# Diuretics

Diuretics are drugs that increase the volume of urine excreted. Most diuretic agents are inhibitors of renal ion transporters that decrease the reabsorption of $Na^+$ at different sites in the nephron. As a result, $Na^+$ and other ions, such as $Cl^-$, enter the urine in greater than normal amounts along with water, which is carried passively to maintain osmotic equilibrium.

Diuretics cause

- increase the volume of urine
- Change in urine pH.
- Changes in the ionic composition of the urine and blood.

The diuretic effect of the different classes of diuretics varies considerably, with the increase in Na+ secretion varying from less than 2% for the weak potassium-sparing diuretics to over 20% for the potent loop diuretics. In addition to the ion transport inhibitors, other types of diuretics include osmotic diuretics, aldosterone antagonists, and carbonic anhydrase inhibitors.

Diuretics are most commonly used for management of abnormal fluid retention (edema) or treatment of hypertension.

## Normal Regulation of Fluids and Electrolytes by Kidney

Approximately 16% to 20% of the blood plasma entering the kidneys is filtered from the glomerular capillaries into Bowman's capsule. The filtrate, although normally free of proteins and blood cells, contains most of the low molecular weight plasma components in concentrations similar to that in the plasma. These include glucose, sodium bicarbonate, amino acids, and other organic solutes, as well as electrolytes, such as $Na^+$, $K^+$, and $Cl^-$.

The kidney regulates the ionic composition and volume of urine by active reabsorption or secretion of ions and/or passive reabsorption of water at five functional zones along the nephron figure (1):

1) The proximal convoluted tubule,
2) The descending loop of Henle
3) The ascending loop of Henle
4) The distal convoluted tubule
5) The collecting tubule and duct

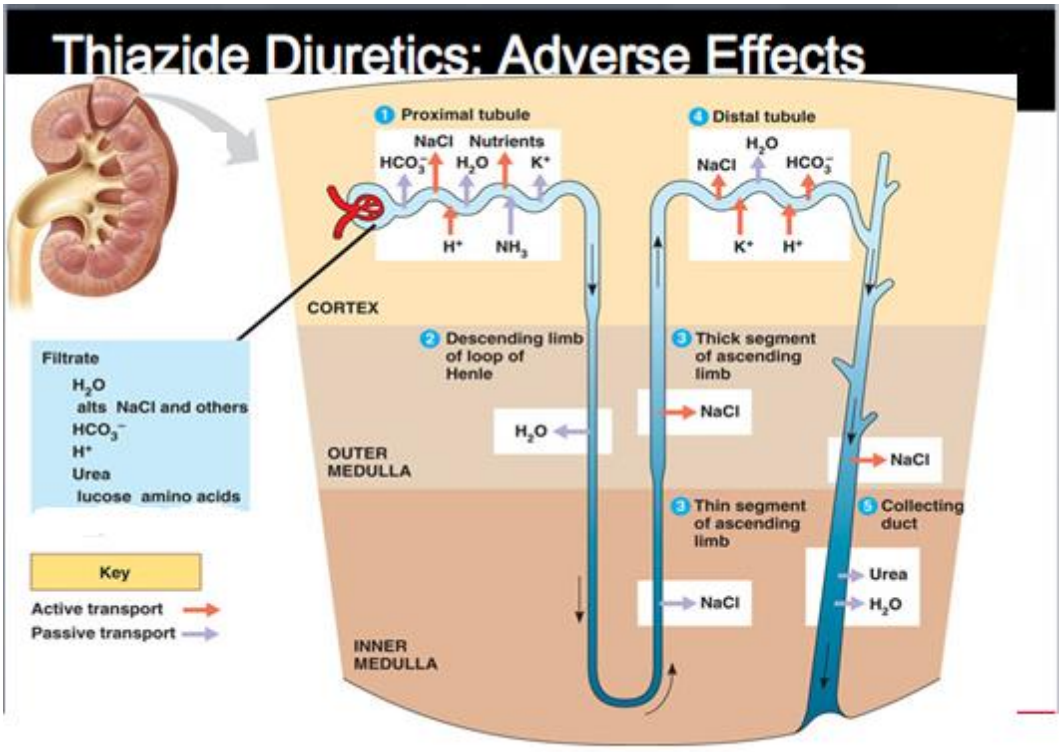
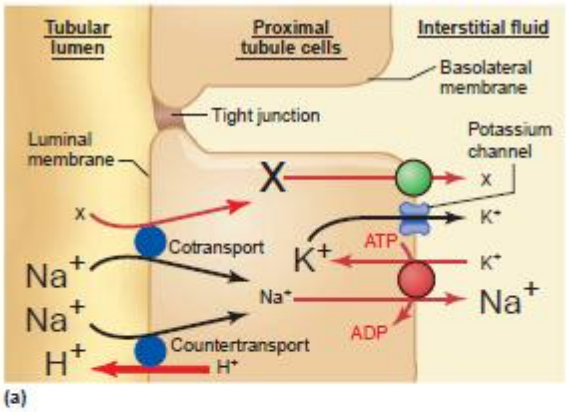



Figure (1): Regulation of Fluids and Electrolytes by Kidney

## A. Proximal Convoluted tubule

1. Almost all the glucose, bicarbonate, amino acids, and other metabolites are reabsorbed.
2. Approximately **<u>two-thirds</u>** of the $Na^+$ is reabsorbed.

3. Chloride enters the lumen of the tubule in exchange for an anion, such as oxalate, as well as para-cellular through the lumen.
4. Water follows passively from the lumen to the blood to maintain osmolar equality.
5. The $Na^+$ that is reabsorbed is pumped into the interstitial by $Na^+/K^+$-adenosine triphosphatase (ATPase) pump, thereby maintaining normal levels of $Na^+$ and $K^+$ in the cell.
6. Carbonic anhydrase in the luminal membrane and cytoplasm of the proximal tubular cells modulates the reabsorption of bicarbonate.
7. The proximal tubule is the site of the organic acid and base secretory systems. It secretes a variety of
   - organic acids, such as uric acid
   - some antibiotics
   - Diuretics, the secretion occur from the bloodstream into the proximal tubular lumen. Most diuretic drugs are delivered to the tubular fluid via this system.
8. Number of other interactions can also occur. For example, *probenecid* interferes with *penicillin* secretion.



**B. Descending loop of Henle**

1. The osmolarity increases along the descending portion of the loop of Henle because of the **countercurrent mechanism** that is responsible for **water reabsorption**.
2. A tubular fluid with a threefold increase in salt concentration.

**C. Ascending loop of Henle**

1. The cells of the ascending tubular epithelium are unique in being **impermeable to water**.
2. Active reabsorption of $Na^+$, $K^+$, and $Cl^-$ is mediated by a **$Na^+/K^+/2Cl-$ co-transporter.**
3. Both $Mg^{2+}$ and $Ca^{2+}$ enter the interstitial fluid via the paracellular pathway.
4. Approximately **25% to 30%** of the tubular sodium chloride returns to the interstitial fluid, thereby helping to maintain high osmolarity.
5. Because the ascending loop of Henle is a major site for salt reabsorption, drugs affecting this site, such as loop diuretics, have the greatest diuretic effect.

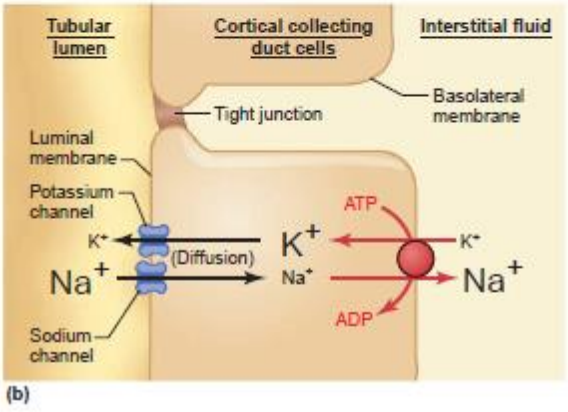
**D. Distal convoluted tubule**

1. The cells of the distal convoluted tubule are also **impermeable to water**.
2. About **10%** of the filtered sodium chloride is reabsorbed via a $Na^+/Cl^-$ transporter that is sensitive to thiazide diuretics.
3. Calcium reabsorption is mediated by passage through a channel and then transported by a $Na^+/Ca^{2+}$-exchanger into the interstitial fluid.

**E. Collecting tubule and duct**

1. Responsible for $Na^+$, $K^+$, and water transport, whereas the intercalated cells affect $H^+$ secretion.

2. Sodium enters the principal cells through channels (epithelial sodium channels). Once inside the cell, Na+ reabsorption relies on a $Na^+/K^+$-ATPase pump to be transported into the blood.
3. Aldosterone receptors in the principal cells influence Na+ reabsorption and $K^+$ secretion. Aldosterone increases the synthesis of Na+ channels and of the $Na^+/K^+$-ATPase pump, which when combined increase $Na^+$ reabsorption.
4. Antidiuretic hormone (ADH; vasopressin) receptors promote the reabsorption of water from the collecting tubules and ducts.



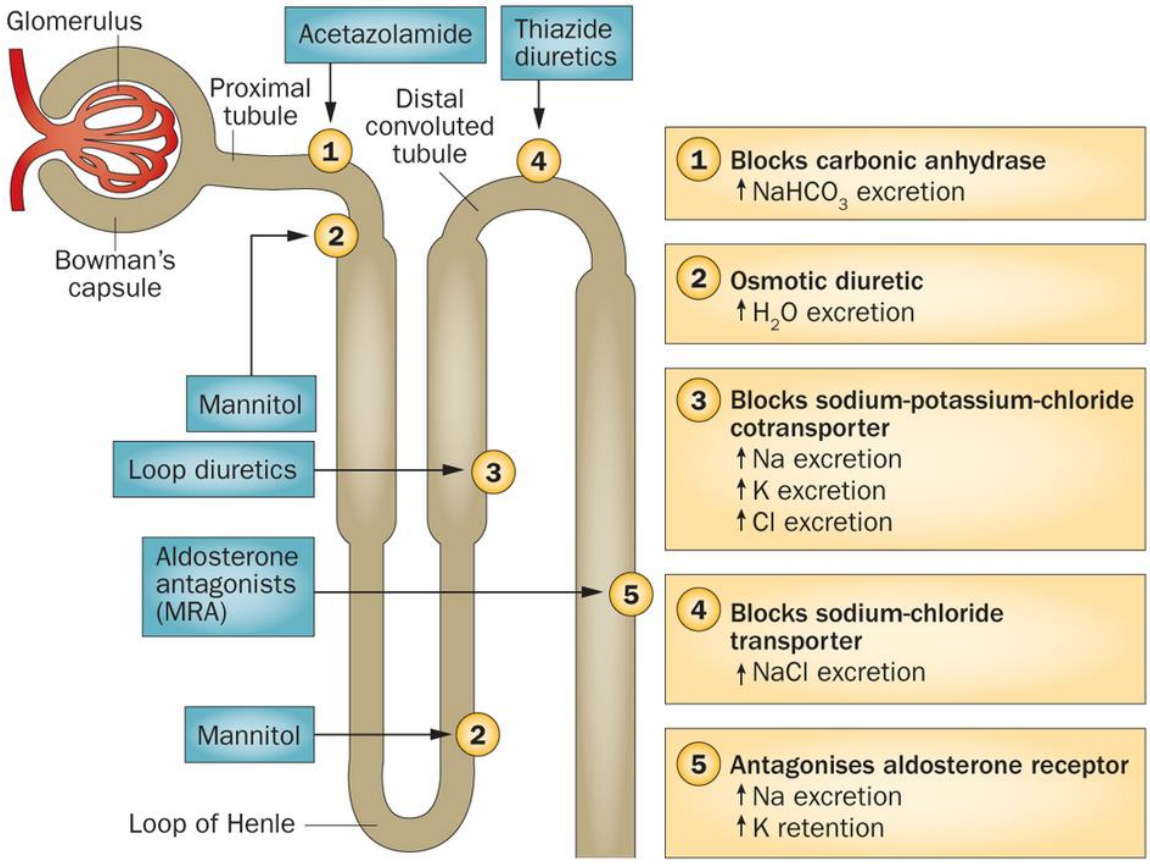

## Types of Diuretics

Diuretic drugs increase urine output by the kidney (i.e., promote diuresis). This is accomplished by altering how the kidney handles sodium. If the kidney excretes more sodium, then water excretion will also increase. Most diuretics produce diuresis by inhibiting the reabsorption of sodium at different segments of the renal tubular system. Sometimes a combination of two diuretics is given because this can be significantly more effective than either compound alone (synergistic effect). The reason for this is that one nephron segment can compensate for altered sodium reabsorption at another

nephron segment; therefore, blocking multiple nephron sites significantly enhances efficacy.

## Site and Mechanisms of Actions of Diuretics

| Diuretics | Site of Action | Mechanism |
|---|---|---|
| Osmotic Diuretic | 1. Proximal tubules<br>2. Loop of Henle<br>3. Collecting duct | Inhibition of water and Na+ reabsorption |
| Carbonic Anhydrase Inhibitor (CA-I) | Proximal tubules | Inhibition of bicarbonate reabsorption |
| Loop Diuretic | Loop of Henle (*thick ascending limb*) | Inhibition of $Na^+$, $K^+$, $Cl^-$ cotransport |
| Thiazide | Early distal tubule | Inhibition of $Na^+$, $Cl^-$ cotransport |
| $K^+$ sparing diuretics | Late distal tubule<br>Collecting duct | Inhibition of Na+ reabsorption and $K^+$ secretion |

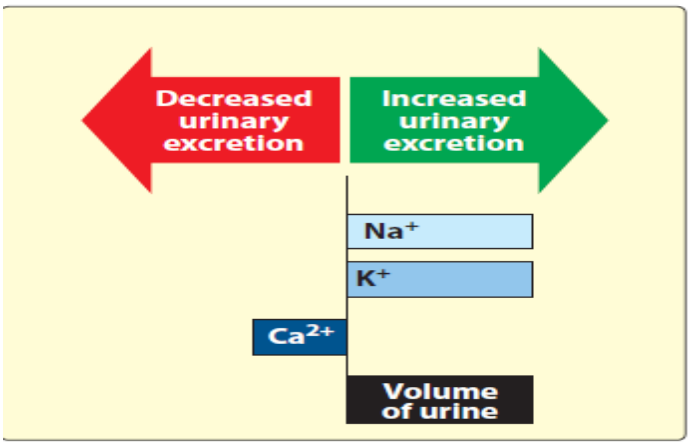


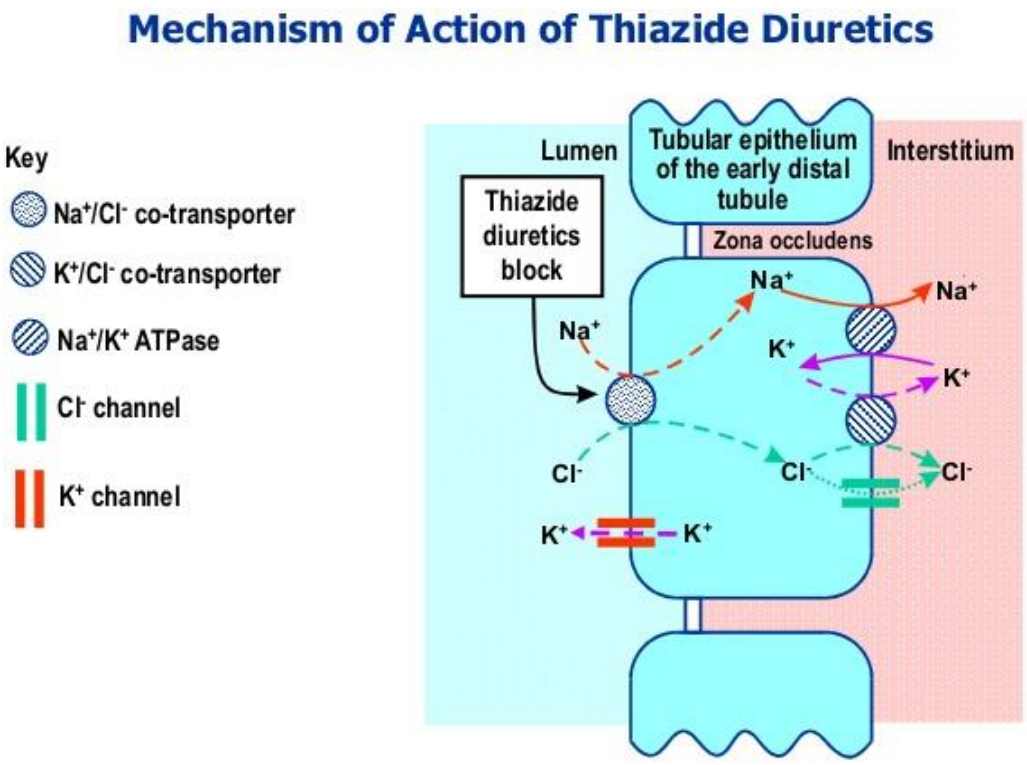
# Thiazides and related agents

1. All thiazides affect the distal convoluted tubule,
2. All have equal maximum diuretic effects, differing only in potency.
3. Thiazides are sometimes called "**low ceiling diuretics**" because increasing the dose above normal therapeutic doses does not promote further diuretic response.
4. Examples: chlorothiazide, hydrochlorothiazide, chlorthalidone.

**Mechanism of Action:**

1. The thiazide and thiazide-like diuretics act mainly in the cortical region of the ascending loop of Henle and the distal convoluted tubule
2. Decrease the reabsorption of $Na^+$, apparently by inhibition of a $Na^+/Cl^-$ co-transporter on the luminal membrane of the tubules.
3. They have a lesser effect in the proximal tubule.
4. As a result, these drugs increase the concentration of $Na^+$ and $Cl^-$ in the tubular fluid.
5. The efficacy of these agents may be diminished with concomitant use of NSAIDs, such as *indomethacin*, which inhibit production of renal prostaglandins, thereby reducing renal blood flow.






**Actions:**

**a. Increased excretion of $Na^+$ and $Cl^-$:**

Cause diuresis with increased $Na^+$ and $Cl^-$ excretion, which can result in the excretion of very hyperosmolar (concentrated) urine. This latter effect is unique, as the other diuretic classes are unlikely to produce a hyperosmolar urine.

**b. Loss of $K^+$:**

it increase $Na^+$ in the filtrate arriving at the distal tubule, more $K^+$ is also exchanged for $Na^+$, resulting in a continual loss of $K^+$ from the body with prolonged use of these drugs.

**C. Loss of $Mg^{2+}$.**

**D. Decreased urinary calcium excretion:**

Decrease the $Ca^{2+}$ content of urine by promoting the reabsorption of $Ca^{2+}$ in the distal convoluted tubule where parathyroid hormone regulates

reabsorption. This effect contrasts with the loop diuretics, which increase the $Ca^{2+}$ concentration in the urine

**E. Reduced peripheral vascular resistance:**

An initial reduction in blood pressure results from a decrease in blood volume and, therefore, a decrease in cardiac output. With continued therapy, volume recovery occurs.

**Therapeutic uses:**

a. Hypertension:

b. Heart failure

c. Hypercalciuria.

d. Diabetes insipidus.

## Adverse effect

**a. Potassium depletion:**

$K^+$ can be supplemented by dietary measures such as increasing the consumption of citrus fruits, bananas, and prunes. In some cases, $K^+$ supplementation may be necessary.

Thiazides decrease the intravascular volume, resulting in activation of the renin–angiotensin–aldosterone system. Increased aldosterone contributes significantly to urinary $K^+$ losses.

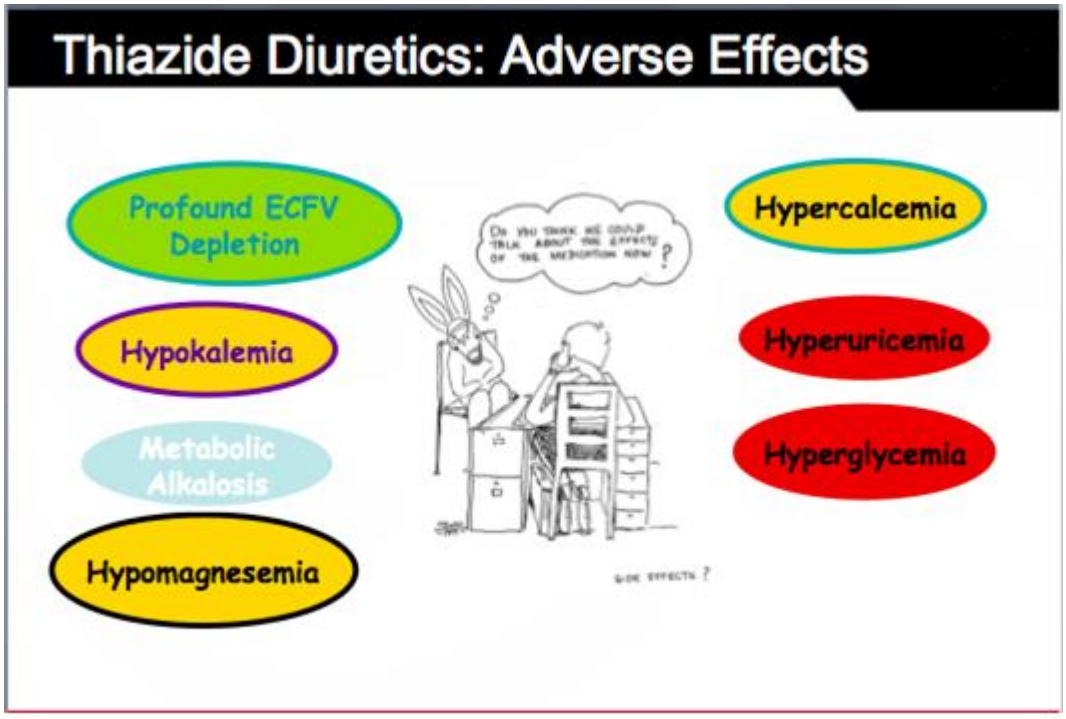
**b. Hypernatremia:** Hypernatremia may develop due to elevation of ADH as a result of hypovolemia, as well as diminished diluting capacity of the kidney and increased thirst.

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

**d. Volume depletion:** This can cause orthostatic hypotension or light-headedness.

**e. Hypercalcemia:** The thiazides inhibit the secretion of $Ca^{2+}$, sometimes leading to hypercalcemia (elevated levels of $Ca^{2+}$ in the blood).

**f. Hyperglycemia:** Therapy with thiazides can lead to glucose intolerance, possibly due to impaired release of insulin and tissue uptake of glucose.

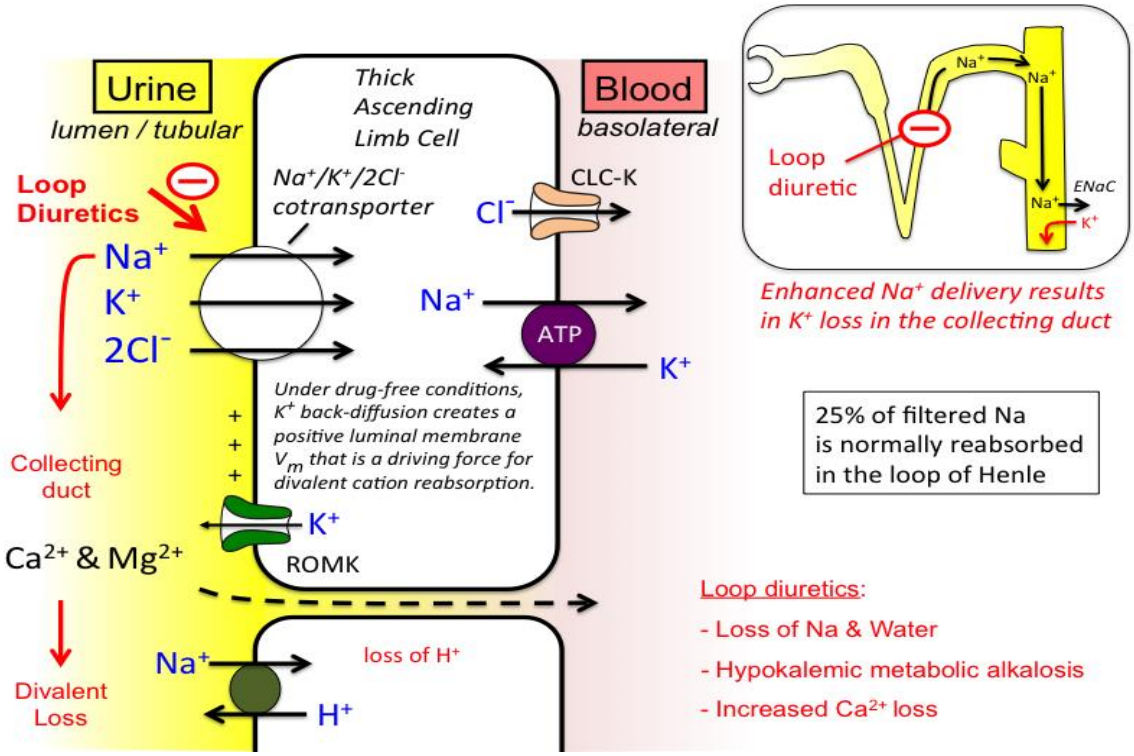


# Loop or High-Ceiling Diuretics

1. This group have their major diuretic action on the ascending limb of the loop of Henle.
2. Of all the diuretics, these drugs have the highest efficacy in mobilizing $Na^+$ and $Cl^-$ from the body.
3. They produce copious amounts of urine.

**Mechanism of action:**

- Loop diuretics inhibit the co-transport of $Na^+/K^+/2Cl^-$ in the luminal membrane in the ascending limb of the loop of Henle. Therefore, reabsorption of these ions is decreased.
- These agents have the greatest diuretic effect of all the diuretic drugs (**why??**), since the ascending limb accounts for reabsorption of 25% to 30% of filtered NaCl, and downstream sites are unable to compensate for the increased Na+ load.



**Actions:**

1. Loop diuretics act promptly, even in patients with poor renal function or lack of response to other diuretics.
2. Unlike thiazides, loop diuretics increase the Ca2+ content of urine. In patients with normal serum $Ca^{2+}$ concentrations, hypocalcaemia does not result (**why??**), because $Ca^{2+}$ is reabsorbed in the distal convoluted tubule.
3. The loop diuretics may increase renal blood flow, possibly by enhancing prostaglandin synthesis. NSAIDs inhibit renal prostaglandin synthesis and can reduce the diuretic action of loop diuretics.

**Therapeutic uses:**

1. The loop diuretics are the drugs of choice for reducing acute pulmonary edema
2. Acute/Chronic peripheral edema caused from heart failure or renal impairment.
3. Because of their rapid onset of action, particularly when given intravenously, the drugs are useful in emergency situations such as acute pulmonary edema.
4. Loop diuretics (along with hydration) are also useful in treating hypercalcemia, because they stimulate tubular $Ca^{2+}$ excretion.
5. They also are useful in the treatment of hyperkalemia.

**Adverse effects:**

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

**b. Hyperuricemia:** *Furosemide* compete with uric acid for the renal secretory systems, thus blocking its secretion and, in turn, causing or exacerbating gouty attacks.

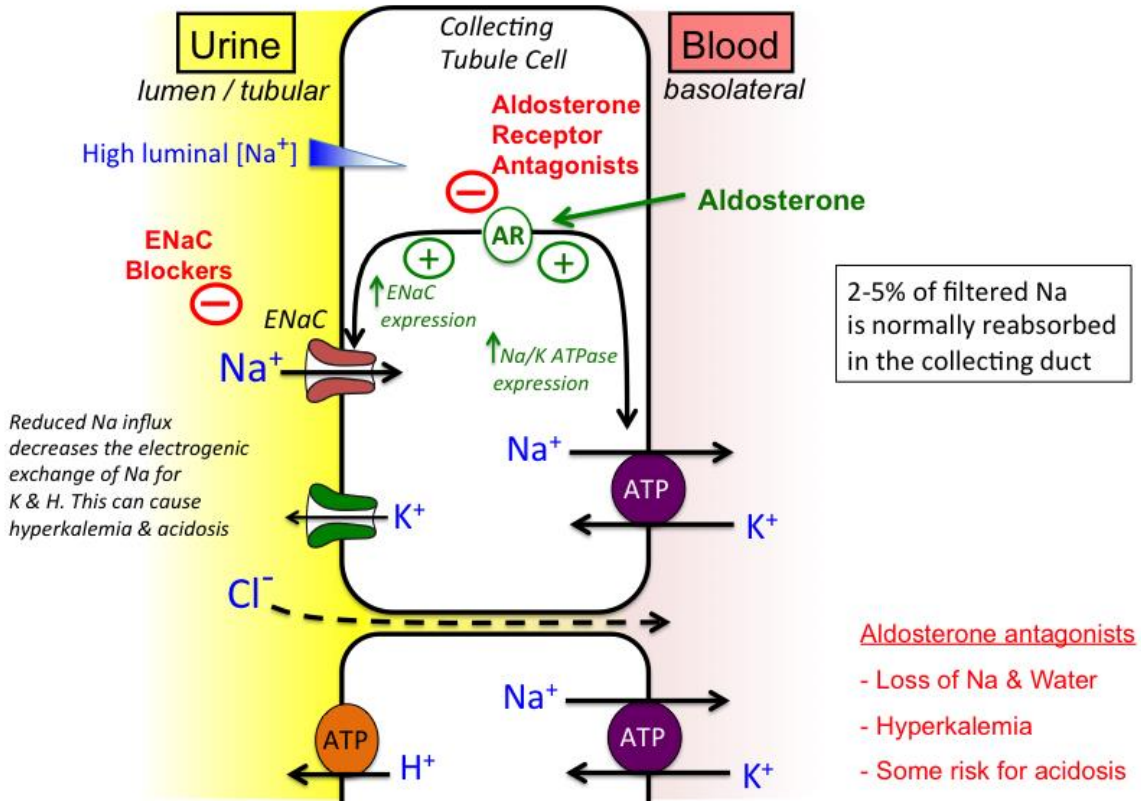
**c. Acute hypovolemia:** Loop diuretics can cause a severe and rapid reduction in blood volume, with the possibility of hypotension, shock, and cardiac arrhythmias.

**d. 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.

**e. Hypomagnesemia:**

## Potassium-Sparing Diuretics

- Potassium-sparing diuretics act in the collecting tubule to inhibit $Na^+$ reabsorption and $K^+$ excretion.
- The major use of potassium sparing agents is in the treatment of hypertension (most often in combination with a thiazide) and in heart failure (aldosterone antagonists).
- It is extremely important that potassium levels are closely monitored in patients treated with potassium-sparing diuretics.
- These drugs should be avoided in patients with renal dysfunction (**why??)** Because of the increased risk of hyperkalemia.
- Within this class, there are drugs with two distinct mechanisms of action: aldosterone antagonists and sodium channel blockers.




**1. Aldosterone antagonists: Spironolactone**

**Mechanism of action:**

- *Spironolactone* is a synthetic steroid that antagonizes aldosterone at intracellular cytoplasmic receptor sites rendering the spironolactone–receptor complex inactive.
- It prevents translocation of the receptor complex into the nucleus of the target cell, ultimately resulting in a failure to produce mediator proteins that normally stimulate the $Na^+/K^+$-exchange sites of the collecting tubule. Thus, a lack of mediator proteins prevents Na+ reabsorption and, therefore, $K^+$ and $H^+$ secretion.

**Actions**

- In most edematous states, blood levels of aldosterone are high, causing retention of $Na^+$. *Spironolactone* antagonizes the activity of aldosterone, resulting in retention of $K^+$ and excretion of $Na^+$.
- Similar to thiazides and loop diuretics, the effect of these agents may be diminished by administration of NSAIDs.

**Therapeutic uses:**

**a. Diuretic:** These agents are often given in conjunction with thiazide or loop diuretics to prevent $K^+$ excretion that would otherwise occur with these drugs.

**b. Secondary hyperaldosteronism:** *Spironolactone* is particularly effective in clinical situations associated with secondary hyperaldosteronism, such as hepatic cirrhosis and nephrotic syndrome. In contrast, in patients who have no significant circulating levels of aldosterone, such as in Addison disease (primary adrenal insufficiency), there is no diuretic effect with the use of this drug.

**c. Heart failure:** Aldosterone antagonists prevent remodeling that occurs as compensation for the progressive failure of the heart.

**d. Resistant hypertension:**

**e. Ascites:** Accumulation of fluid in the abdominal cavity (ascites) is a common complication of hepatic cirrhosis.

**f. Polycystic ovary syndrome:** It blocks androgen receptors and inhibits steroid synthesis at high doses, thereby helping to offset increased androgen levels seen in this disorder.

**Adverse effects:**

1. Because it chemically resembles some of the sex steroids, *spironolactone* may induce gynecomastia in male patients and menstrual irregularities in female patients.
2. Hyperkalemia,
3. Nausea, lethargy, and mental confusion can occur.
4. Potassium-sparing diuretics should be used with caution with other medications that can induce hyperkalemia, such as angiotensin-converting enzyme inhibitors and potassium supplements.

**2. Amiloride**

- Block Na+ transport channels, resulting in a decrease in $Na^+/K^+$ exchange.
- Although they have a K+-sparing diuretic action similar to that of the aldosterone antagonists, their ability to block the $Na^+/K^+$-exchange site in the collecting tubule does not depend on the presence of aldosterone.
- Like the aldosterone antagonists, these agents are not very efficacious diuretics.
- *amiloride* commonly used in combination with other diuretics, usually for their potassium sparing properties.

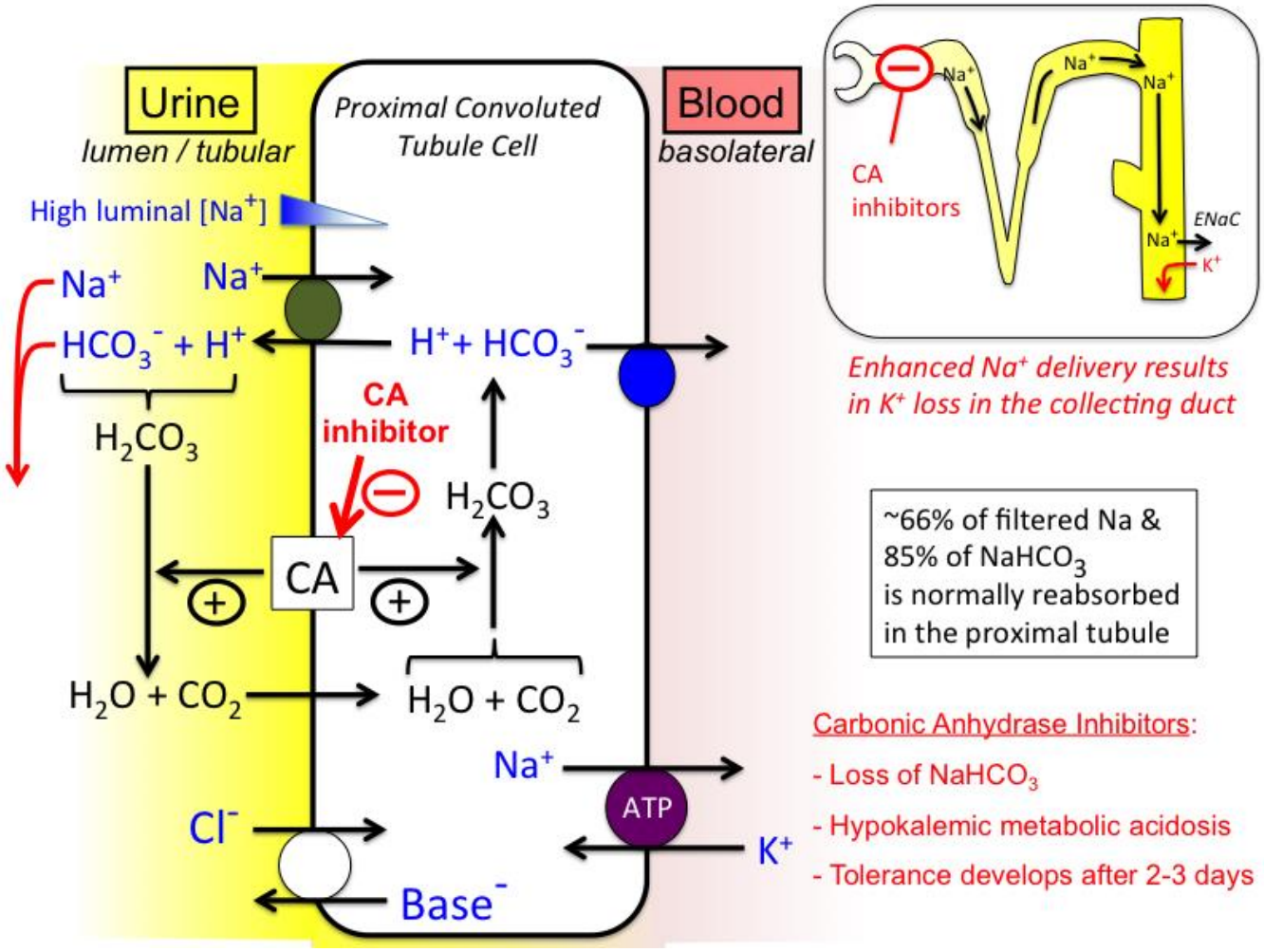
**Carbonic Anhydrase Inhibitor**

*Acetazolamide* more often used for their other pharmacologic actions than for their diuretic effect, because they are much less efficacious than the thiazide or loop diuretics.

**Mechanism of action:**

- *Acetazolamide* inhibits carbonic anhydrase located intracellularly (cytoplasm) and on the apical membrane of the proximal tubular epithelium.

- Carbonic anhydrase catalyzes the reaction of $CO_2$ and$H_2O$, leading to $H_2CO_3$, which spontaneously ionizes to $H^+$ and $HCO^{3-}$ (bicarbonate).
- The decreased ability to exchange $Na^+$ for $H^+$ in the presence of *acetazolamide* results in a mild diuresis.
- $HCO^{3-}$ is retained in the lumen, with marked elevation in urinary pH.
- The loss of $HCO^{3-}$ causes a hyperchloremic metabolic acidosis and decreased diuretic efficacy following several days of therapy.

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**Therapeutic uses:**

**a. Glaucoma:** *Acetazolamide* decreases the production of aqueous humor and reduces intraocular pressure in patients with chronic open-angle glaucoma, probably by blocking carbonic anhydrase in the ciliary body of the eye.

**b. Mountain sickness:** *Acetazolamide* can be used in the prophylaxis of acute mountain sickness.

**Adverse effects:**

1.Metabolic acidosis (mild),

2.potassium depletion

3. renal stone formation

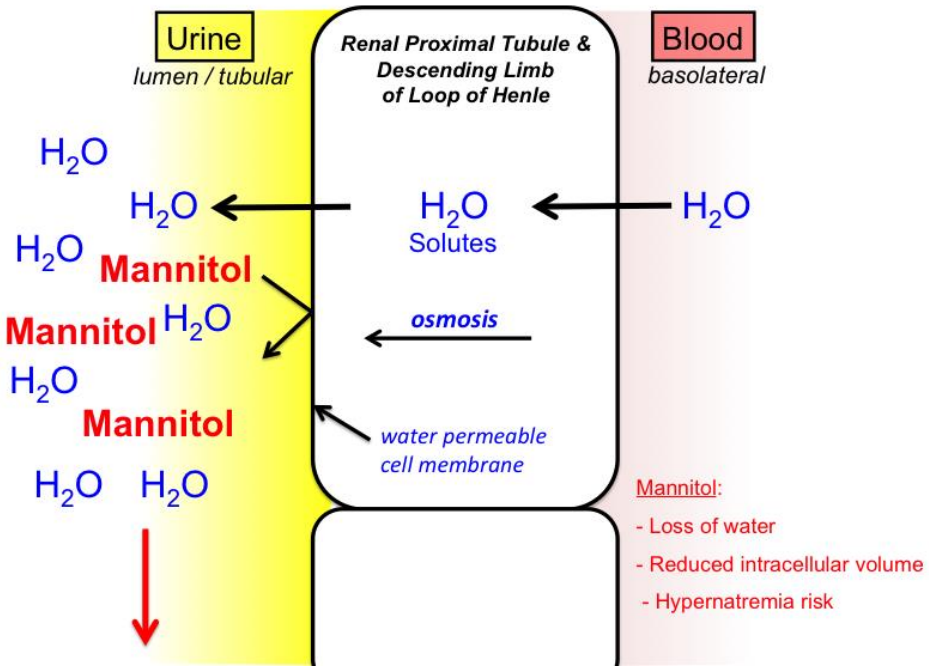
4. drowsiness,

5.The drug should be avoided in patients with hepatic cirrhosis, because it could lead to a decreased excretion of $NH^{4+}$.

**OSMOTIC DIURETICS**

- A number of simple, hydrophilic chemical substances that are filtered through the glomerulus, such as *mannitol* and *urea* result in some degree of diuresis.
- Filtered substances that undergo little or no reabsorption will cause an increase in urinary output.
- The presence of these substances results in a higher osmolarity of the tubular fluid and prevents further water reabsorption, resulting in osmotic diuresis.
- Only a small amount of additional salt may also be excreted. Because osmotic diuretics are used to increase water excretion rather than Na+ excretion,

- They are not useful for treating conditions in which Na+ retention occurs.
- They are used to maintain urine flow following acute toxic ingestion of substances capable of producing acute renal failure.
- Osmotic diuretics are a mainstay of treatment for patients with increased intracranial pressure or acute renal failure due to shock, drug toxicities, and trauma.
- Maintaining urine flow preserves long-term kidney function and may save the patient from dialysis.




**Adverse effects**

- extracellular water expansion and dehydration,
- hypo- or hypernatremia. The expansion of extracellular water results because the presence of *mannitol* in the extracellular fluid extracts water from the cells and causes hyponatremia until diuresis occurs.

# Antihypertensive Drug

Hypertension is defined as either a sustained systolic blood pressure of greater than 140 mm Hg or a sustained diastolic blood pressure of greater than 90 mm Hg.

Hypertension results from increased peripheral vascular arteriolar smooth muscle tone, which leads to

1. increased arteriolar resistance
2. Reduced capacitance of the venous system.

In most cases, the cause of the increased vascular tone is unknown.

Elevated blood pressure is a common disorder, affecting approximately 30% of adults in the United States. Although many patients have no symptoms, chronic hypertension can lead to heart disease and stroke.

Hypertension is also an important risk factor in the development of chronic kidney disease and heart failure. The incidence of morbidity and mortality significantly decreases when hypertension is diagnosed early and is properly treated.

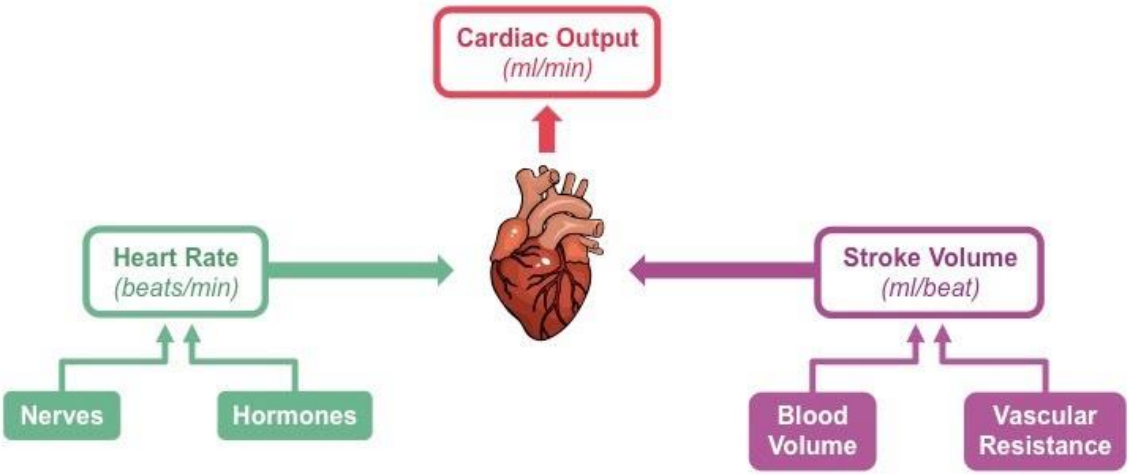
Hypertension is classified into four categories for the purpose of treatment management.

| Classification | Systolic Blood Pressure (mmHg) | | Diastolic Blood Pressure (mmHg) |
|---|---|---|---|
| **Normal** | <120 | AND | <80 |
| **Prehypertension** | 120-139 | OR | 80-89 |
| **Stage I HTN** | 140-159 | OR | 90-99 |
| **Stage 2 HTN** | ≥160 | OR | ≥100 |

# Mechanisms for Controlling Blood Pressure

Arterial blood pressure is regulated within a narrow range to provide adequate perfusion of the tissues without causing damage to the vascular system, particularly the arterial intima (endothelium).

Cardiac output depend **on heart rate and stroke volume**

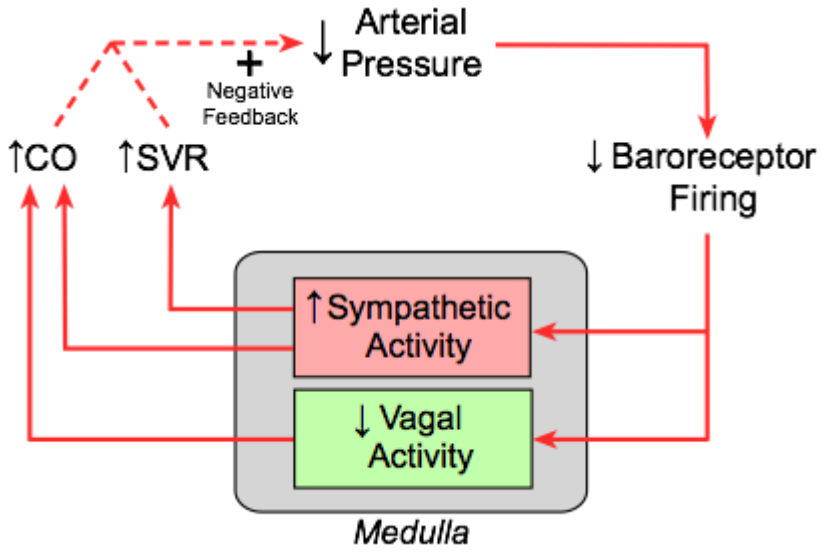



- To regulate the Arterial blood pressure we need to control:
    1. Cardiac output.
    2. Peripheral vascular resistance.
- Cardiac output and peripheral resistance are controlled mainly by
    1. The baro-reflexes and the sympathetic nervous system
    2. The renin–angiotensin–aldosterone system.
- Most antihypertensive drugs lower blood pressure by
    1. Reducing cardiac output.
    2. Decreasing peripheral resistance.

## A. Baroreceptors and the sympathetic nervous system

Baroreflexes act by changing the activity of the sympathetic nervous system. Therefore, 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.



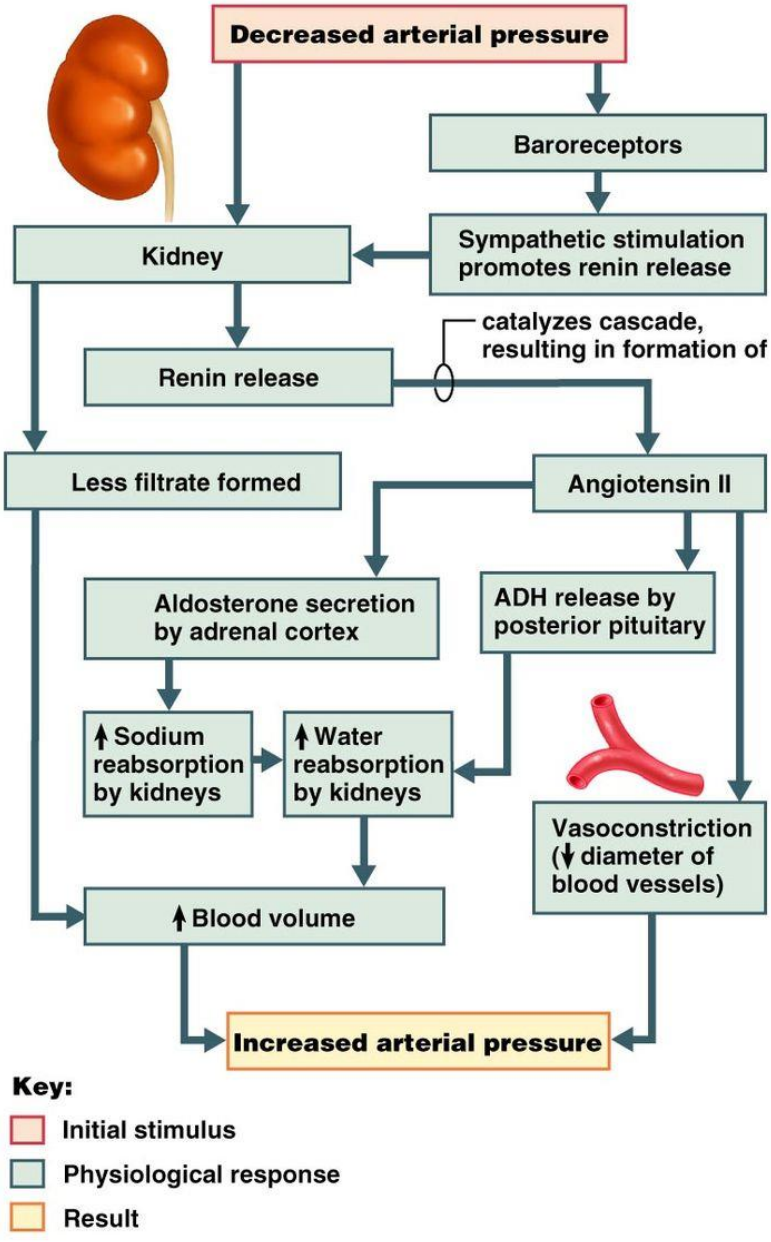

**B. Renin–angiotensin–aldosterone system**

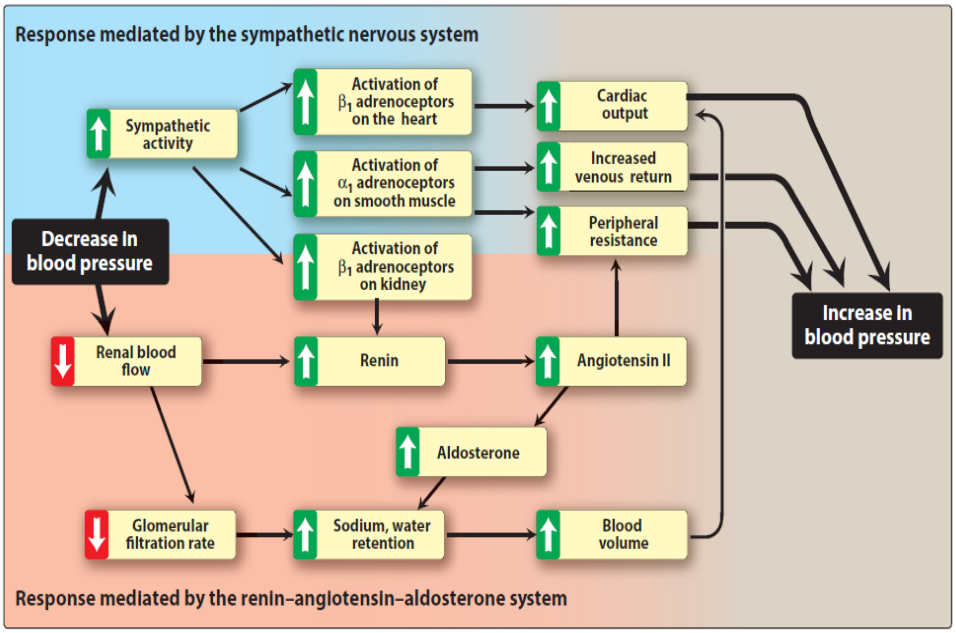
The kidney provides long-term control of blood pressure by altering the blood volume. Baroreceptors in the kidney respond to reduced arterial pressure (and to sympathetic stimulation of β1-adrenoceptors) by releasing the enzyme renin. Low sodium intake and greater sodium loss also increase renin release.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

Angiotensin II cause

1. Vasoconstrictor, constricting both arterioles and veins, resulting in an increase in blood pressure.
2. Preferential vasoconstrictor action on the efferent arterioles of the renal glomerulus, increasing glomerular filtration.

3. Stimulates aldosterone secretion, leading to increased renal sodium reabsorption and increased blood volume, which contribute to a further increase in blood pressure.






# Medications use in hypertension treatment

## Classification of Antihypertensive Drugs

**1) Diuretics**
- Thiazides and congeners.
- Loop diuretics.
- Potassium-sparing diuretics.

**2) Sympatholytic drugs**
- Centrally acting antiadrenergic agents.
- Alpha adrenergic blockers.
- Beta adrenergic blockers.
- Alpha-beta adrenergic blockers.

**3) Vasodilators**
- Nitric oxide releasers.
- Potassium channel openers.
- Calcium channel blockers
- D1-dopamine receptor agonists.

**4) Angiotensin inhibitors and antagonists**
- Angiotensin Converting Enzyme (ACE) inhibitors.
- Angiotensin receptor antagonists.

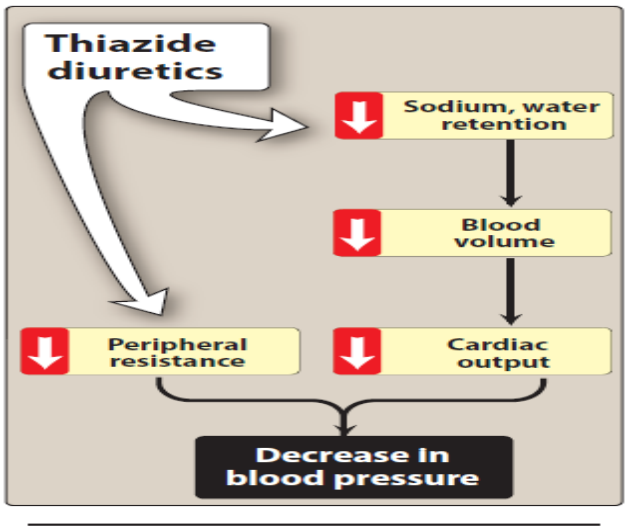
- **Diuretics**

Thiazide diuretics can be used as **initial drug therapy for hypertension unless there are compelling reasons to choose another agent**. Regardless of class, the initial mechanism of action of diuretics is based upon decreasing blood volume, which ultimately leads to decreased blood pressure.

Low-dose diuretic therapy is safe, inexpensive, and effective in preventing stroke, myocardial infarction, and heart failure. Routine serum electrolyte monitoring should be done for all patients receiving diuretics

**A. Thiazide diuretics**

- Its 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.
- Thiazides are useful in combination therapy with a variety of other antihypertensive agents, including β-blockers, ACE inhibitors, ARBs, and potassium-sparing diuretics.
- Thiazide diuretics can induce hypokalemia, hyperuricemia and, to a lesser extent, hyperglycemia in some patients.




**B. Loop diuretics**

- The loop diuretics 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.
- Unlike thiazides, loop diuretics increase the Ca2+ 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.

**C. Potassium-sparing diuretics**

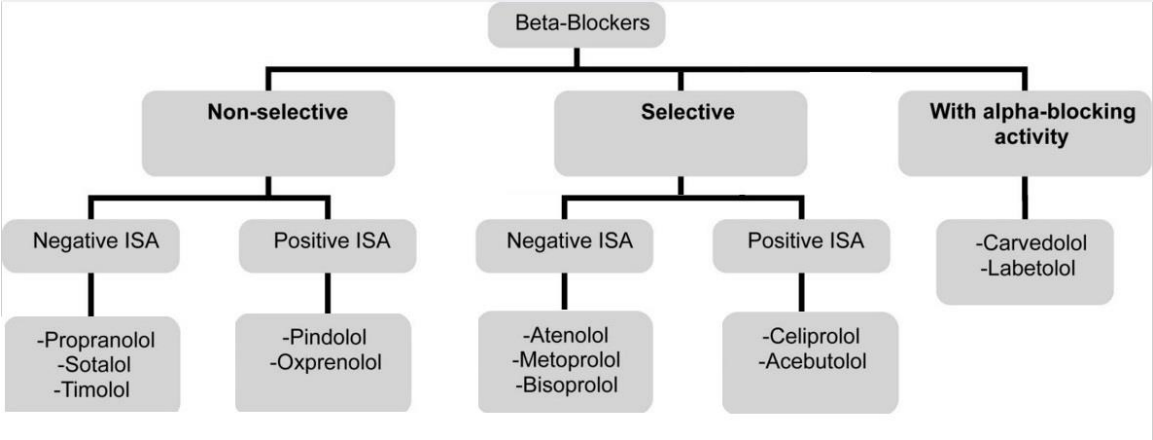
*Amiloride* (inhibitors of epithelial sodium transport at the late distal and collecting ducts) as well as *spironolactone* (aldosterone receptor antagonists) reduce potassium loss in the urine.

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.

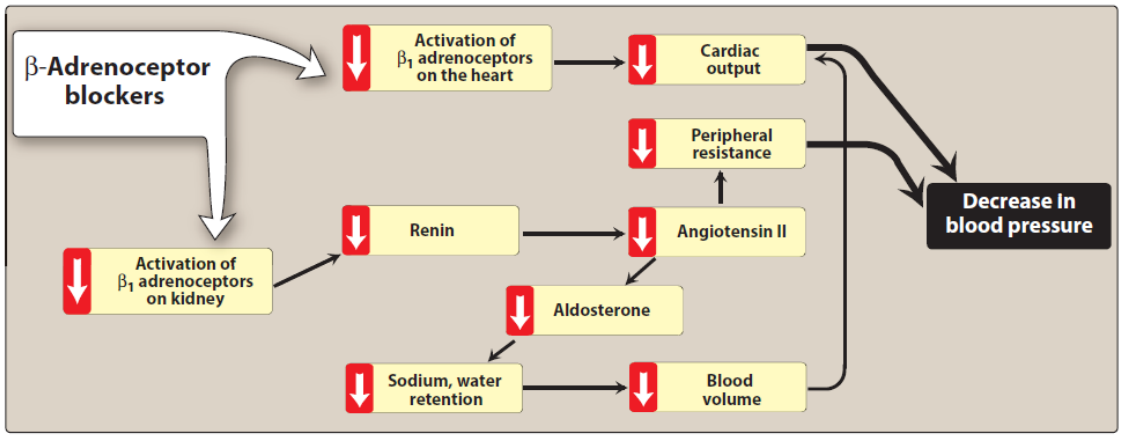
## 2- β-Adrenoceptor–Blocking Agents

β-Blockers are a treatment option for hypertensive patients with concomitant heart disease or heart failure .




## A. Actions

The β-blockers reduce blood pressure primarily by decreasing cardiac output. They may also decrease sympathetic outflow from the central nervous system (CNS) and inhibit the release of renin from the kidneys, thus decreasing the formation of angiotensin II and the secretion of aldosterone.




The type's β-blocker are

- propranolol which acts at both β1 and β2 receptors.
- Selective blockers of β1 receptors, such as metoprolol and atenolol, are among the most commonly prescribed β-blockers.
- Nebivolol is a selective blocker of β1 receptors, which also increases the production of nitric oxide, leading to vasodilation.

## Notes

1. The selective β-blockers may be administered cautiously to hypertensive patients who also have asthma.
2. The nonselective β-blockers are contraindicated in patients with asthma due to their blockade of β2-mediated bronchodilator.
3. B-Blockers should be used cautiously in the treatment of patients with acute heart failure or peripheral vascular disease.

**B. Therapeutic uses**

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, angina pectoris, 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.

**D. Adverse effects**

**1. Common effects:** The β-blockers may cause bradycardia, hypotension, and CNS side effects such as fatigue, lethargy, and insomnia. The β-blockers may decrease libido and cause erectile dysfunction, which can severely reduce patient compliance.

**2. Alterations in serum lipid patterns:** Non cardio-selective β-blockers may disturb lipid metabolism, decreasing high-density lipoprotein cholesterol and increasing triglycerides.

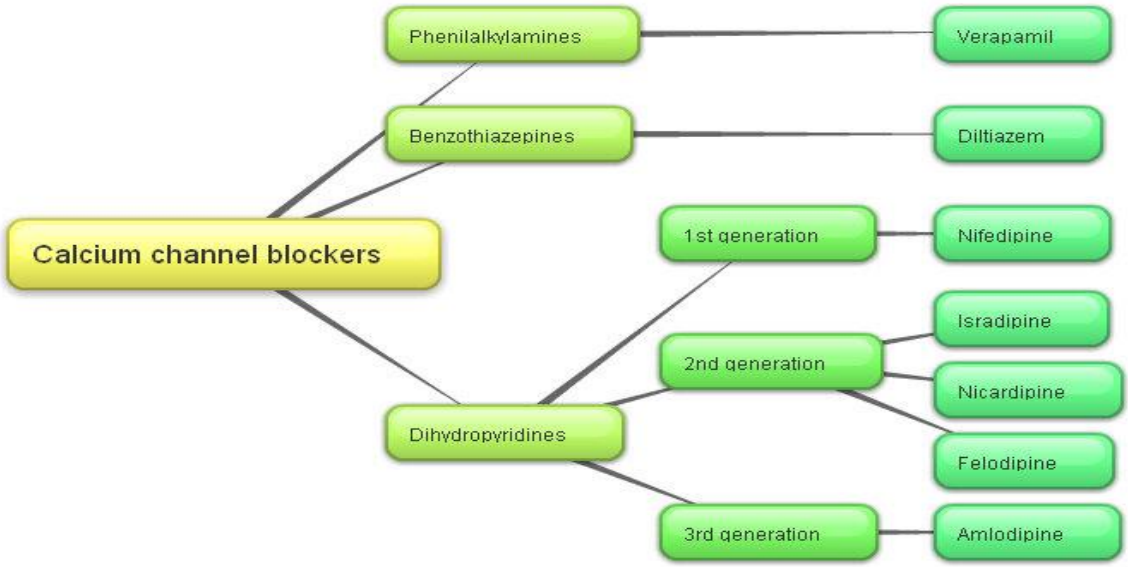
**3. Drug withdrawal:** Abrupt withdrawal may induce angina, myocardial infarction, and even sudden death in patients with ischemic heart disease. Therefore, these drugs must be tapered over a few weeks in patients with hypertension and ischemic heart disease.

## 3- Calcium Channel Blockers

Calcium channel blockers are a recommended treatment option in hypertensive patients with diabetes or angina. High doses of short-acting calcium channel blockers should be avoided because of increased risk of myocardial infarction due to excessive vasodilation and marked reflex cardiac stimulation.

### A. Classes of calcium channel blockers

The calcium channel blockers are divided into three chemical classes, each with different pharmacokinetic properties and clinical indications



**1. Diphenylalkylamines:** *Verapamil* is the only member of this class that is available in the United States. *Verapamil* is the **least selective** of any calcium channel blocker and has **significant effects on both cardiac and vascular smooth muscle cells**. It is also used to treat angina and supraventricular tachyarrhythmias and to prevent migraine and cluster headaches.

**2. Benzothiazepines:** *Diltiazem* is the only member of this class that is currently approved in the United States. Like *verapamil*, *diltiazem* affects **both cardiac and vascular smooth muscle cells**, but it has a **less pronounced negative inotropic effect on the heart compared to that of *verapamil***. *Diltiazem* has a favorable side effect profile.

**3. Dihydropyridines:** This class of calcium channel blockers includes *nifedipine*, *amlodipine*, *felodipine*. These agents differ in pharmacokinetics, approved uses, and drug interactions. All dihydropyridines have a much **greater affinity for vascular calcium channels than for calcium channels in the heart**. They are, therefore, particularly 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.

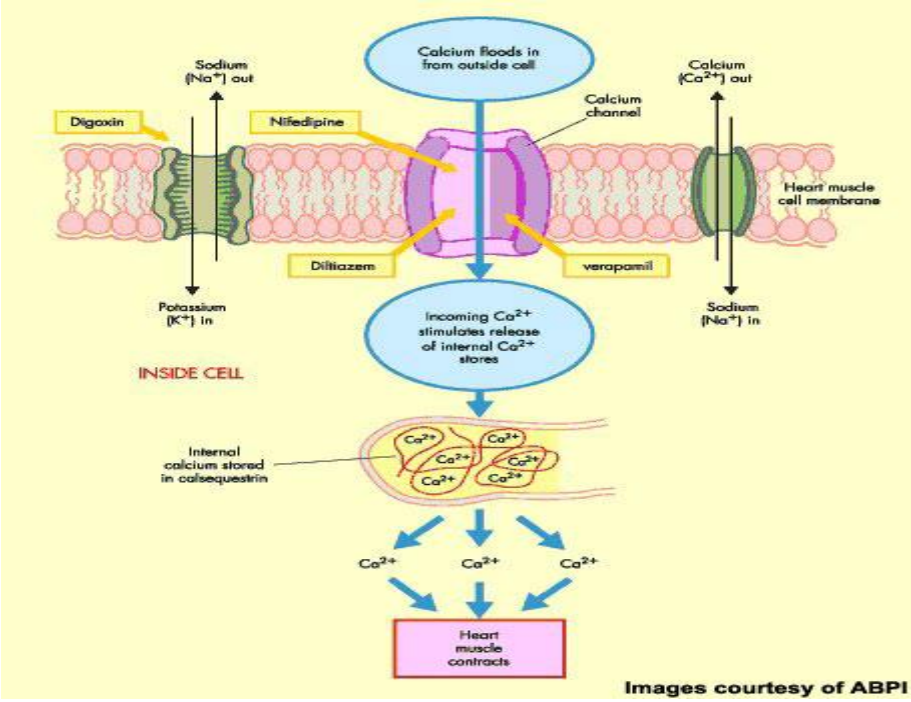
**B. Actions**

The intracellular concentration of calcium plays an important role in

1. maintaining the tone of smooth muscle
2. The contraction of the myocardium.

Calcium enters muscle cells through special voltage sensitive calcium channels. This triggers release of calcium from the sarcoplasmic reticulum and mitochondria, which further increases the cytosolic level of calcium.

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.




## C. Therapeutic uses

In the management of hypertension, CCBs may be used as an initial therapy or as add-on therapy. They are useful in the treatment of hypertensive patients who also have asthma, diabetes, and/or peripheral vascular disease, because unlike β-blockers, they do not have the potential to adversely affect these conditions. All CCBs are useful in the treatment of angina. In addition, *diltiazem* and *verapamil* are used in the treatment of atrial fibrillation.

## E. 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 side effect of dihydropyridines.
- dihydropyridines may cause gingival hyperplasia.

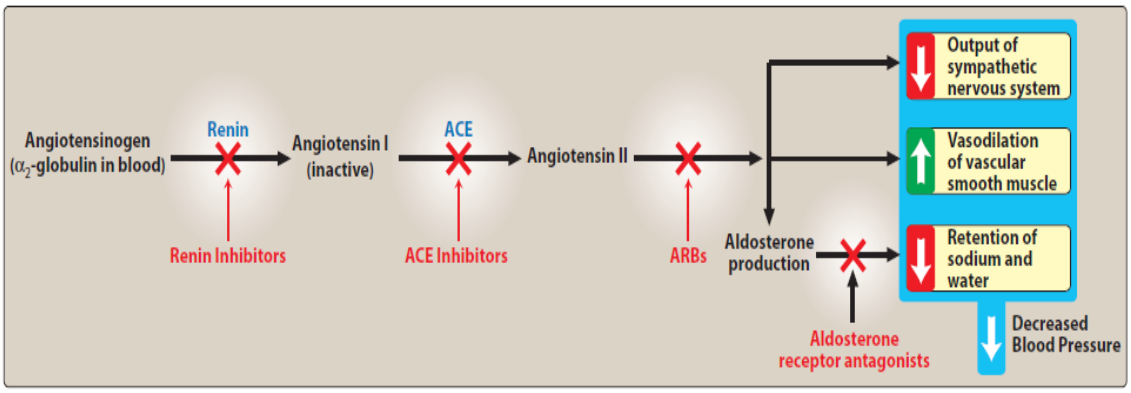
# 4- Angiotensin Converting Enzyme Inhibitor (ACE inhibitors)

- The ACE inhibitors, such as *enalapril* and *lisinopril*
- Recommended as first-line treatment of hypertension inpatients with a variety of compelling indications, including high coronary disease risk or history of diabetes, stroke, heart failure, myocardial infarction, or chronic kidney disease.

**A. Actions**

The ACE inhibitors lower blood pressure by reducing peripheral vascular resistance **without** reflexively increasing cardiac output, heart rate, or contractility.

- These drugs block the enzyme ACE which cleaves angiotensin I to form the potent vasoconstrictor angiotensin II.
- ACE is also responsible for the breakdown of **bradykinin**, a peptide that increases the production of nitric oxide and prostacyclin by the blood vessels. Both nitric oxide and prostacyclin are potent vasodilators. ACE inhibitors decrease angiotensin II and increase bradykinin levels.
- Vasodilation of both arterioles and veins occurs as a result of decreased vasoconstriction (from diminished levels of angiotensin II) and enhanced vasodilation (from increased bradykinin).
- ACE inhibitors also decrease the secretion of aldosterone, resulting in decreased sodium and water retention.
- ACE inhibitors reduce both cardiac preload and afterload, thereby decreasing cardiac work.




**B. Therapeutic uses**

1. ACE inhibitors slow the progression of diabetic nephropathy and decrease albuminuria and, thus, have a compelling indication for use in patients with diabetic nephropathy. **Beneficial effects** on renal function may result from decreasing intra-glomerular pressures, due to efferent arteriolar vasodilation.
2. ACE inhibitors are a standard in the care of a patient following a myocardial infarction and first-line agents in the treatment of patients with systolic dysfunction.
3. Chronic treatment with ACE inhibitors achieves sustained blood pressure reduction, regression of left ventricular hypertrophy, and prevention of ventricular remodeling after a myocardial infarction.
4. ACE inhibitors are **first-line drugs** for treating heart failure, hypertensive patients with chronic kidney disease, and patients at increased risk of coronary artery disease.
5. All of the ACE inhibitors are **equally effective** in the treatment of hypertension at equivalent doses.

**D. Adverse effects**

Common side effects include

1. dry cough is thought to be due to increased levels of bradykinin and substance P in the pulmonary tree and resolves within a few days of discontinuation
2. Rash.
3. Fever.
4. Altered taste.
5. Hypotension (in hypovolemic states).
6. Hyperkalemia **(why??).** Potassium levels must be monitored while on ACE inhibitors, and potassium supplements and potassium-sparing diuretics should be used with caution due to the risk of hyperkalemia
7. Angioedema is a rare but potentially life-threatening reaction that may also be due to increased levels of bradykinin.
8. Serum creatinine levels should also be monitored, particularly in patients with underlying renal disease. However, an increase in serum creatinine of up to 30% above baseline is acceptable.
9. ACE inhibitors can induce **fetal malformations** and should not be used by pregnant women.

## 5- Angiotensin Receptor Blockers (ARBs)

- The ARBs, such as *losartan* and *irbesartan*,
- alternatives to the ACE inhibitors.
- These drugs 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 and decreasing salt and water retention**.

- ARBs do not increase bradykinin levels.
- 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**.
- ARBs **should not** be combined with an ACE inhibitor for the treatment of hypertension due to similar mechanisms and adverse effects.
- These agents are also teratogenic and should **not be used** by pregnant women.

## 6- Renin inhibitors

- A selective 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.
- It lowers blood pressure about as effectively as ARBs, ACE inhibitors, and thiazides.
- *Aliskiren* should not be routinely combined with an ACE inhibitor or ARB.
- *Aliskiren* can cause diarrhea, especially at higher doses, and can also cause cough and angioedema, but probably less often than ACE inhibitors.
- As with ACE inhibitors and ARBs, *aliskiren* is contraindicated during pregnancy.

## 7-α-Adrenoceptor Blocking Agents

- *Prazosin, doxazosin,* and *terazosin* 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**.
- These drugs cause only **minimal changes** in cardiac output, renal blood flow, and glomerular filtration rate.
- 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(why??)**.
- 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.
- $\alpha_1$-blockers with greater selectivity for prostate muscle are used in the treatment of benign prostatic hyperplasia.

### 8- α/β Adrenoceptors Blocking Agents

- *Labetalol* and *carvedilol* block $\alpha_1$, $\beta_1$, and $\beta_2$ receptors.
- *Carvedilol,* although an effective antihypertensive, is mainly used in the treatment of heart failure.
- *Carvedilol,* as well as *metoprolol succinate,* and *bisoprolol* have been shown to reduce morbidity and mortality associated with heart failure.
- *Labetalol* is used in the management of gestational hypertension and hypertensive emergencies.

## 9- Centrally acting adrenergic drugs

**A. Clonidine**

- *Clonidine* acts centrally as a **$\alpha_2$ agonist** to produce inhibition of sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery. This leads to reduced total peripheral resistance and decreased blood pressure.
- *Clonidine* is used primarily for the treatment of hypertension that has not responded adequately to treatment with two or more drugs.
- *Clonidine* does **not** decrease renal blood flow or glomerular filtration and, therefore, **is useful in the treatment of hypertension complicated by renal disease** (**why??**).
- Adverse effects include sedation, dry mouth, and constipation. Rebound hypertension occurs following abrupt withdrawal of *clonidine.*

**B. Methyldopa**

- *Methyldopa* is an **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.
- Its use is limited due to adverse effects and the need for multiple daily doses.
- It is mainly used for management of hypertension in pregnancy, where it has a record of safety.

## 10- 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.
- 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**(why??).**

- Vasodilators also **increase** plasma renin concentration, resulting in sodium and water retention.
- These undesirable side effects can be blocked by concomitant use of a diuretic and a β-blocker. For example, *hydralazine* is almost always administered in combination with a β-blocker, such as *propranolol*, *metoprolol*, or *atenolol* (to balance the reflex tachycardia) and a diuretic (to decrease sodium retention). Together, the three drugs decrease cardiac output, plasma volume, and peripheral vascular resistance.
- *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.

## 11- Combination therapy

- Combination therapy with separate agents or a fixed-dose combination pill may lower blood pressure more quickly with minimal adverse effects.
- Initiating therapy with two antihypertensive drugs should be considered in patients with blood pressures that are more than 20/10 mm Hg above the goal.

- A variety of combination formulations of the various pharmacologic classes are available to increase ease of patient adherence to treatment regimens that require multiple medications to achieve the blood pressure goal

## Resistance hypertension

Resistant hypertension is defined as blood pressure that remains elevated despite administration of an optimal three-drug regimen that includes a diuretic.

The most common causes of resistant hypertension

1. Poor compliance.
2. Excessive ethanol intake.
3. Concomitant conditions (diabetes, obesity, sleep apnea, hyperaldosteronism, high salt intake, and/or metabolic syndrome).
4. Concomitant medications (sympathomimetics, nonsteroidal anti-inflammatory drugs, or antidepressant medications).
5. Insufficient dose and/or drugs.
6. Use of drugs with similar mechanisms of action.

# Anti-Anginal Drugs

- Atherosclerotic disease of the coronary arteries, also known as coronary artery disease (CAD) or ischemic heart disease (IHD), is the most common cause of mortality worldwide.
- Atherosclerotic lesions in coronary arteries can obstruct blood flow, leading to an imbalance in myocardial oxygen supply and demand that presents as stable angina or an acute coronary syndrome (myocardial infarction [MI] or unstable angina).
- Spasms of vascular smooth muscle may also impede cardiac blood flow, reducing perfusion and causing ischemia and angina pain.
- Typical angina pectoris is a characteristic sudden, severe, crushing chest pain that may radiate to the neck, jaw, back, and arms. Patients may also present with dyspnea or atypical symptoms such as indigestion, nausea, vomiting, or diaphoresis.
- Transient, self-limited episodes of myocardial ischemia (stable angina) do not result in cellular death; however, acute coronary syndromes and chronic ischemia can lead to deterioration of cardiac function, heart failure, arrhythmias, and sudden death.
- All patients with IHD and angina should receive guideline-directed medical therapy with emphasis on lifestyle modifications (smoking cessation, physical activity, weight management) and management of modifiable risk factors (hypertension, diabetes, dyslipidemia) to reduce cardiovascular morbidity and mortality

## Types of angina

Angina pectoris has three patterns:

1) Stable, effort-induced, classic, or typical angina.

2) Unstable angina.

3) Prinzmetal, variant, vasospastic, or rest angina.

### A. Stable angina, effort-induced angina, classic or typical angina

- It is usually characterized by a short-lasting burning, heavy, or squeezing feeling in the chest.
- Some ischemic episodes may present "atypically"—with extreme fatigue, nausea, or diaphoresis—while others may not be associated with any symptoms (silent angina).
- Classic angina is caused by the reduction of coronary perfusion due to a **fixed obstruction of a coronary artery produced by atherosclerosis**. Due to the fixed obstruction, the blood supply cannot increase, and the heart becomes susceptible to ischemia whenever there is **increased demand**, such as that produced by physical activity, emotional stress or excitement, or any other cause of increased cardiac workload.
- Typical angina pectoris is promptly relieved by rest or ***nitroglycerin***.
- When the pattern of the chest pains and the amount of effort needed to trigger the chest pains do not vary over time, the angina is named "stable angina".

### B. Unstable angina

- Unstable angina is classified between stable angina and MI.
- In unstable angina, chest pain occurs with increased frequency, duration, and intensity and can be precipitated by progressively less effort.

- Any episode of rest angina longer than 20 minutes, any new-onset angina, any increasing angina, or even sudden development of shortness of breath is suggestive of unstable angina.
- The symptoms are not relieved by rest or *nitroglycerin*.
- Unstable angina is a form of acute coronary syndrome and requires hospital admission and more aggressive therapy to prevent progression to MI and death.

**C. Prinzmetal, variant, vasospastic, or rest angina**

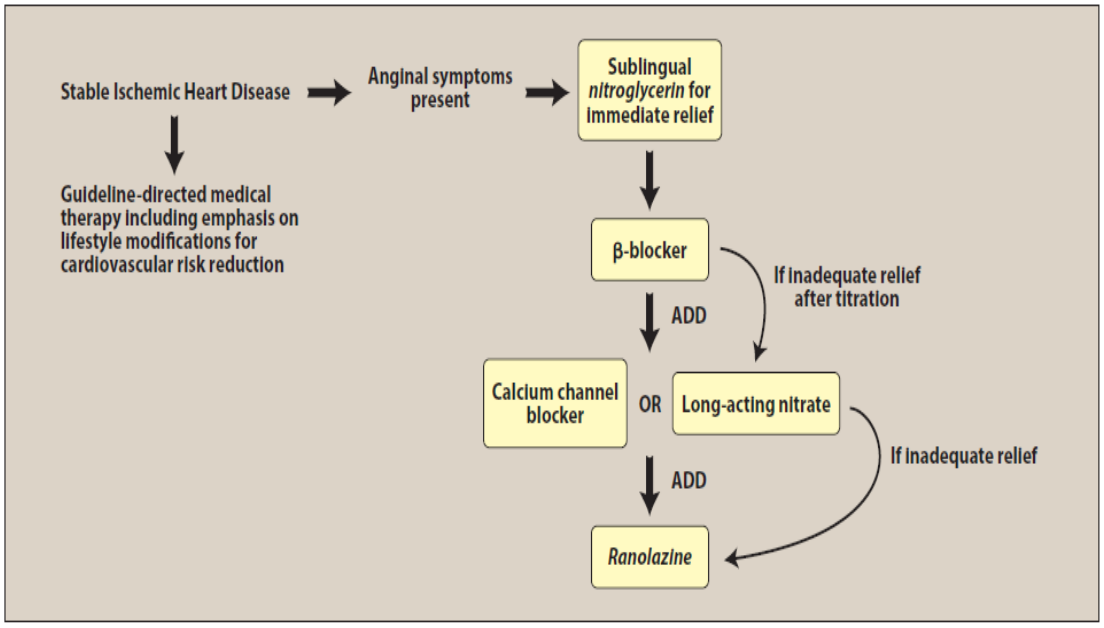
- Prinzmetal angina is an uncommon pattern of episodic angina that occurs at rest and is due to coronary artery spasm.
- Symptoms are caused by decreased blood flow to the heart muscle from the spasm of the coronary artery.
- Although individuals with this form of angina may have significant coronary atherosclerosis, the angina attacks are unrelated to physical activity, heart rate, or blood pressure.
- Prinzmetal angina generally responds promptly to coronary vasodilators, such as *nitroglycerin* and calcium channel blockers.

**D. Acute coronary syndrome**

- Acute coronary syndrome is an emergency that commonly results from rupture of an atherosclerotic plaque and partial or complete thrombosis of a coronary artery.
- Most cases occur from disruption of an atherosclerotic lesion, followed by platelet activation of the coagulation cascade and vasoconstriction. This process culminates in intraluminal thrombosis and vascular occlusion. If the thrombus occludes most of the blood vessel, and, if the occlusion is untreated, necrosis of the cardiac muscle may ensue.

## Treatment strategies

- Four types of drugs, used either alone or in combination, are commonly used to manage patients with stable angina: **β-blockers**, **calcium channel blockers**, **organic nitrates**, and the **sodium channel–blocking drug**.
- These agents help to balance the cardiac oxygen supply and demand equation by affecting blood pressure, venous return, heart rate, and contractility.




### 1- B-adrenergic blockers

- The β-adrenergic blockers decrease the oxygen demands of the myocardium by blocking β1 receptors, resulting in decreased heart rate, contractility, cardiac output, and blood pressure.
- These agents reduce myocardial oxygen demand during exertion and at rest. As such, they can reduce both the frequency and severity of angina attacks.
- B-Blockers can be used to increase exercise duration and tolerance in patients with effort-induced angina.

- B-Blockers are recommended as initial antianginal therapy in all patients unless contraindicated. [Note: The exception to this rule is vasospastic angina, in which β-blockers are ineffective and may actually worsen symptoms.]
- β-Blockers reduce the risk of death and MI in patients who have had a prior MI and also improve mortality in patients with hypertension and heart failure with reduced ejection fraction.
- *Propranolol* is the prototype for this class of compounds, but it is not cardio-selective. Thus, other β-blockers, such as *metoprolol* and *atenolol*, are preferred. [Note: All β-blockers are nonselective at high doses and can inhibit β2 receptors.]
- β-Blockers should be avoided in patients with severe bradycardia; however, they can be used in patients with diabetes, peripheral vascular disease, and chronic obstructive pulmonary disease, as long as they are monitored closely.

**2-Calcium channel blockers**

- Calcium is essential for muscular contraction. Calcium influx is increased in ischemia because of the membrane depolarization that hypoxia produces. In turn, this promotes the activity of several ATP-consuming enzymes, thereby depleting energy stores and worsening the ischemia.
- The calcium channel blockers protect the tissue by inhibiting the entrance of calcium into cardiac and smooth muscle cells of the coronary and systemic arterial beds.
- All calcium channel blockers are, therefore, arteriolar vasodilators that cause a decrease in smooth muscle tone and vascular resistance.

- These agents primarily affect the resistance of peripheral and coronary arteriolar smooth muscle. In the treatment of effort-induced angina, calcium channel blockers reduce myocardial oxygen consumption by decreasing vascular resistance, thereby decreasing afterload.
- Their efficacy in vasospastic angina is due to relaxation of the coronary arteries.

**A. Dihydropyridine calcium channel blockers**

- *Amlodipine* an oral dihydropyridine, functions mainly as an arteriolar vasodilator.
- This drug has minimal effect on cardiac conduction.
- The vasodilatory effect of *amlodipine* is useful in the treatment of variant angina caused by spontaneous coronary spasm.
- *Nifedipine* is another agent in this class; it is usually administered as an extended-release oral formulation.

**B. Non-dihydropyridine calcium channel blockers**

- *Verapamil* slows atrioventricular (AV) conduction directly and decreases heart rate, contractility, blood pressure, and oxygen demand.
- *Verapamil* has greater negative inotropic effects than *amlodipine*, but it is a weaker vasodilator.
- *Verapamil* is contraindicated in patients with preexisting depressed cardiac function or AV conduction abnormalities.
- *Diltiazem* also slows AV conduction, decreases the rate of firing of the sinus node pacemaker, and is also a coronary artery vasodilator.
- *Diltiazem* can relieve coronary artery spasm and is particularly useful in patients with variant angina.

- Nondihydropyridine calcium channel blockers can worsen heart failure due to their negative inotropic effect, and their use should be avoided in this population.

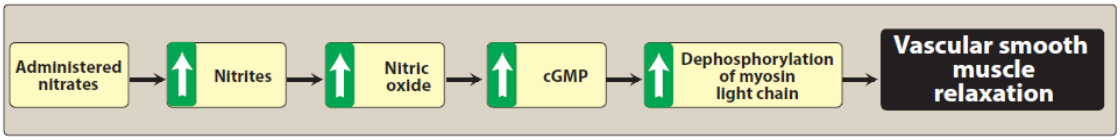
**3- Organic Nitrates**

These compounds cause a reduction in myocardial oxygen demand, followed

by relief of symptoms. They are effective in stable, unstable, and variant angina.

**A. Mechanism of action**

- Organic nitrates relax vascular smooth muscle by their intracellular conversion to nitrite ions and then to nitric oxide, which activates guanylate cyclase and increases the cells' cyclic guanosine monophosphate (cGMP).
- Elevated cGMP ultimately leads to dephosphorylation of the myosin light chain, resulting in vascular smooth muscle relaxation.
- Nitrates such as *nitroglycerin* cause dilation of the large veins, which reduces preload (venous return to the heart) and, therefore, reduces the work of the heart.
- This is believed to be their main mechanism of action in the treatment of angina. Nitrates also dilate the coronary vasculature, providing an increased blood supply to the heart muscle.




**Adverse effects**

- Headache is the most common adverse effect of nitrates.
- High doses of nitrates can also cause postural hypotension.

- Facial flushing.
- Tachycardia.
- Phosphodiesterase type 5 inhibitors such as *sildenafil* potentiate the action of the nitrates.
- Tolerance to the actions of nitrates develops rapidly as the blood vessels become desensitized to vasodilation. Tolerance can be overcome by providing a daily "nitrate-free interval" to restore sensitivity to the drug. This interval of 10 to 12 hours is usually taken at night because demand on the heart is decreased at that time.
- *Nitroglycerin* patches are worn for 12 hours and then removed for 12 hours.
- Variant angina worsens early in the morning, perhaps due to circadian catecholamine surges. Therefore, the nitrate-free interval in these patients should occur in the late afternoon.

**4. Sodium Channel Blocker**

- *Ranolazine* inhibits the late phase of the sodium current (late INa), improving the oxygen supply and demand equation.
- Inhibition of late INa reduces intracellular sodium and calcium overload, thereby improving diastolic function.
- *Ranolazine* has antianginal as well as antiarrhythmic properties. It is indicated for the treatment of chronic angina and may be used alone or in combination with other traditional therapies.
- It is most often used in patients who have failed other antianginal therapies.

| DRUG CLASS | COMMON ADVERSE EFFECTS | DRUG INTERACTIONS | NOTES |
|---|---|---|---|
| β-blockers<br><br>*atenolol*<br>*metoprolol*<br>*propranolol* | Bradycardia, worsening peripheral vascular disease, fatigue, sleep disturbance, depression, blunt hypoglycemia awareness, inhibit $\beta_2$-mediated bronchodilation in asthmatics | $\beta_2$ agonists (blunted effect); non-dihydropyridine calcium-channel blockers (additive effects) | $\beta_1$-selective agents preferred (*atenolol, metoprolol*). Avoid agents with ISA for angina therapy (*pindolol*). |
| Dihydropyridine calcium-channel blockers<br><br>*amlodipine*<br>*felodipine*<br>*nifedipine* | Peripheral edema, headache, flushing, rebound tachycardia (immediate release formulations), hypotension | CYP 3A4 substrates (will increase drug concentrations) | Avoid short-acting agents as they can worsen angina (may use extended-release formulations) |
| Non-dihydropyridine calcium-channel blockers<br><br>*diltiazem*<br>*verapamil* | Bradycardia, constipation, heart failure exacerbations, gingival hyperplasia (*verapamil*), edema (*diltiazem*) | CYP 3A4 substrates (will increase drug concentrations); increase *digoxin* levels; β-blockers and other drugs affecting AV node conduction (additive effects) | Avoid in patients with heart failure<br><br>Adjust dose of both agents in patients with hepatic dysfunction |
| Organic nitrates<br><br>*Isosorbide dinitrate*<br>*Isosorbide mononitrate*<br>*nitroglycerin* | Headache, hypotension, flushing, tachycardia | Contraindicated with PDE5 inhibitors (*sildenafil* and others) | Ensure nitrate-free interval to prevent tolerance |
| Sodium-channel inhibitor<br><br>*ranolazine* | Constipation, headache, edema, dizziness, QT interval prolongation | Avoid use with CYP 3A4 inducers (*phenytoin, carbamazepine, St. John's wort*) and strong inhibitors (*clarithromycin*, azole antifungals) and agents that prolong QT interval (*citalopram, quetiapine*, others) | No effect on hemodynamic parameters |

CYP = cytochrome P450; ISA = intrinsic sympathomimetic activity; PDE5 = phosphodiesterase type 5

# Anticoagulant and Antiplatelet

Thrombosis, the formation of an unwanted clot within a blood vessel, is the most common abnormality of hemostasis. Thrombotic complication are

- include acute myocardial infarction (MI)
- deep vein thrombosis (DVT)
- pulmonary embolism (PE)
- Acute ischemic stroke.

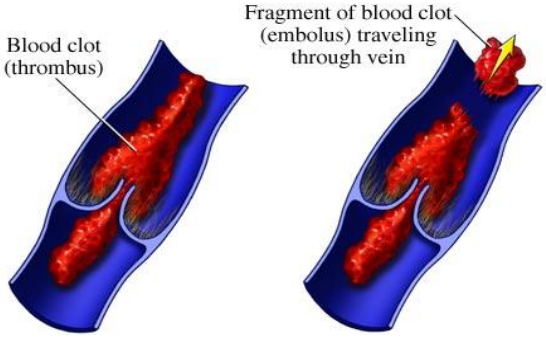
These conditions are treated with drugs such as anticoagulants and fibrinolysis.

Bleeding disorders involving the failure of hemostasis are **less common** than thromboembolic diseases. These disorders include hemophilia, which is treated with transfusion of recombinant factor VIII, and vitamin K deficiency, which is treated with vitamin K supplementation

**Thrombus versus Embolus**

A clot that adheres to a vessel wall is called a "thrombus," whereas an intravascular clot that floats in the blood is termed an "embolus." Thus, a detached thrombus becomes an embolus.

Arterial thrombosis usually consists of a platelet-rich clot. Venous thrombosis typically involves a clot that is rich in fibrin, with fewer platelets than are observed with arterial clots.



**Platelet Response to Vascular Injury**

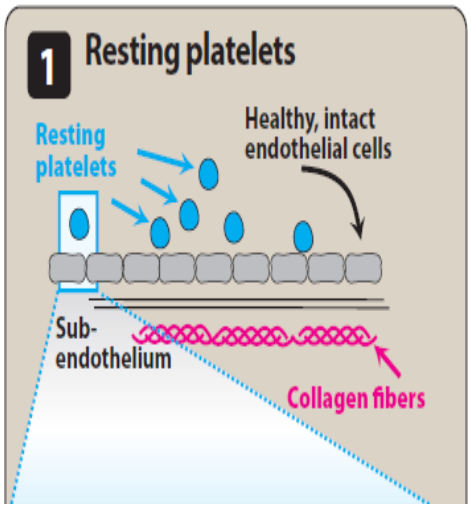
- Physical trauma to the vascular system, such as a puncture or a cut, initiates a complex series of interactions between **platelets**, **endothelial cells**, and the **coagulation cascade**.
- These interactions lead to hemostasis or the cessation of blood loss from a damaged blood vessel.
- Platelets are central in this process.

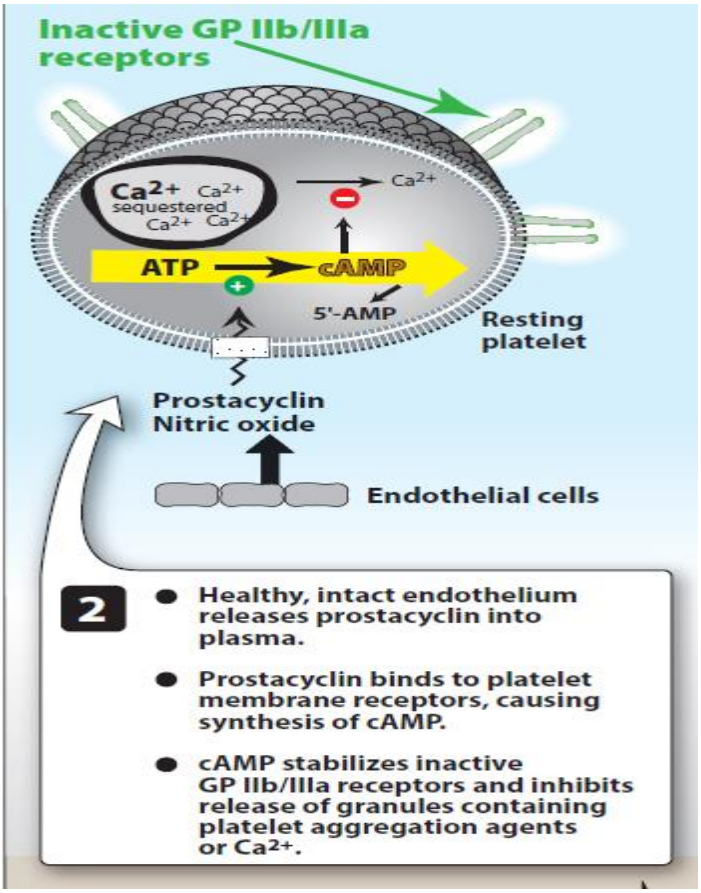
1. There is vasospasm of the damaged blood vessel to prevent further blood loss.
2. The next step involves the formation of a platelet–fibrin plug at the site of the puncture.

The creation of an unwanted thrombus involves many of the same steps as normal clot except that the triggering stimulus is a pathologic condition in the vascular system, rather than external physical trauma.

**A. Resting platelets**

Platelets act as vascular guards, monitoring the integrity of the vascular endothelium. In the absence of injury, resting platelets circulate freely, because the balance of chemical signals indicates that the vascular system is not damaged.




**1. Chemical mediators Synthesized by endothelial cells:**

Chemical mediators, such as

1) prostacyclin (prostaglandin I2)
2) nitric oxide

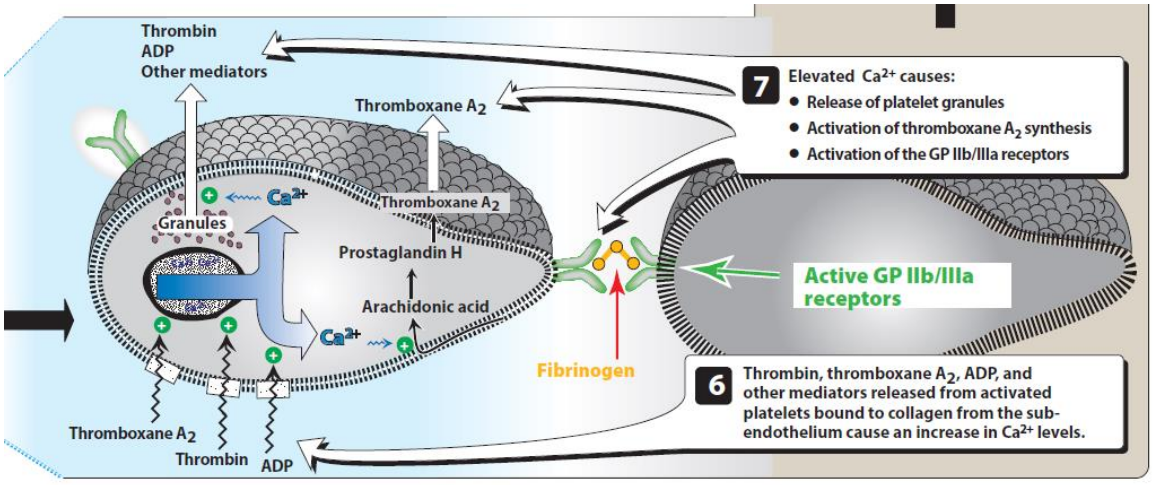
They are synthesized by **intact endothelial** cells and act as **<u>inhibitors of Platelet Aggregation.</u>**

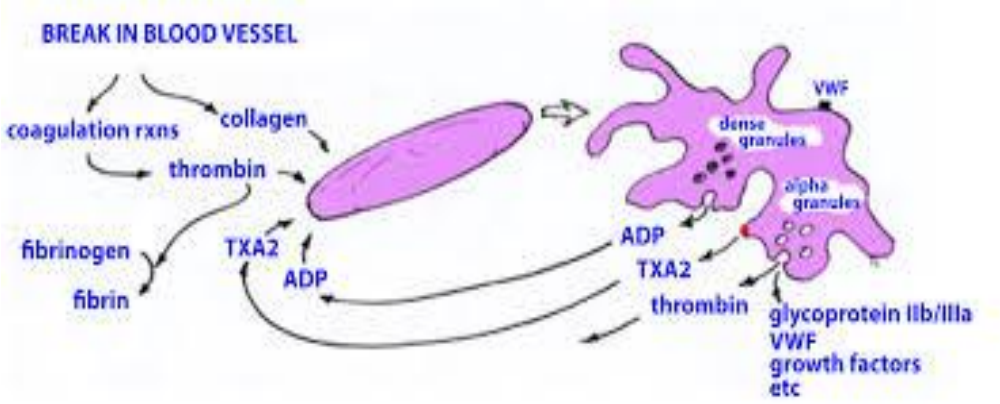
- Prostacyclin (prostaglandin I2) acts by binding to platelet membrane receptors that are coupled to the synthesis of cyclic adenosine monophosphate (cAMP), an intracellular messenger.

- Elevated levels of intracellular cAMP are associated with a decrease in intracellular calcium. This prevents platelet activation and the subsequent release of platelet aggregation agents.
- Damaged endothelial cells synthesize less prostacyclin than healthy cells, resulting in lower prostacyclin levels. Since there is less prostacyclin to bind platelet receptors, less intracellular cAMP is synthesized, which leads to platelet aggregation.

**2. Roles of Thrombin, Thromboxane, and Collagen:**

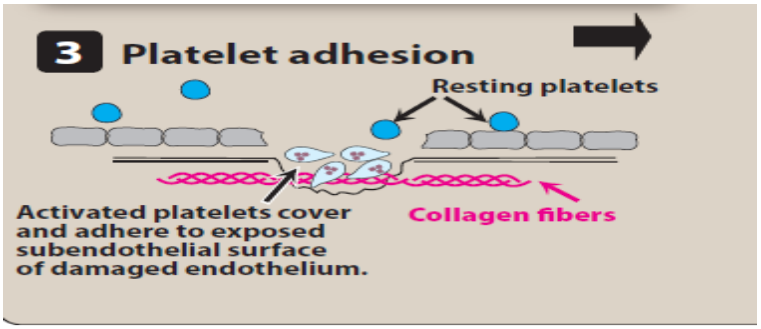
- The platelet membrane also contains receptors that can bind thrombin, thromboxane, and exposed collagen.
- In the intact, normal vessel, circulating levels of thrombin and thromboxane are low, and the intact endothelium covers the collagen in the sub-endothelial layers.
- The corresponding platelet receptors are, thus, **unoccupied**, and as a result, platelet activation and aggregation are not initiated.
- However, when occupied, each of these receptor types triggers a series of reactions leading to the release into the circulation of intracellular granules by the platelets. This ultimately stimulates platelet aggregation.






**B. Platelet Adhesion**

When the endothelium is injured, platelets adhere to and virtually cover the exposed collagen of the sub-endothelium. This triggers a complex series of chemical reactions, resulting in platelet activation.



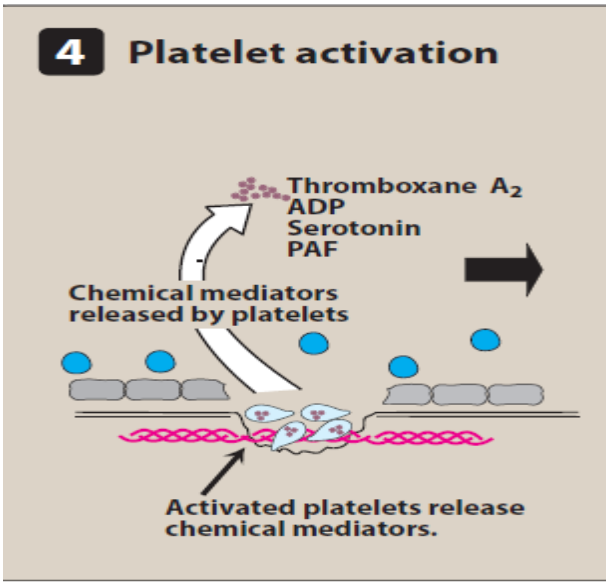

**C. Platelet Activation**

- Receptors on the surface of the adhering platelets are activated by the collagen of the underlying connective tissue.
- This causes morphologic changes in platelets and the release of platelet granules containing chemical mediators;

1) Adenosine diphosphate (ADP).
2) Thromboxane A2.
3) Serotonin.
4) Platelet activation factor.
5) Thrombin.

- These signaling molecules bind to receptors in the outer membrane of resting platelets circulating nearby. These receptors function as sensors that are activated by the signals sent from the adhering platelets. The previously dormant platelets become activated and start to aggregate.

These actions are mediated by several messenger systems that ultimately result in elevated levels of calcium and a decreased concentration of cAMP within the platelet.




**D. Platelet Aggregation**

The increase in cytosolic calcium accompanying activation is due to a release of sequestered stores within the platelet.

This leads to

1) The release of platelet granules containing mediators, such as ADP and serotonin that activate other platelets;

2) Activation of thromboxane A2 synthesis;

3) Activation of glycoprotein (GP) IIb/IIIa receptors that bind fibrinogen and, ultimately, regulate platelet–platelet interaction and thrombus formation.

- Fibrinogen, a soluble plasma GP, simultaneously binds to GP IIb/IIIa receptors on two separate platelets, resulting in platelet cross-linking and platelet aggregation. This leads to an avalanche of platelet aggregation, because each activated platelet can recruit other platelets

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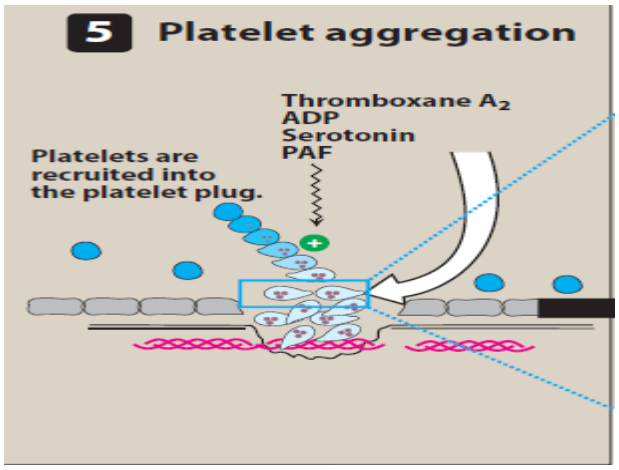
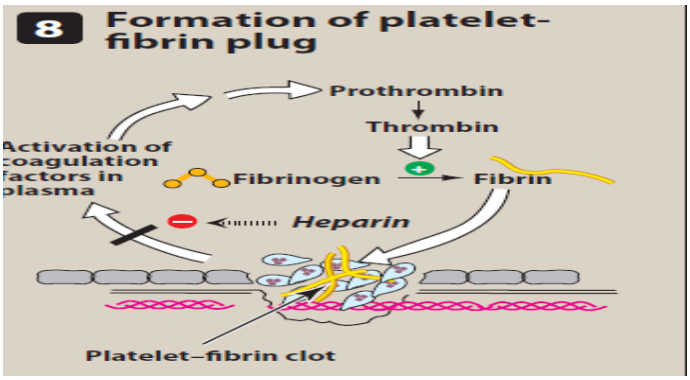


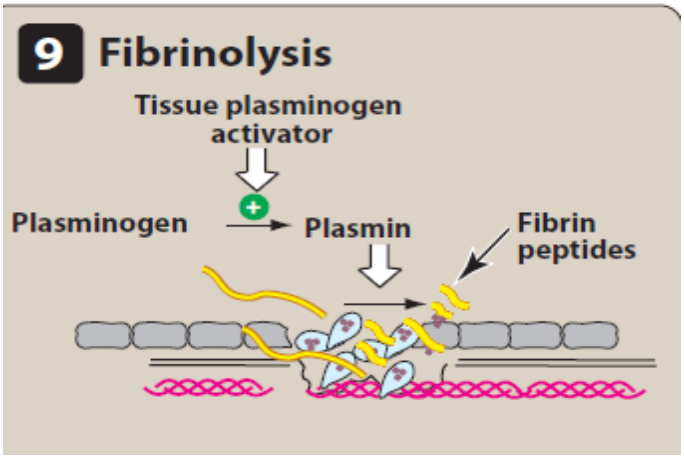

**E. Formation of a Clot**

Local stimulation of the coagulation cascade by **tissue factors** released from the injured tissue and by mediators on the surface of platelets results in the formation of thrombin (factor IIa). In turn, thrombin, a serine protease, catalyzes the hydrolysis of fibrinogen to fibrin, which is incorporated into the clot. Subsequent cross-linking of the fibrin strands stabilizes the clot and forms a hemostatic platelet–fibrin plug.



**F. Fibrinolysis**

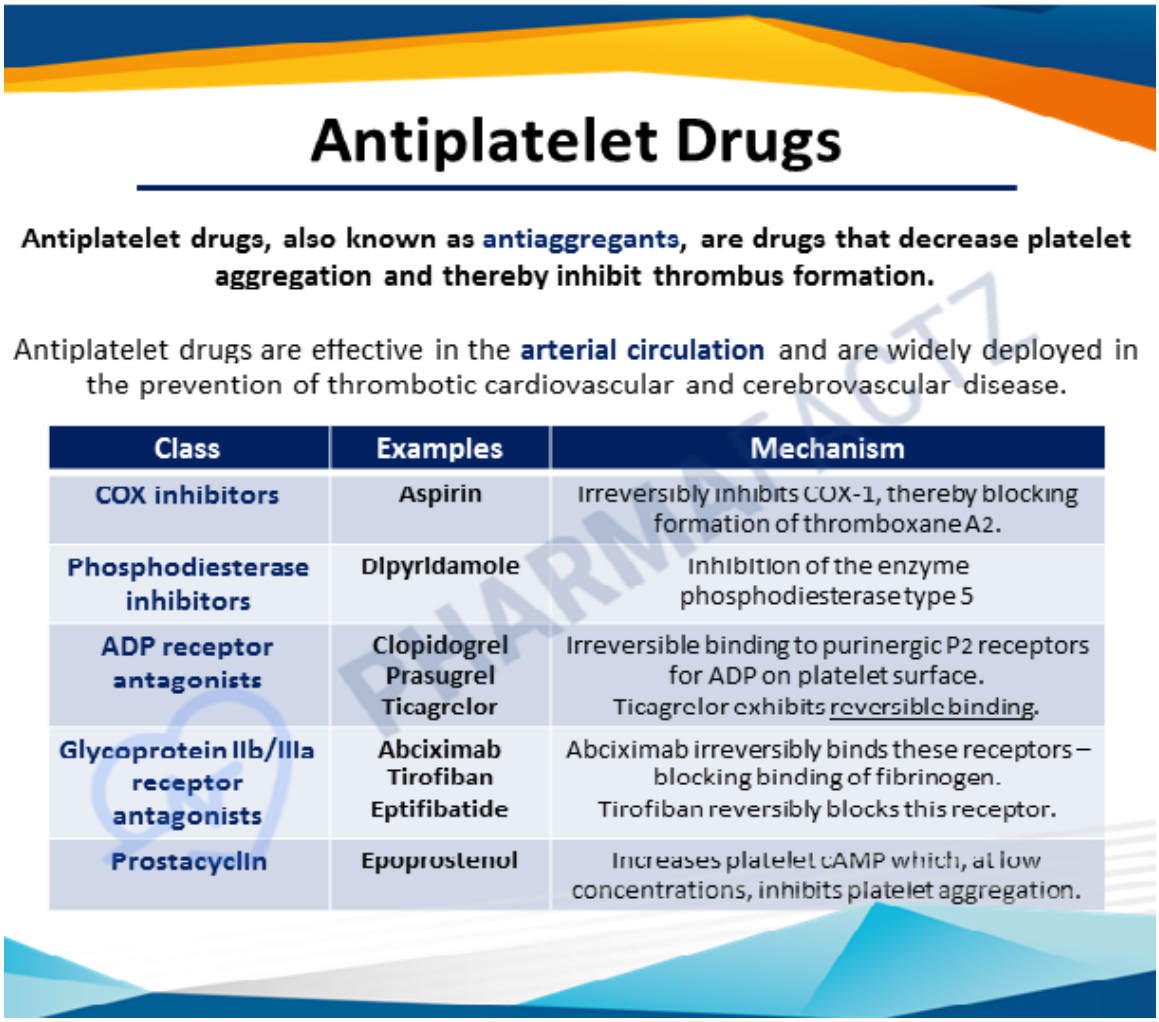
During clot formation, the fibrinolytic pathway is locally activated. Plasminogen is enzymatically processed to plasmin (fibrinolysin) by plasminogen activators in the tissue. Plasmin limits the growth of the clot and dissolves the fibrin network as wounds heal.




**Platelet Aggregation Inhibitors**

Platelet aggregation inhibitors decrease the formation of a platelet-rich clot or decrease the action of chemical signals that promote platelet aggregation. The platelet aggregation inhibitors described below **inhibit cyclooxygenase-1 (COX-1) or block GP IIb/IIIa or ADP receptors**, thereby interfering with the signals that promote platelet aggregation.

Because these agents have different mechanisms of actions, synergistic or additive effects may be achieved when agents from different classes are combined. These agents are beneficial in the prevention and treatment of occlusive cardiovascular diseases, in the maintenance of vascular grafts and arterial patency, and as adjuncts to thrombin inhibitors or thrombolytic therapy in MI.



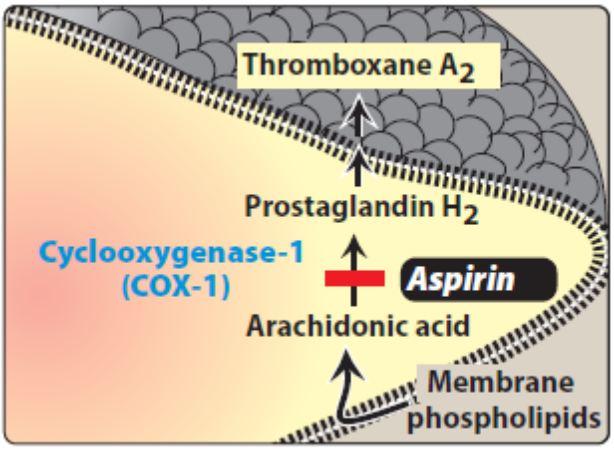

## A. Aspirin

**Mechanism of action:**

Stimulation of platelets by thrombin, collagen, and ADP results in activation of platelet membrane phospholipases that liberate arachidonic acid from membrane phospholipids. Arachidonic acid is first converted to prostaglandin H2 by COX-1 . Prostaglandin H2 is further metabolized to thromboxane A2, which is released into plasma. Thromboxane A2 promotes the aggregation process that is essential for the rapid formation of a hemostatic plug.

*Aspirin* inhibits thromboxane A2 synthesis by acetylation of a serine residue on the active site of COX-1, thereby **irreversibly inactivating the enzyme**. This shifts the balance of chemical mediators to favor the anti-aggregator effects of prostacyclin, thereby preventing platelet aggregation. The inhibitory effect is rapid, and *aspirin*-induced suppression of thromboxane A2 and the resulting suppression of platelet aggregation last for the life of the platelet, which is **approximately 7 to 10 days**.

Repeated administration of *aspirin* has a cumulative effect on the function of platelets. ***Aspirin* is the only antiplatelet agent that irreversibly inhibits platelet function**.




**Therapeutic use:**

*Aspirin* is used in the prophylactic treatment of transient cerebral ischemia, to reduce the incidence of recurrent MI, and to decrease mortality in the setting of primary and secondary prevention of MI.

**Adverse effects:**

1) Bleeding time is prolonged by *aspirin* treatment, causing complications that include an increased incidence of hemorrhagic stroke and gastrointestinal (GI) bleeding, especially at higher doses of the drug.

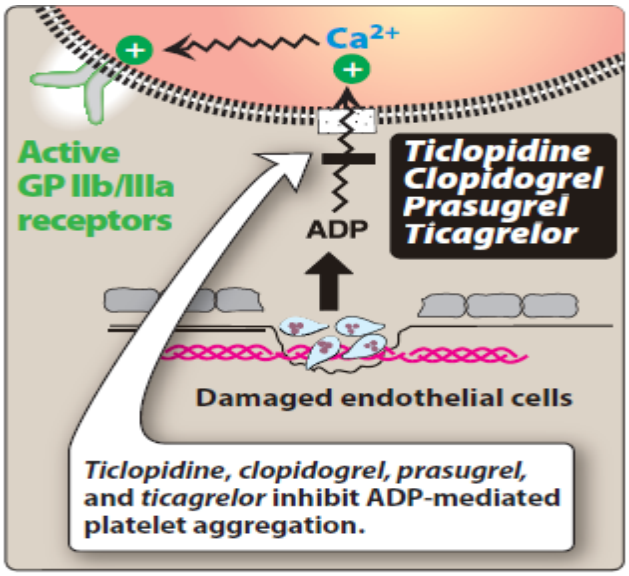
2) Non-steroidal anti-inflammatory drugs, such as *ibuprofen*, inhibit COX-1 by transiently competing at the catalytic site. *Ibuprofen*, if taken within the 2 hours prior to *aspirin*, can obstruct the access of *aspirin* to the serine residue and, thereby, antagonize platelet inhibition by *aspirin*. Therefore, immediate release *aspirin* should be taken at least 60 minutes before or at least 8 hours after *ibuprofen*.
3) Although *celecoxib* does not interfere with the anti-aggregation activity of *aspirin*, there is some evidence that it may contribute to cardiovascular events by shifting the balance of chemical mediators in favor of thromboxane A2.

**B. Ticlopidine, Clopidogrel.**

*Ticlopidine* , *clopidogrel* are P2Y12 ADP receptor inhibitors that also block platelet aggregation but by a mechanism different from that of *aspirin*.

**Mechanism of action:**

These drugs inhibit the binding of ADP to its receptors on platelets and, thereby, inhibit the activation of the GP IIb/IIIa receptors required for platelets to bind to fibrinogen and to each other . These agents bind irreversibly.




**Therapeutic use:**

1) *Clopidogrel* is approved for prevention of atherosclerotic events in patients with a recent MI or stroke and in those with established peripheral arterial disease.
2) It is also approved for prophylaxis of thrombotic events in acute coronary syndromes (unstable angina or non–ST-elevation MI).
3) *clopidogrel* is used to prevent thrombotic events associated with percutaneous coronary intervention (PCI) with or without coronary stenting.
4) *ticlopidine* is generally reserved for patients who are intolerant to other therapies.

**Adverse effects:**

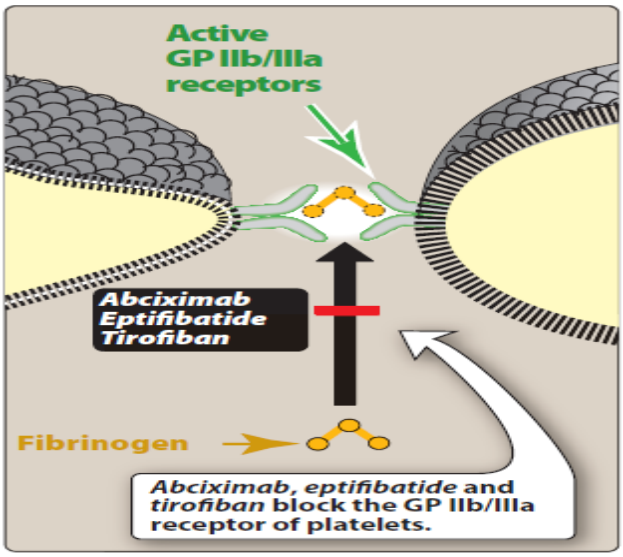
- These agents can cause prolonged bleeding for which there is no antidote.
- *Ticlopidine* is associated with severe hematologic reactions that limit its use, such as agranulocytosis, thrombotic thrombocytopenic purpura
- Aplastic anemia.

- *Clopidogrel* causes fewer adverse reactions, and the incidence of neutropenia is lower.

## Abciximab.

**Mechanism of action:**

The GP IIb/IIIa receptor plays a key role in stimulating platelet aggregation. A monoclonal antibody, *abciximab*, inhibits the GP IIb/IIIa receptor complex. By binding to GP IIb/IIIa, *abciximab* blocks the binding of fibrinogen and, consequently, aggregation does not occur




**Adverse effects:**

The major adverse effect of these agents is bleeding, especially if used with anticoagulants.

## Dipyridamole

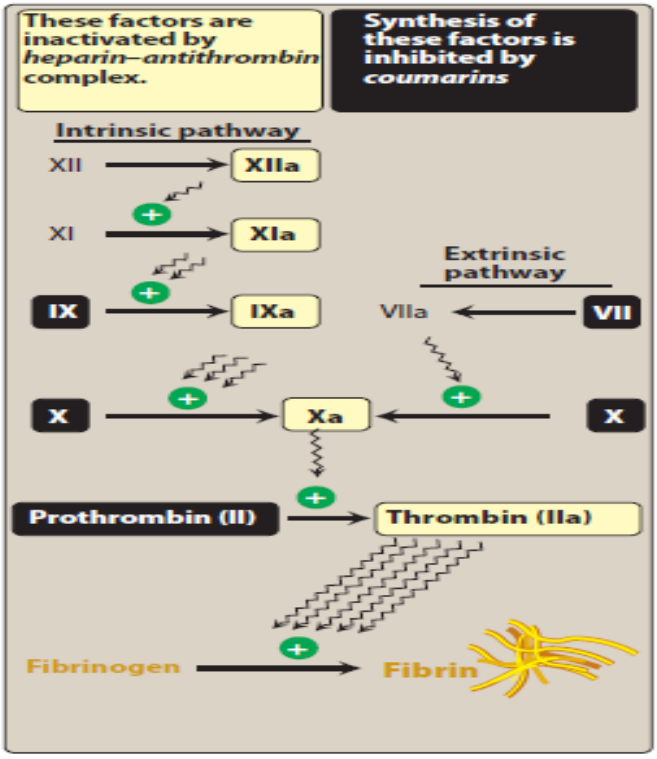
- *Dipyridamole*, a coronary vasodilator, increases intracellular levels of cAMP by inhibiting phosphodiesterase, thereby resulting in decreased thromboxane A2 synthesis.
- The drug may potentiate the effect of prostacyclin to antagonize platelet stickiness and, therefore, decrease platelet adhesion to thrombogenic surfaces

# BLOOD COAGULATION

- The coagulation process that generates thrombin consists of two interrelated Pathways, the extrinsic and the intrinsic systems.
- **The extrinsic system** is initiated by the activation of clotting factor VII by tissue factor. Tissue factor is a membrane protein that is normally separated from the blood by the endothelial cells that line the vasculature. However, in response to vascular injury, tissue factor becomes exposed to blood. There it can bind and activate factor VII, initiating the extrinsic pathway.
- **The intrinsic system** is triggered by the activation of clotting factor XII. This occurs when blood comes into contact with the collagen in the damaged wall of a blood vessel.

**A. Formation of fibrin**

- Both the extrinsic and the intrinsic systems involve a cascade of enzyme reactions that sequentially transform various plasma factors (proenzymes) to their active (enzymatic) forms.
- factor Xa is produced, which converts prothrombin (factor II) to thrombin (factor IIa).
- Thrombin plays a key role in coagulation, because it is responsible for generation of fibrin, which forms the mesh-like matrix of the blood clot.
- If thrombin is not formed or if its function is impeded (for example, by antithrombin III), coagulation is inhibited.




**B. Inhibitors of coagulation**

- It is important that coagulation is restricted to the local site of vascular injury.
- Endogenously, there are several **inhibitors of coagulation factors**, including **protein C**, **protein S**, **antithrombin III**, and **tissue factor pathway inhibitor**.
- The mechanism of action of several anticoagulant agents, including *heparin* and heparin-related products, involves activation of these endogenous inhibitors (primarily antithrombin III).

## ANTICOAGULANTS

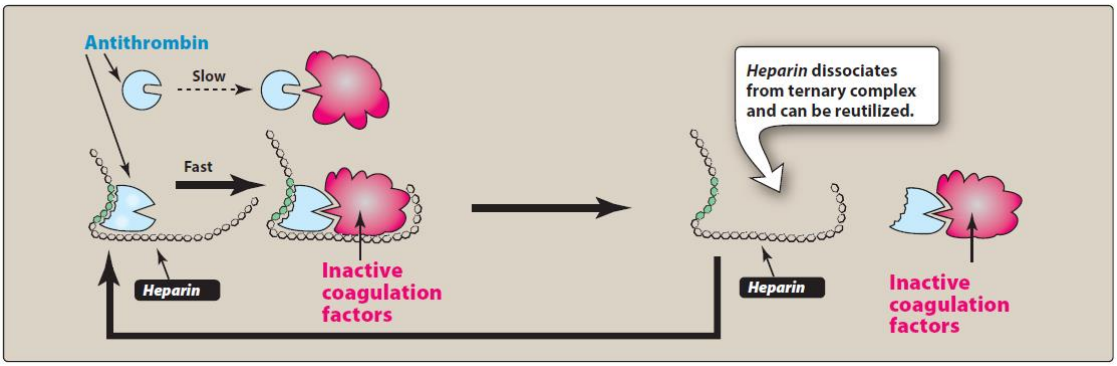
The anticoagulant drugs inhibit either the action of the coagulation factors (for example, *heparin*) or interfere with the synthesis of the coagulation factors (for example, vitamin K antagonists such as *warfarin*).

**A. Heparin and low molecular weight heparins**

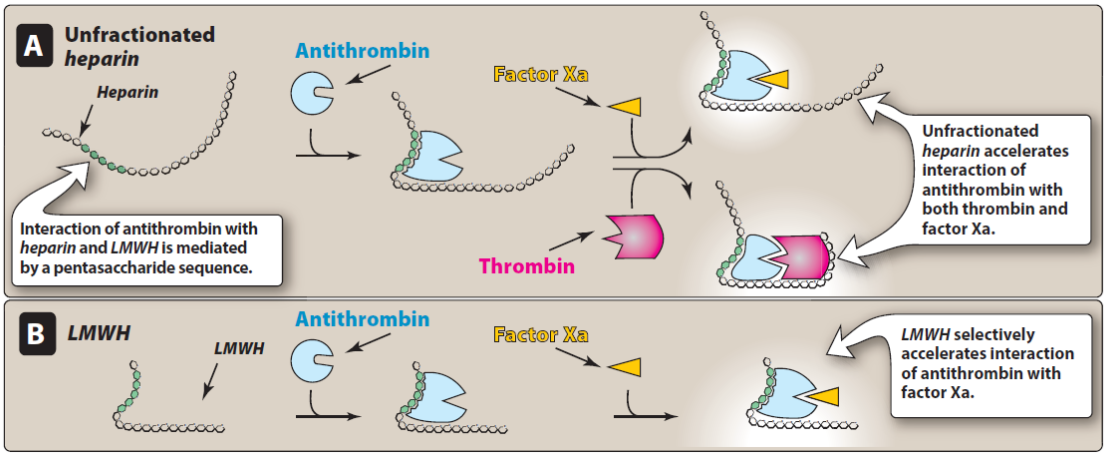
- *Heparin* is an injectable, rapidly acting anticoagulant that is often used acutely to interfere with the formation of thrombi.
- *Heparin* occurs naturally as a macromolecule complexes with histamine in mast cells, where its physiologic role is unknown.
- Unfractionated *heparin* is a mixture of straight-chain, anionic glycosaminoglycans with a wide range of molecular weights.
- It is strongly acidic because of the presence of sulfate and carboxylic acid groups.
- The realization that low molecular weight forms of *heparin* (*LMWHs*) can also act as anticoagulants led to the isolation of *enoxaparin*, produced by enzymatic depolymerization of unfractionated *heparin*. Other LMWHs include *dalteparin* and *tinzaparin* . The *LMWHs* are heterogeneous compounds about one-third the size of unfractionated *heparin*.

**Mechanism of action:**

- *Heparin* acts at a number of molecular targets, but its anticoagulant effect is a consequence of binding to antithrombin III, with the subsequent rapid inactivation of coagulation factors .
- Antithrombin III is that inhibits serine proteases of thrombin (factor IIa) and factor Xa. In the absence of *heparin*, antithrombin III interacts very slowly with thrombin and factor Xa.
- When *heparin* molecules bind to antithrombin III, a conformational change occurs that catalyzes the inhibition of thrombin about 1000-fold.




- *LMWHs* complex with antithrombin III and inactivate factor Xa (including that located on platelet surfaces but do not bind as avidly to thrombin. A unique pentasaccharide sequence contained in *heparin* and *LMWH*s permits their binding to antithrombin III.




**Adverse effects:**

- The chief complication of *heparin* and *LMWH* therapy is bleeding. Careful monitoring of the patient and laboratory parameters is required to minimize bleeding. Excessive bleeding may be managed by discontinuing the drug or by treating with *protamine sulfate*. When infused slowly, the latter combines ionically with *heparin* to form a stable, 1:1 inactive Complex. It is very important that the dosage of *protamine sulfate* is carefully titrated (1 mg for every 100 units of *heparin* administered), because *protamine sulfate* is a

weak anticoagulant, and excess amounts may trigger bleeding episodes or worsen bleeding potential.

- Chills, fever, urticaria, and anaphylactic shock.
- *Heparin*-induced thrombocytopenia (HIT) is a serious condition, in which circulating blood contains an abnormally low number of platelets. This reaction is immune-mediated and carries a risk of venous and arterial embolism. *Heparin* therapy should be discontinued when patients develop HIT or show severe thrombocytopenia.
- In addition, osteoporosis has been observed in patients on long-term *heparin* therapy.
- *Heparin* and *LMWHs* are contraindicated in patients who have hypersensitivity to *heparin*, bleeding disorders, alcoholism, or who have had recent surgery of the brain, eye, or spinal cord.

## Warfarin

- The coumarin anticoagulants owe their action to the ability to antagonize the cofactor functions of vitamin K.
- The only therapeutically relevant coumarin anticoagulant is *warfarin* .
- Initially used as a rodenticide, *warfarin* is now widely used clinically as an oral anticoagulant.
- The INR is the standard by which the anticoagulant activity of *warfarin* therapy is monitored. The INR corrects for variations that occur with different thromboplastin reagents used to perform testing at various institutions.
- The goal of *warfarin* therapy is an INR of 2 to 3 for most indications, with an INR of 2.5 to 3.5 targeted for some mechanical valves and other indications.

- *Warfarin* has a narrow therapeutic index. Therefore, it is important that the INR is maintained within the optimal range as much as possible, and frequent monitoring may be required.

**Mechanism of action:**

- Factors II, VII, IX, and X require vitamin K as a cofactor for their synthesis by the liver. These factors undergo vitamin K–dependent posttranslational modification, whereby a number of their glutamic acid residues are carboxylated to form γ-carboxyglutamic acid residues.
- The γ-carboxyglutamyl residues bind calcium ions, which are essential for interaction between the coagulation factors and platelet membranes. In the carboxylation reactions, the vitamin K– dependent carboxylase fixes CO2 to form the new COOH group on glutamic acid.
- The reduced vitamin K cofactor is converted to vitamin K epoxide during the reaction. Vitamin K is regenerated from the epoxide by vitamin K epoxide reductase, the enzyme that is inhibited by *warfarin*.
- *Warfarin* treatment results in the production of clotting factors with diminished activity (10% to 40% of normal), due to the lack of sufficient γ-carboxyglutamyl side chains.
- Unlike *heparin*, the anticoagulant effects of *warfarin* are not observed immediately after drug administration. Instead, peak effects may be delayed for 72 to 96 hours, which is the time required to deplete the pool of circulating clotting factors.
- The anticoagulant effects of *warfarin* can be overcome by the administration of *vitamin K*. However reversal following administration of *vitamin K* takes approximately 24 hours (the time necessary for degradation of already synthesized clotting factors).

**Adverse effects:**

- The principal adverse effect of *warfarin* is hemorrhage, and the agent has a black box warning for bleeding risk. Therefore, it is important to frequently monitor the INR and adjust the dose of *warfarin*. Minor bleeding may be treated by withdrawal of the drug or administration of oral *vitamin K1*, but severe bleeding may require greater doses of *vitamin K* given intravenously. Whole blood, frozen plasma, and plasma concentrates of blood factors may also be used for rapid reversal of *warfarin*.
- Skin lesions and necrosis are rare complications of *warfarin* therapy. Purple toe syndrome, a rare, painful, blue-tinged discoloration of the toe caused by cholesterol emboli from plaques, has also been observed with *warfarin* therapy. *Warfarin* is teratogenic and should never be used during pregnancy. If anticoagulant therapy is needed during pregnancy, *heparin* or *LMWH* may be administered.

## THROMBOLYTIC DRUGS

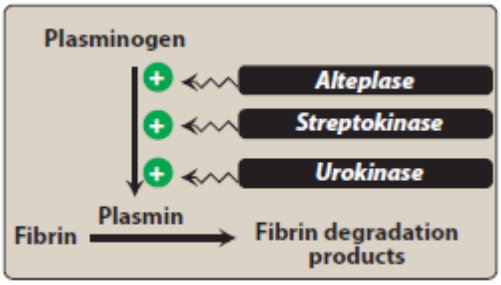
- Acute thromboembolic disease in selected patients may be treated by the administration of agents that activate the conversion of plasminogen to plasmin, a serine protease that hydrolyzes fibrin and, thus, dissolves clots.
- *Streptokinase*, one of the first such agents to be approved, causes a systemic fibrinolytic state that can lead to bleeding problems.
- *Alteplase* acts more locally on the thrombotic fibrin to produce fibrinolysis.
- *Urokinase* is produced naturally in human kidneys and directly converts plasminogen into active plasmin.
- Fibrinolytic drugs may lyse both normal and pathologic thrombi.

## A. Common characteristics of thrombolytic agents

### 1. Mechanism of action:

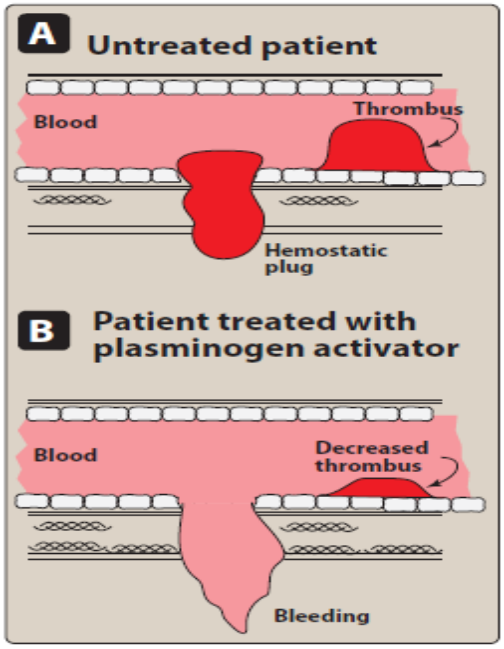
The thrombolytic agents share some common features.

1. All act either directly or indirectly to convert plasminogen to plasmin, which, in turn, cleaves fibrin, thus lysing thrombi.
2. Clot dissolution and reperfusion occur with a higher frequency when therapy is initiated early after clot formation because clots become more resistant to lysis as they age.
3. Unfortunately, increased local thrombi may occur as the clot dissolves, leading to enhanced platelet aggregation and thrombosis. Strategies to prevent this include administration of antiplatelet drugs, such as *aspirin*, or antithrombotics such as *heparin*.




### 3. Adverse effects:

- The thrombolytic agents do not distinguish between the fibrin of an unwanted thrombus and the fibrin of a beneficial hemostatic plug. Thus, hemorrhage is a major side effect. For example, a previously unsuspected lesion, such as a gastric ulcer, may hemorrhage following injection of a thrombolytic agent.
- These drugs are contraindicated in pregnancy, and in patients with healing wounds, a history of cerebrovascular accident, brain tumor, head trauma, intracranial bleeding, and metastatic cancer.



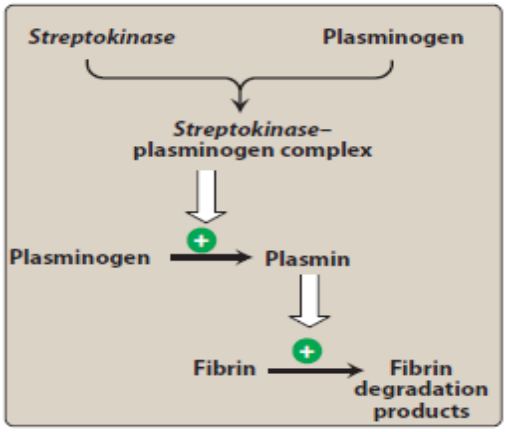

**Alteplase, reteplase, and tenecteplase**

- *Alteplase* (formerly known as *tissue plasminogen activator* or *tPA*) is a serine protease originally derived from cultured human melanoma cells. It is now obtained as a product of recombinant DNA technology
- *Reteplase* is a genetically engineered, smaller derivative of recombinant tPA. *Tenecteplase* is another recombinant tPA with a longer half-life and greater binding affinity for fibrin than *alteplase*.
- *Alteplase* has a low affinity for free plasminogen in the plasma, but it rapidly activates plasminogen that is bound to fibrin in a thrombus or a hemostatic plug. Thus, *alteplase* is said to be "fibrin selective" at low doses.
- *Alteplase* is approved for the treatment of MI, massive PE, and acute ischemic stroke. *Reteplase* and *tenecteplase* are approved only for use in acute MI, although *reteplase* may be used off-label in DVT and massive PE.

- *Alteplase* may cause orolingual angioedema, and there may be an increased risk of this effect when combined with angiotensin-converting enzyme (ACE) inhibitors.

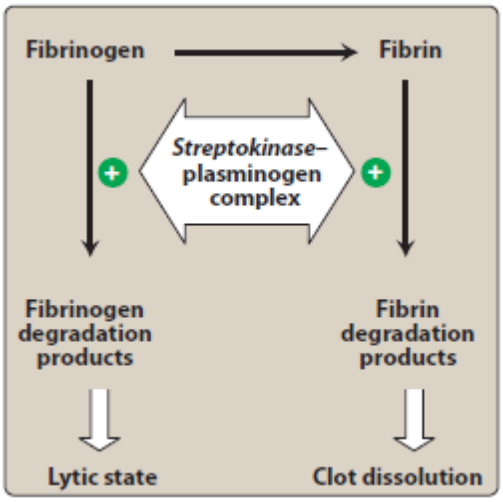
**C. Streptokinase**

*Streptokinase* is an extracellular protein purified from culture broths of group C β-hemolytic streptococci. It forms an active one-to-one complex with plasminogen. This enzymatically active complex converts uncomplexed plasminogen to the active enzyme plasmin.




In addition to the hydrolysis of fibrin plugs, the complex also catalyzes the degradation of fibrinogen, as well as clotting factors V and VII .

With the advent of newer agents, *streptokinase* is rarely used and is no longer available in many markets




**D. Urokinase**

*Urokinase* is produced naturally in the body by the kidneys. Therapeutic *urokinase* is isolated from cultures of human kidney cells and has low antigenicity. *Urokinase* directly cleaves the arginine–valine bond of plasminogen to yield active plasmin.

**Drugs Used to Treat Bleeding**

- Bleeding problems may have their origin in naturally occurring pathologic conditions, such as hemophilia, or as a result of fibrinolytic states that may arise after GI surgery or prostatectomy.
- The use of anticoagulants may also give rise to hemorrhage. Certain natural proteins and *vitamin K*, as well as synthetic antagonists, are effective in controlling this bleeding.
- Concentrated preparations of coagulation factors are available from human donors. However, these preparations carry the risk of transferring viral infections. Blood transfusion is also an option for treating severe hemorrhage.

**A. Aminocaproic acid and tranexamic acid**

Fibrinolytic states can be controlled by the administration of *aminocaproic* acid or *tranexamic* acid. Both agents are synthetic, and inhibit plasminogen activation. *Tranexamic acid* is 10 times more potent than *aminocaproic acid*. A potential side effect is intravascular thrombosim

**B. Protamine sulfate**

*Protamine* sulfate antagonizes the anticoagulant effects of *heparin*. The positively charged *protamine* interacts with the negatively charged *heparin*, forming a stable complex without anticoagulant activity.

**C. Vitamin K**

*Vitamin K1* (*phytonadione*) administration can stop bleeding problems due to *warfarin* by increasing the supply of active *vitamin K1*, thereby inhibiting the effect of *warfarin*. *Vitamin K1* may be administered via the oral, subcutaneous, or intravenous route. [Note: Intravenous *vitamin K* should be administered by slow IV infusion to minimize the risk of hypersensitivity or anaphylact reactions.] For the treatment of bleeding, the subcutaneous route of *vitamin K1* is not preferred, as it is not as effective as oral or IV administr

# THROMBOLYTIC DRUGS

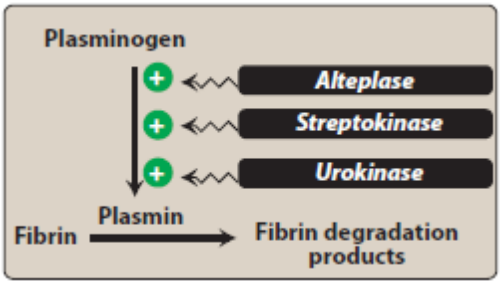
- Acute thromboembolic disease in selected patients may be treated by the administration of agents that activate the conversion of plasminogen to plasmin, a serine protease that hydrolyzes fibrin and, thus, dissolves clots.
- *Streptokinase*, one of the first such agents to be approved, causes a systemic fibrinolytic state that can lead to bleeding problems.
- *Alteplase* acts more locally on the thrombotic fibrin to produce fibrinolysis.
- *Urokinase* is produced naturally in human kidneys and directly converts plasminogen into active plasmin.
- Fibrinolytic drugs may lyse both normal and pathologic thrombi.

## A. Common characteristics of thrombolytic agents

### 1. Mechanism of action:

The thrombolytic agents share some common features.

1. All act either directly or indirectly to convert plasminogen to plasmin, which, in turn, cleaves fibrin, thus lysing thrombi.
2. Clot dissolution and reperfusion occur with a higher frequency when therapy is initiated early after clot formation because clots become more resistant to lysis as they age.
3. Unfortunately, increased local thrombi may occur as the clot dissolves, leading to enhanced platelet aggregation and thrombosis. Strategies to prevent this include administration of antiplatelet drugs, such as *aspirin*, or antithrombotics such as *heparin*.




### 2. Therapeutic use:

Originally used for the treatment of DVT and serious PE, thrombolytic drugs are now being used less frequently for these conditions. Their tendency to cause bleeding has also blunted their use in treating acute

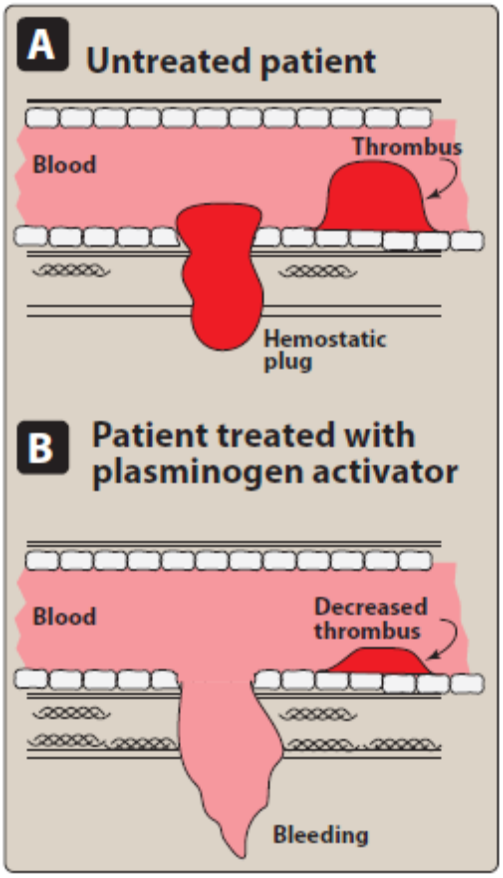
peripheral arterial thrombosis or MI. For MI, intracoronary delivery of the drugs is the most reliable in terms of achieving recanalization. However, cardiac catheterization

may not be possible in the 2- to 6-hour "therapeutic window," beyond which significant myocardial salvage becomes less likely.

Thus, thrombolytic agents are usually administered intravenously. Thrombolytic agents are helpful in restoring catheter and shunt function, by lysing clots causing occlusions. They are also used to dissolve clots that result in strokes.

**3. Adverse effects:**

- The thrombolytic agents do not distinguish between the fibrin of an unwanted thrombus and the fibrin of a beneficial hemostatic plug. Thus, hemorrhage is a major side effect. For example, a previously unsuspected lesion, such as a gastric ulcer, may hemorrhage following injection of a thrombolytic agent.
- These drugs are contraindicated in pregnancy, and in patients with healing wounds, a history of cerebrovascular accident, brain tumor, head trauma, intracranial bleeding, and metastatic cancer.



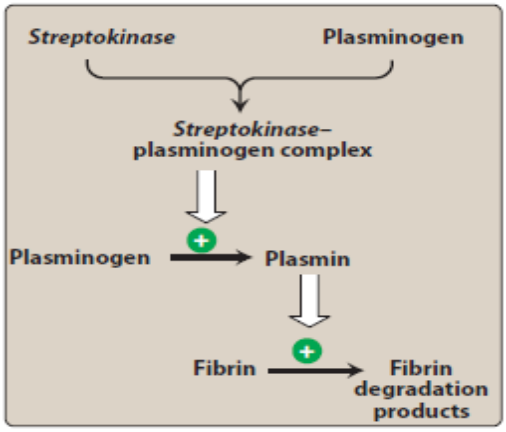

**Alteplase, reteplase, and tenecteplase**

- *Alteplase* (formerly known as *tissue plasminogen activator* or *tPA*) is a serine protease originally derived from cultured human melanoma cells. It is now obtained as a product of recombinant DNA technology
- *Reteplase* is a genetically engineered, smaller derivative of recombinant tPA. *Tenecteplase* is another recombinant tPA with a longer half-life and greater binding affinity for fibrin than *alteplase*.
- *Alteplase* has a low affinity for free plasminogen in the plasma, but it rapidly activates plasminogen that is bound to fibrin in a thrombus or a hemostatic plug. Thus, *alteplase* is said to be "fibrin selective" at low doses.
- *Alteplase* is approved for the treatment of MI, massive PE, and acute ischemic stroke. *Reteplase* and *tenecteplase* are approved only for use in acute MI, although *reteplase* may be used off-label in DVT and massive PE.

- *Alteplase* may cause orolingual angioedema, and there may be an increased risk of this effect when combined with angiotensin-converting enzyme (ACE) inhibitors.

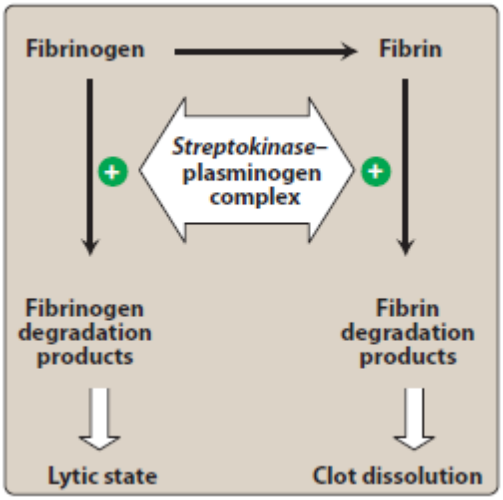
**C. Streptokinase**

*Streptokinase* is an extracellular protein purified from culture broths of group C β-hemolytic streptococci. It forms an active one-to-one complex with plasminogen. This enzymatically active complex converts uncomplexed plasminogen to the active enzyme plasmin.




In addition to the hydrolysis of fibrin plugs, the complex also catalyzes the degradation of fibrinogen, as well as clotting factors V and VII .

With the advent of newer agents, *streptokinase* is rarely used and is no longer available in many markets

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**D. Urokinase**

*Urokinase* is produced naturally in the body by the kidneys. Therapeutic *urokinase* is isolated from cultures of human kidney cells and has low antigenicity. *Urokinase* directly cleaves the arginine–valine bond of plasminogen to yield active plasmin.

**Drugs Used to Treat Bleeding**

- Bleeding problems may have their origin in naturally occurring pathologic conditions, such as hemophilia, or as a result of fibrinolytic states that may arise after GI surgery or prostatectomy.
- The use of anticoagulants may also give rise to hemorrhage. Certain natural proteins and *vitamin K*, as well as synthetic antagonists, are effective in controlling this bleeding.
- Concentrated preparations of coagulation factors are available from human donors. However, these preparations carry the risk of transferring viral infections. Blood transfusion is also an option for treating severe hemorrhage.

**A. Aminocaproic acid and tranexamic acid**

Fibrinolytic states can be controlled by the administration of *aminocaproic* acid or *tranexamic* acid. Both agents are synthetic, and inhibit plasminogen activation. *Tranexamic acid* is 10 times more potent than *aminocaproic acid*. A potential side effect is intravascular thrombosis.

**B. Protamine sulfate**

*Protamine* sulfate antagonizes the anticoagulant effects of *heparin*. The positively charged *protamine* interacts with the negatively charged *heparin*, forming a stable complex without anticoagulant activity. Adverse effects of drug administration include hypersensitivity as well as dyspnea, flushing, bradycardia, and hypotension when rapidly injected.

**C. Vitamin K**

*Vitamin K1* (*phytonadione*) administration can stop bleeding problems due to *warfarin* by increasing the supply of active *vitamin K1*, thereby inhibiting the effect of *warfarin*. *Vitamin K1* may be administered via the oral, subcutaneous, or intravenous route. [Note: Intravenous *vitamin K* should be administered by slow IV infusion to minimize the risk of hypersensitivity or

anaphylact reactions.] For the treatment of bleeding, the subcutaneous route of *vitamin K1* is not preferred, as it is not as effective as oral or IV administration.

# Drugs for Hyperlipidemia

Hyperlipidemia is abnormally elevated levels of one or all lipids (cholesterol, triglyceride) or lipoproteins (VLDL, LDL) in the blood.

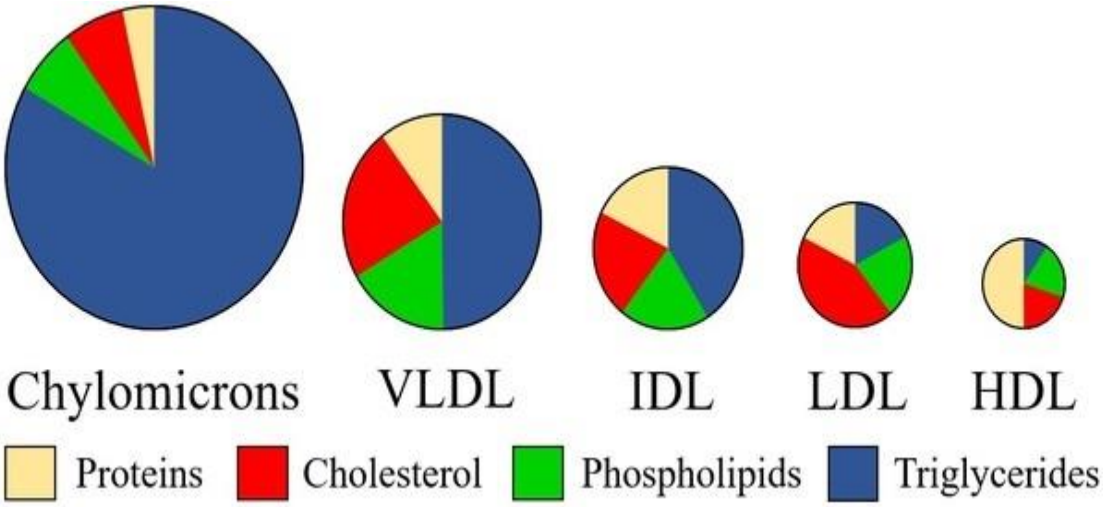
Hyperlipidemias are divided into **primary** and **secondary** subtypes.

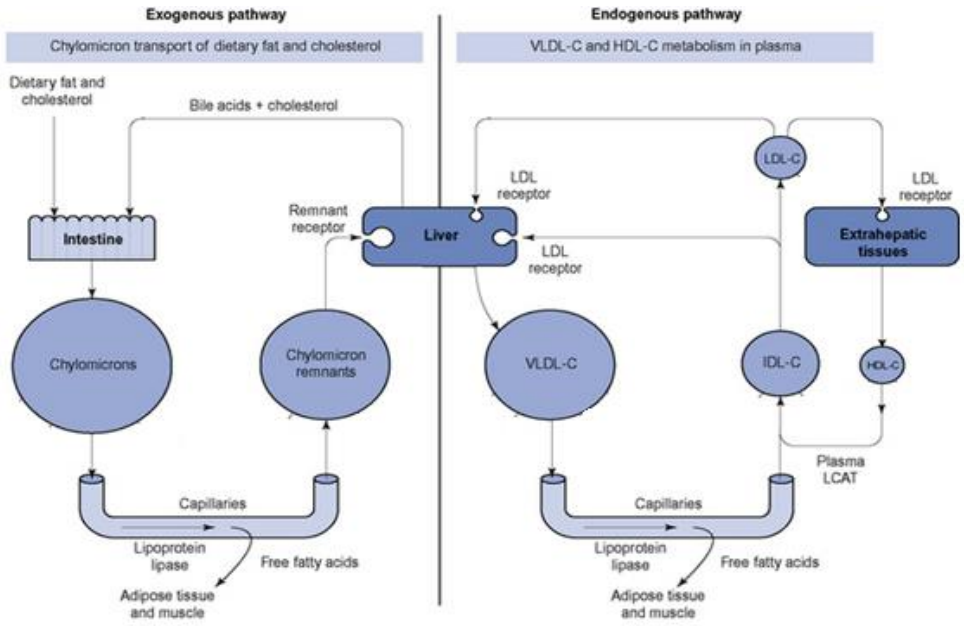
1. Primary hyperlipidemia is usually due to genetic causes (such as a mutation in a receptor protein).
2. Secondary hyperlipidemia arises due to other underlying causes such as diabetes.

Lipid and lipoprotein abnormalities are common in the general population and are regarded as modifiable risk factors for cardiovascular disease due to their influence on atherosclerosis. In addition, some forms may predispose to acute pancreatitis.

**Treatment goals**

- Plasma lipids consist mostly of **lipoproteins**, which are spherical complexes of lipids and specific proteins (apolipoproteins). The clinically important lipoproteins are LDL, VLDL, chylomicrons and HDL.
- The occurrence of coronary heart disease is positively associated with high total cholesterol and more strongly with elevated LDL, meanwhile, high levels of HDL have been associated with a decreased risk for heart disease.
- Reduction of LDL is the **primary goal** of cholesterol-lowering therapy.




## A. Treatment options for hypercholesterolemia

- Lifestyle changes, such as diet, exercise, and weight reduction, can lead to modest decreases in LDL and increases in HDL.

- However most patients are unable to achieve significant LDL reductions with lifestyle modifications alone, and drug therapy may be required.
- Treatment with HMG-CoA reductase inhibitors (statins) is the primary treatment option for hypercholesterolemia.

**B. Treatment options for hypertriglyceridemia**

- Elevated triglycerides are **independently** associated with increased risk of CHD.
- Diet and exercise are the primary modes of treating hypertriglyceridemia. If indicated, *niacin* and fibric acid derivatives are the most efficacious in lowering triglycerides.
- Omega-3 fatty acids (fish oil) in adequate doses may also be beneficial.
- Triglyceride reduction is a secondary benefit of the statins, with the primary benefit being reduction of LDL.

## Drugs for hyperlipidemia

Antihyperlipidemic drugs include the statins, *niacin*, fibrates, bile acid–binding resins, a cholesterol absorption inhibitor, and omega-3 fatty acids. These agents may be used alone or in combination. However, drug therapy should always be accompanied by lifestyle modifications, such as exercise and a diet low in saturated fats.

**A. HMG-CoA reductase inhibitors**

3-Hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (commonly known as statins) lower elevated LDL, resulting in a substantial reduction in coronary events and death from coronary heart disease. They are considered first-line treatment for patients with elevated risk of atherosclerosis.

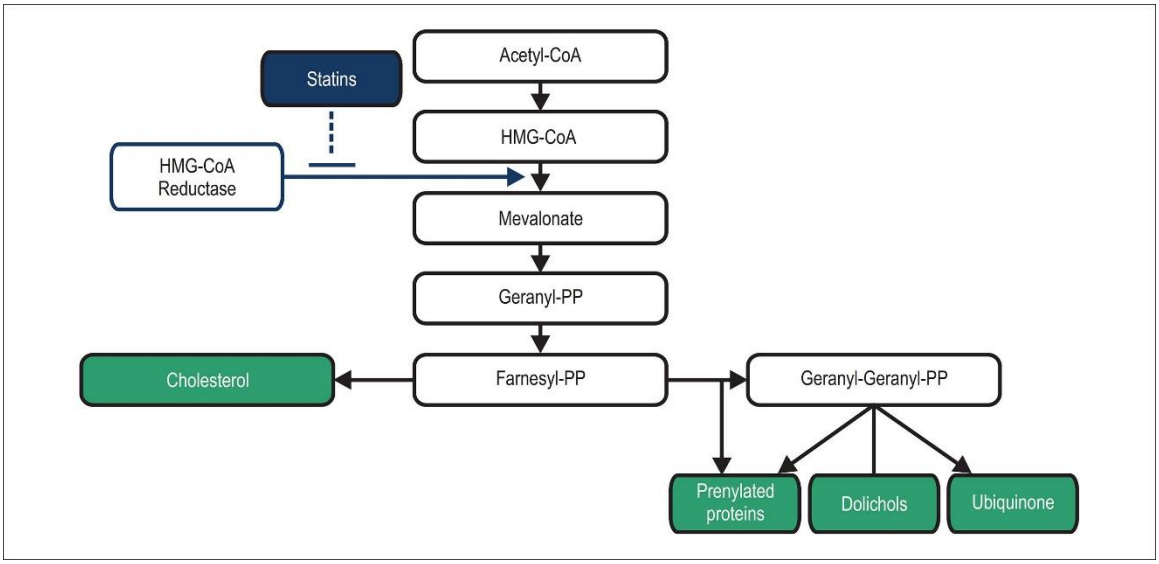
**Therapeutic benefits** include

- plaque stabilization,
- improvement of coronary endothelial function
- inhibition of platelet thrombus formation
- Anti-inflammatory activity.

The value of lowering LDL with statins has been demonstrated in patients with and without established CHD.

1. **Mechanism of action:**

- *Lovastatin* , *simvastatin* , *pravastatin* , *atorvastatin* , *fluvastatin* , *pitavastatin* , and *rosuvastatin* are competitive inhibitors of HMG-CoA reductase, **the rate-limiting step in cholesterol synthesis**.
- By inhibiting de novo cholesterol synthesis, they deplete the intracellular supply of cholesterol.
- Depletion of intracellular cholesterol causes the cell to increase the number of cell surface LDL receptors that can bind and internalize circulating LDLs. Thus, plasma cholesterol is reduced, by both decreased cholesterol synthesis and increased LDL catabolism.
- *Pitavastatin*, *rosuvastatin*, and *atorvastatin* are the most potent LDL cholesterol–lowering statins, followed by *simvastatin*, *pravastatin*, and then *lovastatin* and *fluvastatin*. [Note: Because these agents undergo a marked first-pass extraction by the liver, their dominant effect is on that organ.] The HMG-CoA reductase inhibitors also decrease triglyceride levels and may increase HDL cholesterol levels in some patients.




## 2. Therapeutic uses:

These drugs are effective in lowering plasma cholesterol levels in all types of hyperlipidemias. However, patients who are homozygous for familial hypercholesterolemia lack LDL receptors and, therefore, benefit much less from treatment with these drugs.

## 3. Adverse effects:

- Elevated liver enzymes may occur with statin therapy. Therefore, liver function should be evaluated prior to starting therapy and if a patient has symptoms consistent with liver dysfunction. [Note: Hepatic insufficiency can cause drug accumulation.]
- Myopathy and rhabdomyolysis (disintegration of skeletal muscle; rare) have been reported. In most of these cases, patients usually had renal insufficiency or were taking drugs such as *erythromycin*, *gemfibrozil*, or *niacin*. *Simvastatin* is metabolized by cytochrome P450 3A4, and inhibitors of this enzyme may increase the risk of rhabdomyolysis.
- Plasma creatine kinase levels should be determined in patients with muscle complaints. The HMG-CoA reductase inhibitors may also increase the effect of *warfarin*. Thus, it is important to evaluate

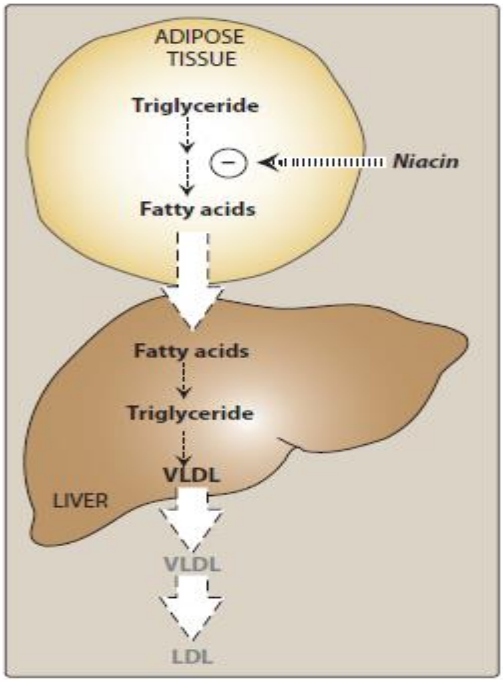
international normalized ratio (INR) frequently. These drugs are contraindicated during pregnancy and lactation.

**B. Niacin (nicotinic acid)**

*Niacin* can reduce LDL by 10% to 20% and is the most effective agent for increasing HDL. It also lowers triglycerides by 20% to 35% at typical doses of 1.5 to 3 grams/day. *Niacin* can be used in combination with statins, and a fixed-dose combination of *lovastatin* and long-acting *niacin* is available.

1. **Mechanism of action:**

At gram doses, *niacin* strongly inhibits lipolysis in adipose tissue, thereby reducing production of free fatty acids. The liver normally uses circulating free fatty acids as a major precursor for triglyceride synthesis. Reduced liver triglyceride levels decrease hepatic VLDL production, which in turn reduces LDL plasma concentrations.



**2. Therapeutic uses:**

Since *niacin* lowers plasma levels of both cholesterol and triglycerides, it is useful in the treatment of familial hyperlipidemias. It is also used to treat other severe hypercholesterolemias, often in combination with other agents.

**3. Adverse effects:**

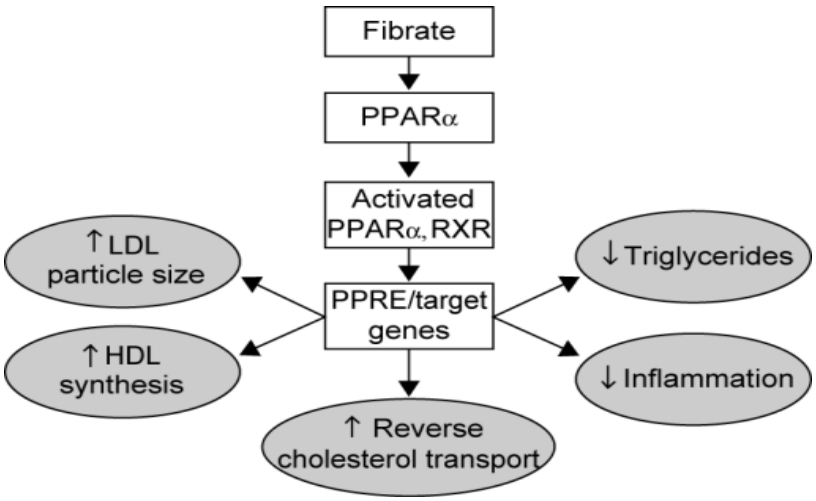
- The most common side effects of *niacin* are an intense cutaneous flush (accompanied by an uncomfortable feeling of warmth) and pruritus.
- Administration of *aspirin* prior to taking *niacin* decreases the flush, which is prostaglandin mediated.
- Some patients also experience nausea and abdominal pain. Slow titration of the dosage or usage of the 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.

## C. Fibrates

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

### 1. Mechanism of action:

- The peroxisome proliferator–activated receptors (PPARs) are members of the nuclear receptor family that regulates lipid metabolism.
- PPARs function as ligand-activated transcription factors.
- Upon binding to their natural ligands (fatty acids or eicosanoids) or antihyperlipidemic drugs, PPARs are activated.
- They then bind to peroxisome proliferator response elements, which ultimately leads to
  1. Induction of lipoprotein lipolysis.
  2. Induction of hepatic fatty acid (FA) uptake and reduction of hepatic triglyceride production.
  3. Increased removal of LDL particles.
  4. Reduction in neutral lipid (cholesteryl ester and triglyceride) exchange between VLDL and HDL may result from decreased plasma levels of TRL.
  5. Increase in HDL production and stimulation of reverse cholesterol transport.




2. *Fenofibrate* is more effective than *gemfibrozil* in lowering triglyceride levels.
3. **Therapeutic uses:**

The fibrates are used in the treatment of hypertriglyceridemias. They are particularly useful in treating type III hyperlipidemia (dysbetalipoproteinemia), in which intermediate density lipoprotein particles accumulate.

4. **Adverse effects:**

- The most common adverse effects are mild gastrointestinal (GI) disturbances. These lessen as the therapy progresses.
- Because these drugs increase biliary cholesterol excretion, there is a predisposition to form gallstones.
- Myositis (inflammation of a voluntary muscle) can occur, and muscle weakness or tenderness should be evaluated.
- Patients with renal insufficiency may be at risk. Myopathy and rhabdomyolysis have been reported in patients taking *gemfibrozil* and statins together.
- The use of *gemfibrozil* is contraindicated with *simvastatin*.

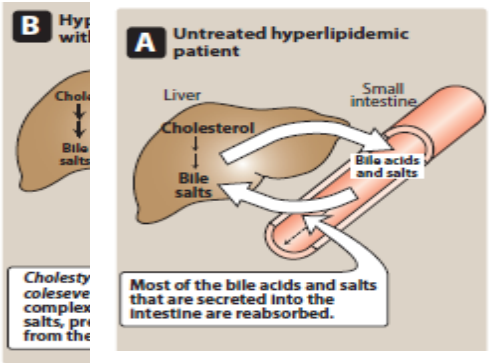
- Both fibrates may increase the effects of *warfarin*. INR should, therefore, be monitored more frequently when a patient is taking both drugs.
- Fibrates should not be used in patients with severe hepatic or renal dysfunction or in patients with preexisting gallbladder disease

**D. Bile acid–binding resins**

Bile acid sequestrates (resins) have significant LDL cholesterol–lowering effects, although the benefits are less than those observed with statins.

**1. Mechanism of action:**

- *Cholestyramine* , *colestipol* , and *colesevelam* are anion-exchange resins that bind negatively charged bile acids and bile salts in the small intestine .
- The resin/bile acid complex is excreted in the feces, thus lowering the bile acid concentration.
- This causes hepatocytes to increase conversion of cholesterol to bile acids, which are essential components of the bile. Consequently, intracellular cholesterol concentrations decrease, which activates an increased hepatic uptake of cholesterol-containing LDL particles, leading to a fall in plasma LDL-C. [Note: This increased uptake is mediated by an up-regulation of cell surface LDL receptors.]



**2. Therapeutic uses:**

The bile acid–binding resins are useful (often in combination with diet or *niacin*) for treating hyperlipidemias. [Note: In those rare individuals who are homozygous for type IIA and functional LDL receptors are totally lacking, these drugs have little effect on plasma LDL levels.] *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.

**3. Adverse effects:**

- The most common side effects are GI disturbances, such as constipation, nausea, and flatulence.
- *Colesevelam* has fewer GI side effects than other bile acid sequestrants.
- These agents may impair the absorption of the fat-soluble vitamins (A, D, E, and K), and they interfere with the absorption of many drugs (for example, *digoxin*, *warfarin*, and thyroid hormone). Therefore, other drugs should be taken at least 1 to 2 hours before, or 4 to 6 hours after, the bile acid–binding resins. These agents may raise triglyceride levels and are contraindicated in patients with significant hypertriglyceridemia (≥400 mg/dL).

**E. 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%. Due its modest LDL-lowering effects, *ezetimibe* is often used as an adjunct to statin therapy or in statin-intolerant patients.
- Patients with moderate to severe hepatic insufficiency should not be treated with *ezetimibe*. Adverse effects are uncommon with use of *ezetimibe*.

**F. Omega-3 fatty acids**

- Omega-3 polyunsaturated fatty acids (PUFAs) are essential fatty acids that are predominately used for triglyceride lowering.
- Essential fatty acids inhibit VLDL and triglyceride synthesis in the liver. The omega-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are found in marine sources such as tuna, halibut, and salmon.
- Approximately 4 g of marine-derived omega-3 PUFAs daily decreases serum triglyceride concentrations by 25% to 30%, with small increases in LDL-C and HDL-C.
- Over-the-counter or prescription fish oil capsules (EPA/DHA) can be used for supplementation, as it is difficult to consume enough omega-3 PUFAs from dietary sources alone.
- *Icosapent ethyl* is a prescription product that contains only EPA and, unlike other fish oil supplements, does not significantly raise LDL-C.
- Omega-3 PUFAs can be considered as an adjunct to other lipid-lowering therapies for individuals with significantly elevated triglycerides (≥500 mg/dL).

- Although effective for triglyceride lowering, omega-3 PUFA supplementation has not been shown to reduce cardiovascular morbidity and mortality.
- The most common side effects of omega-3 PUFAs include GI effects (abdominal pain, nausea, and diarrhea) and a fishy aftertaste.
- Bleeding risk can be increased in those who are concomitantly taking anticoagulants or antiplatelets.

**G. Combination drug therapy**

It is often necessary to use two antihyperlipidemic drugs to achieve treatment goals in plasma lipid levels. The combination of an HMG CoA reductase inhibitor with a bile acid–binding agent has been shown to be very useful in lowering LDL-C levels.

*Simvastatin* and *ezetimibe*, as well as *simvastatin* and *niacin*, are currently available combined in one pill to treat elevated LDL cholesterol. However, more clinical information is needed to determine whether combination therapy produces better long-term benefits than the use of a high-dose statin. Until this uncertainty is resolved, many experts recommend maximizing statin dosages and adding *niacin* or fibrates only in those with persistently elevated triglycerides (greater than 500 mg/dL) or those with low HDL cholesterol levels (less than 40 mg/dL). Combination drug therapy is not without risks. Liver and muscle toxicity occurs more frequently with lipid-lowering drug combinations. Figure 23.12 summarizes some actions of the antihyperlipidemic drugs.

| TYPE OF DRUG | EFFECT ON LDL | EFFECT ON HDL | EFFECT ON TRIGLYCERIDES |
|---|---|---|---|
| HMG CoA reductase inhibitors (statins) | ↓↓↓↓ | ↑↑ | ↓↓ |
| Fibrates | ↓ | ↑↑↑ | ↓↓↓↓ |
| *Niacin* | ↓↓ | ↑↑↑↑ | ↓↓↓ |
| Bile acid sequestrants | ↓↓↓ | ↑ | ↑ |
| Cholesterol absorption inhibitor | ↓ | ↑ | ↓ |

# Antiarrhythmic

- In contrast to skeletal muscle, which contracts only when it receives a stimulus, the heart contains specialized cells that **exhibit automaticity**. That is, they intrinsically generate rhythmic action potentials in the absence of external stimuli.
- These "pacemaker" cells differ from other myocardial cells in showing a slow, spontaneous depolarization during diastole (phase 4), caused by an inward positive current carried by sodium and calcium ions.
- This depolarization is fastest in the sinoatrial (SA) node (the normal initiation site of the action potential), and it decreases throughout the normal conduction pathway through the atrioventricular (AV) node to the bundle of His and the Purkinje system.
- Dysfunction of impulse **generation or conduction** at any of a number of sites in the heart can cause an abnormality in cardiac rhythm

## Introduction to the Arrhythmias

- The arrhythmias are dysfunctions cause abnormalities in impulse formation and conduction in the myocardium.
- However, in the clinical setting, arrhythmias present as a complex family of disorders with a variety of symptoms.
- To make sense of this large group of disorders, it is useful to organize the arrhythmias into groups according to the anatomic site of the abnormality: the atria, the AV node, or the ventricles.

### A. Causes of arrhythmias

Most arrhythmias arise either from aberrations in impulse generation (abnormal automaticity) or from a defect in impulse conduction.

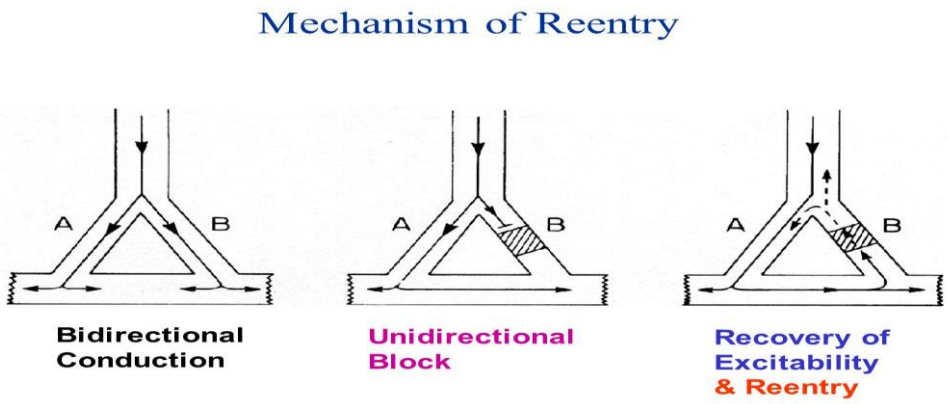
#### 1. Abnormal automaticity:

- The SA node shows the fastest rate of phase 4 depolarization and, therefore, exhibits a higher rate of discharge than that occurring in other pacemaker cells exhibiting automaticity.
- Thus, the SA node normally sets the pace of contraction for the myocardium. If cardiac sites other than the SA node show enhanced automaticity, they may generate competing stimuli, and arrhythmias may arise.

- Most of the antiarrhythmic agents **suppress automaticity by blocking either $Na^+$ or $Ca^{2+}$ channels to reduce the ratio of these ions to $K^+$.**
- This decreases the slope of phase 4 (diastolic) depolarization and/or raises the threshold of discharge to a less negative voltage.
- Antiarrhythmic drugs cause the frequency of discharge to decrease. This effect is more pronounced in cells with ectopic pacemaker activity than in normal cells.

**2. Abnormalities in impulse conduction:**

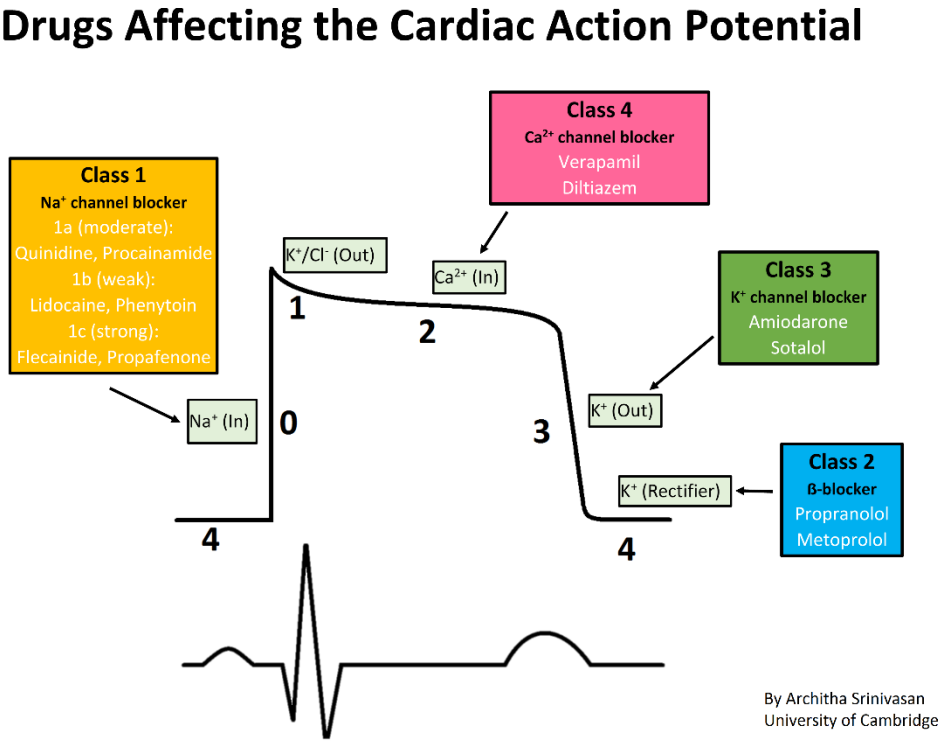
- Impulses from higher pacemaker centers are normally conducted down pathways that split to activate the entire ventricular surface.
- A phenomenon called **reentry** can occur if a
  1. unidirectional block caused by myocardial injury
  2. Prolonged refractory period results in an abnormal conduction pathway.




- Reentry is the most common cause of arrhythmias, and it can occur at any level of the cardiac conduction system. This short-circuit pathway results in re-excitation of the ventricular muscle, causing premature contraction or sustained ventricular arrhythmia.
- Antiarrhythmic agents prevent reentry by
  1. slowing conduction (class I drugs)
  2. Increasing the refractory period (class III drugs), thereby converting a unidirectional block into a bidirectional block.

## Antiarrhythmic drugs

- Antiarrhythmic drugs can
  1. modify impulse generation and conduction to prevent arrhythmias from occurring
  2. Reduce symptoms associated with arrhythmias.
- Unfortunately, many of the antiarrhythmic agents are known to have dangerous pro-arrhythmic actions—that is, to cause arrhythmias.
- Inhibition of potassium ($K^+$) channels (typically thought of as class III activity) 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 .
- The most common cause of **QT prolongation** is drug-induced, although other conditions (for example, ischemia and hypokalemia) and genetic profiles may contribute. QT prolongation is not only seen with class III antiarrhythmics.
- Many drugs are known to prolong the QT interval, such as macrolide antibiotics and antipsychotics.
- Caution should be employed when combining drugs with additive effects on the QT interval or when giving QT-prolonging antiarrhythmic drugs with drugs known to inhibit their metabolism.
- As such, the benefit of antiarrhythmic drugs must always be compared to the potential for serious adverse effects or drug interactions.




## III. CLASS I ANTIARRHYTHMIC DRUGS

Antiarrhythmic drugs can be classified according to their predominant effects on the action potential.

| 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 |

Although this classification is convenient, it is not entirely clear-cut, because many drugs have actions relating to more than one class or may have active metabolites with a different class of action. Class I antiarrhythmic drugs act by blocking voltage- sensitive sodium (Na+) channels. The use of sodium channel blockers has declined due to their pro-arrhythmic effects, particularly in patients with reduced left ventricular function and ischemic heart disease.

**Class IA antiarrhythmic drugs: Quinidine and procainamide**

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

**Mechanism of action:**

- *Quinidine* binds to open and inactivated sodium channels and prevents sodium influx, thus slowing the rapid upstroke during phase 0.
- It decreases the slope of phase 4 spontaneous depolarization, inhibits potassium channels, and blocks calcium channels. Because of these actions, it slows conduction velocity and increases refractoriness.
- *Quinidine* also has mild α-adrenergic blocking and anticholinergic actions.

**3.** *Procainamide* have actions similar to those of *quinidine*.

**Adverse effects:**

- 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.

**C. Class IB antiarrhythmic drugs: Lidocaine**

The class IB agents rapidly associate and dissociate from sodium channels. Thus, the actions of class IB agents are manifested when the cardiac cell is depolarized or firing rapidly. The class IB drugs *lidocaine* are useful in treating ventricular arrhythmias.

**Mechanism of action:** In addition to sodium channel blockade, *lidocaine* shorten phase 3 repolarization and decrease the duration of the action potential.

**Adverse effects:**

- *Lidocaine* has a fairly wide therapeutic index. It shows little impairment of left ventricular function and has no negative inotropic effect.
- 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.

**D. Class IC antiarrhythmic drugs: Flecainide**

These drugs slowly dissociate from resting sodium channels and show prominent effects even at normal heart rates. Several studies have cast serious doubts on the safety of the class IC drugs, particularly in patients with structural heart disease.

**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 potassium channels leading to increased action potential duration.

**Adverse effects:**

*Flecainide* is generally well tolerated, with blurred vision, dizziness, and nausea occurring most frequently.

**IV. CLASS II ANTIARRHYTHMIC DRUGS**

- Class II agents are β-adrenergic antagonists, or β-blockers.
- These drugs diminish phase 4 depolarization and, thus, depress automaticity, prolong AV conduction, and decrease heart rate and contractility.
- In contrast to the sodium channel blockers, β-blockers and class III compounds, such as *sotalol* and *amiodarone,* are increasing in use.
- *Metoprolol* is the β-blocker most widely used in the treatment of cardiac arrhythmias. Compared to nonselective β-blockers, such as *propranolol,* it reduces the risk of bronchospasm.

**V. CLASS III ANTIARRHYTHMIC DRUGS**

- Class III agents block potassium channels and, thus, diminish the outward potassium 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**

**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.

**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.

**VI. CLASS IV ANTIARRHYTHMIC DRUGS**

- Class IV drugs are the nondihydropyridine calcium channel blockers *verapamil* and *diltiazem.*
- Although voltage- sensitive calcium channels occur in many different tissues, the major effect of calcium channel blockers is on vascular smooth muscle and the heart.
- *Verapamil* shows greater action on the heart than on vascular smooth muscle, and *diltiazem* is intermediate in its actions.
- In the heart, *verapamil* and *diltiazem* bind only to open depolarized voltage-sensitive channels, thus decreasing the inward current carried by calcium.
- They prevent repolarization until the drug dissociates from the channel, resulting in a decreased rate of phase 4 spontaneous depolarization. These drugs are therefore use-dependent.
- They also slow conduction in tissues that are dependent on calcium currents, such as the AV and SA nodes.

**VII. 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. [Note: Serum trough concentrations of 1.0 to 2.0 ng/mL are desirable for atrial fibrillation or flutter, whereas lower concentrations of 0.5 to 0.8 ng/mL are targeted for systolic heart failure.]