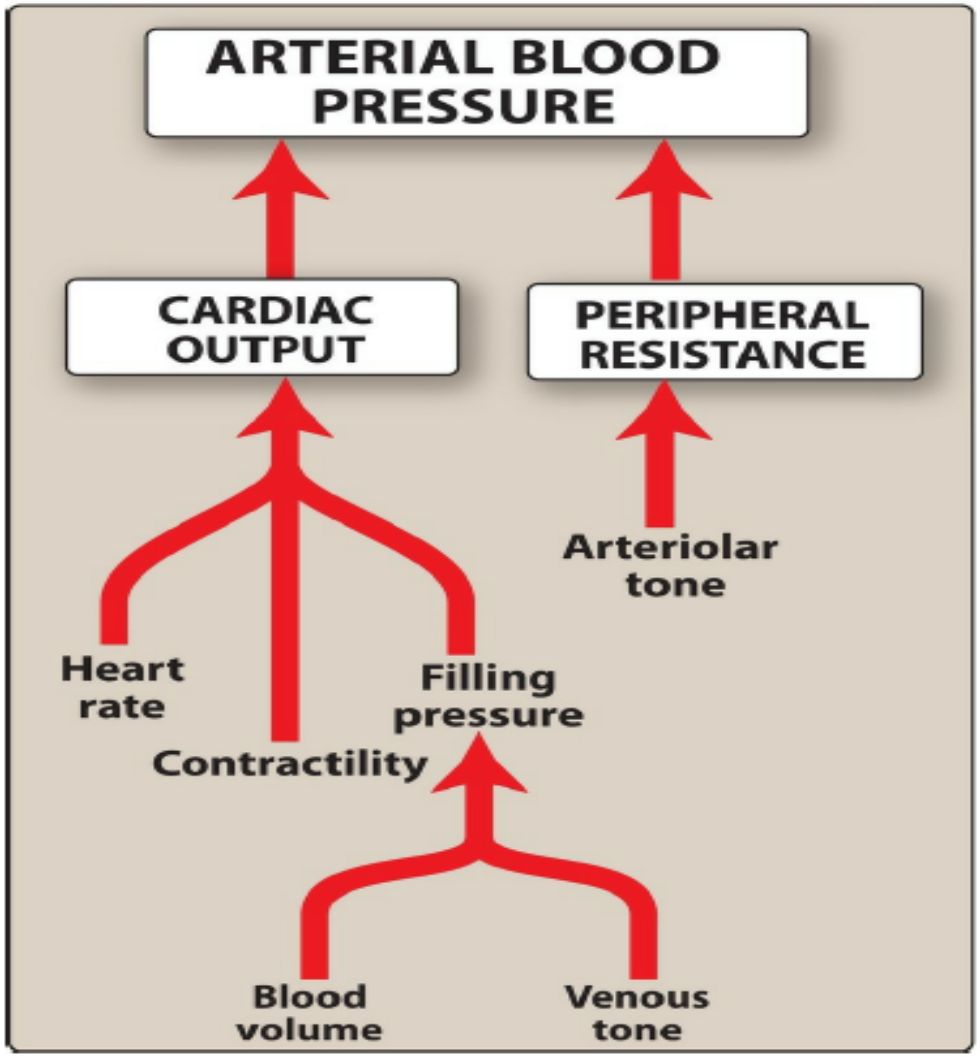
Drugs for hypertension

YASMINE ZOHAIR ALSHORAFA

Hypertension

- It is a sustained elevation of systemic arterial blood pressure
- It is defined as systolic blood pressure more than or equals 140 mm Hg or diastolic blood pressure more than or equals 90 mm Hg
- Hypertension results from increased peripheral vascular arteriolar smooth muscle tone, which leads to increased arteriolar resistance and reduced capacitance of the venous System
- chronic hypertension can lead to heart disease and stroke, the top two causes of death in the world.
- Hypertension is also an important risk factor in the development of chronic kidney disease and heart failure


ARTERIAL BLOOD PRESSURE
CARDIAC OUTPUT
PERIPHERAL RESISTANCE
Arteriolar tone
Heart rate
Contractility
Filling pressure
Blood volume
Venous tone

Classification of blood pressure

	Systolic mm Hg		Diastolic mm Hg
Normal	<120	and	<80
Elevated	120–129	or	<80
Stage 1 hypertension	130–139	or	80–89
Stage 2 hypertension	≥140	or	≥90

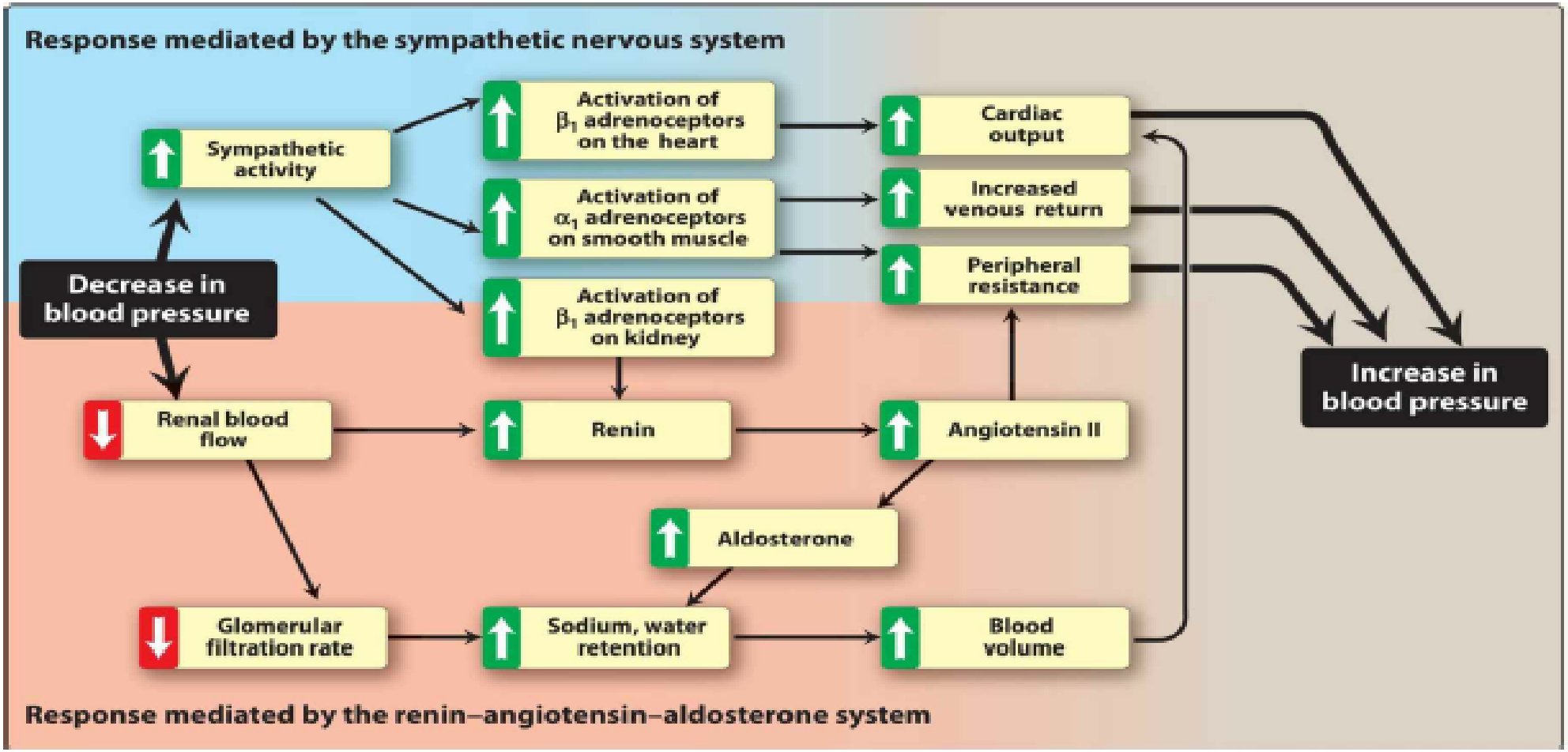


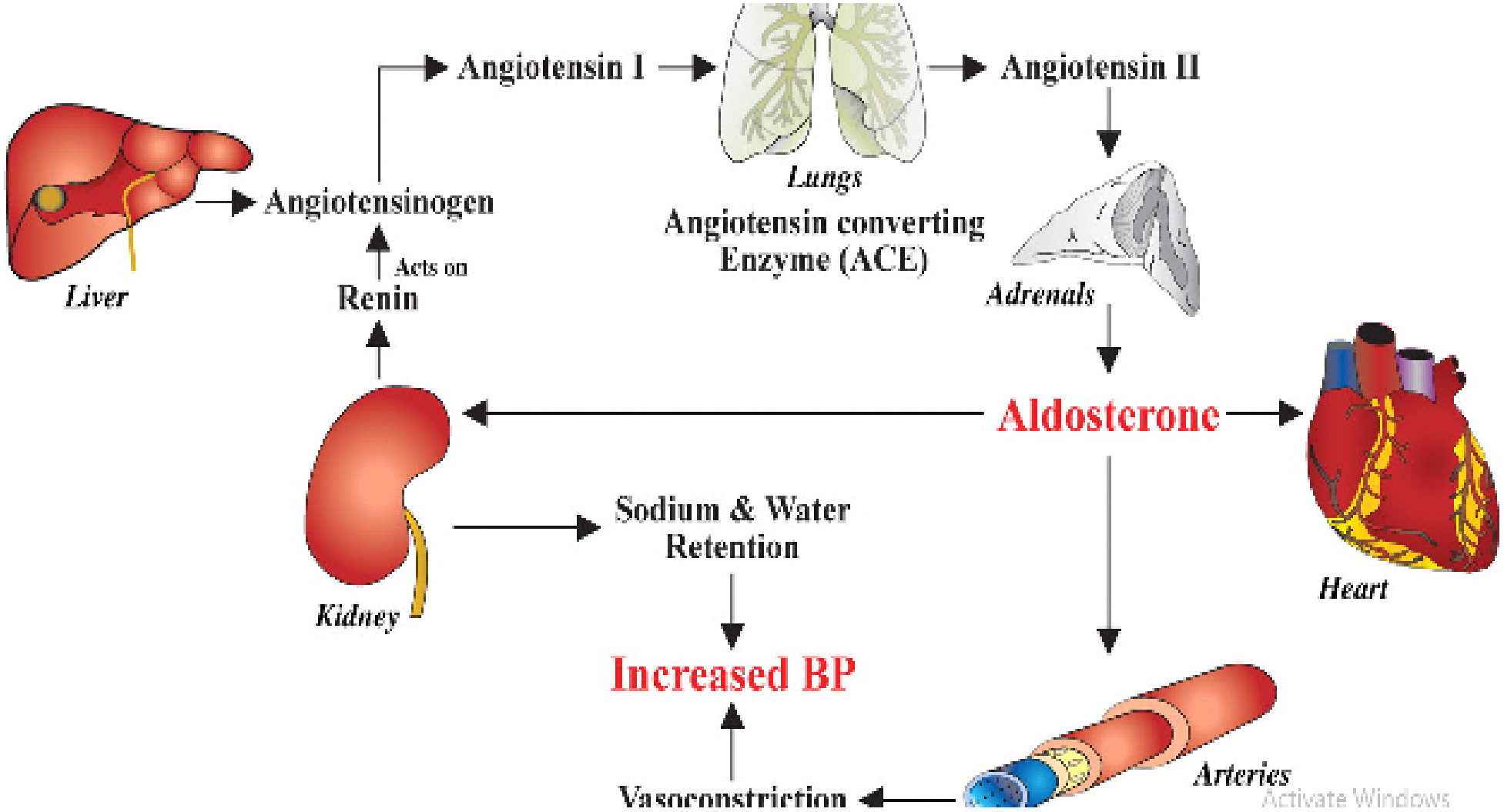
Figure 16.4 Response of the autonomic nervous system and the renin–angiotensin–aldosterone system to a decrease in blood pressure.

Baroreceptors and the sympathetic nervous system

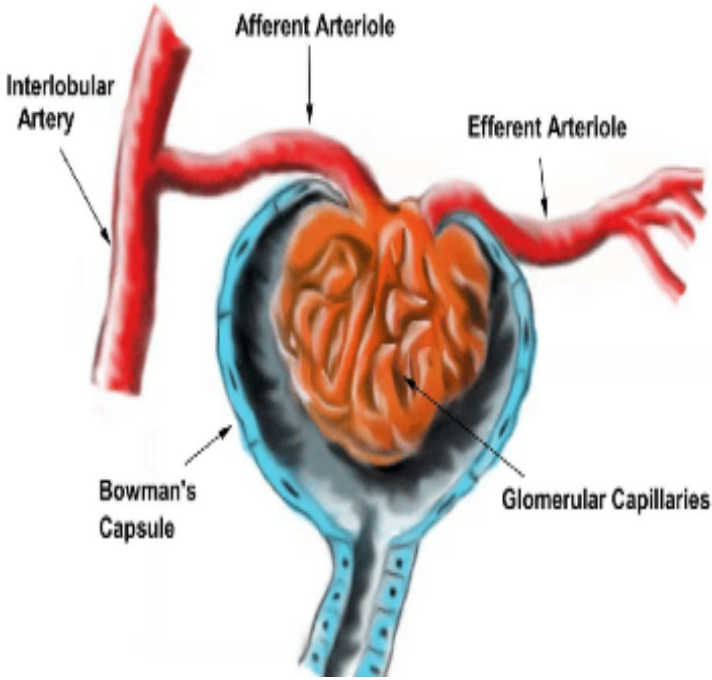
- Baroreflexes act by changing the activity of the sympathetic and parasympathetic nervous system.
- They are responsible for the rapid, moment-to-moment regulation of blood pressure. A fall in blood pressure causes pressure-sensitive neurons (**baroreceptors in the aortic arch and carotid sinuses**) to send fewer impulses to cardiovascular centers in the spinal cord.
- This prompts a reflex response of increased sympathetic and decreased parasympathetic output to the heart and vasculature, resulting in vasoconstriction and increased cardiac output.
- These changes result in a compensatory rise in blood pressure

Renin–angiotensin–aldosterone system

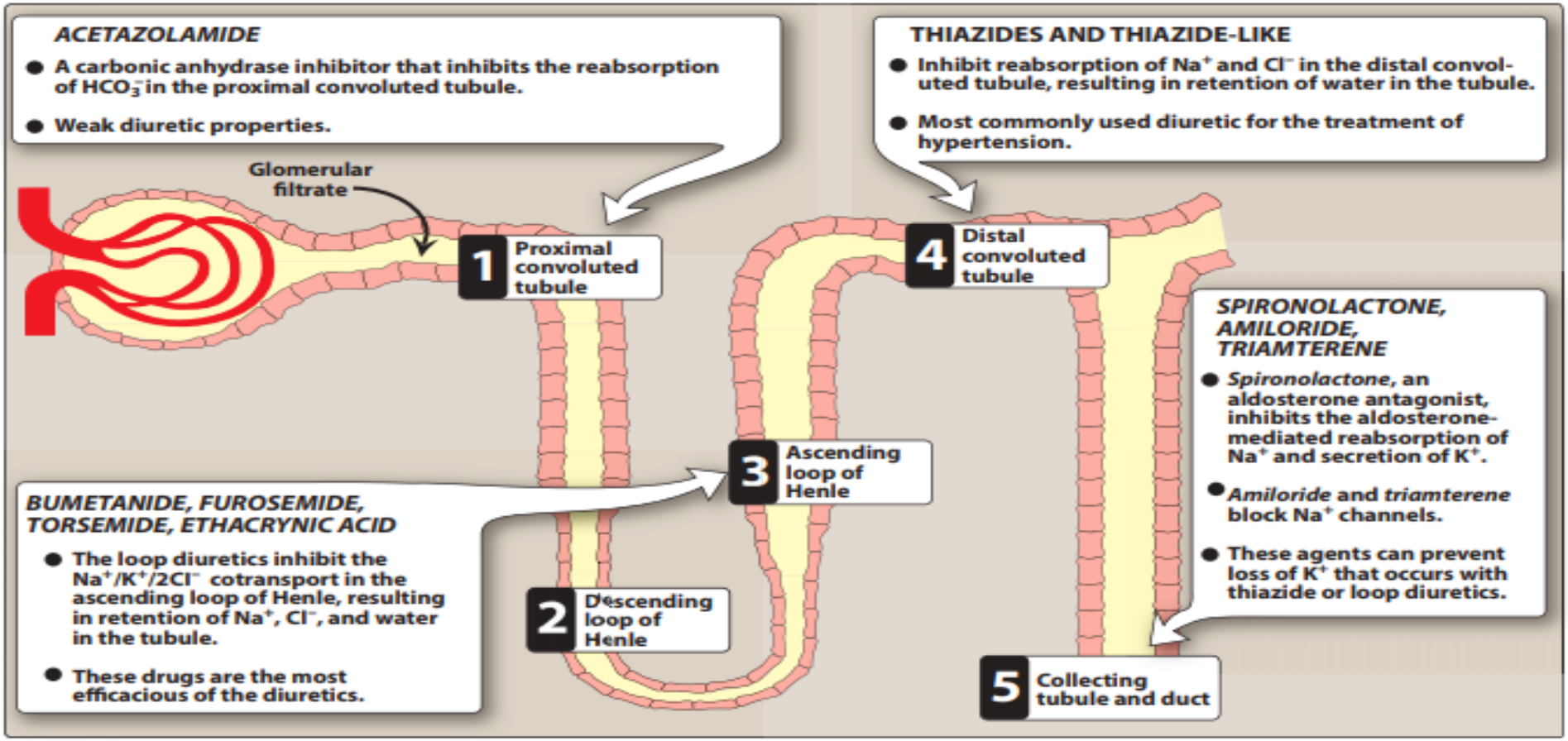
- The kidney provides long-term control of blood pressure by altering the blood volume. Baroreceptors in the kidney respond to reduced arterial pressure (and to sympathetic stimulation of β1-adrenoceptors) by releasing the enzyme renin
- Low-sodium intake and greater sodium loss also increase renin release.
- Renin converts angiotensinogen to angiotensin I, which is converted in turn to angiotensin II, in the presence of angiotensin converting enzyme (ACE).



- Angiotensin II is a potent circulating vasoconstrictor, constricting both arterioles and veins, resulting in an increase in blood pressure.
- **Angiotensin II exerts a preferential vasoconstrictor action on the efferent arterioles of the renal glomerulus, increasing glomerular filtration.**
- Furthermore, angiotensin II stimulates aldosterone secretion, leading to increased renal sodium reabsorption and increased blood volume, which contribute to a further increase in blood pressure. These effects of angiotensin II are mediated by stimulation of angiotensin II type 1 (AT1) receptors

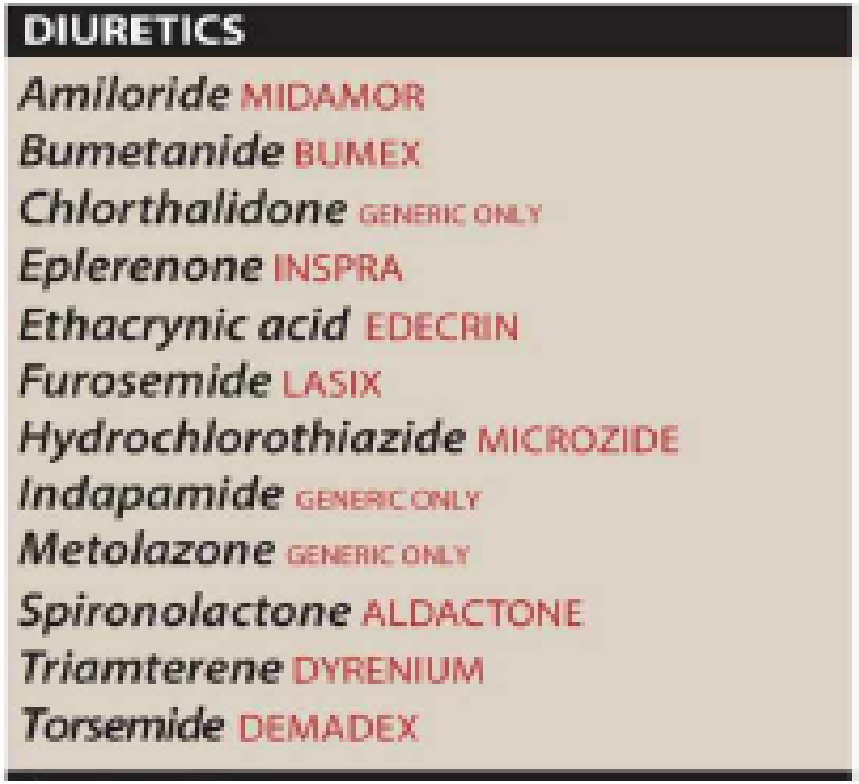


Diuretics


ACETAZOLAMIDE
A carbonic anhydrase inhibitor that inhibits the reabsorption of HCO_3^- in the proximal convoluted tubule.
Weak diuretic properties.
THIAZIDES AND THIAZIDE-LIKE
Inhibit reabsorption of Na^+ and Cl^- in the distal convoluted tubule, resulting in retention of water in the tubule.
Most commonly used diuretic for the treatment of hypertension.
Glomerular filtrate
1 Proximal convoluted tubule
2 Descending loop of Henle
3 Ascending loop of Henle
4 Distal convoluted tubule
5 Collecting tubule and duct
BUMETANIDE, FUROSEMIDE, TORSEMIDE, ETHACRYNIC ACID
The loop diuretics inhibit the $Na^+/K^+/2Cl^-$ cotransport in the ascending loop of Henle, resulting in retention of Na^+, Cl^-, and water in the tubule.
These drugs are the most efficacious of the diuretics.
SPIRONOLACTONE, AMILORIDE, TRIAMTERENE
Spironolactone, an aldosterone antagonist, inhibits the aldosterone-mediated reabsorption of Na^+ and secretion of K^+.
Amiloride and triamterene block Na^+ channels.
These agents can prevent loss of K^+ that occurs with thiazide or loop diuretics.

Thiazide diuretics

- *hydrochlorothiazide* and *chlorthalidone*, lower blood pressure initially by increasing sodium and water excretion.
- This causes a decrease in extracellular volume, resulting in a decrease in cardiac output and renal blood flow .
- With long-term treatment, plasma volume approaches a normal value, but a hypotensive effect persists that is related to a decrease in peripheral resistance.
- Thiazide diuretics are not effective in patients with inadequate kidney function (estimated glomerular filtration rate less than 30 mL/min/ m2)..



Actions

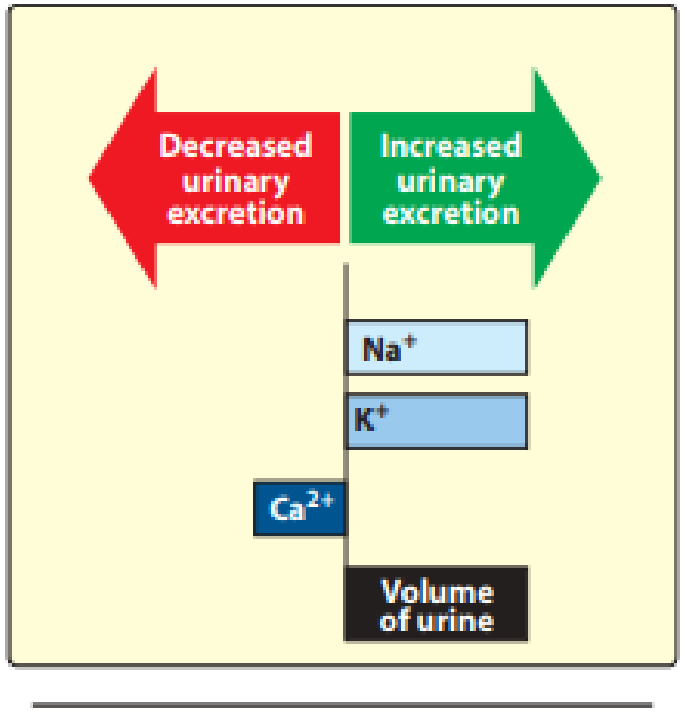
Increased excretion of Na+ and Cl−

Loss of K+

Loss of Mg2+

Decreased urinary calcium excretion :

Thiazide and thiazidelike diuretics



Adverse effects

Potassium depletion: the most frequent problem with the thiazide diuretics, and it can predispose patients who are taking digoxin to ventricular arrhythmias

Hyponatremia: Hyponatremia may develop due to elevation of ADH as a result of hypovolemia, as well as diminished diluting capacity of the kidney and increased thirst

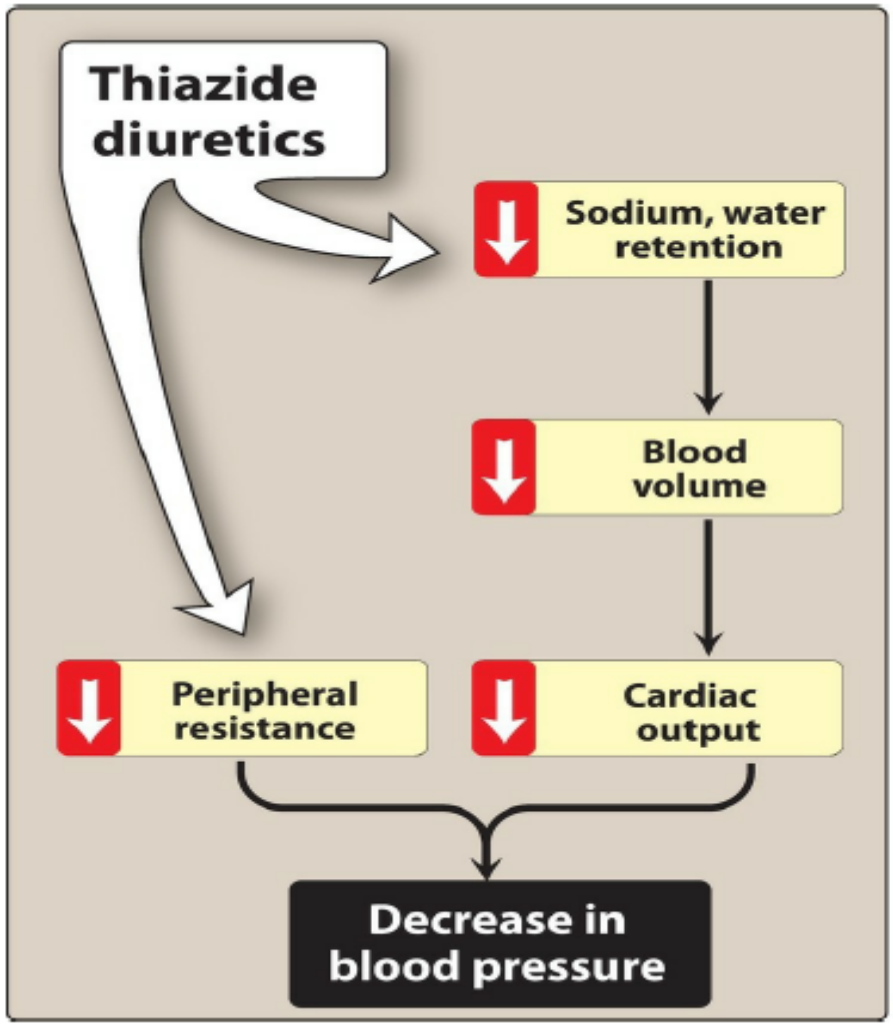
Limiting water intake and lowering the diuretic dose can prevent hyponatremia

Hyperuricemia: Thiazides increase serum uric acid by decreasing the amount of acid excreted by the organic acid secretory system

Volume depletion

Hypercalcemia

Hyperglycemia: lead to glucose intolerance, possibly due to impaired release of insulin and tissue uptake of glucose.


Thiazide diuretics
Sodium, water retention
Blood volume
Peripheral resistance
Cardiac output
Decrease in blood pressure

Loop diuretics

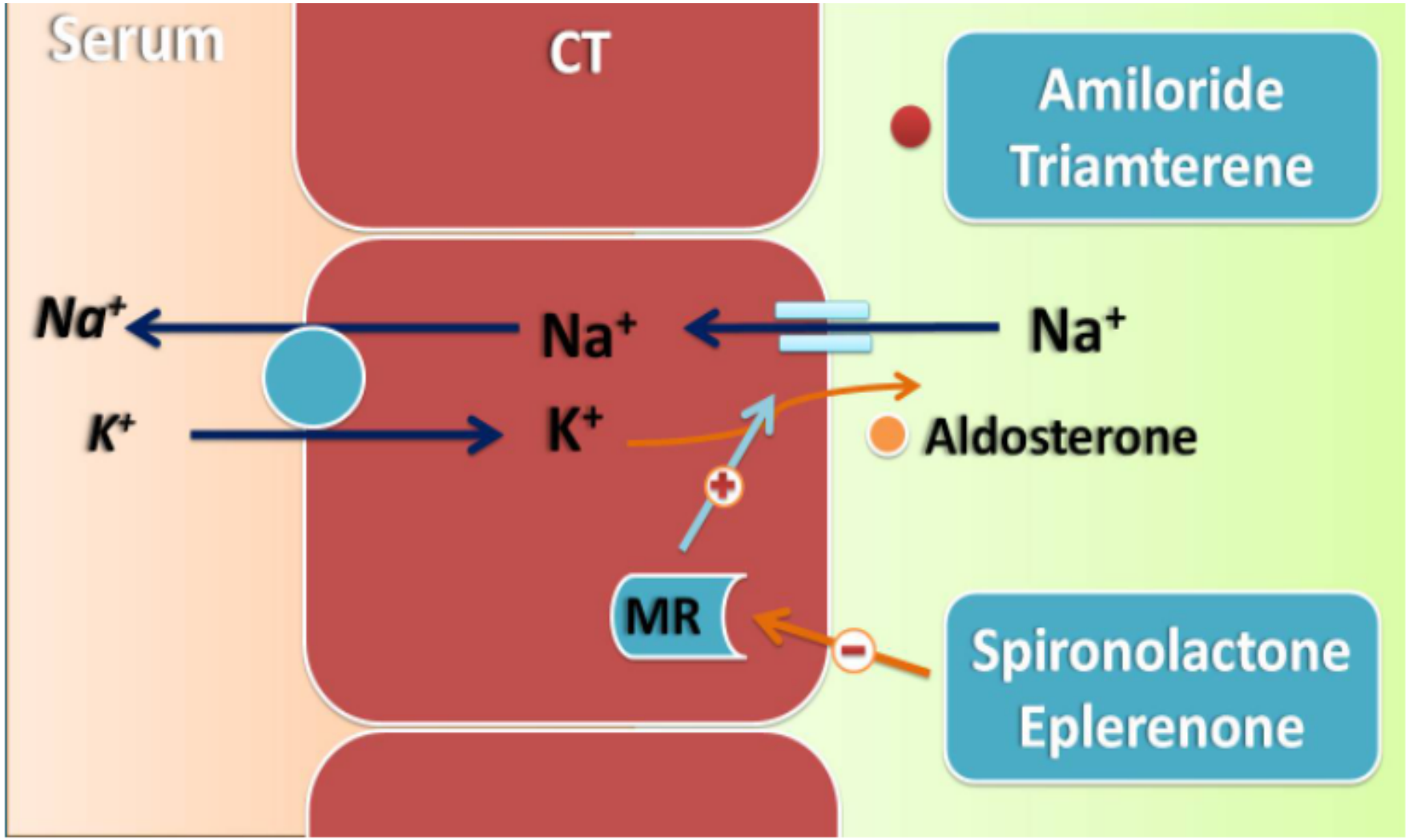
- The loop diuretics (***furosemide, torsemide, bumetanide,*** and ***ethacrynic acid***) act promptly by
- blocking sodium and chloride reabsorption in the kidneys, even in patients with poor renal function or those who have not responded to thiazide diuretics.
- Loop diuretics cause decreased renal vascular resistance and increased renal blood flow.
- Like thiazides, they can cause hypokalemia.
- However, unlike thiazides, loop diuretics increase the calcium content of urine, whereas thiazide diuretics decrease it.
- These agents are rarely used alone to treat hypertension, but they are commonly used to manage symptoms of heart failure and edema.

Potassium-sparing diuretics

- *Amiloride* and *triamterene* are inhibitors of epithelial sodium transport at the late distal and collecting ducts.
- *spironolactone* and *eplerenone* are aldosterone receptor antagonists.
- All of these agents reduce potassium loss in the urine. ‘
- Aldosterone antagonists have the additional benefit of diminishing the cardiac remodeling that occurs in heart failure
- Potassium-sparing diuretics are sometimes used in combination with loop diuretics and thiazides to reduce the amount of potassium loss induced by these diuretics.

- Sodium entry in these segments occur through aldosterone sensitive sodium channels
- The reabsorption of cationic sodium without an anion creates a lumen negative electrical gradient that then favors the secretion of potassium and hydrogen ions.
- Thus inhibition of sodium reabsorption at this site can lead to hyperkalemia and metabolic acidosis

Amiloride and triametrene are cations that directly block sodium channels but don't affect mineralocorticoid receptor.

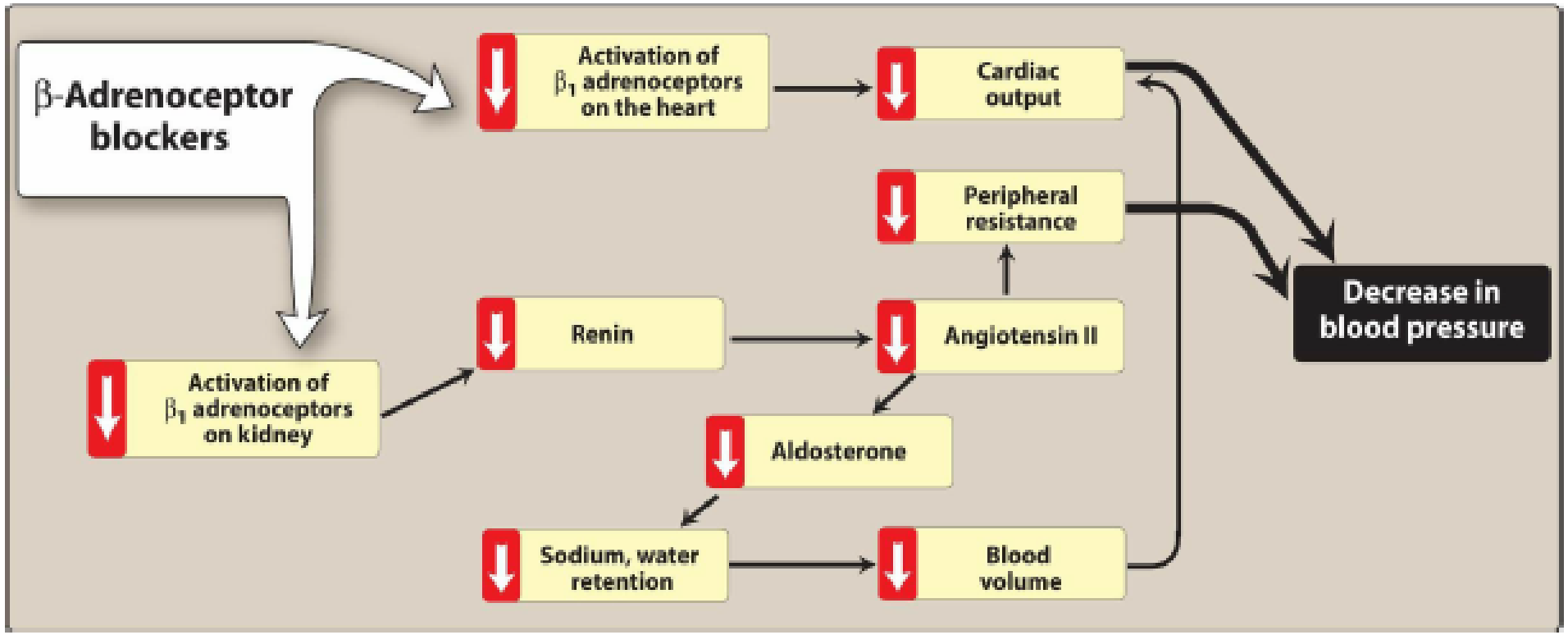

Serum
CT
Amiloride
Triamterene
Na+
Na+
Na+
K+
K+
Aldosterone
MR
Spironolactone
Eplerenone

Spironolactone and eplerenone competitively inhibit the mineralocorticoid receptor

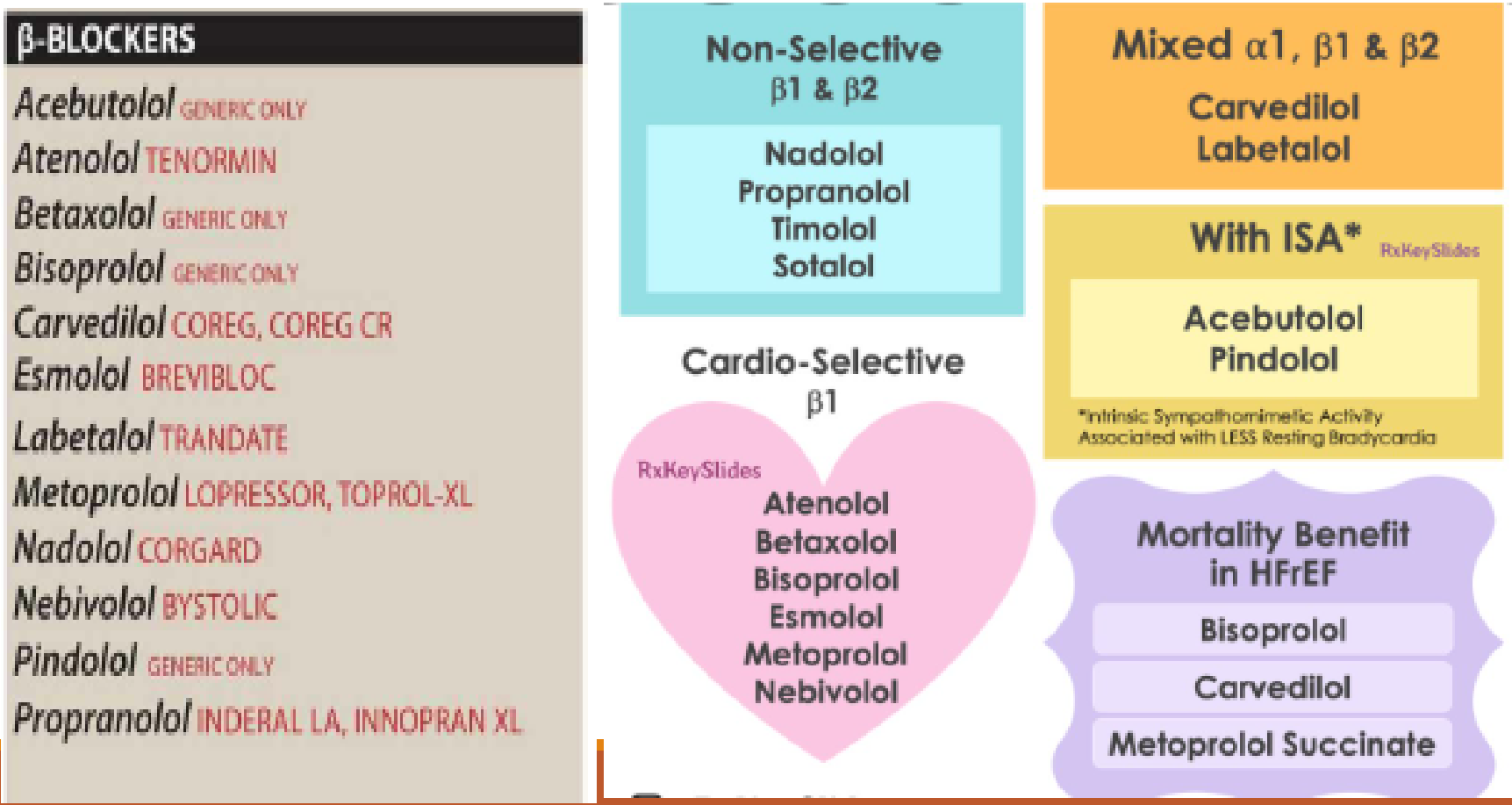
Eplerenone is better tolerated than spironolactone , as it has lower incidence of endocrine side effects (gynecomastia, menstrual abnormalities, impotence)

Spironolactone has non selective binding to estrogen and progesterone receptors.

β-Adrenoceptor–Blocking Agents



β-Adrenoceptor–Blocking Agents



- The primary therapeutic benefits of β-blockers are seen in hypertensive patients with concomitant heart disease, such as supraventricular tachyarrhythmia (for example, atrial fibrillation), previous myocardial infarction, stable ischemic heart disease, and chronic heart failure.

- Conditions that discourage the use of β-blockers include reversible bronchospastic disease such as asthma, second- and third-degree heart block, and severe peripheral vascular disease

Adverse effects


Sexual dysfunction

Hypotension


Bradycardia


Fatigue


Insomnia

- Non cardioselective β-blockers may disturb lipid metabolism, decreasing high-density lipoprotein cholesterol and increasing triglycerides.
- Hyperkalemia (minor elevation of less than 0.5 meq/L)
- Lipophilic beta blockers (propranolol and metoprolol) >>> CNS effects

Drug withdrawal

Abrupt withdrawal may induce severe hypertension, angina,

myocardial infarction, and even sudden death in patients with ischemic heart disease.

Therefore, these drugs must be tapered over a few weeks in patients with

hypertension and ischemic heart disease.

Drugs for hypertension part 2

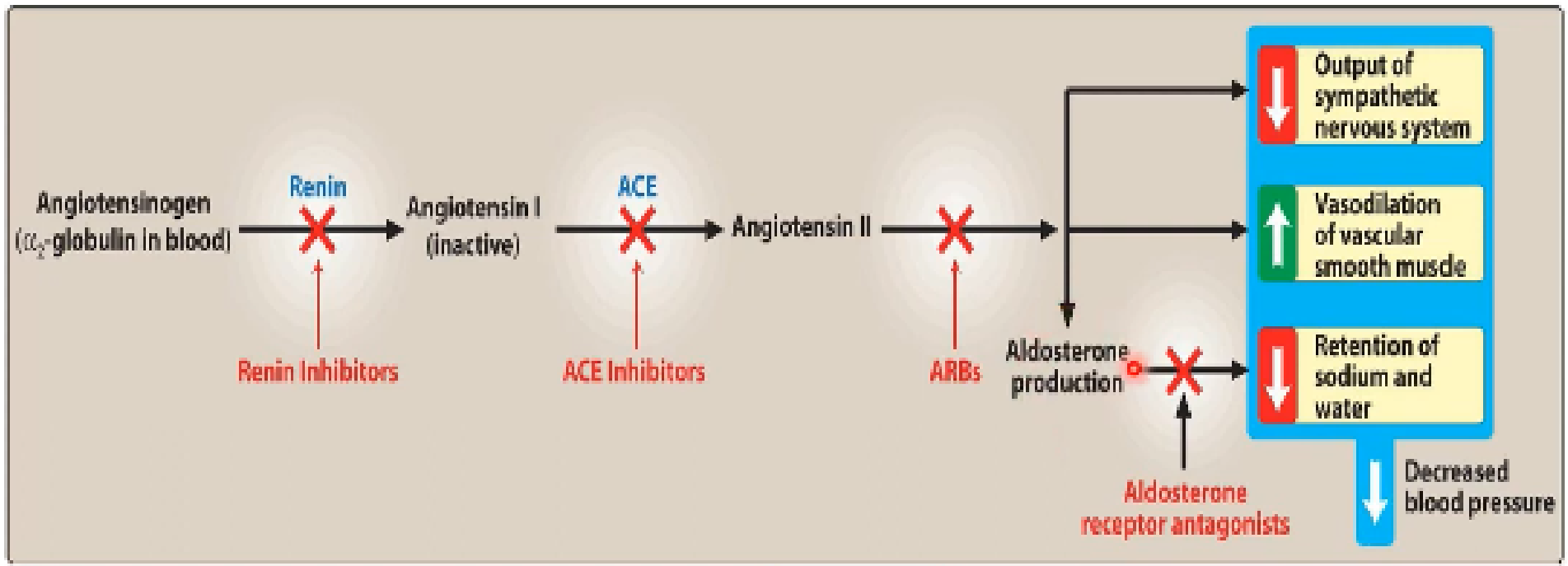
YASMINE ZOHAIR ALSHORAFA

ACE Inhibitors

ACE inhibitors are recommended as first-line treatment of hypertension in patients with a variety of compelling indications, including high coronary disease risk or history of diabetes, stroke, heart failure, myocardial infarction, or chronic kidney disease

ACE INHIBITORS
Benazepril LOTENSIN
Captopril GENERIC ONLY
Enalapril VASOTEC
Fosinopril GENERIC ONLY
Lisinopril PRINIVIL, ZESTRIL
Moexipril GENERIC ONLY
Quinapril ACCUPRIL
Perindopril GENERIC ONLY
Ramipril ALTACE
Trandolapril GENERIC ONLY

ACE Inhibitors



Angiotensin II

Bradykinin

nitric oxide and prostacyclin by the blood vessels)

Therapeutic uses

- Slow the progression of diabetic nephropathy and decrease albuminuria
- Standard in the care of a patient following a myocardial infarction and first-line agents in the treatment of patients with systolic dysfunction
- Regression of left ventricular hypertrophy, and prevention of ventricular remodeling after a myocardial infarction.
- Hypertensive patients with chronic kidney disease.

Adverse effects

dry cough

Angioedema

Hyperkalemia.

Increase in serum creatinine of up to 30% above baseline

Fetal malformations in pregnant women

Angiotensin II Receptor Blockers

- ARBs block the AT1 receptors, decreasing the activation of AT1 receptors by angiotensin II.
- Their pharmacologic effects are similar to those of ACE inhibitors in that they produce arteriolar and venous dilation and block aldosterone secretion, thus lowering blood pressure.
- They may be used as first-line agents for the treatment of hypertension, especially in patients with a compelling indication of diabetes, heart failure, or chronic kidney disease.
- Adverse effects are similar to those of ACE inhibitors, although the risks of cough and angioedema are significantly decreased.

ANGIOTENSIN II RECEPTOR BLOCKERS
Azilsartan EDARBI
Candesartan ATACAND
Eprosartan GENERIC ONLY
Irbesartan AVAPRO
Losartan COZAAR
Olmesartan BENICAR
Telmisartan MICARDIS
Valsartan DIOVAN

Renin Inhibitor

Aliskiren , is available for the treatment of hypertension.

Aliskiren directly inhibits renin and, thus, acts earlier in the renin–angiotensin–aldosterone system than ACE inhibitors or ARBs

Aliskiren should not be combined with an ACE inhibitor or ARB in the treatment of hypertension.

It also causes cough and angioedema but less often than ACE inhibitors.

As with ACE inhibitors and ARBs, *aliskiren* is contraindicated during pregnancy.

Aliskiren can cause diarrhea, especially at higher doses.

Aliskiren is metabolized by CYP3A4 and is subject to many drug interactions.

Classes of calcium channel blockers

Diphenylalkylamines

- Verapamil
- Acts on cardiac and vascular smooth muscle cells
- Used as anti-angina
- Anti arrhythmic

Benzothiazepines

- diltiazem
- both cardiac and vascular smooth muscle cells
- less pronounced negative
- inotropic effect on the heart compared to that of veraparmil

Dihydropyridines

- Nifedipine
- Amlodipine
- Ielodipine
- Nicardipine
- much greater affinity for vascular calcium channels than for calcium channels in the heart

Dihydropyridines

They are beneficial in treating hypertension.

The dihydropyridines have the advantage in that they show little interaction with other cardiovascular drugs, such as *digoxin* or *warfarin*, which are often used concomitantly with calcium channel blockers.

Calcium channel antagonists block the inward movement of calcium by binding to L-type calcium channels in the heart and in smooth muscle of the coronary and peripheral arteriolar vasculature.

This causes vascular smooth muscle to relax, dilating mainly arterioles. Calcium channel blockers do not dilate veins.

Most of these agents have short half-lives (3 to 8 hours) following an oral dose.

Sustained-release preparations are available and permit once-daily dosing.

Amlodipine has a very long half-life and does not require a sustained-release formulation.

Adverse effects

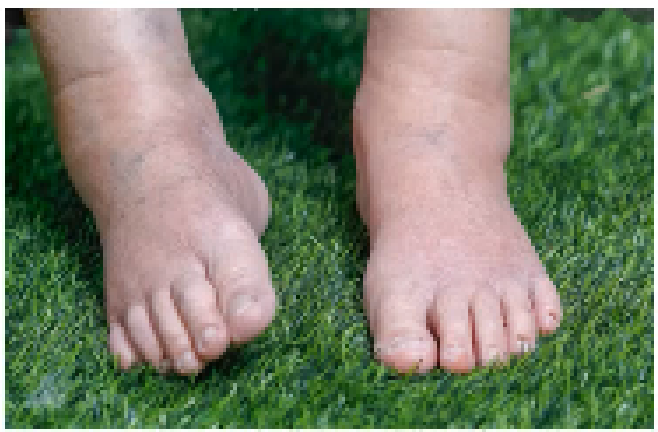
First-degree atrioventricular block and constipation are common dose-dependent side effects of *verapamil*.

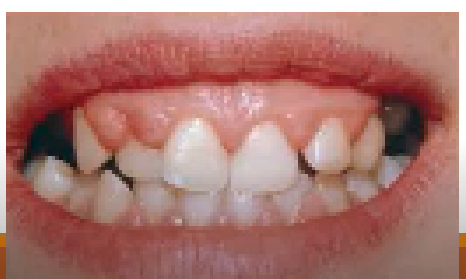
Verapamil and *diltiazem* should be avoided in patients with heart failure or with atrioventricular block due to their negative inotropic (force of cardiac muscle contraction) and dromotropic (velocity of conduction) effects.

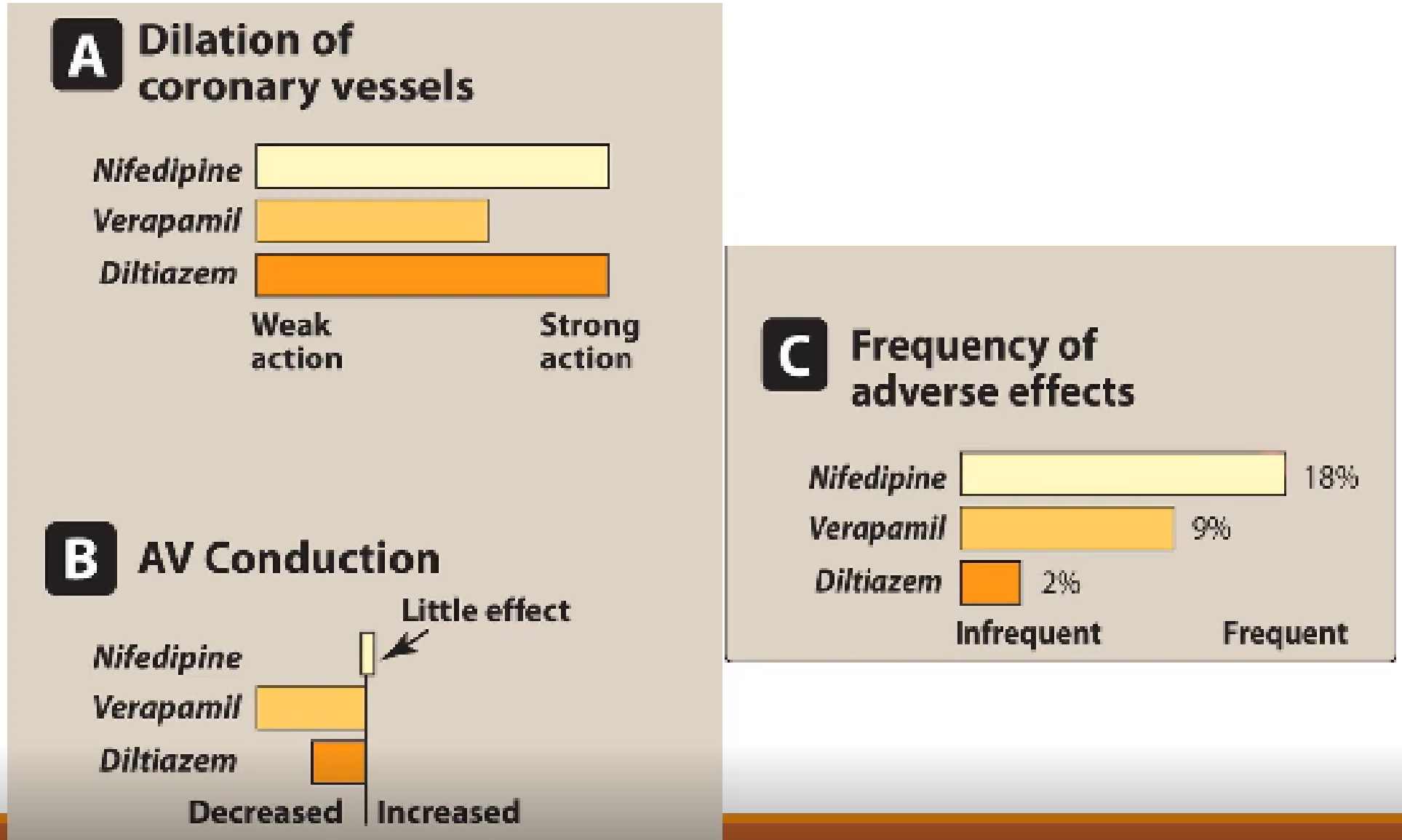
Dizziness, headache, and a feeling of fatigue caused by a decrease in blood pressure are more frequent with **dihydropyridines**

Peripheral edema is another commonly reported side effect of this class.

Nifedipine and other dihydropyridines may cause gingival hyperplasia.






A
Dilation of coronary vessels
Nifedipine
Verapamil
Diltiazem
Weak action
Strong action
B
AV Conduction
Little effect
Nifedipine
Verapamil
Diltiazem
Decreased
Increased
C
Frequency of adverse effects
Nifedipine
18%
Verapamil
9%
Diltiazem
2%
Infrequent
Frequent

α-ADRENOCEPTOR–BLOCKING AGENTS

prazosin, doxazosin* and *terazosin.

These agents produce a competitive block of α1-adrenoceptors. They decrease peripheral vascular resistance and lower arterial blood pressure by causing relaxation of both arterial and venous smooth muscle.

Long-term tachycardia does not occur, but salt and water retention does.

Reflex tachycardia and postural hypotension often occur at the onset of treatment and with dose increases, requiring slow titration of the drug in divided doses.

Due to weaker outcome data and their side effect profile, α-blockers are no longer recommended as initial treatment for hypertension but may be used for refractory cases.

Other α1-blockers with greater selectivity for the prostate are used in the treatment of benign prostatic hyperplasia

a-/b-Adrenoceptor–blocking Agents

- *Labetalol* and *carvedilol* block α1, β1, and β2 receptors.
- *Carvedilol* is indicated in the treatment of heart failure and hypertension. It has been shown to reduce morbidity and mortality associated withmheart failure.
- *Labetalol* is used in the management of gestational hypertension and hypertensive emergencies.

Centrally Acting Adrenergic Drugs

Clonidine

- acts centrally as an α2 agonist to produce inhibition of sympathetic vasomotor centers. decreasing sympathetic outflow to the periphery.
- Adverse effects includes sedation, dry mouth, and constipation

Methyldopa

- α2 agonist that is converted to methylnorepinephrine centrally to diminish adrenergic outflow from the CNS
- The most common side effects of methyldopa are sedation and drowsiness
- It is mainly used for management of hypertension in pregnancy

Vasodilators

- The direct-acting smooth muscle relaxants, such as *hydralazine* and *minoxidil*, are not used as primary drugs to treat hypertension.
- These vasodilators act by producing relaxation of vascular smooth muscle, primarily in arteries and arterioles. This results in decreased peripheral resistance and, therefore, blood pressure.

Side effects

- Both agents produce reflex stimulation of the heart, resulting in the competing reflexes of increased myocardial contractility, heart rate, and oxygen consumption.

  These actions may prompt angina pectoris, myocardial infarction, or cardiac failure in predisposed individuals

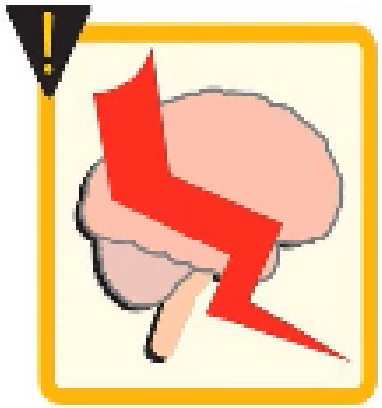
- Vasodilators also increase plasma renin concentration, resulting in sodium and water retention

Hydralazine is an accepted medication for controlling blood pressure in pregnancy-induced hypertension

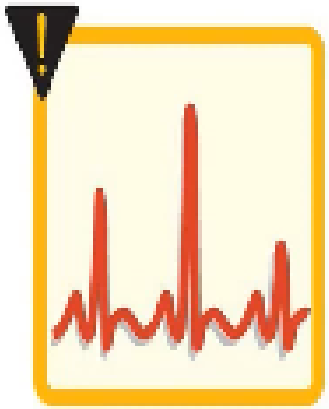
Adverse effects of *hydralazine* include headache, tachycardia, nausea, sweating, arrhythmia, and precipitation of angina .

A lupus-like syndrome can occur with high dosages, but it is reversible upon discontinuation of the drug.

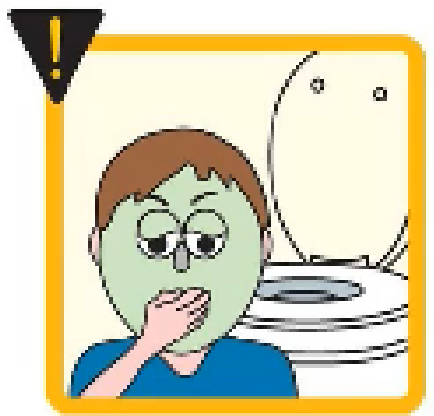
Minoxidil treatment causes **hypertrichosis (the growth of body hair).** This drug is used topically to treat **male pattern baldness**



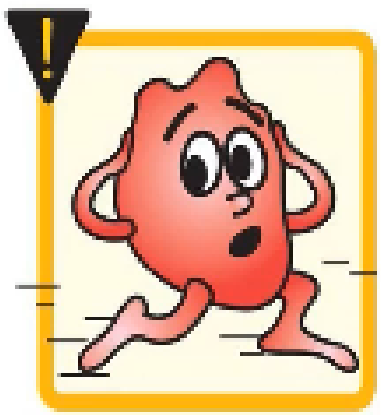
Headache



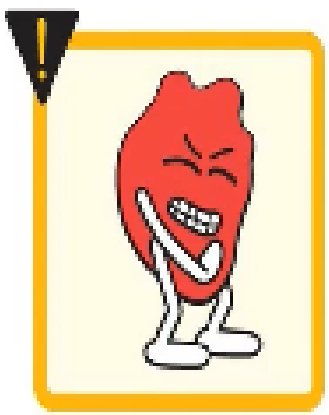
Palpitations



Nausea



Tachycardia



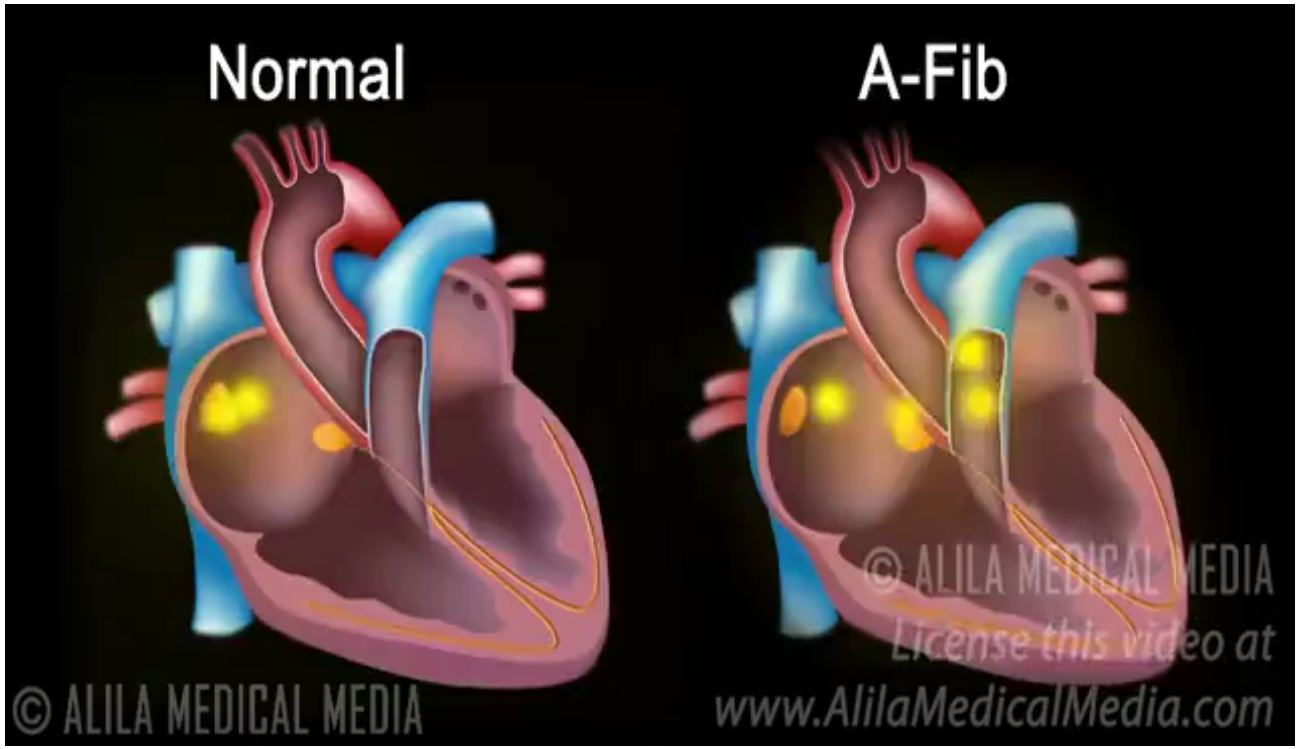
Angina

Antiarrhythmic part 1

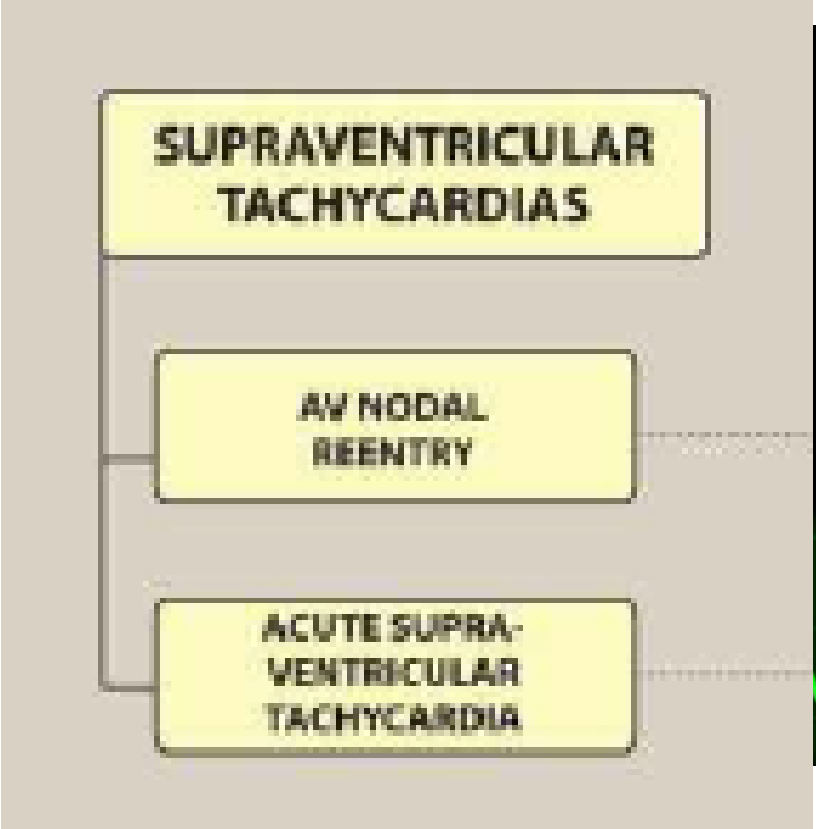
Atrial arrhythmia

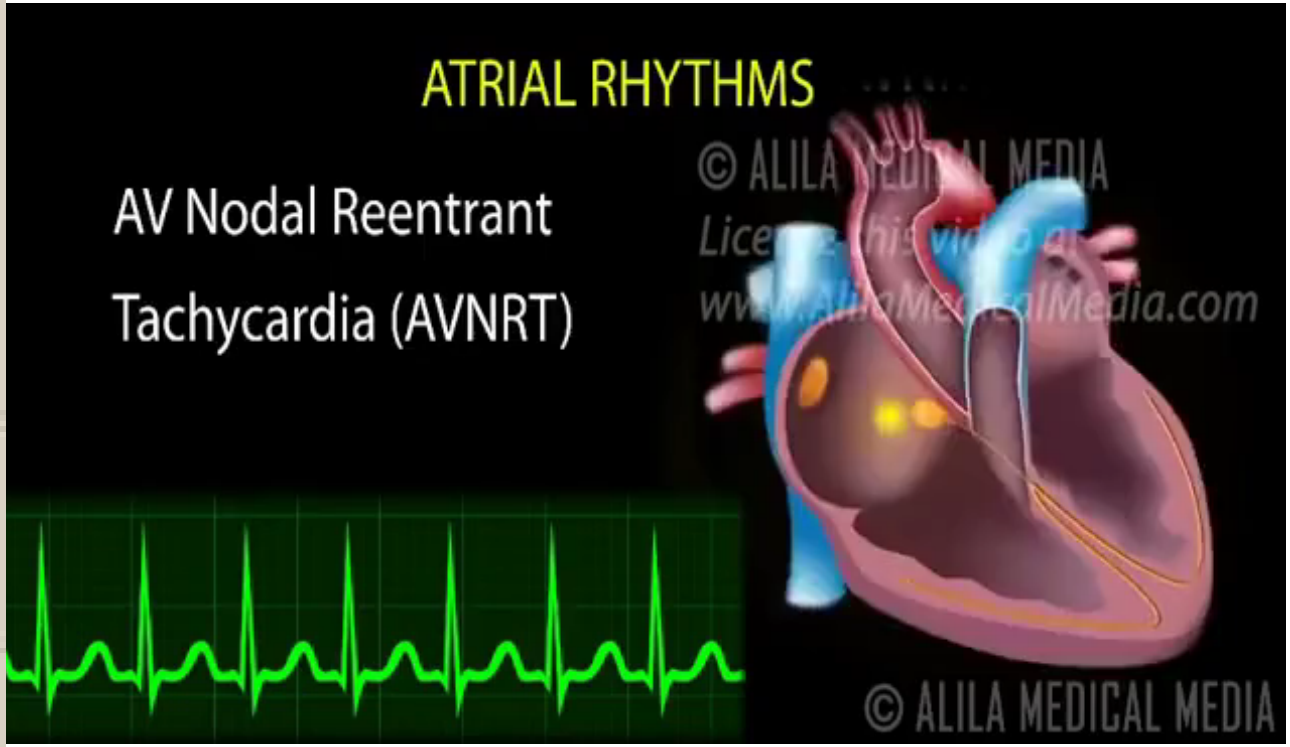
This common arrhythmia involves multiple ectopic foci of atrial cells, creating a chaotic movement of impulses through the atria. The ventricular response may be rapid (100–150 beats per minute) and irregular. Cardiac output is decreased and exercise intolerance is common.

TYPE OF ARRHYTHMIA	Class I
ATRIAL ARRHYTHMIAS	
ATRIAL FLUTTER	
ATRIAL FIBRILLATION	*Propafenone*

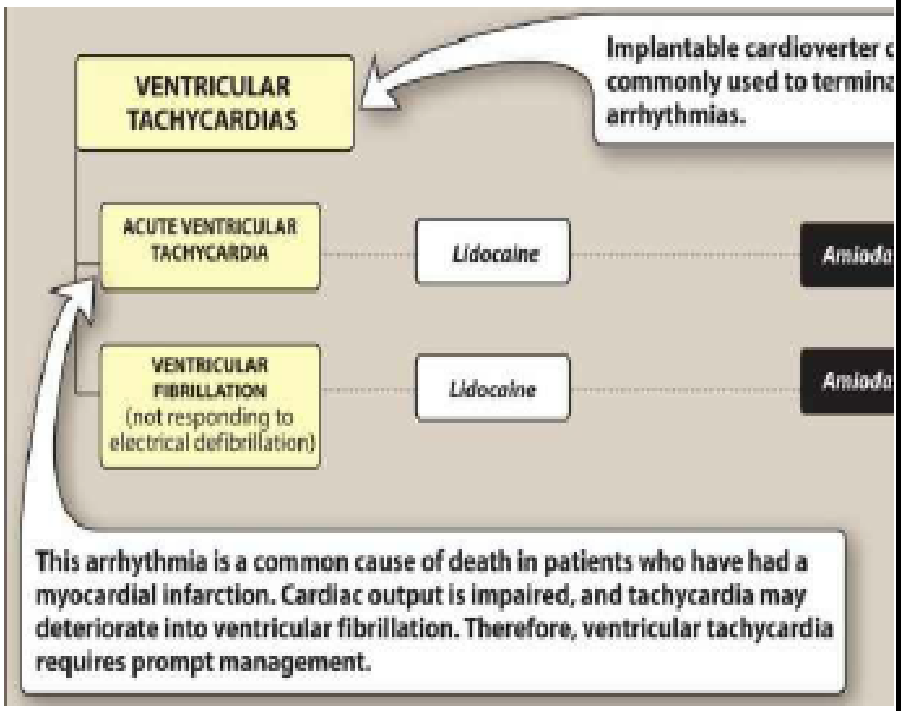


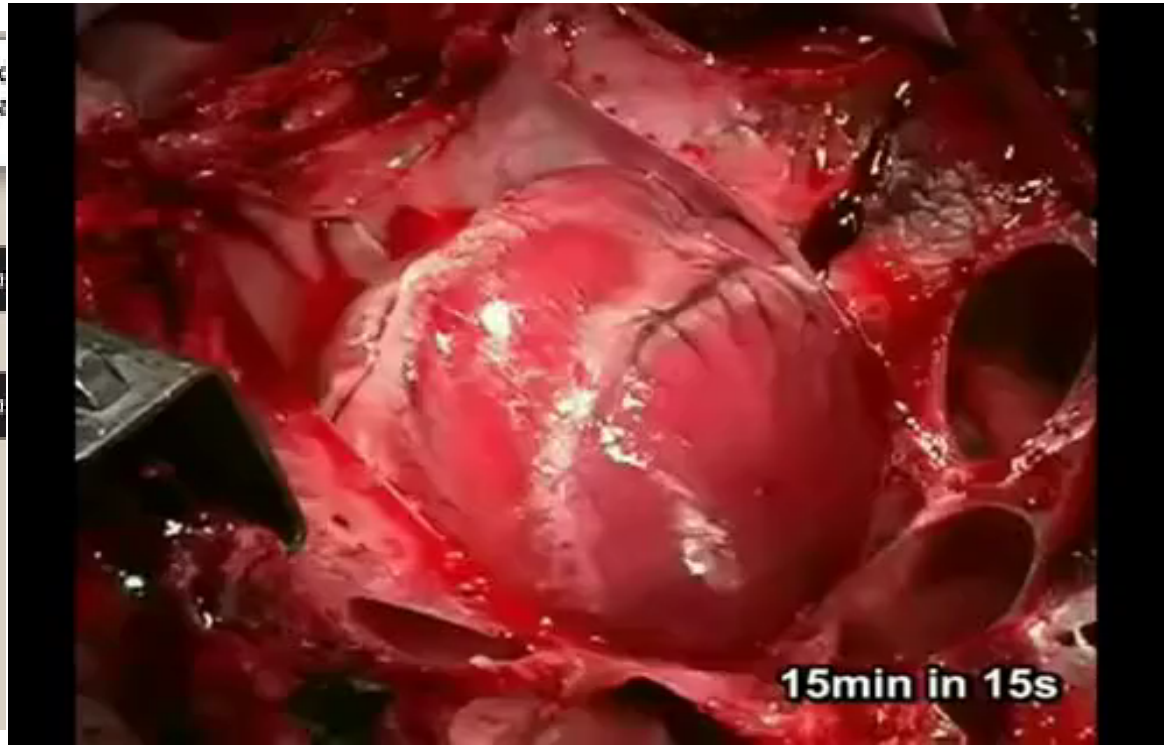
Supraventricular tachycardias





Ventricular tachycardia



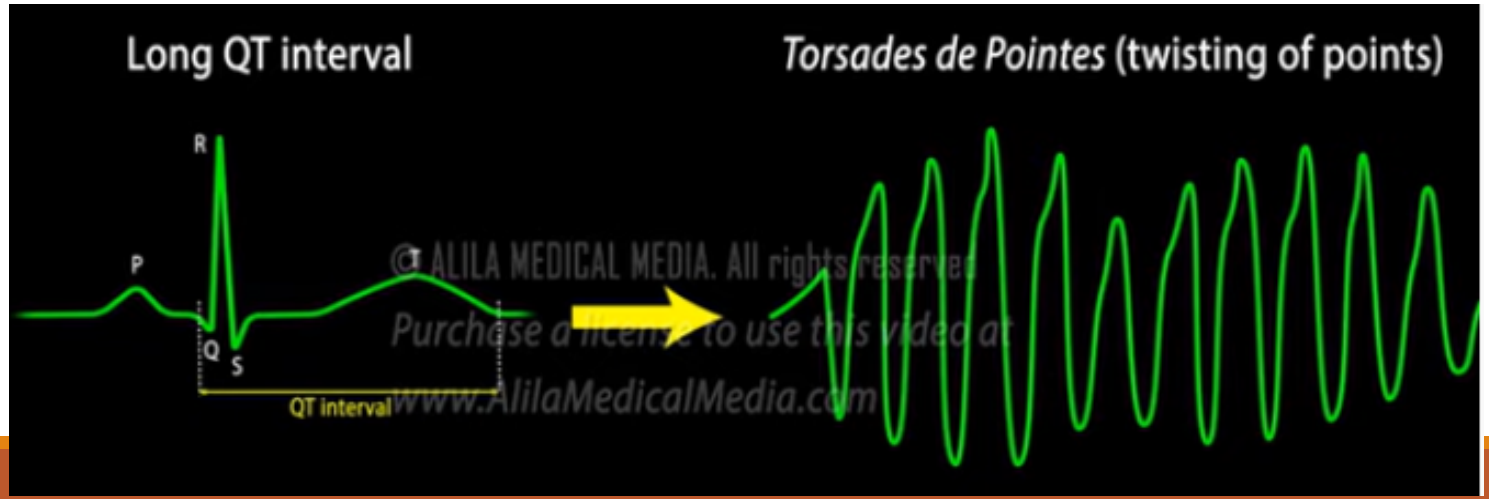


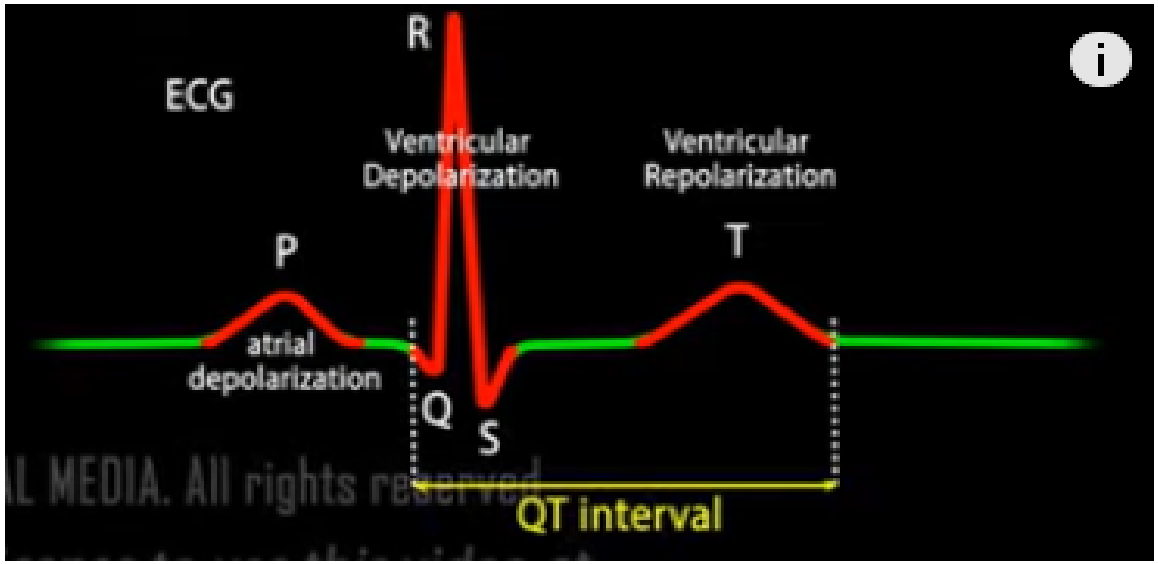
Antiarrhythmic drugs

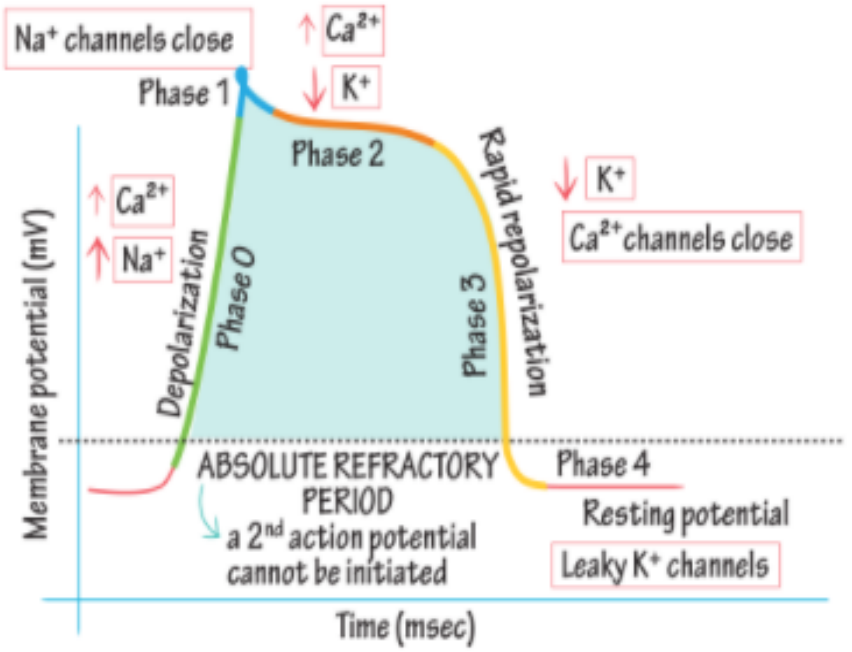
Many of the antiarrhythmic agents are known to have dangerous proarrhythmic actions—that is, to cause arrhythmias

Inhibition of K+ channels widens the action potential and can, thus, prolong the QT interval. If prolongation is excessive, these drugs increase the risk of developing life threatening ventricular tachyarrhythmias (torsades de pointes).

Causes:: drug induced, ischemia and hypokalemia) and genetic abnormalities may contribute.




ECG
R
Ventricular Depolarization
Ventricular Repolarization
P
T
atrial depolarization
Q
S
QT interval


Na+ channels close
↑ Ca2+
↓ K+
Phase 1
Phase 2
Rapid repolarization
↓ K+
↑ Ca2+
↑ Na+
Ca2+ channels close
Depolarization
Phase 0
Phase 3
Membrane potential (mV)
ABSOLUTE REFRACTORY PERIOD
a 2nd action potential cannot be initiated
Phase 4
Resting potential
Leaky K+ channels
Time (msec)

Anti-arrythmic classification

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

Class I

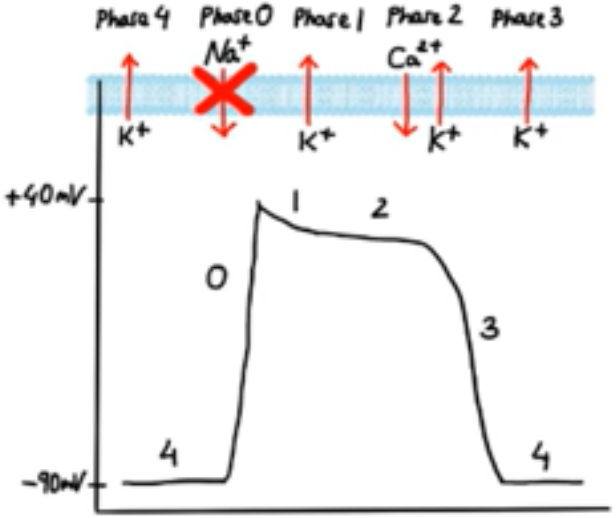
Mechanism of action :: blocking voltage-sensitive Na+ channels.

They bind more rapidly to open or inactivated Na+ channels than to channels that are fully repolarized.

Therefore, these drugs show a greater degree of blockade in tissues that frequently depolarizing.

Use dependence (or state dependence):

It enables these drugs to block cells that are discharging at an abnormall high frequency, without interfering with the normal beating of the heart.



proarrhythmic effects!!!!!!!!

CLASS I (Na^+-channel blockers)

Disopyramide (IA) NORPACE

Flecainide (IC) TAMBOCOR

Lidocaine (IB) XYLOCAINE

Mexiletine (IB) GENERIC ONLY

Procainamide (IA) GENERIC ONLY

Propafenone (IC) RYTHMOL

Quinidine (IA) GENERIC ONLY

Class I

Class IA	Moderate Na channel blocker Prolong action potential and refractory period Slows conduction velocity
Class IB	Weak Na channel blocker shorten phase 3 repolarization and decrease the duration of the action potential
Class IC	Powerful and strong fast Na channel blockers Depress phase 0 depolarization Has limited effect on repolarization and refractory period more potent antiarrhythmics.

Class IA antiarrhythmic drugs: Quinidine, procainamide, and disopyramide

- Because of their concomitant class III activity, they can precipitate arrhythmias that can progress to ventricular fibrillation.
- **Mechanism of action**:

Slowing the rapid upstroke during phase 0

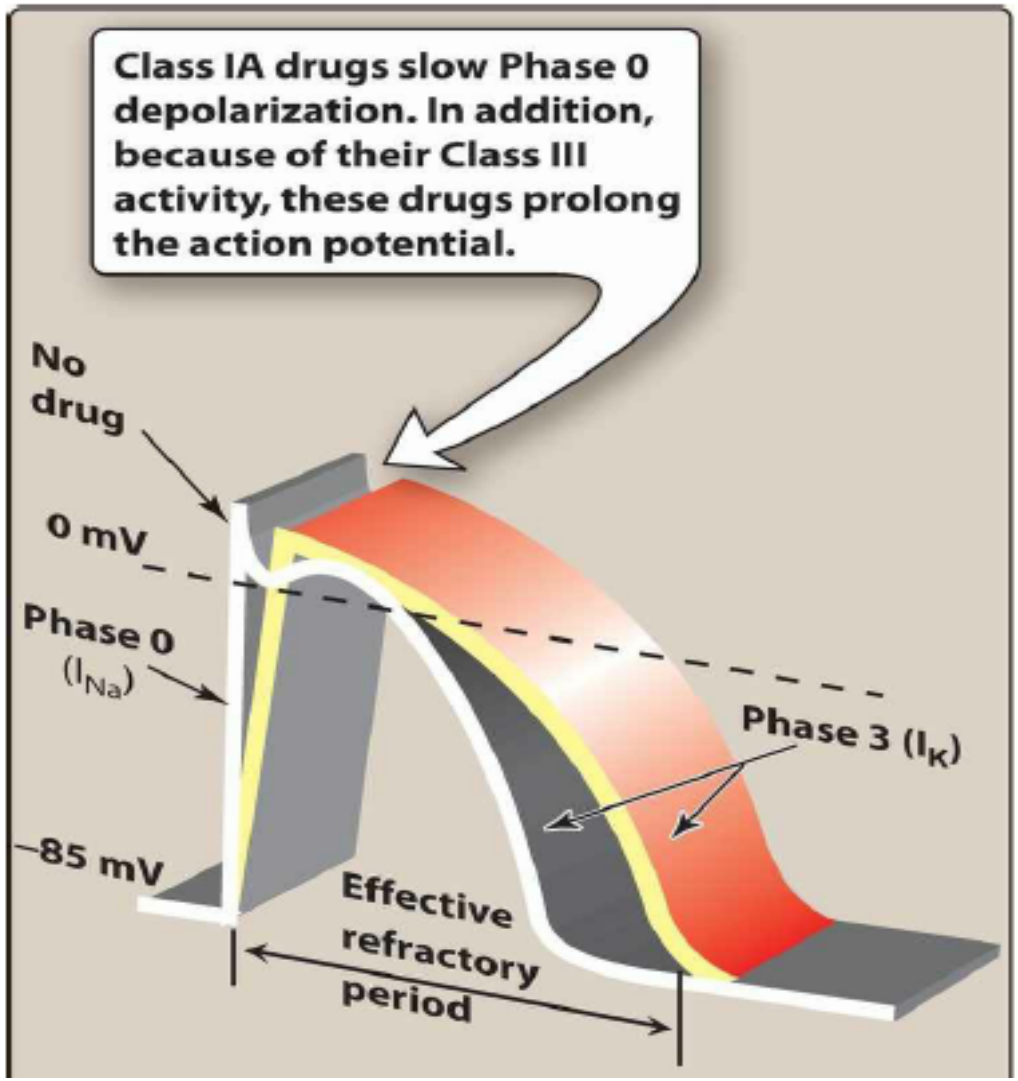
It slows conduction velocity and increases refractoriness

Quinidine also has mild α-adrenergic blocking and anticholinergic actions.

Neither *procainamide* nor *disopyramide* has α-blocking activity

less anticholinergic activity with *procainamide* and more with *disopyramide*

Disopyramide produces a greater negative inotropic effect, and unlike the other drugs, it causes peripheral vasoconstriction


Class IA drugs slow Phase 0 depolarization. In addition, because of their Class III activity, these drugs prolong the action potential.
No drug
0 mV
Phase 0 (I_{Na})
Phase 3 (I_K)
−85 mV
Effective refractory period

Therapeutic uses:

They are used in the treatment of a wide variety of arrhythmias, including atrial, AV junctional, and ventricular tachyarrhythmias

Adverse effects:

- **Enhanced proarrhythmic effects** and ability to worsen heart failure symptoms,

  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)

- 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)

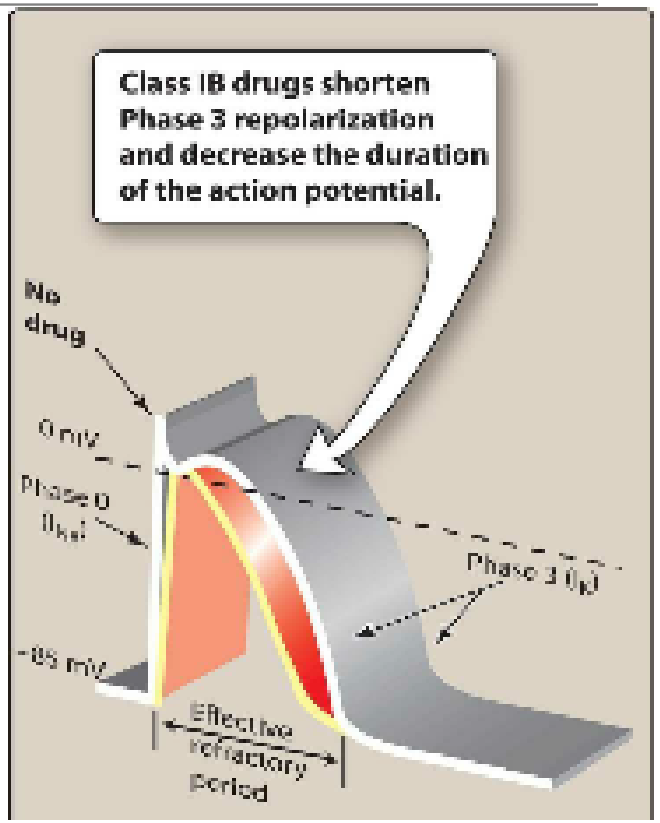
Class IB antiarrhythmic drugs: Lidocaine and mexiletine

- They are useful in treating ventricular arrhythmias
- They have little effect on atrial or AV junction arrhythmias
- Neither drug contributes to negative inotropy

Mechanism of action:

In addition to Na+ channel blockade, *lidocaine* and *mexiletine* shorten phase 3 repolarization and decrease the duration of the action potential

Adverse effects:

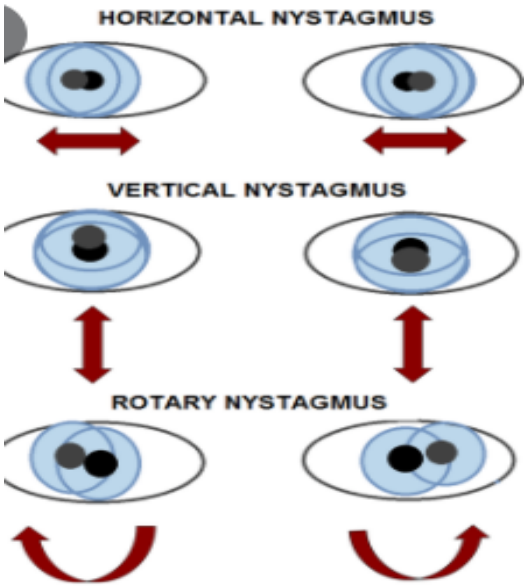


Adverse effects

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. Nausea, vomiting, and dyspepsia are the most common adverse effects.



Class IC antiarrhythmic drugs: Flecainide and propafenone

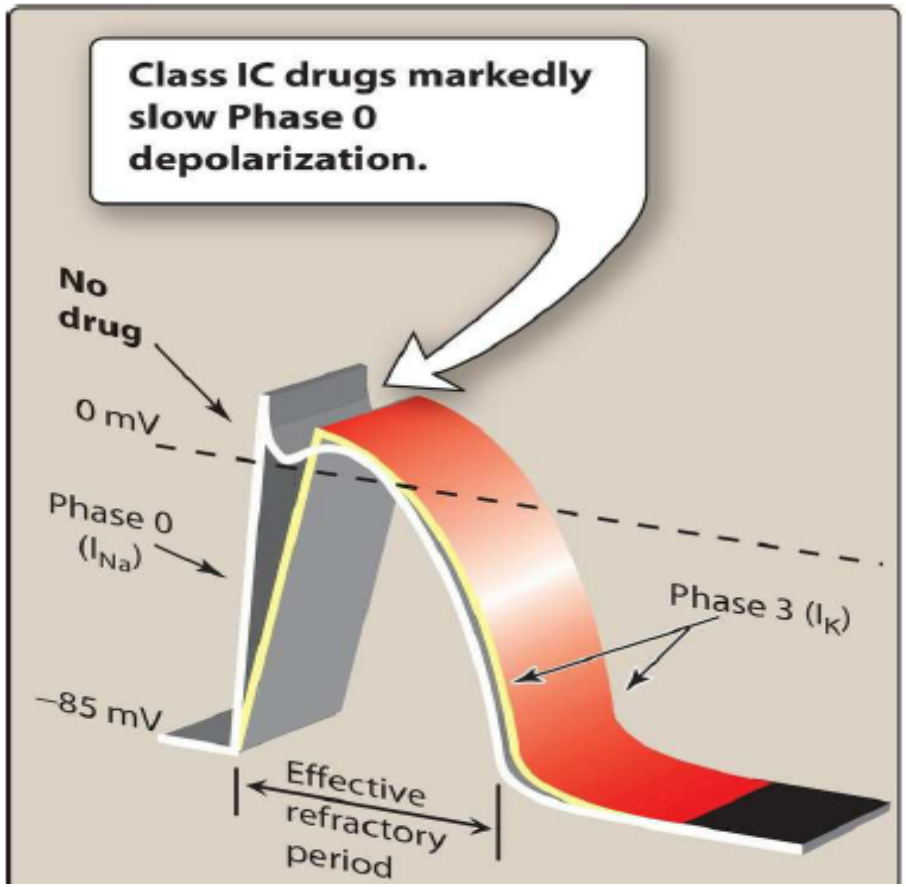
These drugs slowly dissociate from resting Na+ channels and show prominent effects even at normal heart rates.

Due to **their negative inotropic and proarrhythmic effects**!!!!!!

The use of these agents is avoided in patients with structural heart disease (left ventricular hypertrophy, heart failure, atherosclerotic heart disease).

Mechanism of action::

- They suppress phase 0 upstroke in Purkinje and myocardial fibers
- *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.
- propafenone possesses weak β-blocking properties.


Class IC drugs markedly slow Phase 0 depolarization.
No drug
0 mV
Phase 0 (I_{Na})
Phase 3 (I_K)
−85 mV
Effective refractory period

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: rhythm control of atrial fibrillation or flutter and paroxysmal supraventricular tachycardia prophylaxis in patients with AV reentrant tachycardias

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.

Class IA	**Moderate Na channel blocker** **Prolong action potential and refractory period** **Slows conduction velocity**
Class IB	Weak Na channel blocker shorten phase 3 repolarization and decrease the duration of the action potential
Class IC	Powerful and strong fast Na channel blockers Depress phase 0 depolarization Has limited effect on repolarization and refractory period more potent antiarrhythmics.

Anti-arryhthmic part 2

YASMINE Z AL SHORAFA

Class II Antiarrhythmic Drugs

β-blockers.

They are also used for atrial flutter and fibrillation
AV nodal reentrant tachycardia.
Prevent life-threatening ventricular arrhythmias following a myocardial infarction.

Class II Antiarrhythmic Drugs

Mechanism of action :

1- Diminish phase 4 depolarization

2-Depress automaticity,

3-Prolong AV conduction

4-Decrease heart rate and contractility

Common adverse effects:

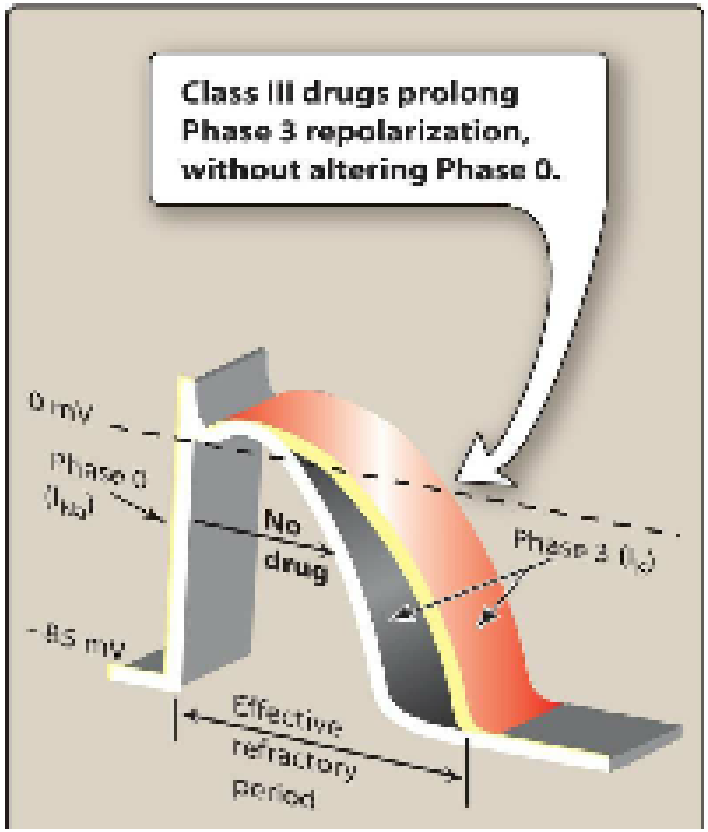
include bradycardia, hypotension, and fatigue

Class III Antiarrhythmic Drugs

- Class III agents block K+ channels and, thus, diminish the outward 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
- They prolong the effective refractory period, increasing refractoriness.
- All class III drugs have the potential to induce arrhythmias.

CLASS III (K^+ channel blockers)

Amiodarone CORDARONE, PACERONE
Dofetilide TIKOSYN
Dronedarone MULTAQ
Ibutilide CORVERT
Sotalol BETAPACE, SORINE



Amiodarone

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

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.

Despite its adverse effect profile, *amiodarone* is thought to be the least proarrhythmic of the class I and III antiarrhythmic drugs.

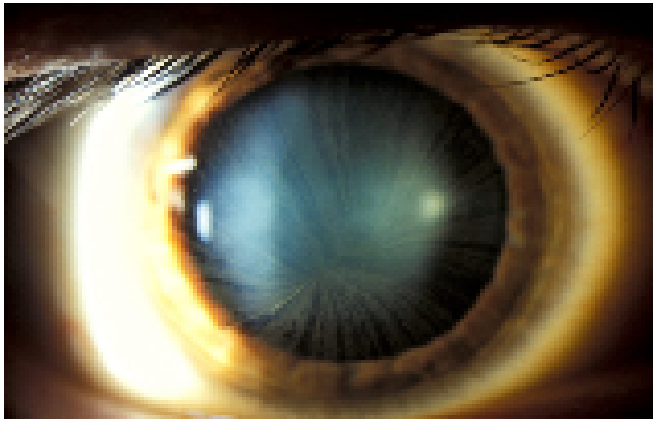
The drug is unusual in having a prolonged half-life of several weeks (25-100 days), and it distributes extensively in tissues.

Full clinical effects may not be achieved until months after initiation of treatment, unless loading doses are employed.

Adverse effects::

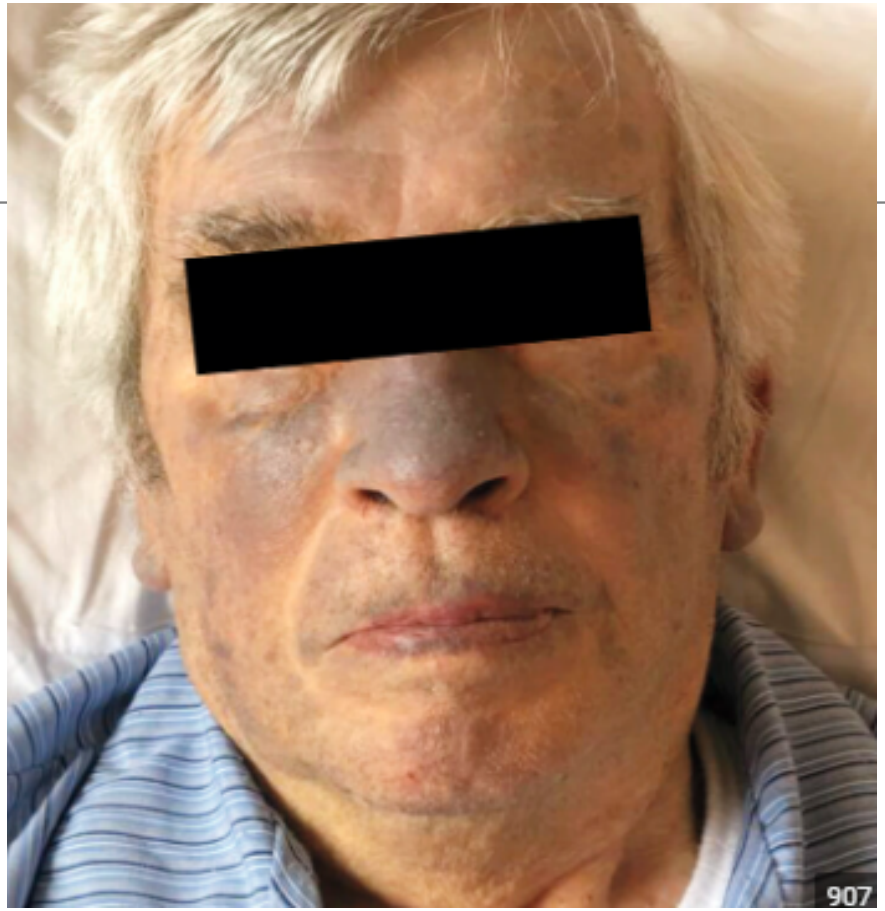
pulmonary fibrosis, neuropathy, hepatotoxicity, corneal deposits,

optic neuritis, blue-gray skin discoloration, and hypo- or hyperthyroidism



Numerous DDIs ::: since it is metabolized by CYP3A4 and

serves as an inhibitor of CYP1A2, CYP2C9, CYP2D6, and P glycoprotein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Dronedarone

- It has a shorter half-life than *amiodarone*.
- It does not have the iodine moieties that are responsible for thyroid dysfunction associated with *amiodarone*.
- *Dronedarone* has a better adverse effect profile than does *amiodarone* but may still cause liver failure.
- It is used to maintain sinus rhythm in atrial fibrillation or flutter, but it is less effective than *amiodarone*.

- **The drug is contraindicated in those with symptomatic heart failure or permanent atrial fibrillation due to an increased risk of death**

Sotalol

- Nonselective β-blocker activity
- *Sotalol* blocks a rapid outward K+ current. This blockade prolongs both repolarization and duration of the action potential, thus lengthening the effective refractory period

Therapeutic use : *Sotalol* is used for maintenance of sinus rhythm in patients with atrial fibrillation, atrial flutter, or refractory paroxysmal supraventricular tachycardia and in the treatment of ventricular arrhythmias

- It has a low rate of adverse effects when compared to other antiarrhythmic agents
- To reduce the risk of proarrhythmic effects, *sotalol* should be initiated in the hospital to monitor QT interval.

Dofetilide

It can be used as a first-line antiarrhythmic agent in patients with persistent atrial fibrillation and heart failure or in those with coronary artery disease.

Because of the risk of proarrhythmia, *dofetilide* initiation is limited to the inpatient setting.

The half-life of this oral drug is 10 hours.

Ibutilide

Ibutilide is a K+ channel blocker that also activates the slow inward Na+ current (mixed class III and IA actions).

Ibutilide is the drug of choice for chemical conversion of atrial flutter.

It is not used orally. Initiation is also limited to the inpatient setting due to the risk of arrhythmia.

Class IV Antiarrhythmic Drugs

Nondihydropyridine Ca2+ channel blockers ***verapamil*** and ***diltiazem***

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

They slow conduction in tissues that are dependent on Ca2+ currents, such as the AV and SA nodes

These agents are more effective against atrial than against ventricular arrhythmias, in treating reentrant supraventricular tachycardia

Common adverse effects include bradycardia, hypotension, and peripheral edema

Other Antiarrhythmic Drugs

Digoxin

Prolonging the effective refractory period and diminishing conduction velocity in the AV node, while shortening the refractory period in atrial and ventricular myocardial cells

Digoxin is used to control ventricular response rate in atrial fibrillation and flutter

At toxic concentrations, *digoxin* causes ectopic ventricular beats that may result in VT and fibrillation.

Note: Serum trough concentrations of 1.0 to 2.0 ng/mL are desirable for atrial fibrillation or flutter

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.

Magnesium sulfate

Magnesium is necessary for the transport of Na+, Ca2+, and K+ 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.

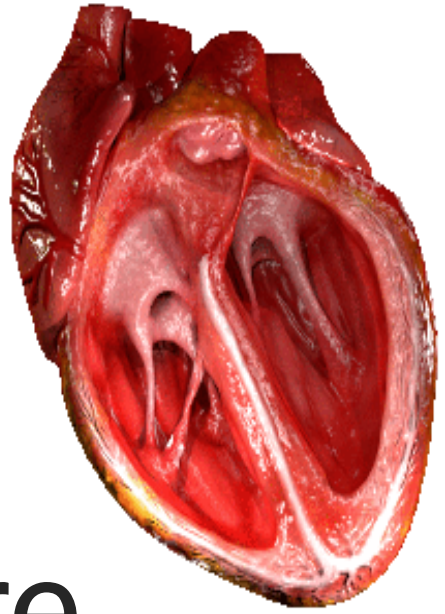
Ranolazine

Ranolazine is an antianginal drug with antiarrhythmic properties similar to *amiodarone*

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.

dizziness and constipation as the most common adverse effects



Drugs for Heart Failure

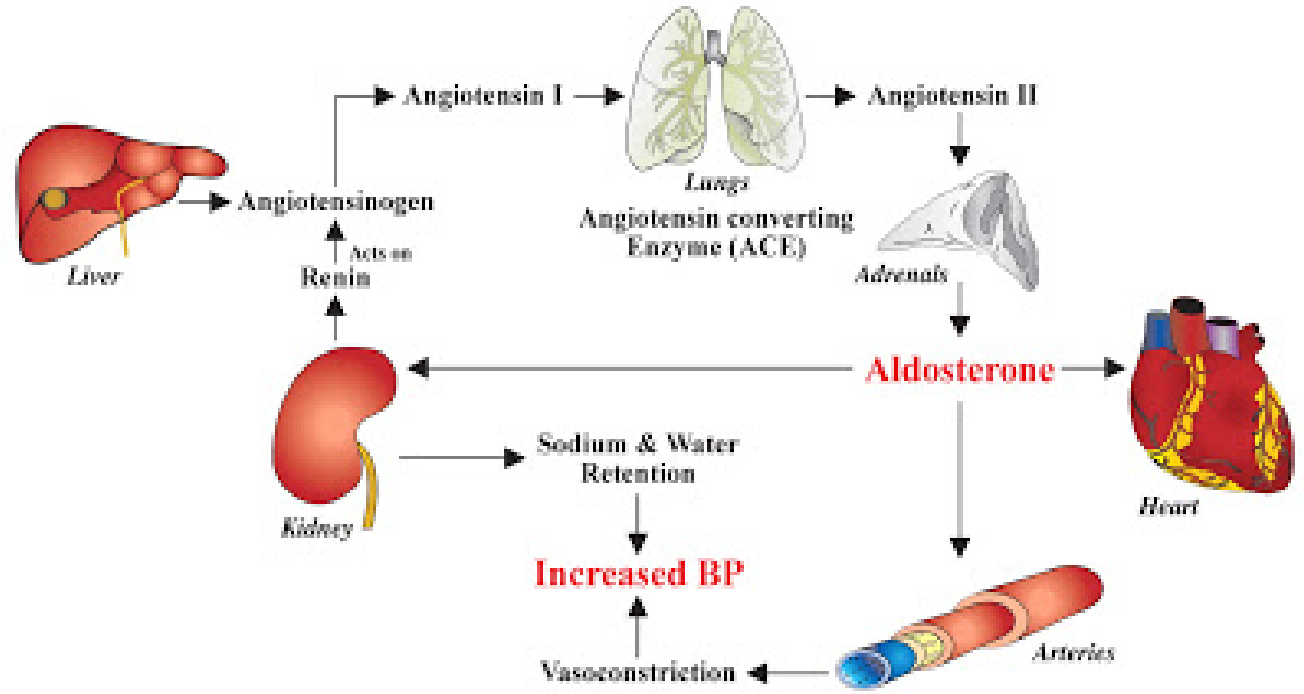
YASMINE AL SHORAFA

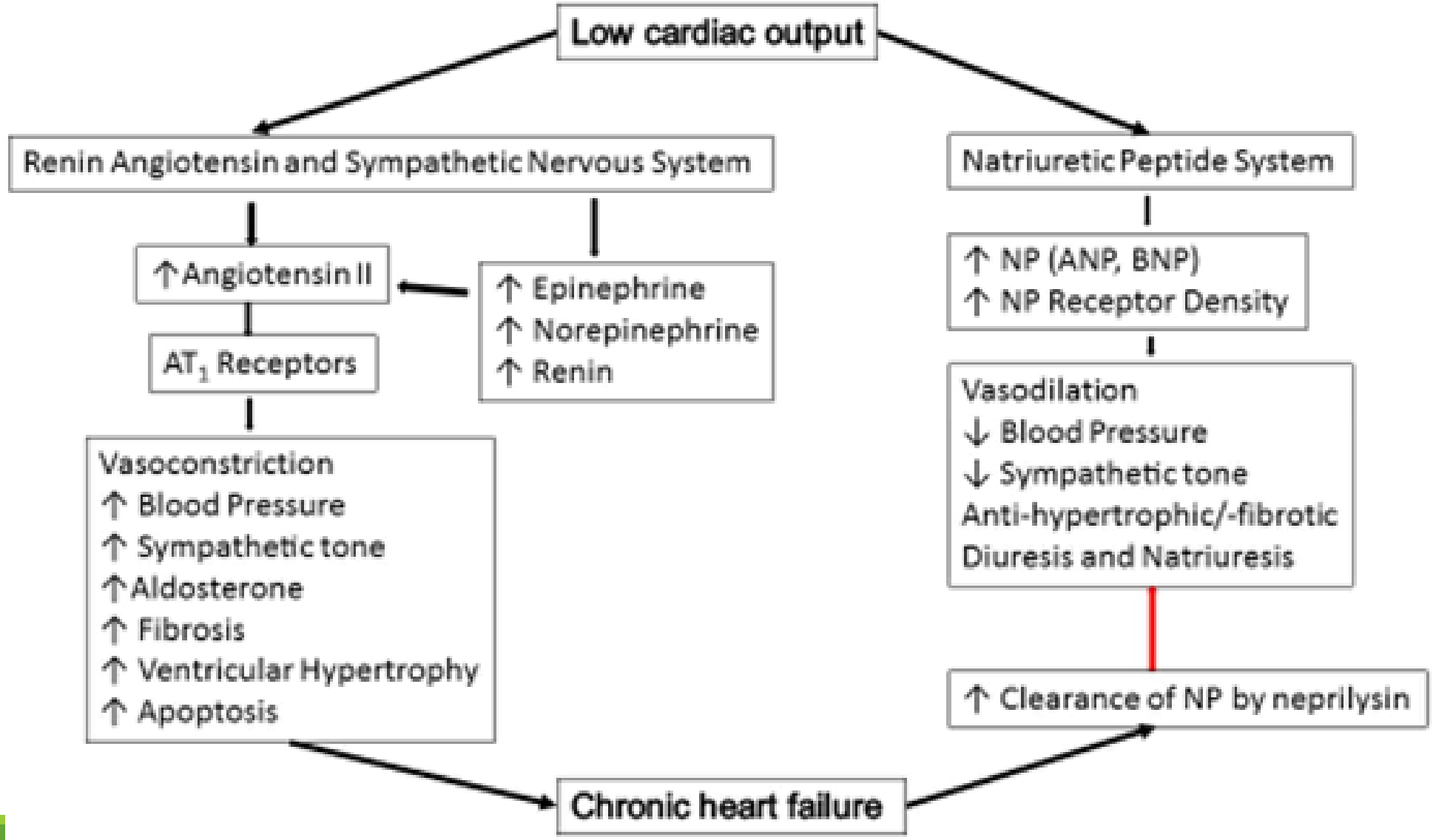
Heart failure (HF)

- It 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.
- HF is due to an impaired ability of the heart to adequately fill with and/or eject blood.
- 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 disea

Role of physiologic compensatory mechanisms in the progression of HF

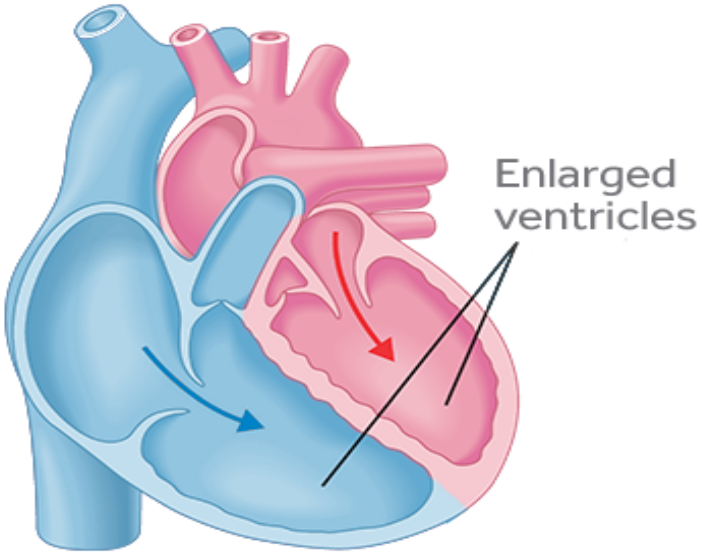
Chronic activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS) is associated with remodeling of cardiac tissue, loss of myocytes, hypertrophy, and fibrosis. This prompts additional neurohormonal activation, creating a vicious cycle that, if




Low cardiac output
Renin Angiotensin and Sympathetic Nervous System
Natriuretic Peptide System
↑ Angiotensin II
↑ Epinephrine
↑ Norepinephrine
↑ Renin
AT_1 Receptors
↑ NP (ANP, BNP)
↑ NP Receptor Density
Vasoconstriction
↑ Blood Pressure
↑ Sympathetic tone
↑ Aldosterone
↑ Fibrosis
↑ Ventricular Hypertrophy
↑ Apoptosis
Vasodilation
↓ Blood Pressure
↓ Sympathetic tone
Anti-hypertrophic/-fibrotic
Diuresis and Natriuresis
↑ Clearance of NP by neprilysin
Chronic heart failure

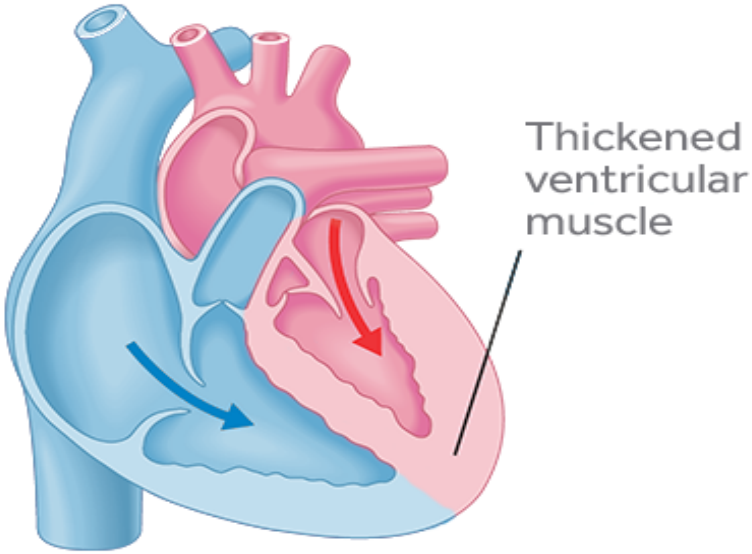
Types of HF

Heart failure(HF) with reduced ejection fraction (Systolic HF)



This results from reduced contraction of the left ventricle such that not enough blood is pumped into the circulation.

Heart failure with preserved ejection fraction (Diastolic HF)



The left ventricle becomes stiff and does not relax normally. As a result, it cannot fill properly, and pressure begins to increase in the left heart chambers and in the lungs.

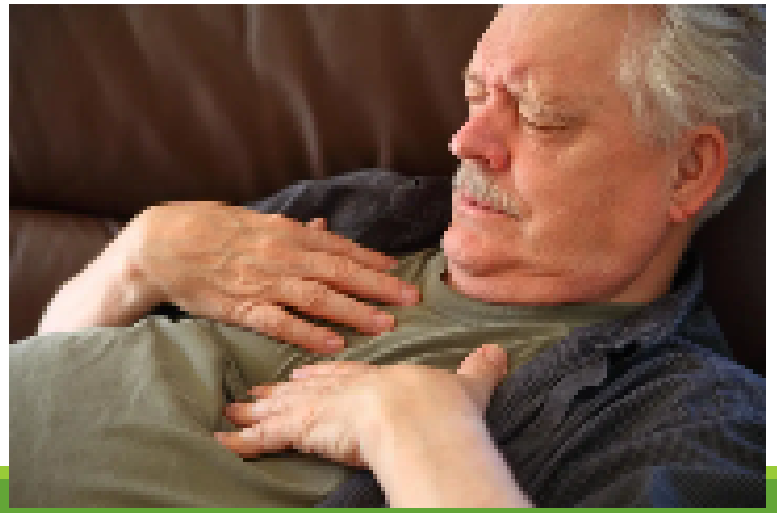
Types of HF

If the compensatory mechanisms adequately restore cardiac output, HF is said to be compensated.

If the compensatory mechanisms fail to maintain cardiac output, HF is decompensated and the patient develops worsening HF signs and symptoms.

Typical HF signs and symptoms include:

Dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, fatigue, and peripheral edema.



Goals of pharmacologic intervention in HF

,,.

- alleviate symptoms
- slow disease progression
- Improve survival

Therapeutic strategies in HF

1-Fluid limitations (less than 1.5 to 2 L daily)

2-Low dietary intake of sodium (less than 2000 mg/

3-Treatment of comorbid conditions

4- judicious use of diuretics.

5- inhibitors of the RAAS,

6- inhibitors of the sympathetic nervous system

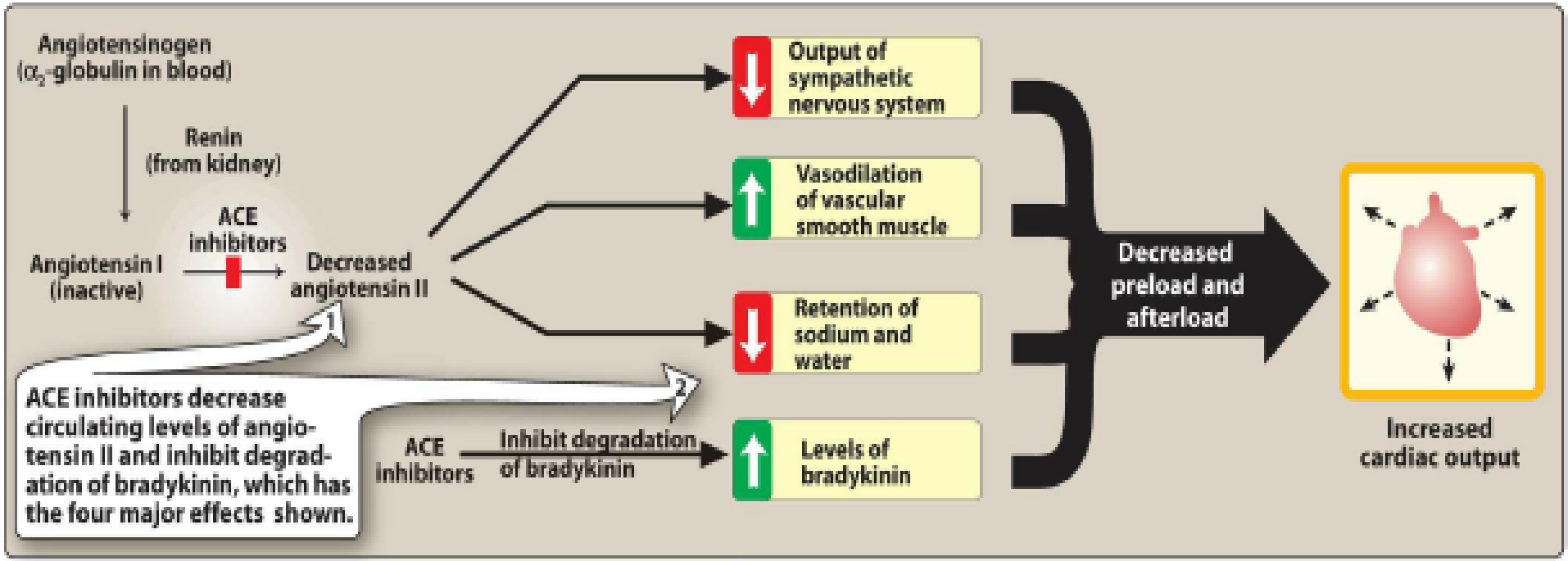
7-drugs that enhance activity of natriuretic peptides

8- Inotropic agents are reserved for acute signs and symptoms of HF and are used mostly in the inpatient setting.

9-Avoid 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

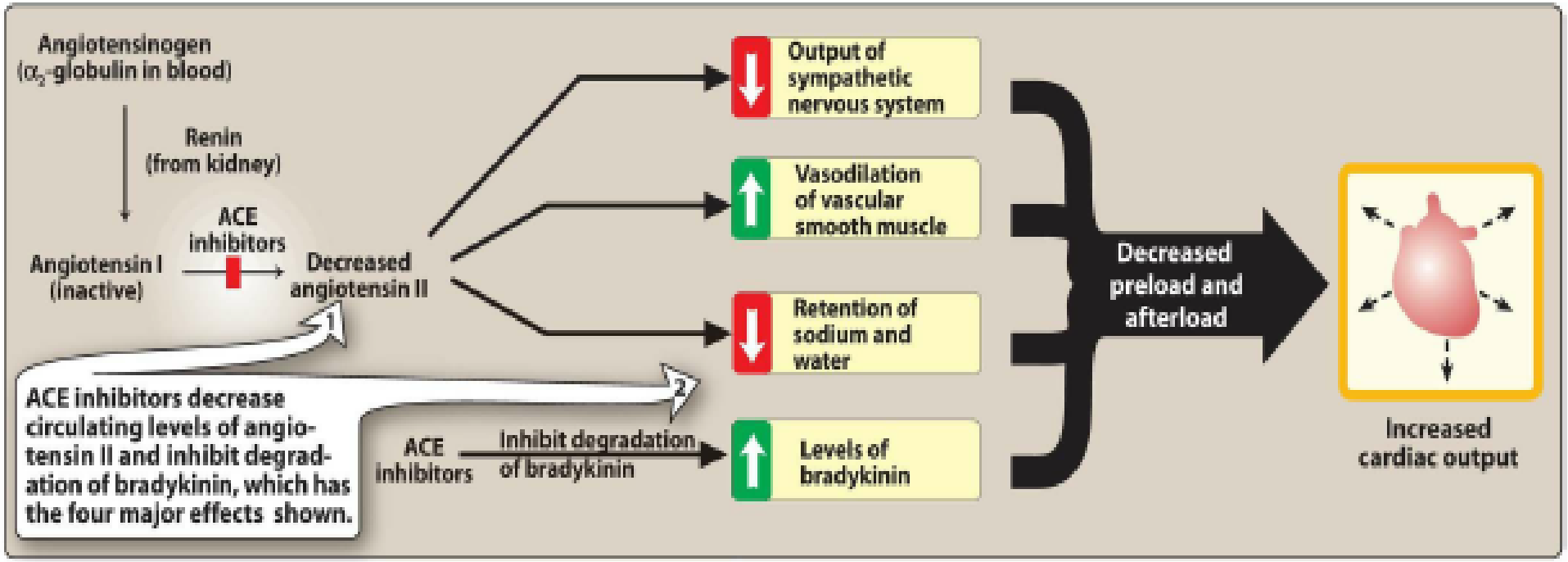
Angiotensin-converting enzyme inhibitors:



Inhibitors of the Renin–Angiotensin–Aldosterone System

ANGIOTENSIN RECEPTOR BLOCKERS
Candesartan ATACAND
Losartan COZAAR
Telmisartan MICARDIS
Valsartan DIOVAN

ACE INHIBITORS
Captopril GENERIC ONLY
Enalapril VASOTEC
Fosinopril GENERIC ONLY
Lisinopril PRINIVIL, ZESTRIL
Quinapril ACCUPRIL
Ramipril ALTACE


Angiotensinogen
(α_2-globulin in blood)
Renin
(from kidney)
ACE
inhibitors
Angiotensin I
(inactive)
Decreased
angiotensin II
1
2
ACE inhibitors decrease circulating levels of angiotensin II and inhibit degradation of bradykinin, which has the four major effects shown.
ACE
inhibitors
Inhibit degradation
of bradykinin
Output of sympathetic nervous system
Vasodilation of vascular smooth muscle
Retention of sodium and water
Levels of bradykinin
Decreased preload and afterload
Increased cardiac output

Actions of ACEIs

- 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.

Therapeutic use

- ACE inhibitors may be considered for patients with asymptomatic and symptomatic HFrEF.
- 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.

ACEIs

Pharmacokinetics

Food may decrease the absorption of *captopril* , so it should be taken on an empty stomach.

Except for *captopril* and injectable *enalaprilat*, ACE inhibitors are prodrugs that require activation by hydrolysis via hepatic enzymes

Adverse effects:

- postural hypotension, if used concomitantly with a diuretic
- Renal insufficiency, . Serum creatinine levels should also be monitored, particularly in patients with underlying renal disease
- Hyperkalemia, the risk of hyperkalemia, potassium levels must be monitored, particularly with concurrent use of potassium supplements, potassium-sparing diuretics, or aldosterone antagonists
- Persistent dry cough, and angioedema

ACE inhibitors are teratogenic and should not be used in pregnant women.

Dysgeusia:: more with captopril >>> reversible loss or alteration of taste sensation

Angiotensin receptor blockers

- Competitive antagonists of the angiotensin II type 1 receptor
- ARBs have the advantage of more complete blockade of the actions of angiotensin II.
- ARBs do not affect bradykinin levels
- ARBs have actions similar to those of ACE inhibitors, they are not therapeutically identical.
- ARBs are a substitute for patients who cannot tolerate ACE inhibitors.

Actions

- Their actions on preload and afterload are similar to ACEis
- Their use in HF is mainly as a substitute in patients who cannot tolerate ACE inhibitors due to cough or angioedema.
- Hypertension

Adverse effects

ARBs have an adverse effect and drug interaction profile similar to that of ACE inhibitors.

ARBs have a lower incidence of cough and angioedema.

Like ACE inhibitors, ARBs are contraindicated in pregnancy.

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.

Eplerenone is more selective for aldosterone receptors and causes less endocrine effects (gynecomastia) than *spironolactone*, which also binds to progesterone and androgen receptors.

β-Blockers

These agents improved systolic function and reverse cardiac remodeling .

How???!!!

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

β–ADRENORECEPTOR BLOCKERS	
Bisoprolol	GENERIC ONLY
Carvedilol	COREG, COREG CR
Metoprolol succinate	TOPROL XL
Metoprolol tartrate	LOPRESSOR

- β-Blockade is recommended for all patients with chronic, stable HFrEF
- *Carvedilol* is a nonselective β-adrenoreceptor antagonist that also blocks α-adrenoreceptors, whereas *bisoprolol* and *metoprolol succinate* are β1-selective antagonists.
- *Bisoprolol*, *carvedilol*, and *metoprolol succinate* reduce morbidity and mortality associated with 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*

Diuretics

Loop diuretics are the most commonly used diuretics in HF.

Diuretics reduce signs and symptoms of volume overload, such as dyspnea on exertion, orthopnea, and peripheral edema.

Diuretics decrease plasma volume and, subsequently, decrease venous return to the heart (preload) . This decreases cardiac workload and oxygen demand. Diuretics may also decrease afterload by reducing plasma volume, thereby decreasing blood pressure.

Diuretics have not been shown to improve survival in HF, they should only be used to treat signs and symptoms of volume excess

Loop diuretics

Bumetanide , furosemide, torsemide , and ethacrynic acid

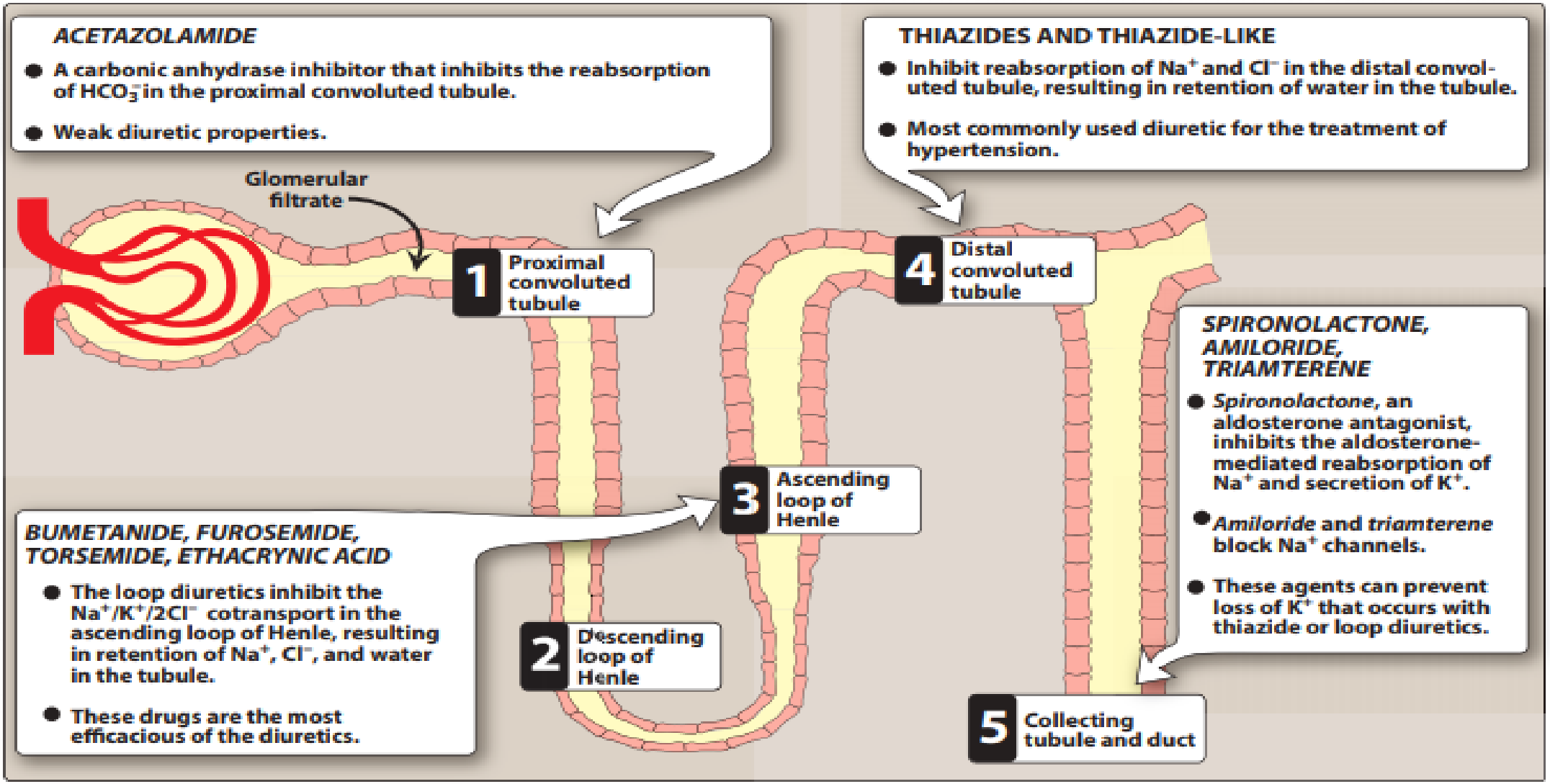
All of them act on ascending limb of the loop of Henle

These agents have the greatest diuretic effect of all the diuretic drugs (25% to 30% of filtered NaCl)

The most commonly used is **furosemide**

The most potent **Bumetanide & torsemide**

Ethacrynic acid is not used frequently due to its side effects >>> most likely to cause deafness


ACETAZOLAMIDE
A carbonic anhydrase inhibitor that inhibits the reabsorption of HCO_3^- in the proximal convoluted tubule.
Weak diuretic properties.
THIAZIDES AND THIAZIDE-LIKE
Inhibit reabsorption of Na^+ and Cl^- in the distal convoluted tubule, resulting in retention of water in the tubule.
Most commonly used diuretic for the treatment of hypertension.
Glomerular filtrate
1 Proximal convoluted tubule
2 Descending loop of Henle
3 Ascending loop of Henle
4 Distal convoluted tubule
5 Collecting tubule and duct
BUMETANIDE, FUROSEMIDE, TORSEMIDE, ETHACRYNIC ACID
The loop diuretics inhibit the $Na^+/K^+/2Cl^-$ cotransport in the ascending loop of Henle, resulting in retention of Na^+, Cl^-, and water in the tubule.
These drugs are the most efficacious of the diuretics.
SPIRONOLACTONE, AMILORIDE, TRIAMTERENE
Spironolactone, an aldosterone antagonist, inhibits the aldosterone-mediated reabsorption of Na^+ and secretion of K^+.
Amiloride and triamterene block Na^+ channels.
These agents can prevent loss of K^+ that occurs with thiazide or loop diuretics.

Adverse effects:

Otoxicity: Reversible or permanent hearing loss may occur with loop diuretics, particularly when used in conjunction with other ototoxic drugs (for example, aminoglycoside antibiotics)

Hyperuricemia: Furosemide and ethacrynic acid compete with uric acid for the renal secretory systems

causing or exacerbating gouty attacks

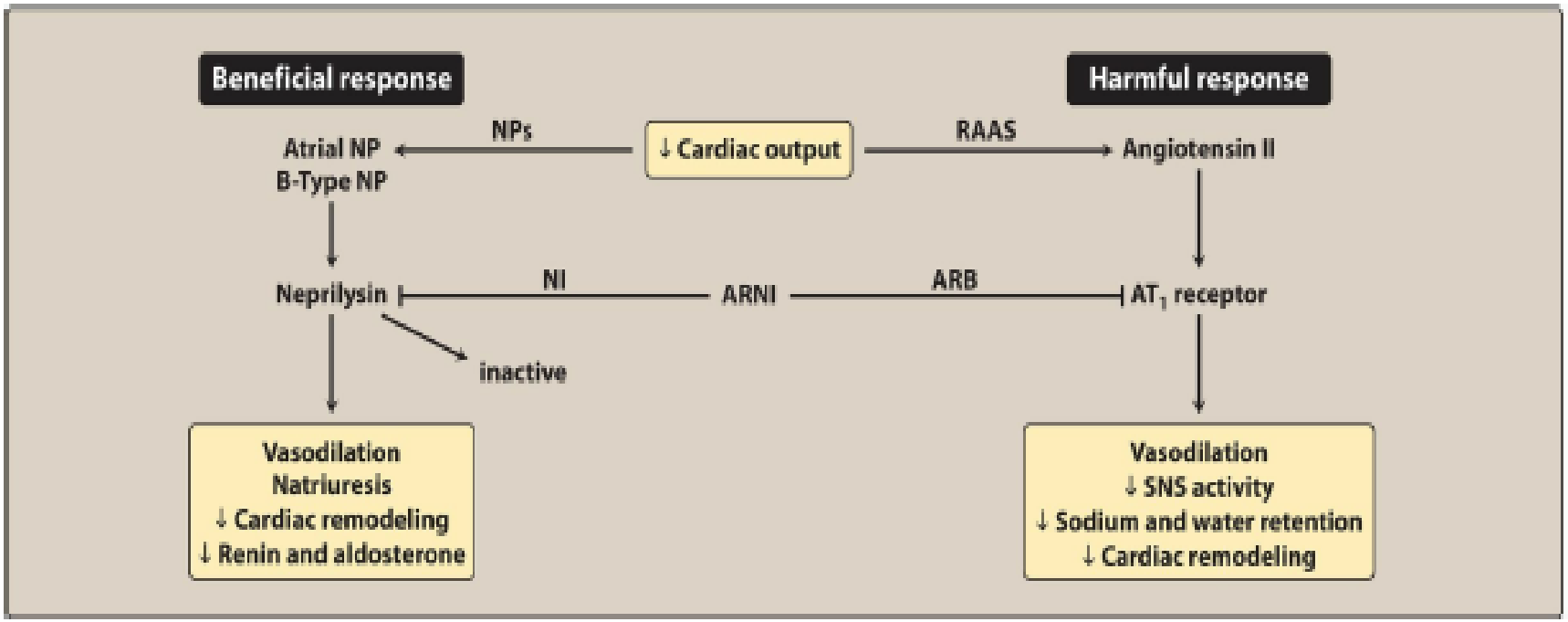
Acute hypovolemia

Potassium depletion: The heavy load of Na+ presented to the collecting tubule results in increased exchange of tubular Na+ for K+, leading to the possibility of hypokalemia. The loss of K+ from cells in exchange for H+ leads to hypokalemic alkalosis.

Hypomagnesemia:

Chronic use of loop diuretics combined with low dietary intake of Mg2+ can lead to hypomagnesemia, particularly in the elderly

Angiotensin Receptor–Neprilysin Inhibitor



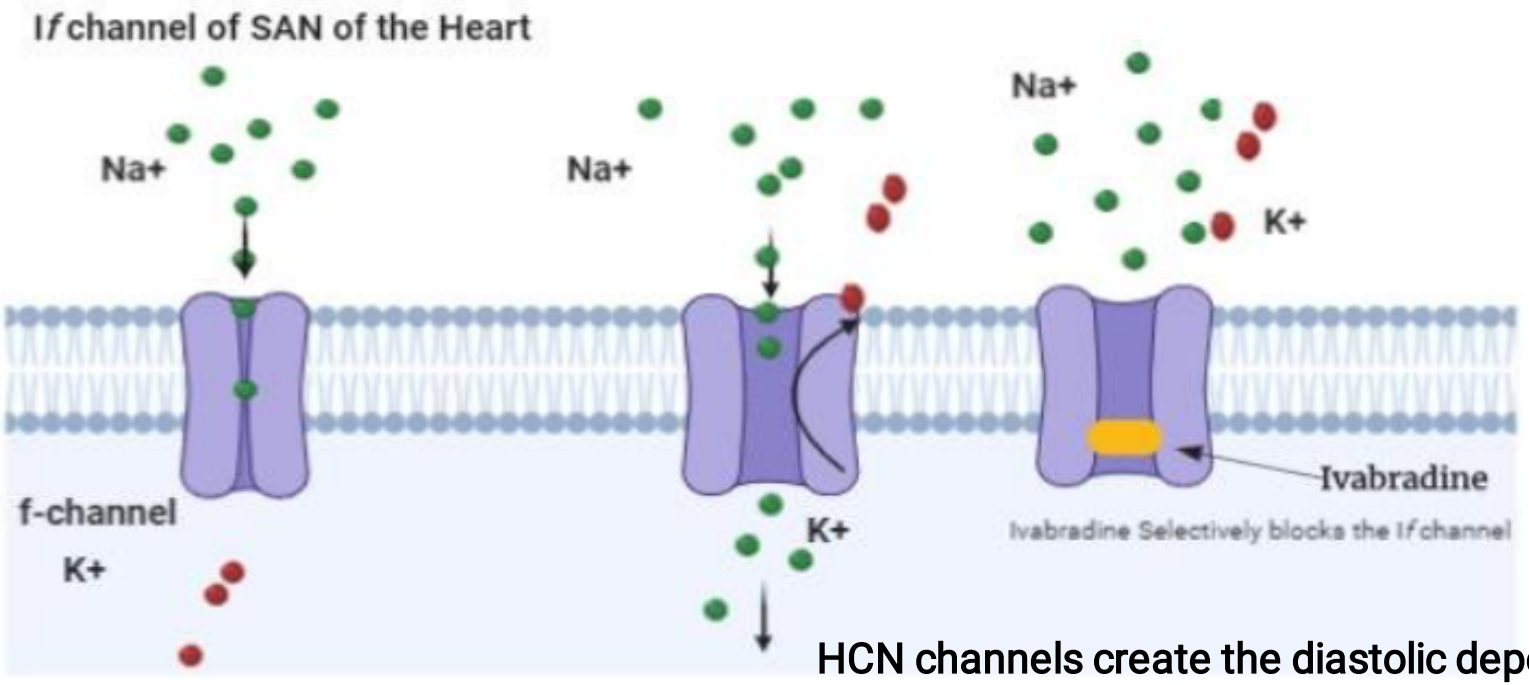
Sacubitril/valsartan

- *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
- *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.

Adverse effects

- similar to that of an ACE inhibitor or ARB.
- 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 angiodema 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 channels create the diastolic depolarization or "funny pacemaker current (I_f) of the sinoatrial node, so termed because it is uniquely activated by the membrane hyperpolarization that follows systolic depolarization

Ivabradine

Actions

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

In patients with HFrEF, a slower heart rate increases stroke volume and improves symptoms of HF.

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.

Specifically, patients should be on an optimal dose of β-blocker or have a contraindication to β-blockers.

Pharmacokinetics

Ivabradine should be administered with meals to increase absorption.

Adverse effects

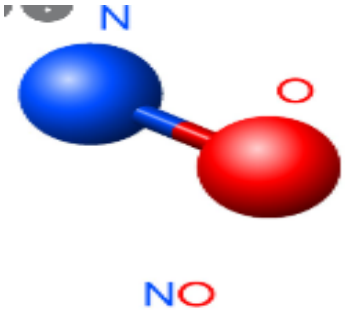
- Bradycardia may occur with *ivabradine*, which may improve with dose reduction.
- It has been shown to increase the risk of atrial fibrillation.
- *Ivabradine* inhibits similar channels in the eye, and luminous phenomena may occur early in therapy. This enhanced brightness may be ameliorated by dose reduction.
- *Ivabradine* should not be used in pregnancy or breast-feeding, with more advanced heart block, or with potent 3A4 inhibitors.

Drugs for heart failure part 2

YASMINE ZOHAIR AL SHORAFA

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, combination of *hydralazine* and *isosorbide dinitrate* may be used.
- A fixed-dose combination of these agents has been shown to improve symptoms and survival in black patients with HFrEF on standard HF treatment (β- blocker plus ACE inhibitor or ARB).
- 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**.

- Although these drugs act by different mechanisms, the inotropic action is the result of an increased cytoplasmic calcium concentration that enhances the contractility of cardiac muscle.

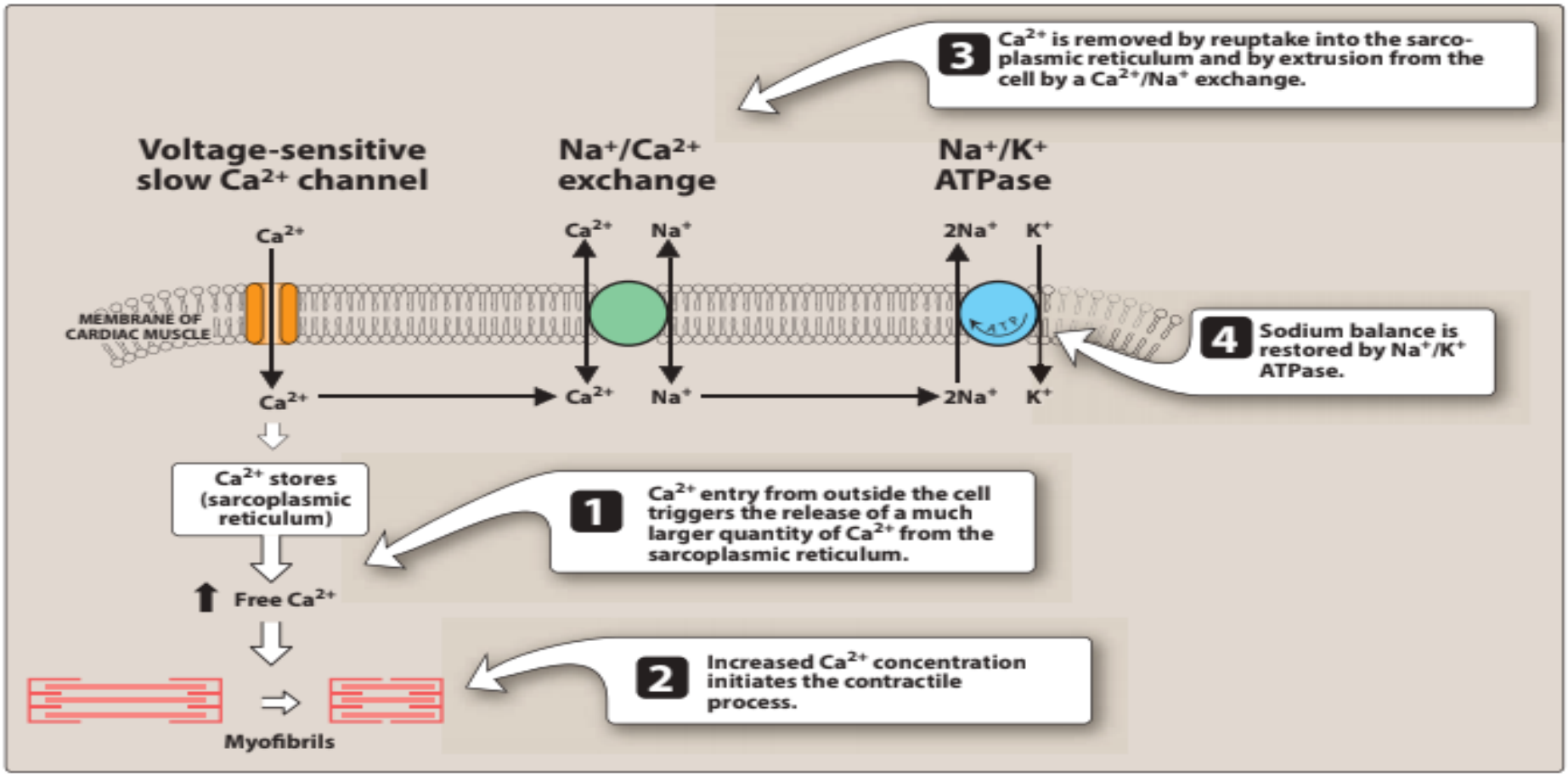
- All positive inotropes in HFrEF that increase intracellular calcium concentration have been associated with reduced survival, especially in patients with HFrEF.

- For this reason, these agents, with the exception of *digoxin*, are only used for a short period mainly in the inpatient setting.

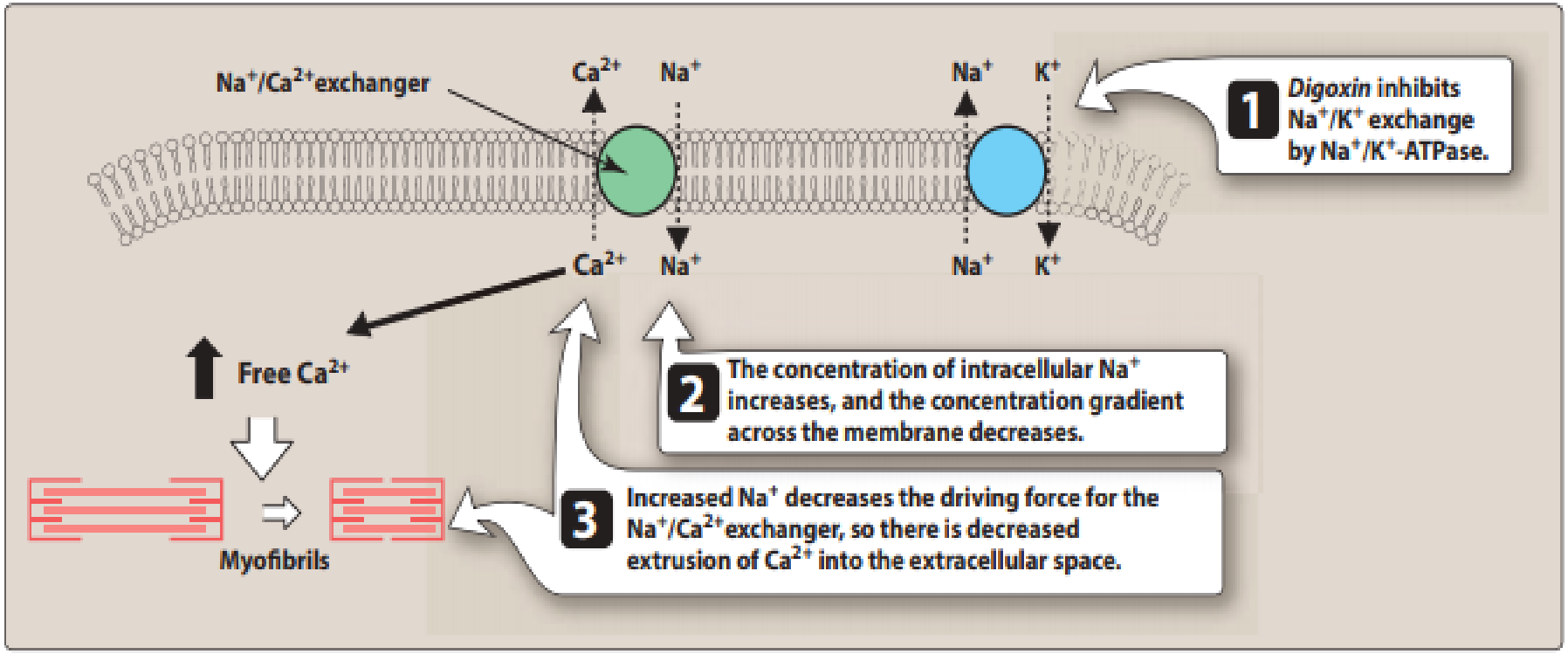
Digitalis glycosides

- The drugs come from the digitalis (foxglove) plant
- The digitalis glycosides have a low therapeutic index
- The most widely used agent is digoxin. Digitoxin is seldom used due to its considerable duration of action

Ion movements during the contraction of cardiac muscle.



Mechanism of action of digoxin



Increased contractility of the cardiac muscle:

Increases the force of cardiac contraction, thereby cardiac output

Increasing cardiac ouput, improves circulation .It has **vagomimetic** action so heart rate and myocardial oxygen demand decrease

Digoxin slows conduction velocity through the AV node, making it useful for atrial fibrillation

Neurohormonal inhibition:

low-dose digoxin inhibits sympathetic activation with minimal effects on contractility

❖ **Therapeutic uses**

Digoxin therapy is indicated in patients with severe HFrEF after initiation of ACE inhibitor, β-blocker, and diuretic therapy

Atrial fibrillation

❖ **Pharmacokinetics**

❖ Digoxin is available in oral and injectable formulations

❖ inotropic effect of digitalis takes hours to develop, even after i.v. administration.

❖ large volume of distribution, because it accumulates in muscle

❖ The dosage is based on lean body weight

❖ Digoxin has a long half-life of 30 to 40 hours

❖ requiring dose adjustment in renal dysfunction as it is excreted unchanged in urine by glomerular filtration

Adverse effects

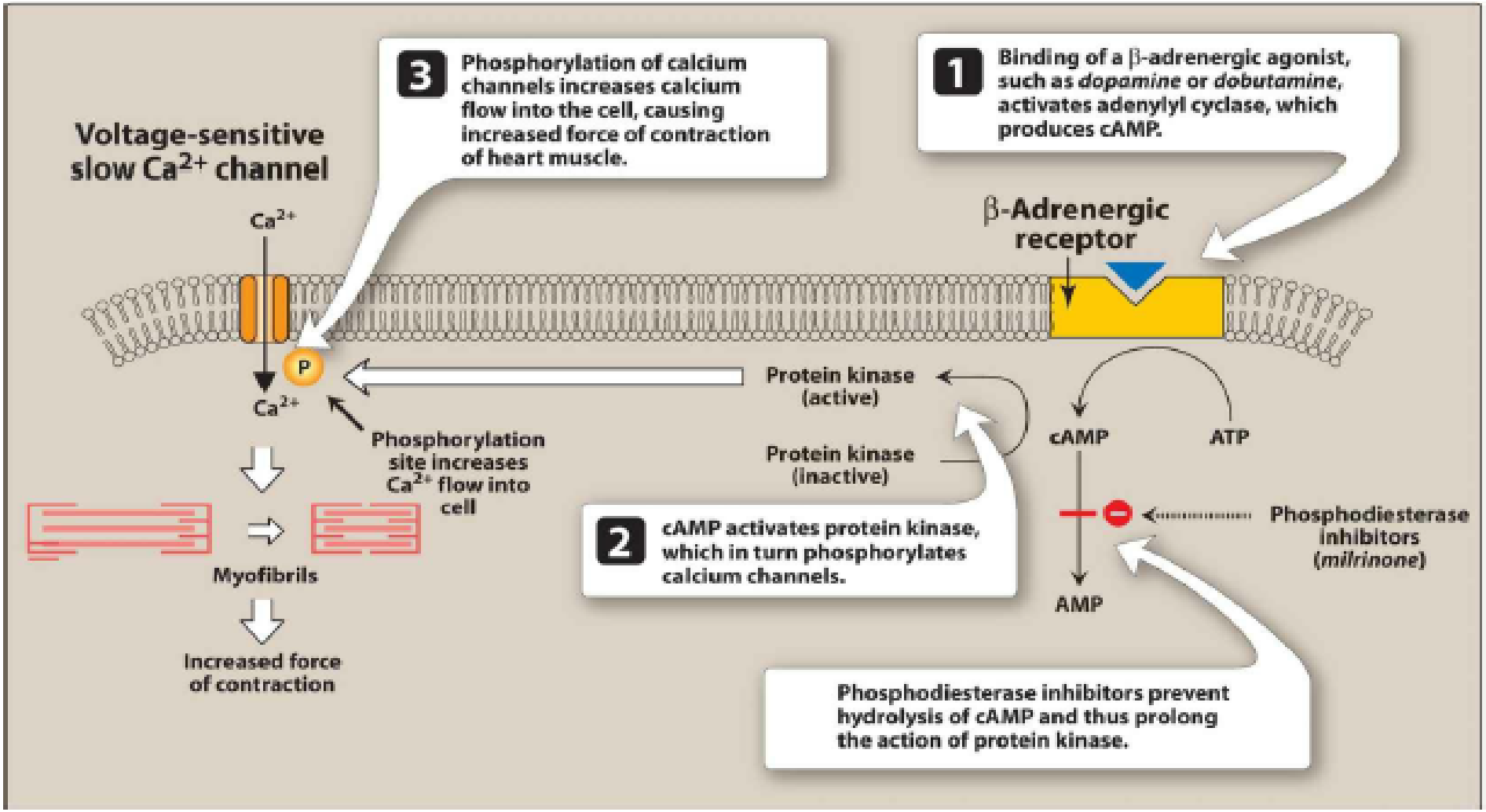
- very narrow therapeutic index, and digoxin toxicity is one of the most common adverse drug reactions leading to hospitalization
- Anorexia, nausea, and vomiting may be initial indicators of toxicity
- Patients may also experience blurred vision, yellowish vision (xanthopsia)
- cardiac arrhythmias due to hyperkalemia (increase extracellular potassium)
- Severe toxicity resulting in ventricular tachycardia may require administration of antiarrhythmic drugs and the use of antibodies to digoxin (digoxin immune Fab), which bind and inactivate the drug

β-Adrenergic agonists

Dobutamine and *Dopamine*, improve cardiac performance by causing positive inotropic effects and vasodilation.

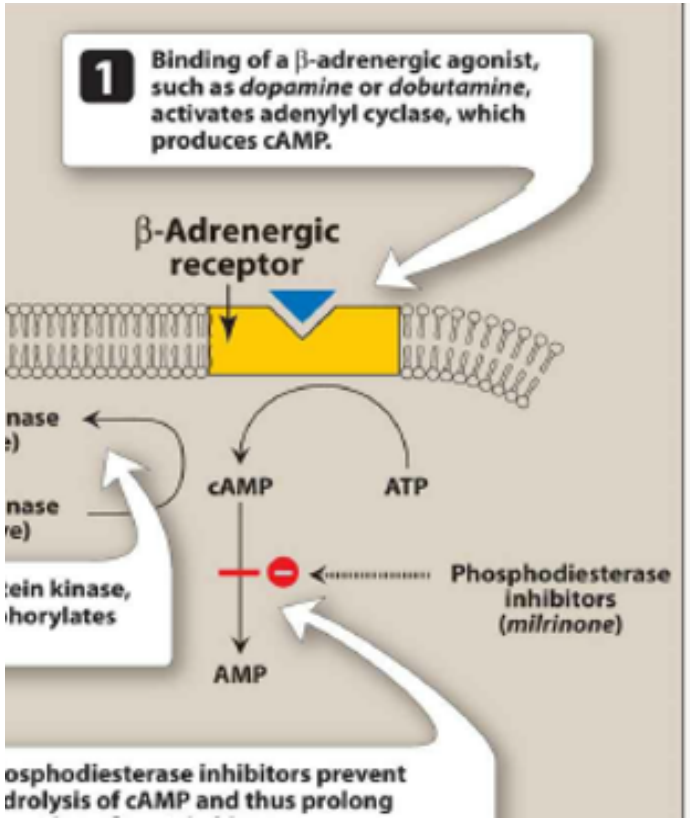
β-Adrenergic agonists ultimately lead to increased entry of calcium ions into myocardial cells and enhanced contraction .

Both drugs must be given by intravenous infusion and are primarily used in the short-term treatment of acute HF in the hospital setting


Voltage-sensitive slow Ca^{2+} channel
3 Phosphorylation of calcium channels increases calcium flow into the cell, causing increased force of contraction of heart muscle.
1 Binding of a β-adrenergic agonist, such as *dopamine* or *dobutamine*, activates adenylyl cyclase, which produces cAMP.
β-Adrenergic receptor
Ca^{2+}
P
Ca^{2+}
Phosphorylation site increases Ca^{2+} flow into cell
Protein kinase (active)
Protein kinase (inactive)
cAMP
ATP
Phosphodiesterase inhibitors (*milrinone*)
2 cAMP activates protein kinase, which in turn phosphorylates calcium channels.
AMP
Myofibrils
Increased force of contraction
Phosphodiesterase inhibitors prevent hydrolysis of cAMP and thus prolong the action of protein kinase.

Phosphodiesterase inhibitors

- Milrinone is a phosphodiesterase inhibitor that increases the intracellular concentration of cAMP .
- Like β-adrenergic agonists, this results in an increase of intracellular calcium and, therefore, cardiac contractility.
- Long-term, milrinone therapy may be associated with a substantial increased risk of mortality.
- However, short-term use of intravenous milrinone is not associated with increased mortality in patients without a history of coronary artery disease.



Recombinant B-type Natriuretic Peptide

- In acute decompensated congestive HF, drugs that reduce preload result in improvement in HF symptoms such as dyspnea.

- When IV diuretics are minimally effective, a recombinant B-type natriuretic peptide (BNP), or *nesiritide*, can be used as an alternative.

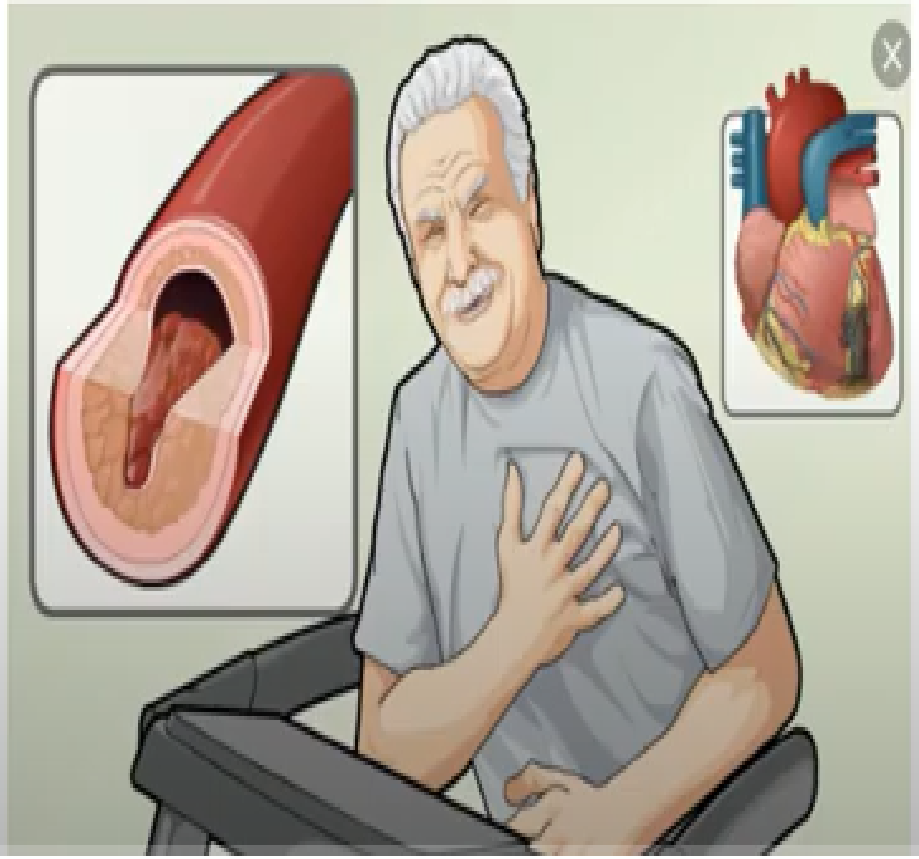
- Through binding to natriuretic peptide receptors, *nesiritide* stimulates natriuresis and diuresis and reduces preload and afterload.

Nesiritide is administered intravenously as a bolus (most often) and continuous infusion.

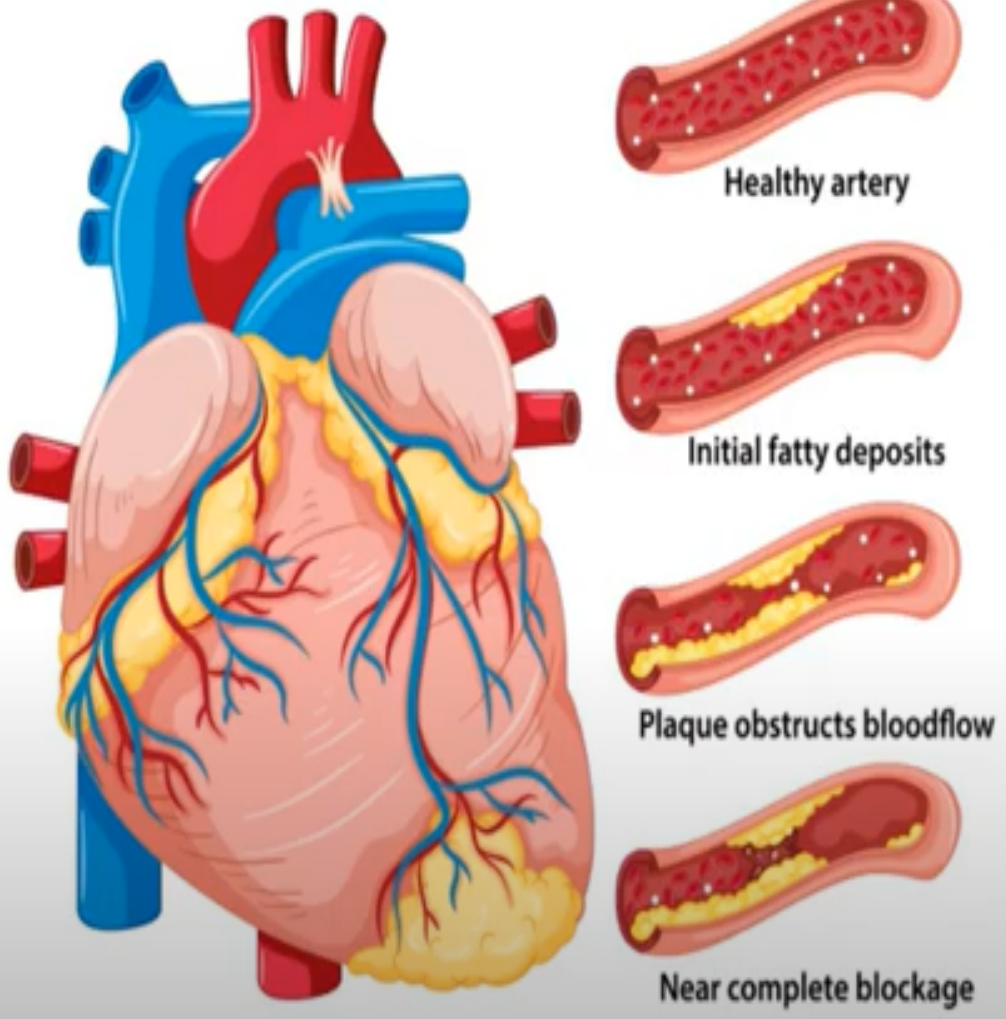
Like endogenous BNP, *nesiritide* has a short half-life of 20 minutes and is cleared by renal filtration, cleavage by endopeptidases and through internalization after binding to natriuretic peptide receptors.

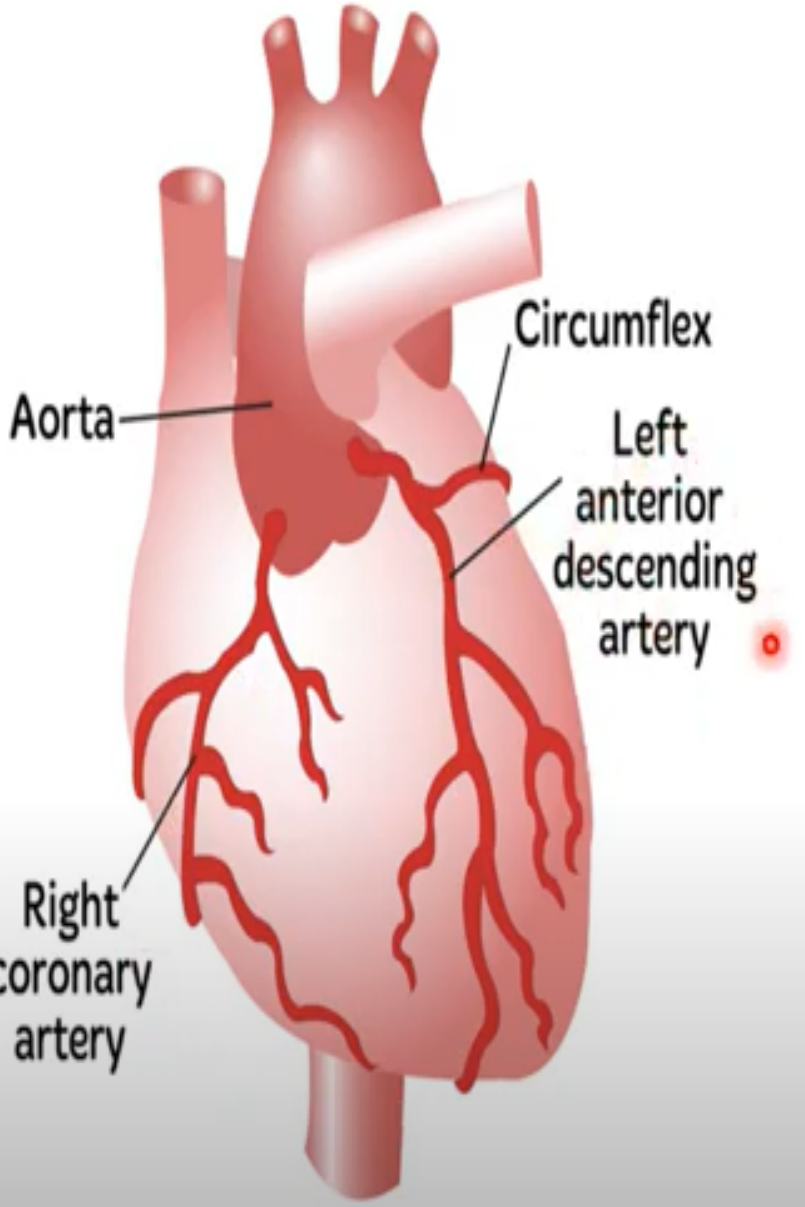
The most common adverse effects are hypotension and dizziness, and like diuretics, *nesiritide* can worsen renal function.

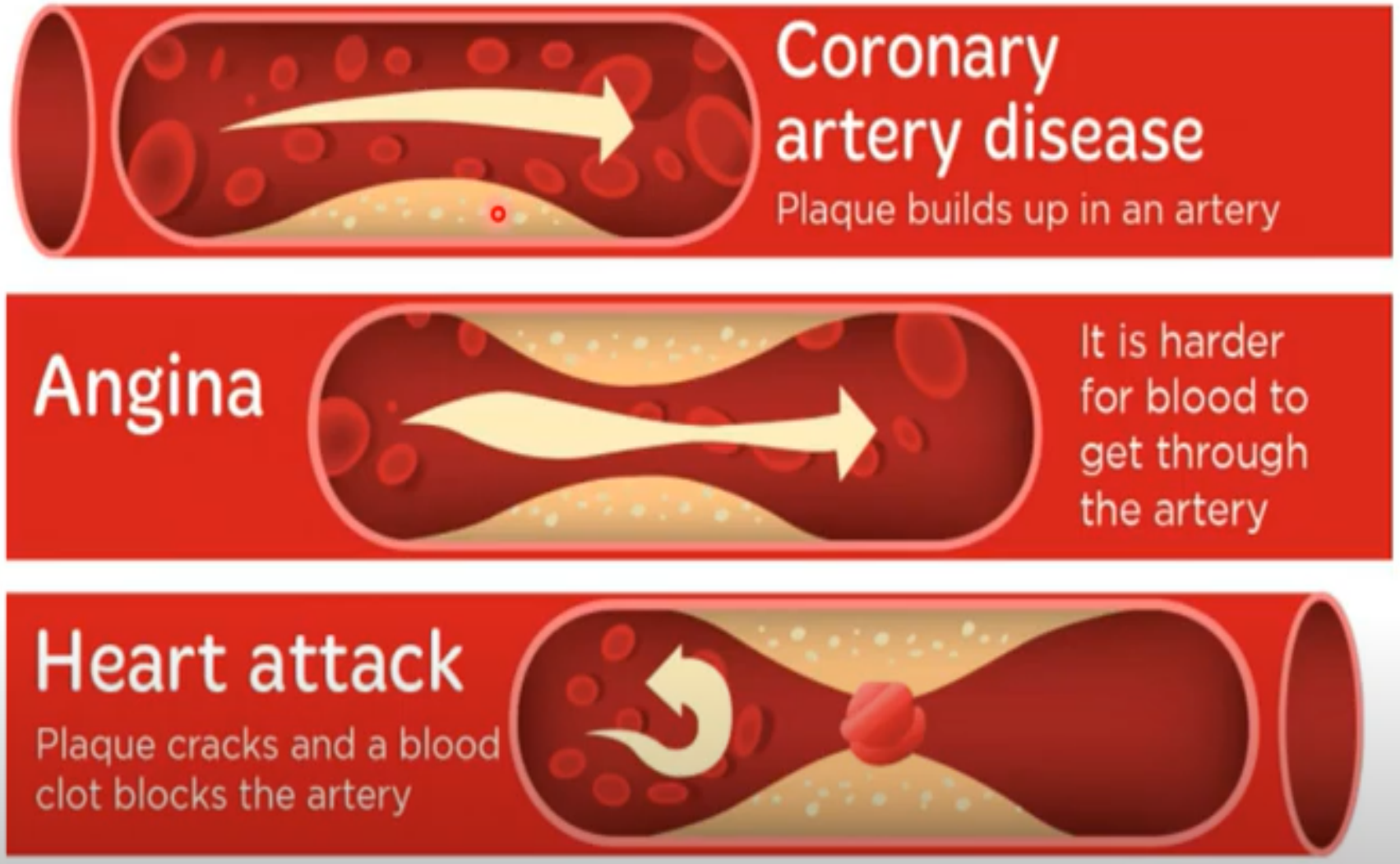
Antianginal Drugs



CORONARY ARTERY DISEASE






Coronary artery disease
Plaque builds up in an artery
Angina
It is harder for blood to get through the artery
Heart attack
Plaque cracks and a blood clot blocks the artery

Anti-anginal Drugs

β-BLOCKERS

Atenolol TENORMIN
Bisoprolol GENERIC ONLY
Metoprolol LOPRESSOR, TOPROL XL
Propranolol INDERAL, INNOPRAN XL

CALCIUM CHANNEL BLOCKERS (DIHYDROPYRIDINES)

Amlodipine NORVASC
Felodipine PLENDIL
Nifedipine ADALAT, PROCARDIA

CALCIUM CHANNEL BLOCKERS (NONDIHYDROPYRIDINE)

Diltiazem CARDIZEM, CARTIA, TIAZAC
Verapamil CALAN, VERELAN

NITRATES

Nitroglycerin MINITRAN, NITRO-DUR, NITROSTAT
Isosorbide dinitrate DILATRATE-SR, ISORDIL
Isosorbide mononitrate GENERIC ONLY

SODIUM CHANNEL BLOCKER

Ranolazine RANEXA

Nitrates

1. *Nitrates*
   (a) *Short acting:* Glyceryl trinitrate (GTN, Nitroglycerine)
   (b) *Long acting:* Isosorbide dinitrate (short acting by sublingual route), Isosorbide mononitrate

Nitrates

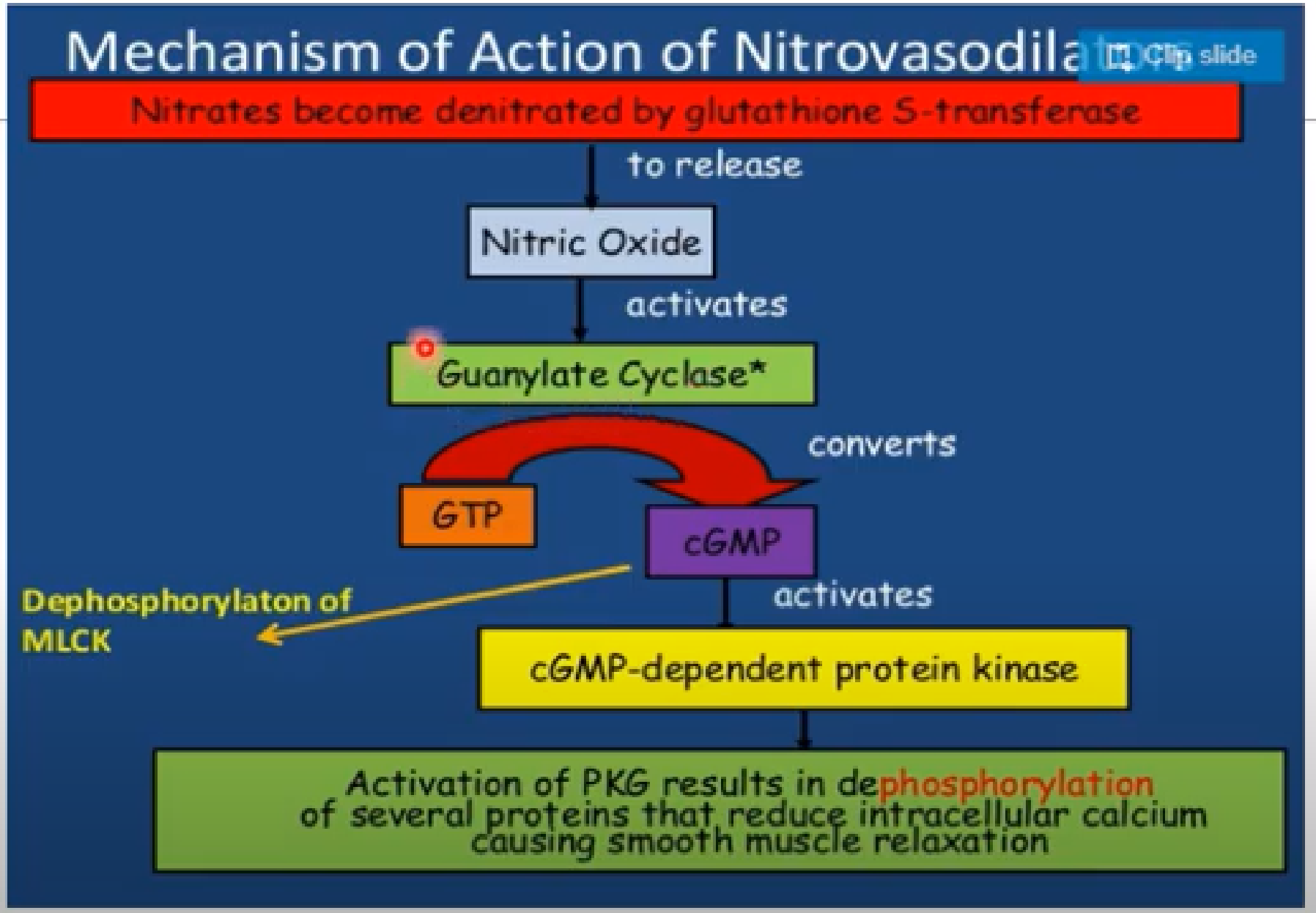
- All organic nitrates share the same action; differ only in time course.

- Preload reduction : It is through their action on **peripheral veins** that nitrates exert major beneficial effects in classical angina. Nitrates dilate veins more than arteries

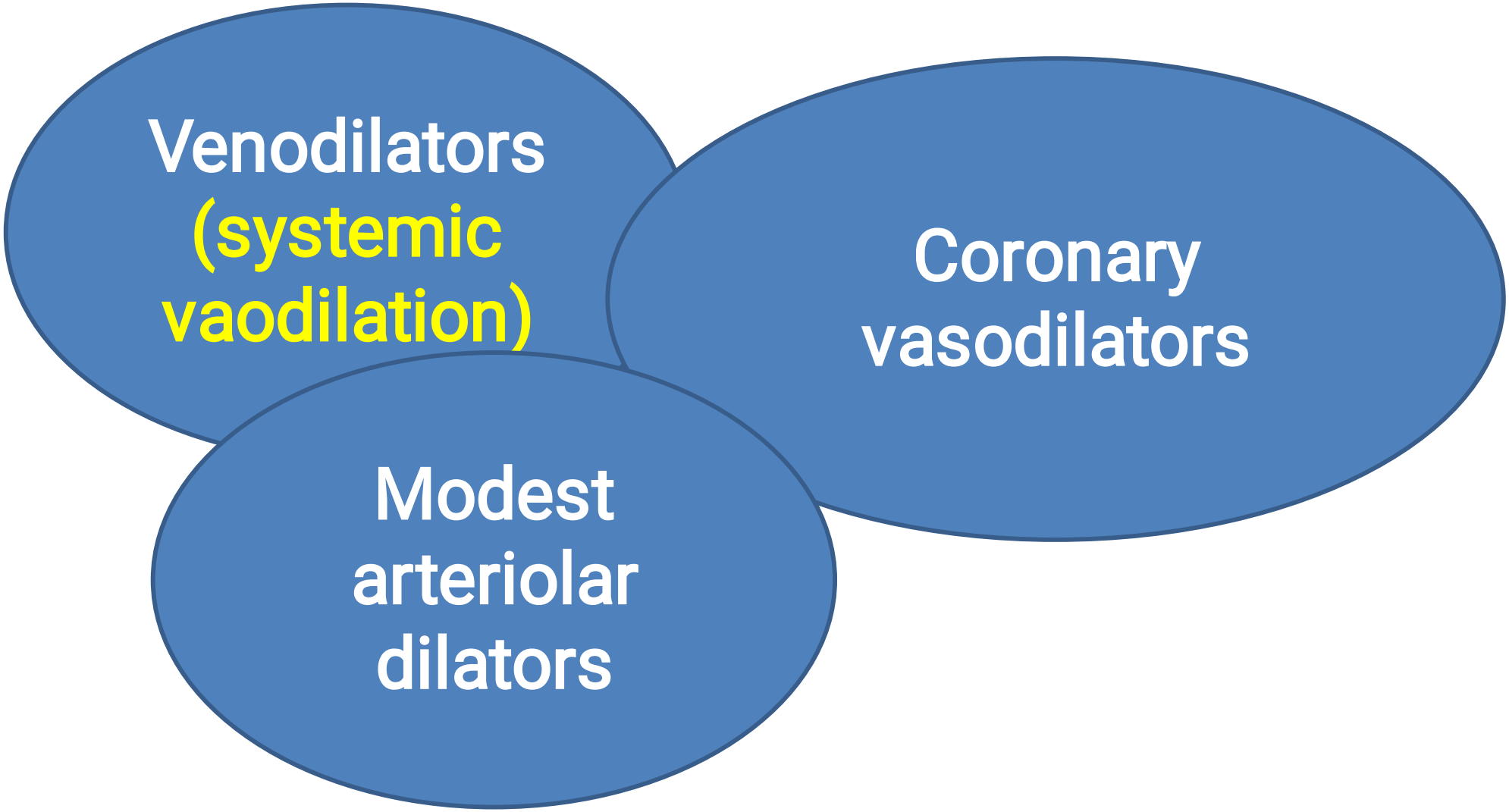
- Afterload reduction: Nitrates also produce some arteriolar dilatation → slightly decrease total peripheral resistance (t.p.r.) or afterload on heart; BP falls.

- With usual doses there is no reflux tachycardia

- With high doses, reflux tachcardia occurs and this would exacerbate angina


Mechanism of Action of Nitrovasodila
Nitrates become denitrated by glutathione S-transferase
to release
Nitric Oxide
activates
Guanylate Cyclase*
converts
GTP
cGMP
Dephosphorylaton of MLCK
activates
cGMP-dependent protein kinase
Activation of PKG results in dephosphorylation of several proteins that reduce intracellular calcium causing smooth muscle relaxation

Nitrates


Venodilators
(systemic
vaodilation)
Coronary
vasodilators
Modest
arteriolar
dilators

- Venodilation >>> lowers preload (left ventricular end diastolic pressure) >>> reduces wall stress >>> decrease myocardial oxygen demand

- Coronary vasodilator>>> relieve ischemia

- Vasospastic angina>>> reduce or reverse coronary vasospasm

Mechanism of relief of angina: due to the relaxant effect on large coronary vessels and therby increasing blood supply to the ischemic heart

By decreasing the work on heart

Mechanism of action::

Organic nitrates are rapidly denitrated enzymatically in the smooth muscle cell to release the reactive free radical nitric oxide (NO)

All nitrates share the same action but differs pharmacokinetically

Nitrates

- Nitrates in the form of sublingual preparation are the first line therapy for the treatment of acute anginal symptoms
- Patients should be instructed to use them at the onset of the attack
- Longer acting nitrates are added to beta blockers or calcium channel blockers to control angina.

Pharmacokinetics

- Nitrates are lipid soluble: well absorbed from buccal mucosa, intestines and skin
- Hepatic metabolism is extensive for nitroglycerin & isosorbide dinitrate
- Isosorbide mononitrates has the highest bioavailability and the least first pass metabolism
- **GTN** short-acting from sublingual but **isosorbide dinitrate** longer-acting from oral route

	GTN	ISDN	ISMN
Half life	2 min	40 min	4-6 h
Bioavailability	<1 %	20%	100%
Route of administration	SL 2 min/transdermal/oral sustained release / IV	SL 5 min /oral sustained	Oral extended release

Adverse effects

Headache is the most common adverse effect of nitrates

Fullness in head, throbbing headache; some degree of tolerance develops on continued use.

Flushing, weakness, sweating, palpitation, dizziness and fainting; these are mitigated by lying down

Drug Drug interactions >>>>>>> with phosphodiesterase type 5 inhibitors such as **sildenafil**

Tolerance:::::

- Attenuation of haemodynamic and anti-ischaemic effect of nitrates occurs in a dose and duration of exposure dependent manner if they are continuously present in the body
- Tolerance weans off rapidly (within hours) when the body is free of the drug
- To prevent nitrate tolerance is to provide nitrate free intervals everyday

Sodium channel blocker

Ranolazine inhibits the late phase of the sodium current, improving the oxygen supply and demand.

Its considered anti angina and anti arrhythmic

It has many drug drug interactions, also it prolongs QT interval

Nicorandil

- Potassium channel activator
- It has an arterial and venous dilator and improves coronary blood flow due to potassium channel opening and nitrate effect
- Can protect the heart from subsequent ischemic attacks

Drugs for Hyperlipidemia

3-Hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors

Statins

First-line treatment for patients with elevated risk of ASCVD

Therapeutic benefits include plaque stabilization, improvement of coronary endothelial function, inhibition of platelet thrombus formation, and anti-inflammatory activity

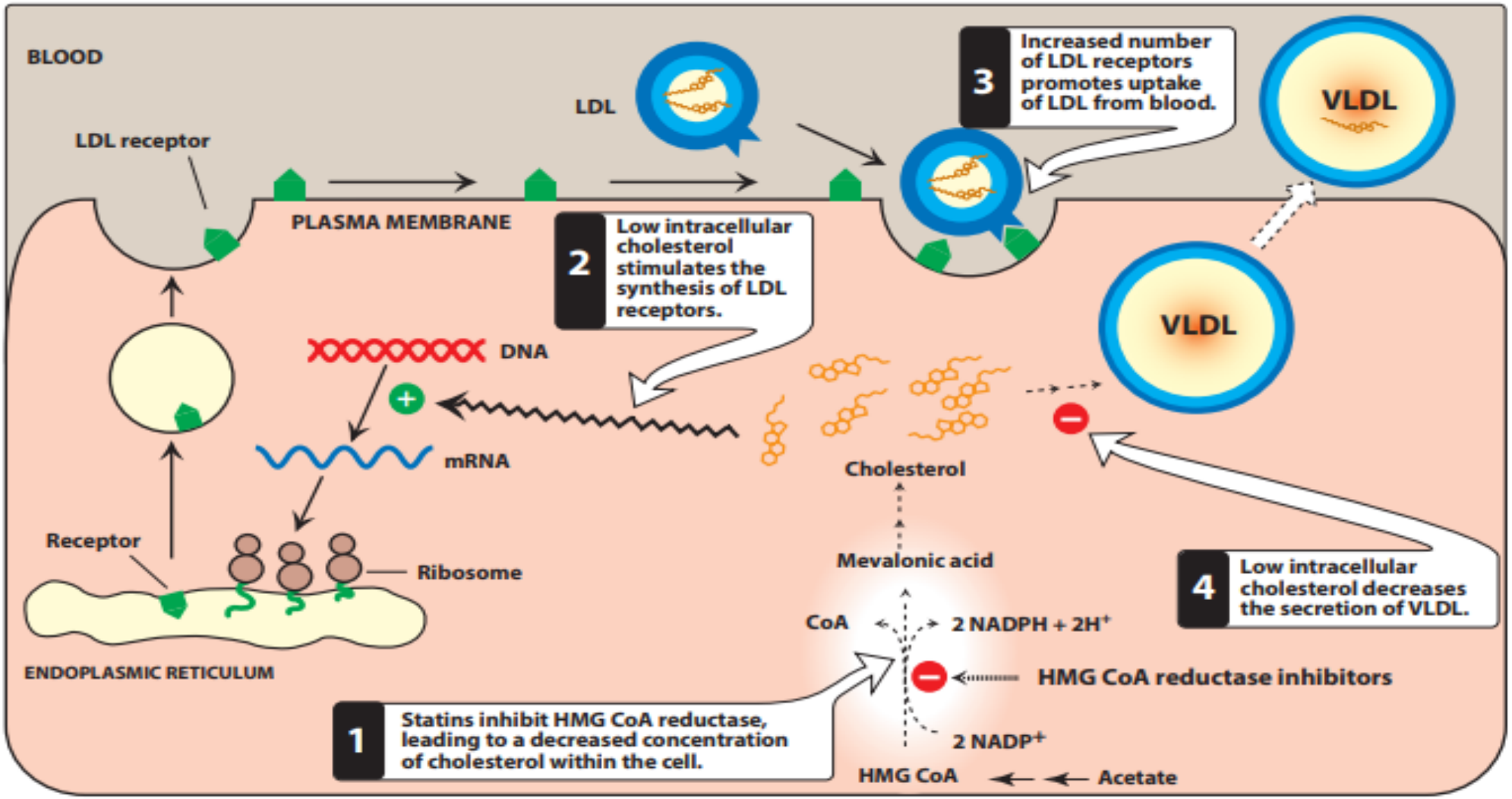
Atorvastatin, lovastatin, simvastatin, pravastatin, Fluvastatin, pitavastatin, rosuvastatin

Mechanism of action

competitive inhibitors of HMG CoA reductase, the rate-limiting step in cholesterol synthesis

Depletion of intracellular cholesterol causes the cell to increase the number of cell surface LDL receptors that can bind and internalize circulating LDLs

plasma cholesterol is reduced, by both decreased cholesterol synthesis and increased LDL catabolism


BLOOD
LDL
3 Increased number of LDL receptors promotes uptake of LDL from blood.
VLDL
LDL receptor
PLASMA MEMBRANE
2 Low intracellular cholesterol stimulates the synthesis of LDL receptors.
VLDL
DNA
mRNA
Cholesterol
Receptor
Ribosome
Mevalonic acid
4 Low intracellular cholesterol decreases the secretion of VLDL.
CoA
2 NADPH + 2H+
ENDOPLASMIC RETICULUM
HMG CoA reductase inhibitors
1 Statins inhibit HMG CoA reductase, leading to a decreased concentration of cholesterol within the cell.
2 NADP+
HMG CoA
Acetate

Pharmacological actions:

Mainly decrease LDL , decrease TG, and may increase HDL

The most potent : atorvastatin, rosuvastatin, pitavastatin

Less potent; simvastatin, pravastatin, Fluvastatin, lovastatin

Therapeutic uses:

All types of hyperlipidemias

Familial hypercholesterolemia lack LDL receptors

Pharmacokinetics:

Lovastatin and simvastatin are prodrugs

All statins are metabolized in the liver, with some metabolites retaining activity. Excretion takes place principally through bile and feces, but some urinary elimination

Characteristic	*Atorvastatin*	*Fluvastatin*	*Lovastatin*	*Pitavastatin*	*Pravastatin*	*Rosuvastatin*	*Simvastatin*
Serum LDL cholesterol reduction produced (%)	55	24	34	43	34	60	41
Serum triglyceride reduction produced (%)	29	10	16	18	24	18	18
Serum HDL cholesterol increase produced (%)	6	8	9	8	12	8	12
Plasma half-life (h)	14	1–2	2	12	1–2	19	1–2
Penetration of central nervous system	No	No	Yes	Yes	No	No	Yes
Renal excretion of absorbed dose (%)	2	<6	10	15	20	10	13

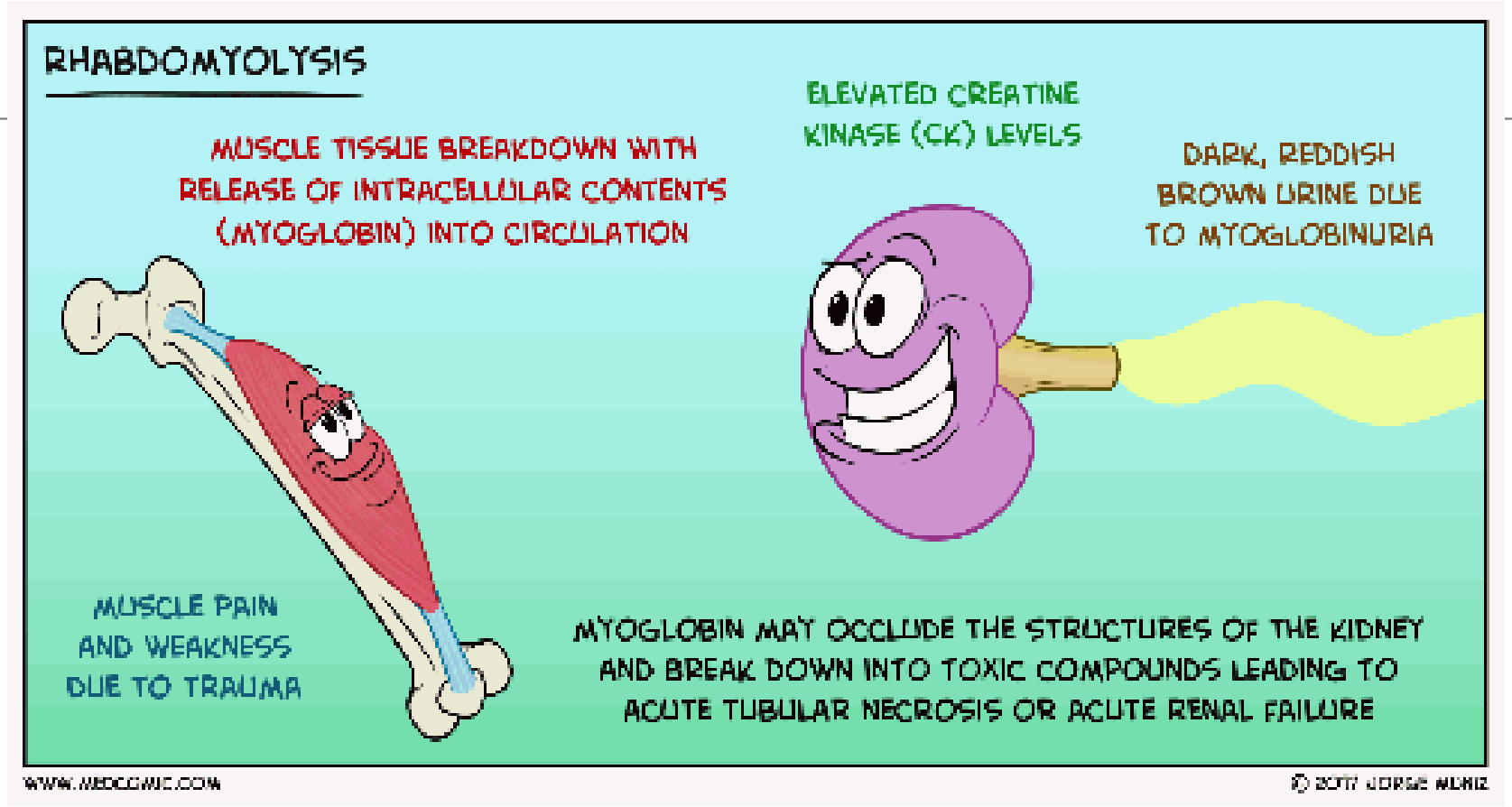
Adverse effects:

Elevated liver enzymes

Myopathy and rhabdomyolysis (disintegration of skeletal muscle;

Simvastatin is metabolized by cytochrome P450 3A4, and inhibitors of this enzyme may increase the risk of rhabdomyolysis (Creatine kinase levels)

These drugs are contraindicated during pregnancy and lactation


RHABDOMYOLYSIS
MUSCLE TISSUE BREAKDOWN WITH RELEASE OF INTRACELLULAR CONTENTS (MYOGLOBIN) INTO CIRCULATION
ELEVATED CREATINE KINASE (CK) LEVELS
DARK, REDDISH BROWN URINE DUE TO MYOGLOBINURIA
MUSCLE PAIN AND WEAKNESS DUE TO TRAUMA
MYOGLOBIN MAY OCCLUDE THE STRUCTURES OF THE KIDNEY AND BREAK DOWN INTO TOXIC COMPOUNDS LEADING TO ACUTE TUBULAR NECROSIS OR ACUTE RENAL FAILURE
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Niacin (nicotinic acid):

Reduce LDL-C by 10% to 20% and is the most effective agent for increasin

lowers triglycerides by 20% to 35%

Mechanism of action: inhibits lipolysis in adipose tissue,

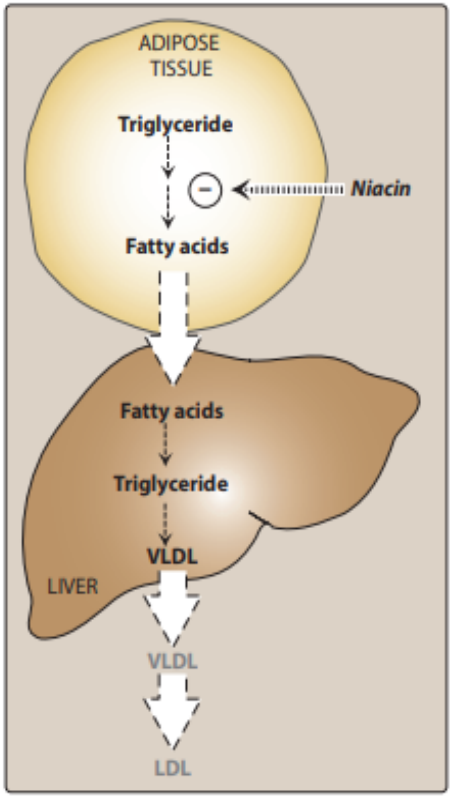
thereby reducing production of free fatty acids

Reduce VLDL production & therefore LDL levels

Therapeutic uses: familial hyperlipidemias

Pharmacokinetics: It is converted in the body to nicotinamide,

which is incorporated into the cofactor nicotinamide adenine dinucleotide (NAD+)



Adverse effects:

The most common side effects of niacin are an intense cutaneous flush (accompanied by an uncomfortable feeling of warmth) and pruritus

Aspirin???

Nausea, abdominal pain

Sustained-release formulation of niacin reduces bothersome initial adverse effects.

Niacin inhibits tubular secretion of uric acid and, thus, predisposes to hyperuricemia and gout.

Impaired glucose tolerance and hepatotoxicity have also been reported.

The drug should be avoided in hepatic disease.

Fibrates

Fenofibrate and gemfibrozil are derivatives of fibric acid that lower serum triglycerides and increase HDL levels.

Fenofibrate is more effective than gemfibrozil in lowering triglyceride levels.

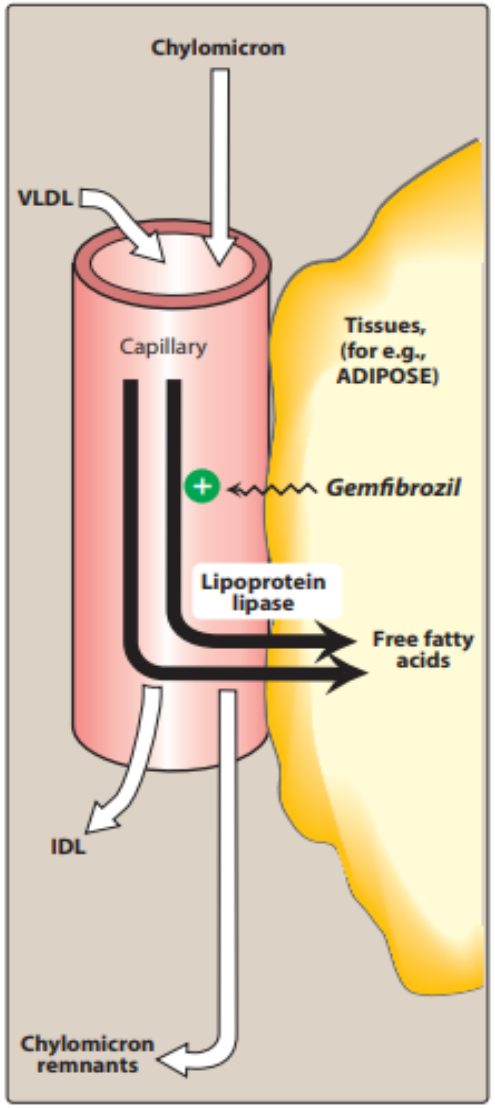
Fibrates also increase the level of HDL cholesterol by increasing the expression of apo AI and apo AIII

MOA:

The peroxisome proliferator–activated receptors (PPARs) are members of the nuclear receptor family that regulates lipid metabolism

Upon binding to their natural ligands (fatty acids or eicosanoids) or antihyperlipidemic drugs, PPARs are activated

increased expression of lipoprotein lipase and decrease expression of apo CIII



Therapeutic uses

Hypertriglyceridemias

Hyperlipidemia

Pharmacokinetics

Fenofibrate is a prodrug, which is converted to the active moiety fenofibric acid

undergo extensive biotransformation and are excreted in the urine

Adverse effects

gastrointestinal (GI) disturbances (most common)

Gallstones...Myositis ....

Myopathy and rhabdomyolysis have been reported in patients taking gemfibrozil and statins together

The use of gemfibrozil is contraindicated with simvastatin.

Both fibrates may increase the effects of warfarin. INR should, therefore, be monitored more frequently when a patient is taking both drugs.

Fibrates should not be used in patients with severe hepatic or renal dysfunction or in patients with preexisting gallbladder disease

Bile acid–binding resins

- significant LDL cholesterol– lowering effects<<< statins
- Cholestyramine, colestipol , and colesevelam
- **Mechanism of action::**
- Anion-exchange resins that bind negatively charged bile acids and bile salts in the small intestine
- resin/bile acid complex is excreted in the feces, thus lowering the bile acid concentration
- Hepatocytes then increase conversion of cholesterol to bile acids, which are essential components of the bile

Therapeutic uses::

The bile acid–binding resins are useful often in combination with diet or niacin for treating type type IIA and type IIB hyperlipidemias

Cholestyramine can also relieve pruritus caused by accumulation of bile acids in patients with biliary stasis.

Colesevelam is also indicated for type 2 diabetes due to its glucose-lowering effects.

Pharmacokinetics

Bile acid sequestrants are insoluble in water and have large molecular weights

Neither absorbed Nor metabolized ,,,, totally excreted in feces

Adverse effects:

GI disturbances, such as constipation, nausea, and flatulence

Colesevelam has fewer GI side effects

They impair the absorption of the fat-soluble vitamins

They interfere with the absorption of many drugs (for example, digoxin, warfarin, and thyroid hormone) ?????

These agents may raise triglyceride levels and are contraindicated in patients with significant hypertriglyceridemia (≥400 mg/dL)

Cholesterol absorption inhibitor

Ezetimibe selectively inhibits absorption of dietary and biliary cholesterol in the small intestine, leading to a decrease in the delivery of intestinal cholesterol to the liver.

This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood.

Ezetimibe lowers LDL cholesterol by approximately 17%.

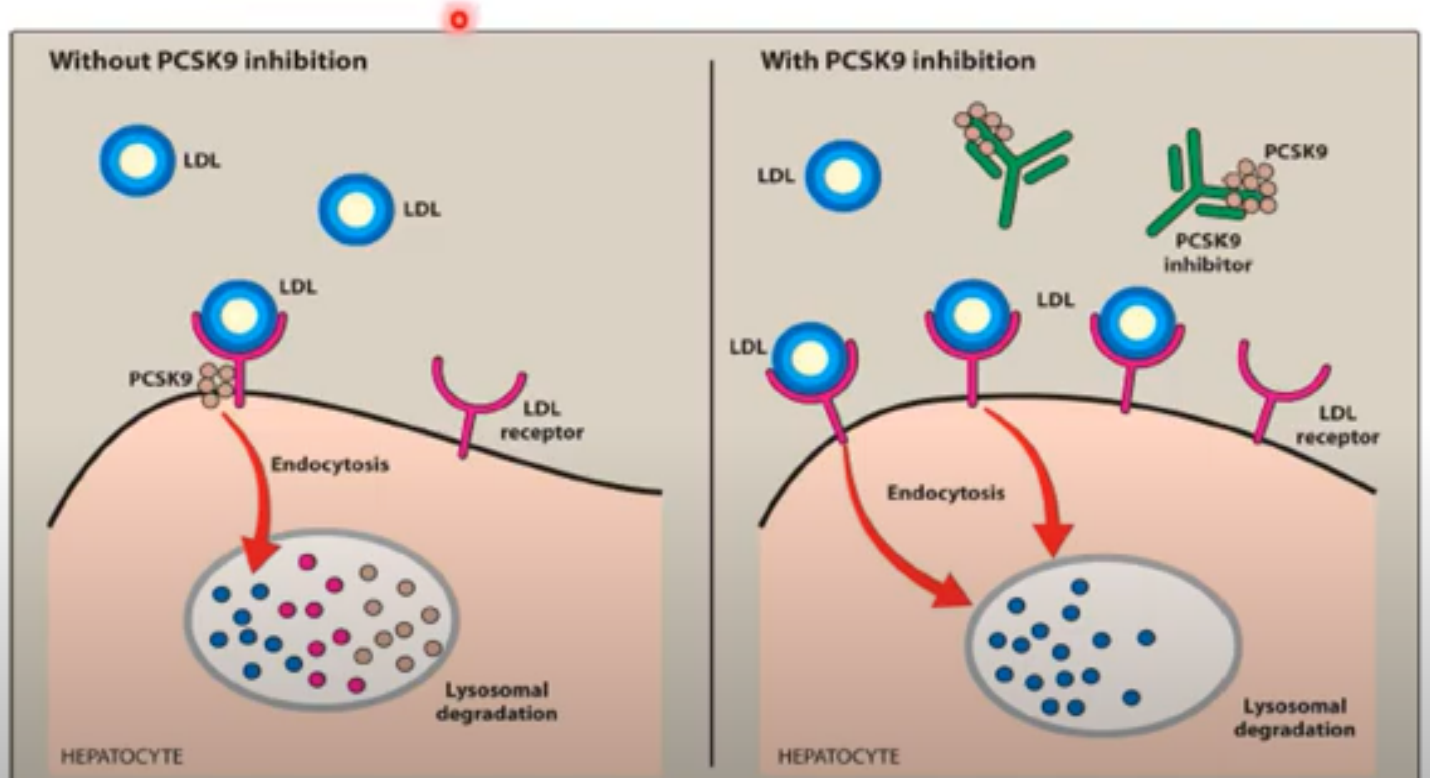
Patients with moderate to severe hepatic insufficiency should not be treated with ezetimibe.

Adverse effects are uncommon with use of ezetimibe

PCSK9 inhibitors (Proprotein convertase subtilisin kexin type 9 inhibitors)

Evolocumab

Alirocumab



When combined with statin therapy, PCSK9 inhibitors provide potent LDL-C lowering (50% to 70%).

They may also be considered for patients with high ASCVD risk and statin intolerance.

PCSK9 inhibitors are only available as subcutaneous injections and are administered every two to four weeks.

The most common adverse drug reactions are injection site reactions, immunologic or allergic reactions, nasopharyngitis, and upper respiratory tract infections.