



REVIEW ON ANTIHYPERTENSIVE DRUGS

RESIST TO HYPERTENSION

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Abstract: Hypertension is the common disease of the world and which is the most important target to the world to oppose it . It can be resist by using some Antihypertensive drugs. It is the disease in which blood pressure pressure increases above the Normal level and leads to Hypertension.

Now this review consists of the main Antihypertensive Drugs,their structures with Mechanism of Action and its Classification for managing the Hypertension.

Keywords: Antihypertensive Drugs, Hypertension, Clinical management, Losartan.

• Introduction

Antihypertensive drugs are the class of drugs that are used to treat the Hypertension i.e.(high blood pressure). It prevent the complication of high blood pressure, such as **Myocardial Infarction** and **Stroke**.

The Hypertension can be occur by reasons as follows:

Stress

Increase in blood pressure.

Evidence suggest that the reduction of blood pressure by 5 mmHg can decrease the risk of stroke by 34% and of ischaemic heart disease by 21% and also decrease the dementia, heart failure from cardiovascular disease. Normal range : 120/80 mmHg ; below its level known as hypotension and above its level known to be hypertension.

CLASSIFICATION :

It can be classified as follows:

A) **ACE Inhibitors** : Captopril, Lisinopril, Ramipril

B) **B-Blocker** : Propranolol,Labetalol, Metoprolol

C) **Alpha blocker**: Prazosin, chlorpromazine

D) **Mixed Alpha +Beta Blocker** : Carvedilol

E) **Diuretics** :

1) Loop Diuretics : Furosemide

2) Thiazide Diuretics : Hydrochlorothiazide, chlorothiazide.

3) Thiazide like Diuretics : Clopamide

4) K-sparing Diuretics: Spironolactone, Amiloride

F) **Ca-channel blockers** : Amlodipine, Nifedifine, Verapamil.

G) **Angiotensin II receptor antagonists** : Losartan,Telmisartan

H) **Vasodilators** : Sodium Nitroprusside, Hydralazine

1) Alpha-2 adrenergic receptor agonists: Clonidine, methyldopa.

History:

Chlorothiazide was discovered in 1957, but first known example is effective from 1947. To treat hypertension using Primaquine, an antimalarial.

Nowadays, **CYT006-AngQb** was only moderately useful successful in studies.

the fundamental goal of treatment should be the prevention of the important endpoints of hypertension, such as heart attack, stroke and Heart failure. Patient age and associated conditions and end organ damage also play a part in determining dosage and type of medication administered.

A) ACE INHIBITORS:

Captopril :

Is the Antihypertensive drug which sold under brand **Capoten**.

It was the first oral ACE inhibitor to treat Hypertension. It is not responsible for causing fatigue as associated with B-Blockers. Due to adverse drug event of causing hyperkalemia, as seen with most ACE inhibitors and medicine usually paired with diuretic.

Route of Administration	Oral
Bioavailability	70-75%
Metabolism	Liver
Elimination Half life	1.9 hrs
Excretion	Kidney

Formula : C₉H₁₅NO₃S

SYNTHESIS:

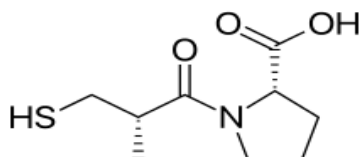
Chemical synthesis of captopril by treatment of L-proline with (2S)-3-acetylthio-2-methylpropanoyl chloride under basic condition NaOH, aminolysis of the protective acetyl group.

Structure activity Relationship (SAR) :

Captopril has an L-proline group which allows for it to be more bioavailable within oral formulations. The thiol moiety within the molecule has been associated with two significance adverse effects: the hapten or immune response. This immune response, also known as agranulocytosis, can explain the adverse drug events which may be seen in captopril with the allergic response, which would be: hives, severe stomach pain, difficulty breathing, swelling of the face, lips, tongue or throat.

The molecule's thiol moiety will attach to the binding site of the ACE enzyme. This will inhibit the port at which the angiotensin-1 molecule would normally bind, therefore inhibiting the downstream effects within the renin-angiotensin system.

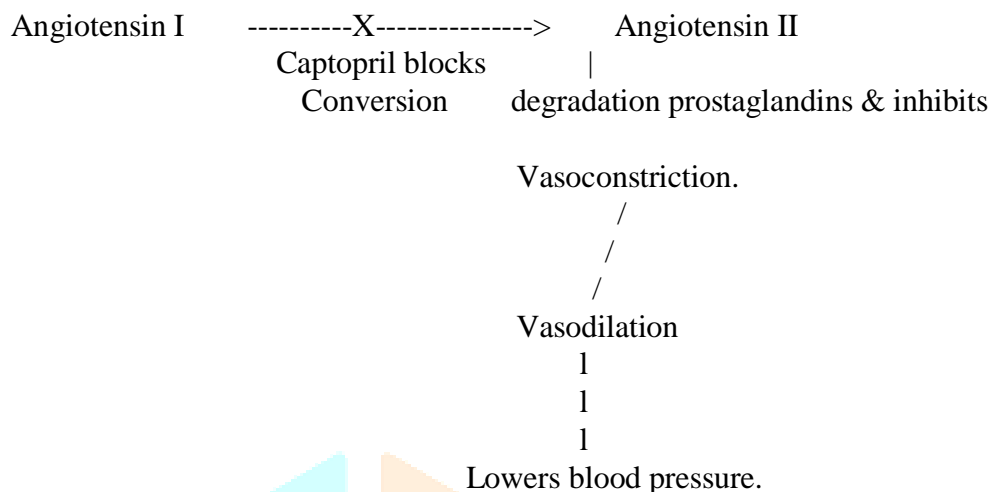
Structure:



Captopril

Mechanism of Action:

Captopril blocks the conversion of angiotensin I to angiotensin II and prostaglandins degradation inhibiting vasoconstriction and promotes vasodilation.

**Uses:**

- 1) To treat hypertension, congestive heart failure.
- 2) To preserve kidney function in diabetic nephropathy.
- 3) To elevate mood .

Adverse effect :

Cough, Headache, Hyperkalemia, Tachycardia.

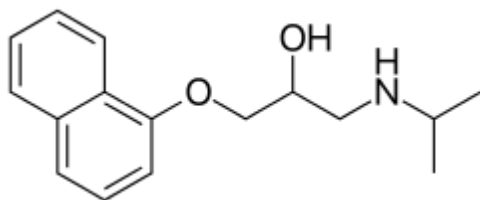
Contraindication :

Tachycardia.

B) B-BLOCKERS :**Propranolol**

Is the Antihypertensive drug effective in hypertension and ischemic heart disease. It was the B-Blocker used in lowering blood pressure in mild to moderate hypertension. Usually B-Blockers are used in preventing reflex tachycardia , to reduce mortality in patients after myocardial infarction and heart failure in some patients.

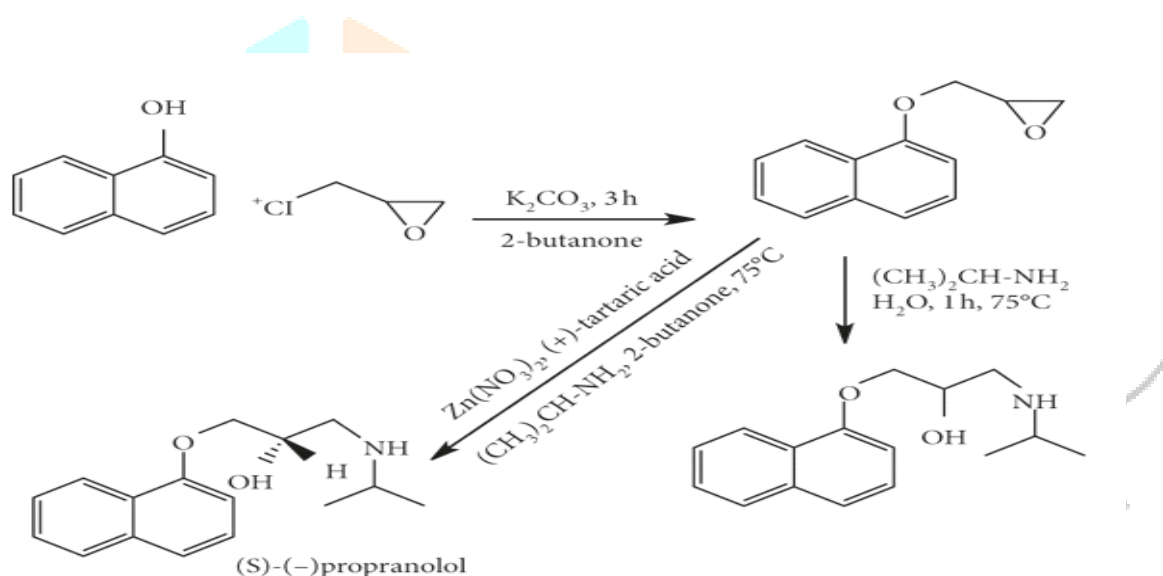
Route of Administration	Oral,Rectal, Intravenous
Bioavailability	26 %
Metabolism	Liver
Elimination Half life	4-5 hrs
Excretion	Kidney (< 1 %)

Structure:

Propranolol

Propranolol:**Formula: C₁₆H₂₁NO₂****Synthesis:**

Propranolol was synthesized from reaction between 1-naphthol and isopropylamine. Typically, 1.25 g of 1-naphthol (8.67 mM) was dissolved in 10 mL of ethanol : water (9:1), followed by adding 0.5 g of KOH into the above mixture under stirring for 30 min.

**Mechanism of action :**

It inhibits sympathetic stimulation of heart which inhibits cAMP synthesis as a result reducing protein kinase activation. Less Ca influx to voltage gated L-type calcium channels and decrease sympathetic effect on heart and blood pressure reduced.

Uses:

- 1) Treats hypertension.
- 2) To treat Angina pectoris, Myocardial infarction.
- 3) Used in treating portal hypertension to lower portal vein pressure.
- 4) In anxiety.

Adverse effects:

- 1) Myasthenia gravis
- 2) Hyperthyroidism

Contraindication :

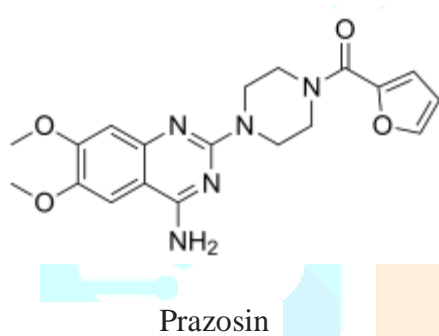
- 1) Bradycardia
- 2) Sick sinus syndrome.

C) ALPHA BLOCKER :

Prazosin:

Prazosin, sold under the brand name Minipress among others, is a medication used to treat high blood pressure, symptoms of an enlarged prostate, and nightmares. It is a less preferred treatment of high blood pressure. Prazosin was patented in 1965 and came into medical use in 1974. Prazosin has an onset of action of 30 to 90 minutes.

Route of Administration	Oral
Bioavailability	60 %
Metabolism	Liver
Elimination Half life	2-3 hrs
Excretion	Kidney (< 1 %)

Structure :

Formula: C₁₉H₂₁N₅O₄.

Synthesis:

Prazosin is synthesized using 2-furoic acid, from which compound 2 is obtained, and this acid can be readily replaced with numerous commercially available carboxylic acids.

Mechanism of Action :

Prazosin inhibits the postsynaptic alpha-1 adrenoceptors. This inhibition blocks the vasoconstricting effect of catecholamines (epinephrine and norepinephrine) on the vessels, leading to peripheral blood vessel dilation.

Prazosin -----> blocks alpha-1 receptor in arterioles -----> decrease sympathetic outflow

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Peripheral resistance <----- Vasodilation

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Decrease blood pressure

Uses:

- 1) Second-line choice for the treatment of high blood pressure.
- 2) Prazosin is also useful in treating urinary hesitancy associated with benign prostatic hyperplasia.
- 3) The drug is usually recommended for severe stings from the Indian red scorpion.

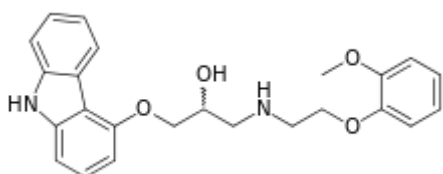
Adverse effects :

- 1) Dizziness, headache, drowsiness, lack of energy, weakness, palpitations, and nausea.
- 2) Vomiting, diarrhea, constipation, edema, orthostatic hypotension, dyspnea, syncope,
- 3) Depression, nervousness.

D) Mixed Alpha +Beta Blocker :**Carvedilol :**

Carvedilol, sold under the brand name Coreg among others, is a medication used to treat high blood pressure, congestive heart failure (CHF). Carvedilol was patented in 1978 and approved for medical use in the United States in 1995.

Route of Administration	Oral
Bioavailability	25-35 %
Metabolism	Liver
Elimination Half life	7-10 hrs
Excretion	Urine, Feces

Structure :

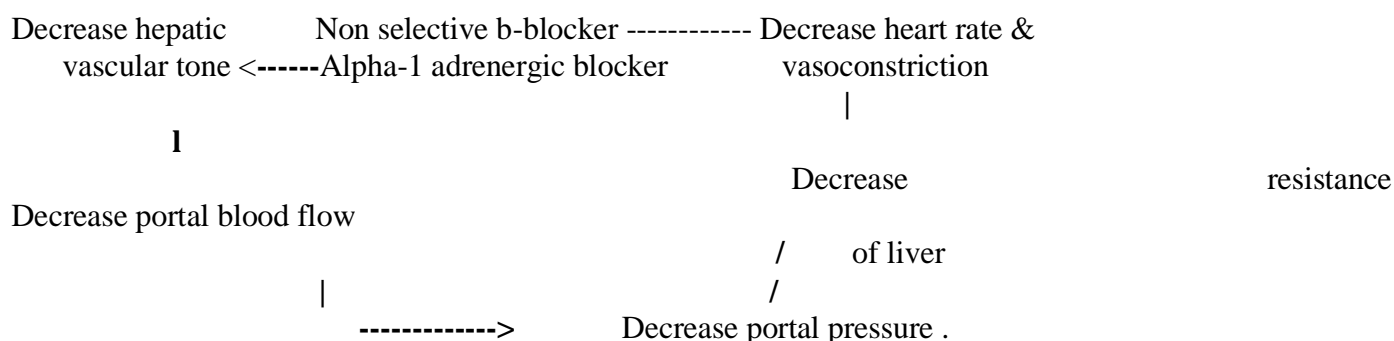
Carvedilol

Formula : C₂₄H₂₆N₂O₄**Synthesis :**

Mixture of two enantiomorphs, R(+)-carvedilol and S(—)-carvedilol. Reaction of 4-oxiranyl-methoxy-9H-carbazole 8 with 2-(2-methoxy-phenoxy)-ethylamine 9 in monoglyme, and compound 8 was produced by the condensation of 4-hydroxy carbazole 6 with epichlorohydrin 7 in the presence of sodium hydroxide in dimethyl sulfoxide (DMSO) medium.

Mechanism of action :

It promotes vasoconstriction by action of b-receptor , as a result portal blood flow decreases. alpha receptor blocked and vascular tone of liver decreases.



Adverse effects :

- 1) Low blood pressure
- 2) Diarrhea
- 3) Weakness, Dizziness
- 4) Slowed heart rate.

Uses:

- 1) Management of congestive heart failure.
- 2) Carvedilol has been used in the treatment of uncomplicated hypertension.
- 3) Adjunct to angiotensin-converting-enzyme inhibitor (ACE inhibitors) and diuretics.

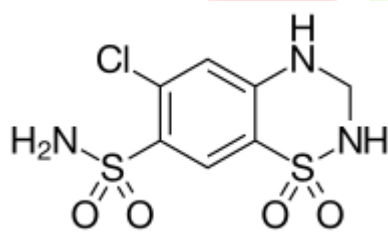
Contraindications :

- 1) Carvedilol should not be used in patients with bronchial asthma or bronchospastic conditions.
- 2) Second or third-degree atrioventricular block, sick sinus syndrome, severe bradycardia.

E) Diuretics :**Hydrochlorothiazide :**

Hydrochlorothiazide is a diuretic medication often used to treat high blood pressure and swelling. Hydrochlorothiazide shows greater effect on systolic blood pressure than diastolic one which can reach 4 mmHg to 6 mmHg pressure reduction.

Route of Administration	Oral
Bioavailability	70 %
Metabolism	Non significant
Elimination Half life	5.6—14.8 hrs
Excretion	Kidney

Structure :

Hydrochlorothiazide

Hydrochlorothiazide :**Formula : C₇H₈ClN₃O₄S₂****Synthesis :**

Hydrochlorothiazide is synthesized by either the reaction of para-formaldehyde with 5-chloro-2,4-disulfamoylaniline in nonaqueous media, or the reaction of formaldehyde with 6-chloro-7-sulfamoyl-2H-1,2,4-benzothiazine-1,1-dioxide in aqueous alkaline solution.

Mechanism of action :

Hydrochlorothiazide inhibits sodium chloride cotransport in the distal convoluted tubule. More sodium is then excreted in the kidney with accompanying fluid. This action leads to a diuretic action that lowers blood pressure and cardiac output.

Hydrochlorothiazide inhibits -----> Na⁺/ Cl⁻ co transport

Decrease lower blood pressure <-----Increase Sodium and Water excretion

Uses :

- 1) Hydrochlorothiazide is used for the treatment of hypertension, congestive heart failure, symptomatic edema, diabetes insipidus, renal tubular acidosis.
- 2) Hydrochlorothiazide is also sometimes used to prevent osteopenia and for treatment of hypoparathyroidism.
- 3) Prevention of kidney stones in those who have high levels of calcium in their urine.

Adverse effects :

- 1) Hypokalemia, or low blood levels of potassium.
- 2) Hyperlipidemia, high cholesterol and triglycerides.
- 3) Headache.
- 4) Nausea/vomiting.

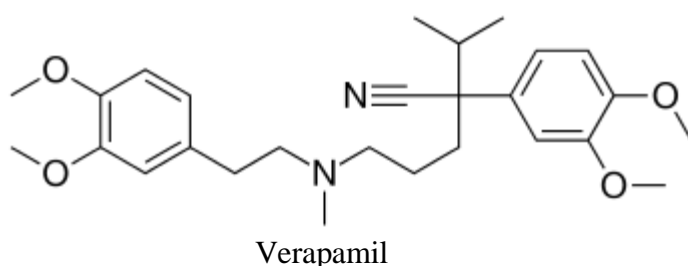
Contraindications :

- 1) Stage 4 CKD, Gout, Acute renal failure.
- 2) Hyponatremia.

F) Ca-channel blockers :**Verapamil :**

It is a calcium channel blocker medication used for the treatment of high blood pressure, angina (chest pain from not enough blood flow to the heart), and supraventricular tachycardia. Verapamil was approved for medical use in the United States in 1981. it was the 151st most commonly prescribed medication in the United States, with more than 3 million prescriptions.

Route of Administration	Oral , Intravenous
Bioavailability	31 %
Metabolism	Liver
Elimination Half life	2.8—7.4 hours
Excretion	Kidney :11 %

Structure :

Mechanism of Action :

Verapamil's mechanism in all cases is to block voltage-dependent calcium channels. verapamil dilate the coronary blood vessels, which increases the supply of blood and oxygen to the heart. They also cause dilatation of systemic peripheral vessels as well, causing a reduction in the workload of the heart, hence the blood pressure decreases.

Verapamil -----> Block L- type Ca⁺⁺ channels -----> Decrease Ca⁺⁺ and entry
 ↓
 ↓
 Decreases heart rate & Vascular smooth muscles relaxed.

Uses :

- 1) For controlling ventricular rate in supraventricular tachycardia and migraine headache prevention.
- 2) Also used intra-arterially to treat cerebral vasospasm.

Adverse effects :

- 1) Dizziness (3.3%), nausea (2.7%), low blood pressure (2.5%), and headache.
- 2) Congestive heart failure, pulmonary edema, fatigue.

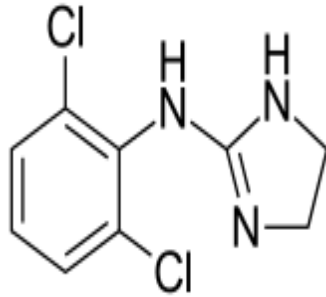
Contraindications :

- 1) Hypotension (systolic blood pressure less than 90 mm Hg), cardiogenic Shock.
- 2) It is also contraindicated in people with atrial flutter or fibrillation and an existing accessory tract such as in Wolff-Parkinson-White syndrome.

I) Alpha-2 adrenergic receptor agonists :**Clonidine :**

Clonidine, sold under the brand name Catapres among others, is an α₂-adrenergic agonist medication used to treat high blood pressure, ADHD. Clonidine was patented in 1961 and came into medical use in 1966. The reduction in circulating norepinephrine by clonidine was used in the past as an investigatory test for pheochromocytoma, which is a catecholamine-synthesizing tumor, usually found in the adrenal medulla. In a clonidine suppression test, plasma catecholamine levels are measured before and 3 hours after a 0.3 mg oral test dose has been given to the patient. A positive test occurs if there is no decrease in plasma levels.

Route of administration	Oral
Bioavailability	70-80 %
Metabolism	Liver
Excretion	Urine
Elimination half life	5-13 hrs

Structure :

Clonidine

Mechanism of action :

Clonidine treats high blood pressure by stimulating α_2 receptors in the brainstem, which decreases peripheral vascular resistance, lowering blood pressure. It has specificity towards the presynaptic α_2 receptors in the vasomotor center in the brainstem. This binding has a sympatholytic effect, suppresses release of norepinephrine, ATP, renin, and neuropeptide Y which if released would increase vascular resistance.

Clonidine also acts as an agonist at imidazoline-1 (I1) receptors in the brain, and it is hypothesized that this effect may contribute to reducing blood pressure.

Clonidine -----> stimulates presynaptic α_2 receptors -----> Inhibits release of NE

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Lowers blood pressure.

Uses :

- 1) Resistant to hypertension.
- 2) Attention deficit hyperactivity disorder.
- 3) Drug withdrawal.

Adverse effects :

- 1) Sedation, dry mouth, and hypotension (low blood pressure).
- 2) Headache (dose-dependent), Fatigue.
- 3) Skin reactions (if given transdermally).

Contraindications:

- 1) In patient with hypersensitivity to clonidine.
- 2) In Diabetic patient with sulphonylurea.
- 3) In Angioedema.

Combination	Possible effects
An alpha or beta adrenergic blocker + Clonidine	Antagonism of clonidine action observed.
Hydralazine + Dihydropyridine	Haemodynamic action
Verapamil + B-blocker	Bradycardia

J) Angiotensin II receptor blocker :

Antihypertensives & pregnancy

Antihypertensives to be avoided during pregnancy	Antihypertensives found safer during pregnancy
ACE inhibitors, ARBs: Risk of foetal damage, growth retardation.	Hydralazine Methyldopa
Diuretics: increase risk of foetal wastage, placental infarcts, miscarriage, stillbirth.	Dihydropyridine CCBs: if used, they should be discontinued before labour as they weaken uterine contractions.
Nonselective β blockers: Propranolol cause low birth weight, decreased placental size, neonatal bradycardia and hypoglycaemia.	Cardioselective β blockers and those with ISA, e.g. atenolol, metoprolol, pindolol, acebutolol: may be used if no other choice.
Sod. nitroprusside: Contraindicated in eclampsia.	Prazosin and clonidine-provided that postural hypotension can be avoided.

Uses:

1) Losartan is used for hypertension, including in people with left ventricular hypertrophy (enlarged heart muscle), and kidney dysfunction among type II diabetics. It may also delay progression of diabetic nephropathy. It is a suitable pharmacological agent for the reduction of renal disease progression in patients with type 2 diabetes, hypertension.

Adverse effects:

- 1) Losartan in adults: upper respiratory infections, dizziness, and back pain. People with type 2 diabetes and kidney disease may experience diarrhea, fatigue, low blood pressure, low blood glucose, elevated potassium, chest pain, or allergic reaction.
- 2) It injures liver.

Contraindications:

- 1) Hypertension.
- 2) Diabetic nephropathy patients.

References:

- [1] https://en.wikipedia.org/wiki/Antihypertensive_drug
- [2] K.D.Tripathi - Essentials of Medical Pharmacology 6th Edition.
- [3] https://www.google.com/search?q=moa+of+carvedilol+for+hypertension+&tbm=isch&ved=2ahUKEwi_e_I711Mn9AhXFieYKHZl
- [4] <https://www.google.com/search?q=verapamil+mechanism+of+action&tbm=isch&ved=2ahUKEwihtvD63sn9AhWZndgFHbaFC>

