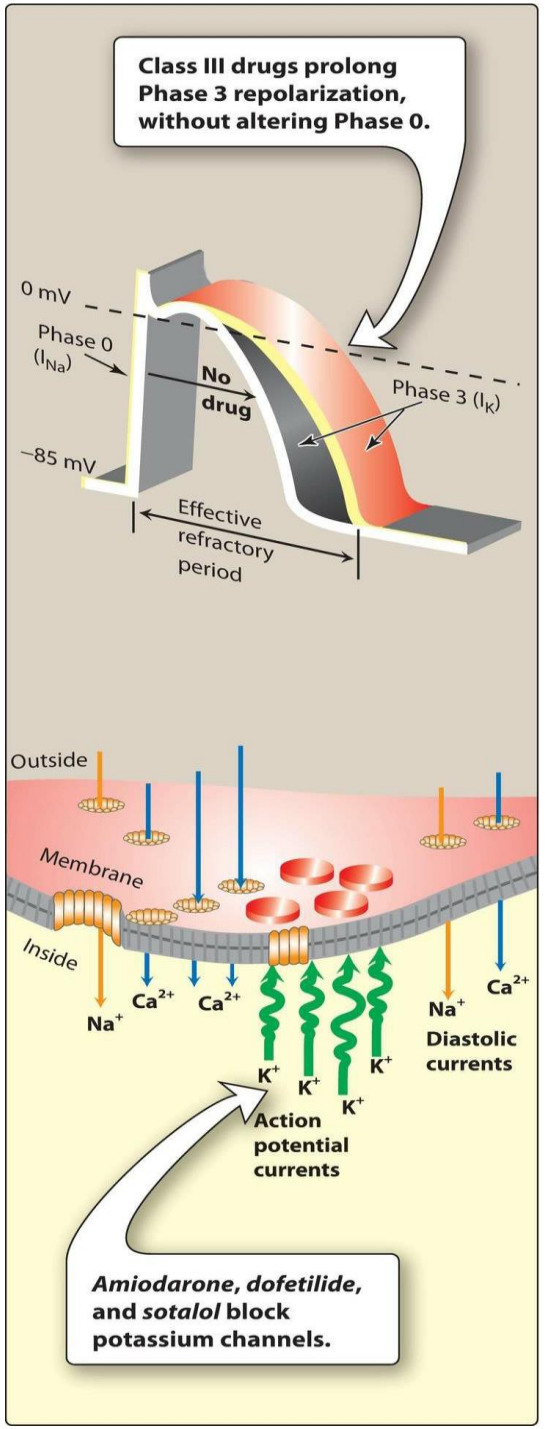
A. Amiodarone

1. Mechanism of action

Amiodarone contains iodine and is related structurally to thyroxine. It has complex effects, showing class I, II, III, and IV actions, as well as α-blocking activity. Its dominant effect is prolongation of the action potential duration and the refractory period by blocking K^+ channels.

2. Therapeutic uses

- Amiodarone is effective in the treatment of severe refractory supraventricular and ventricular tachyarrhythmias.



- Amiodarone has been a mainstay of therapy for the rhythm management of atrial fibrillation or flutter.
- Amiodarone is thought to be the least proarrhythmic of the class I and III antiarrhythmic drugs.

3. Pharmacokinetics

Amiodarone is incompletely absorbed after oral administration. The drug is unusual in having a prolonged half-life of several weeks, and it distributes extensively in tissues.

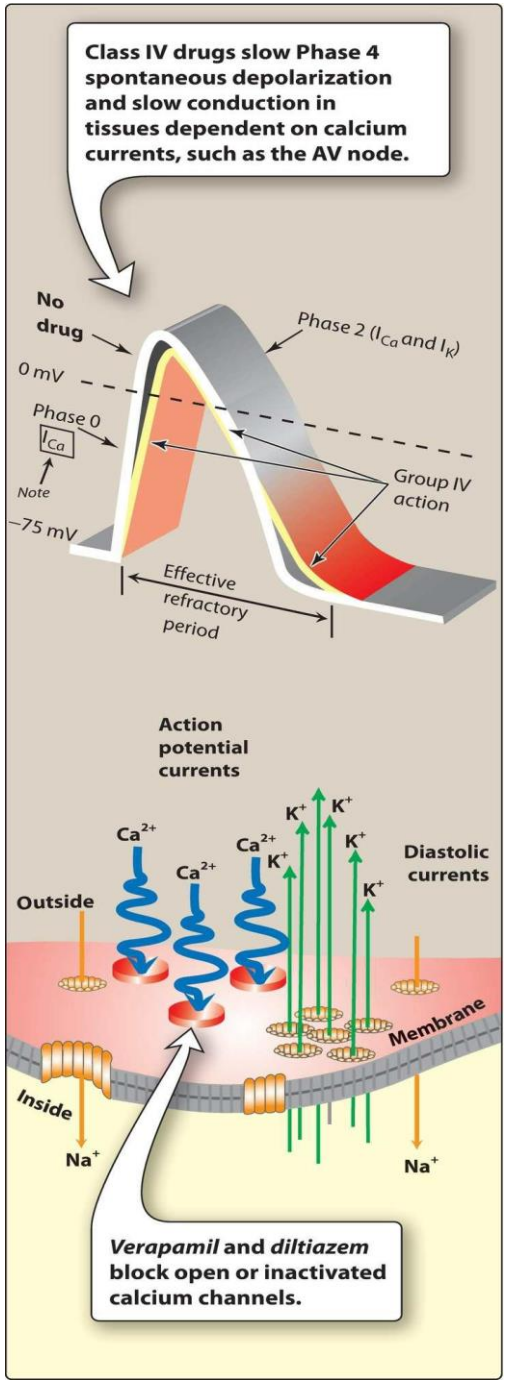
4. Adverse effects

- Amiodarone shows a variety of toxic effects, including pulmonary fibrosis, neuropathy, hepatotoxicity, corneal deposits, optic neuritis, blue-gray skin discoloration, and hypo- or hyperthyroidism.
- However, use of low doses and close monitoring reduce toxicity, while retaining clinical efficacy.
- Amiodarone is subject to numerous drug interactions, since it is metabolized by CYP3A4 and serves as an inhibitor of CYP1A2, CYP2C9, CYP2D6, and P-glycoprotein.

❖ Dronedarone, Sotalol, Dofetilide, Ibutilide are other examples of drugs that are included in this group.

➢ Class IV Antiarrhythmic Drugs

- Class IV drugs are **the nondihydropyridine Ca^{2+} channel blockers verapamil and diltiazem.** Although voltage-sensitive Ca^{2+} channels occur in many different tissues, the major effect of Ca^{2+} channel blockers is on vascular smooth muscle and the heart. Both drugs show greater action on the heart than on vascular smooth muscle, but more so with verapamil.
- In the heart, verapamil and diltiazem bind only to open depolarized voltage-sensitive channels, thus decreasing the inward current carried by Ca^{2+} channels occur in many different tissues, the major effect of Ca^{2+}.
- These drugs are use dependent in that they prevent repolarization until the drug dissociates from the channel, resulting in a decreased rate of phase 4 spontaneous depolarization. They also slow conduction in tissues that are dependent on Ca^{2+} currents, such as the AV and SA nodes.
- These agents are more effective against atrial than against ventricular arrhythmias.
- They are useful in treating reentrant supraventricular tachycardia and in reducing the ventricular rate in atrial flutter and fibrillation.
- Common adverse effects include bradycardia, hypotension, and peripheral edema.
- Both drugs are metabolized in the liver by CYP3A4. Dosage adjustments may be needed in patients with hepatic dysfunction. Both agents are subject to many drug interactions as they are CYP3A4 inhibitors, as well as substrates and inhibitors of P-glycoprotein.



Other Antiarrhythmic Drugs

A. Digoxin

Digoxin **inhibits the Na^+/k^+-ATPase pump**, ultimately shortening the refractory period in atrial and ventricular myocardial cells while prolonging the effective refractory period and diminishing conduction velocity in the AV node. Digoxin is used to control ventricular response rate in atrial fibrillation and flutter; however, sympathetic stimulation easily overcomes the inhibitory effects of digoxin. At toxic concentrations, digoxin causes ectopic ventricular beats that may result in VT and fibrillation.

B. Adenosine

Adenosine is a naturally occurring nucleoside, but at high doses, the drug decreases conduction velocity, prolongs the refractory period, and decreases automaticity in the AV node. Intravenous adenosine is the drug of choice for converting acute supraventricular tachycardias. It has low toxicity but causes flushing, chest pain, and hypotension. Adenosine has an extremely short duration of action (approximately 10 to 15 seconds) due to rapid uptake by erythrocytes and endothelial cells.

C. Magnesium sulfate

Magnesium is necessary for the transport of Na^+ across cell membranes. It slows the rate of SA node impulse formation and prolongs conduction time along the myocardial tissue. Intravenous magnesium sulfate is the salt used to treat arrhythmias, as oral magnesium is not effective in the setting of arrhythmia. Most notably, magnesium is the drug of choice for treating the potentially fatal arrhythmia torsades de pointes and digoxin-induced arrhythmias.

D. Ranolazine

- Ranolazine is an antianginal drug with antiarrhythmic properties similar to amiodarone.
- However, its main effect is to shorten repolarization and decrease the action potential duration similar to mexiletine.
- It is used to treat refractory atrial and ventricular arrhythmias, often in combination with other antiarrhythmic drugs.
- It is well tolerated with dizziness and constipation as the most common adverse effects.
- Ranolazine is extensively metabolized in the liver by CYP3A and CYP2D6 isoenzymes and is mainly excreted by the kidney. Concomitant use with strong CYP3A inducers or inhibitors is contraindicated.


Thank You!