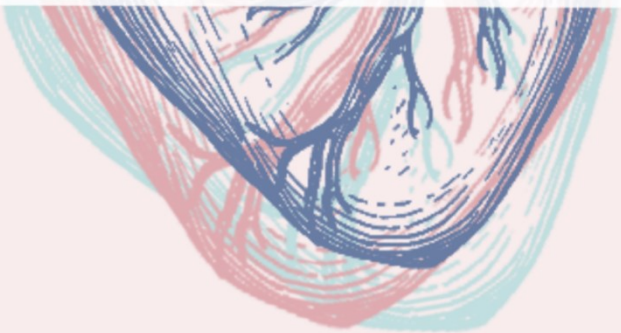
Cardio-Vascular System

2

Pharmacology



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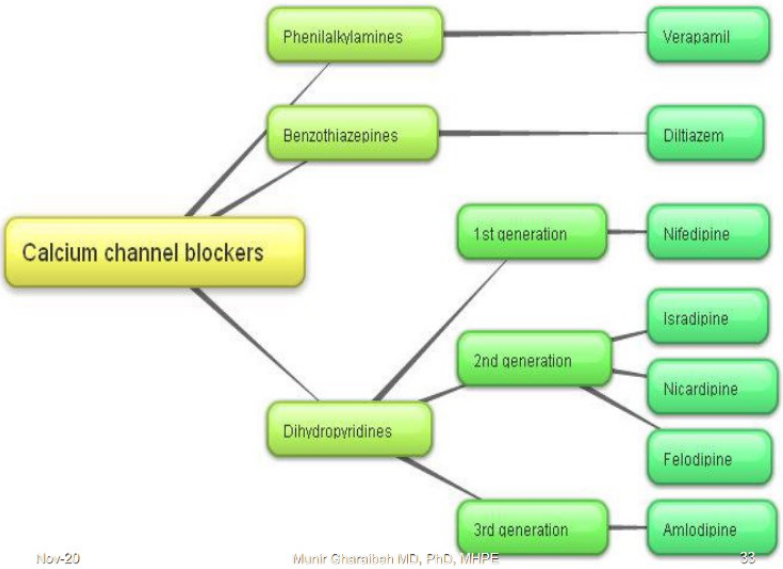
Let's continue talking about antihypertensive drugs.

Calcium channel blockers (CCBs)

Calcium channels are essential part in most cells of the body, especially, calcium is important in cardiovascular function, its involved in cardiac muscle contraction, vascular smooth muscle contraction and other smooth muscles in the body, in the neural function of the CNS, nerve synapses, glandular secretion whether exocrine or endocrine, also in cell division.

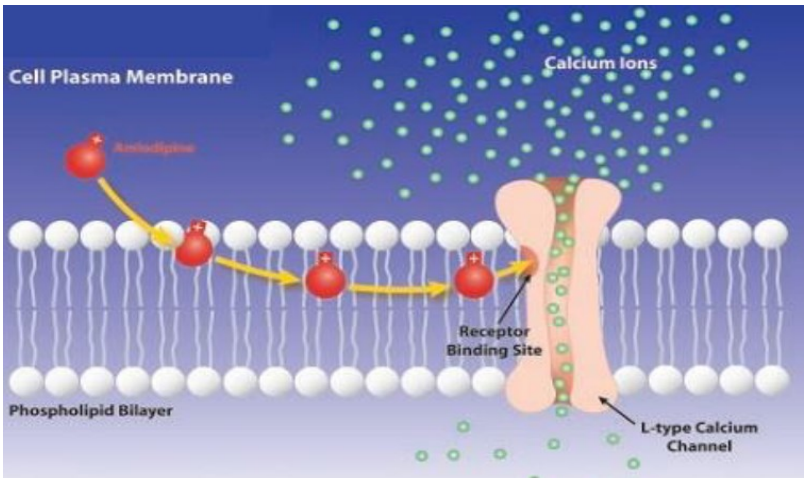
That's why calcium channel blockers are nowadays used for the treatment of many cardiovascular and non-cardiovascular diseases.



The first CCBs discovered were verapamil, diltiazem, nifedipine. Each belong to different chemical groups.

Newer drugs that belong to Dihydropyridines were manufactured, making 1st, 2nd and 3rd generation of this class.

As the name suggests, CCBs blocks calcium entry into the cell through the calcium channels, as you can see the drug passes through the plasma membrane and binds to the calcium channel from the inside rendering it inactive.



The table below shows the different types of calcium channels, their locations, calcium current properties, and what drugs block them.

- Calcium channel blockers have different affinities toward certain types, for example verapamil can block only the L type.
- The most common channel type is the L, its present almost everywhere.

- sFTX are drugs that were used on experimental animals and have proved to block the T type.
- DHP stands for dihydropyridines.

These are not for memorizing at all, just know we have different types, location, current properties, they blocked by different drugs.

Type	Channel Name	Where Found	Properties of the Calcium Current	Blocked By
L	$Ca_V1.1$–$Ca_V1.3$	Cardiac, skeletal, smooth muscle, neurons ($Ca_V1.4$ is found in retina), endocrine cells, bone	Long, large, high threshold	Verapamil, DHPs, Cd^{2+}, -aga-IIIA
T	$Ca_V3.1$–$Ca_V3.3$	Heart, neurons	Short, small, low threshold	sFTX, flunarizine, Ni^{2+}, mibefradil[1]
N	$Ca_V2.2$	Neurons, sperm[2]	Short, high threshold	Ziconotide,[3] gabapentin,[4] -CTX-GVIA, -aga-IIIA, Cd^{2+}
P/Q	$Ca_V2.1$	Neurons	Long, high threshold	-CTX-MVIIC, -aga-IVA
R	$Ca_V2.3$	Neurons, sperm[2]	Pacemaking	SNX-482, -

18-Nov-20 Munir Gharaibeh MD, PhD, MHPE 36

Mechanism of action:

- Calcium channel blockers are used to treat hypertension by primarily acting to reduce peripheral vascular resistance (PVR), by causing vasodilation through preventing vascular smooth muscles contraction.
- They have initial diuretic effect, the vasodilation of the renal arteries might cause some sort of diuresis, especially with the short-acting DHPs. For example, Nifedipine.
- More effective than others in protection against stroke, because they can affect the blood vessels in the brain.
- Effective in the elderly.
- Equally effective in black and nonblack patients. In contrast to diuretics, which were more effective in black patients.

They have different effects on PVR, heart rate HR and cardiac output CO.

	PVR	HR	CO
Nifedipine	---	+++ (Reflexly)	++
Diltiazem	--	-	-
Verapamil	--	--	--

CCBs they also work on the cardiac muscle itself, logically they must also suppress the cardiac muscles, which is true in case of Diltiazem and Verapamil (because they are not as potent as Nifedipine in reducing PVR), but Nifedipine is an exception.

Nifedipine is very potent in reducing PVR, so it acts as a rapid vasodilator, as a result of this rapid vasodilation, the baroreceptors gets activated initiating a reflex, consequently stimulating the sympathetic and inhibiting the parasympathetic systems, which as we know, will stimulate the heart rate and cardiac output.

Therefore, the direct effect of nifedipine on the heart is inhibitory, but as a result of the baroreceptor reflex, it indirectly stimulates the heart.

Side Effects:

- Relatively safe drugs, most of the side effects are due to vasodilation of blood vessels
- Risk of Hypotension. (in drugs like nifedipine)
- Headache, dizziness. (as a result of vasodilation in the brain vessels)
- Flushing, especially with short acting agents.
- Peripheral edema.
- Do NOT cause metabolic disturbances. In contrast with diuretics.

CCBs also differ in pharmacokinetic characteristics, they have different oral bioavailability, half-life, different indications. The doctor only read verapamil, nifedipine and diltiazem.

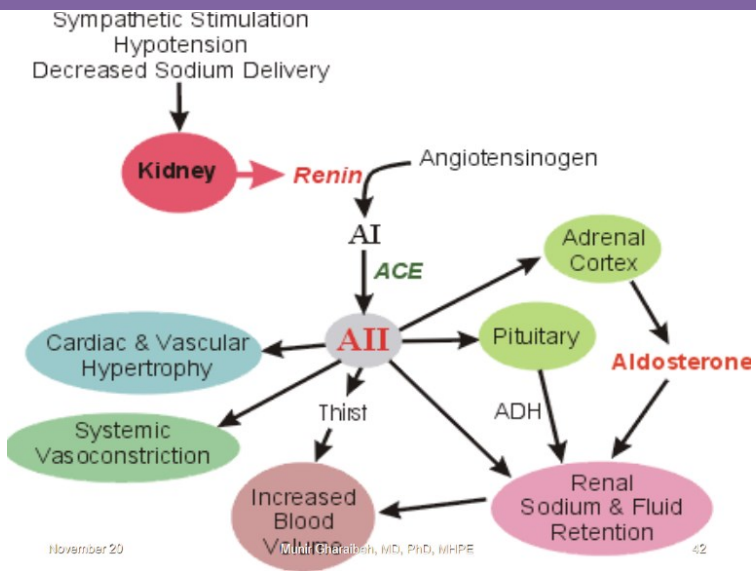
Drug	Oral Bioavailability (%)	Half-Life (hours)	Indication
Dihydropyridines			
Amlodipine	65–90	30–50	Angina, hypertension
Felodipine	15–20	11–16	Hypertension, Raynaud's phenomenon
Isradipine	15–25	8	Hypertension
Nicardipine	35	2–4	Angina, hypertension
Nifedipine	45–70	4	Angina, hypertension, Raynaud's phenomenon
Nimodipine	13	1–2	Subarachnoid hemorrhage
Nisoldipine	< 10	6–12	Hypertension
Nitrendipine	10–30	5–12	Investigational
Miscellaneous			
Diltiazem	40–65	3–4	Angina, hypertension, Raynaud's phenomenon
Verapamil	20–35	6	Angina, hypertension, arrhythmias, migraine

Renin-Angiotensin-Aldosterone System

There are receptors in the afferent arteriole of the kidney that can sense the salt concentration as well as the blood pressure, so if BP drops, this triggers the release of renin from the afferent arteriole.

Now, renin converts angiotensinogen (which is produced from the liver) into angiotensin I.

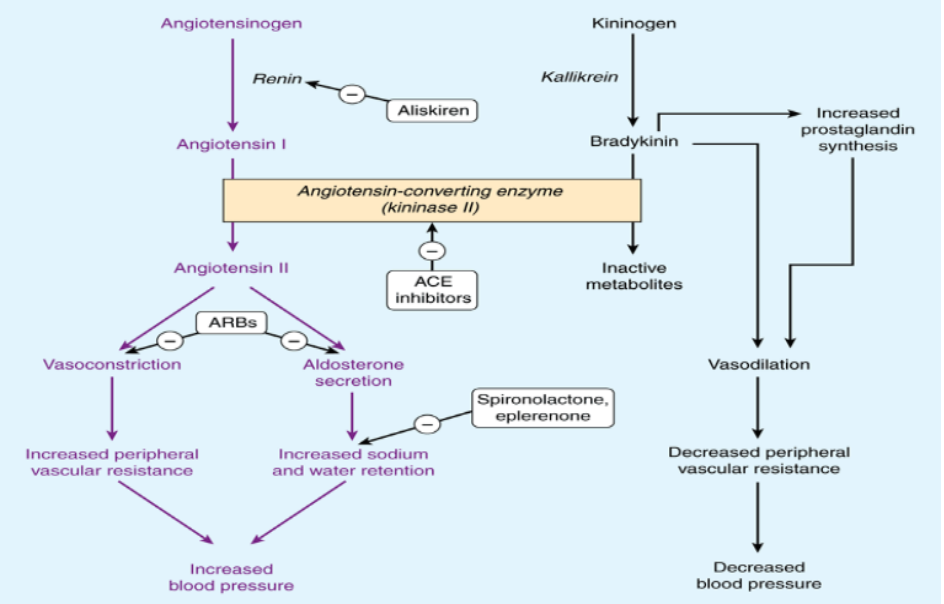
Angiotensin I goes to the lungs and there it meets the enzyme angiotensin-converting enzyme (ACE) which converts it into angiotensin II.



As mentioned in the figure above, angiotensin II has many effects. Please read them!

There many drugs which target this system, Aliskiren (inhibits renin), ACEI (angiotensin-converting enzyme inhibitors), ARBs (angiotensin receptor blockers).

Spironolactone, eplerenone these inhibit aldosterone secretion as well as aldosterone receptors.



ACE also metabolizes bradykinin, bradykinin increases prostaglandin synthesis causing vasodilation. Therefore, inhibiting ACE would not only decrease angiotensin II levels but also stopping bradykinin from being metabolized, resulting in increased levels of bradykinin, which ultimately causes vasodilation, decreased PVR and decreased blood pressure.

Angiotensin II:

Angiotensin II, as a part of the renin-angiotensin-aldosterone system, its major function is to regulate the blood pressure as well as body fluids.

- Potent vasoconstrictor by itself.
- Facilitates release of NE. (acting as neuro-mediator for the sympathetic nervous system, which also increases the blood pressure)
- Central actions to increase BP.
- Promotes release of aldosterone, aldosterone increases the BP by increasing salt and water retention.
- Regulates tubular function in the kidney.
- Regulates intra-renal blood flow.

Angiotensin-Converting Enzyme Inhibitors (ACEI)

These drugs inhibit the enzyme angiotensin-converting enzyme (ACE) which is responsible for converting angiotensin I into angiotensin II.

- Have many applications nowadays, for hypertension and other diseases.
- Inhibit ACE in the lungs.
- Also inhibit kinin metabolism

Cardiorenal Effects of ACE Inhibitors:

- Vasodilation (arterial & venous):
  - Reduces arterial & venous pressure.
  - Reduce ventricular afterload and preload.
- Decreases blood volume (through inhibiting aldosterone), therefore having a natriuretic (induces sodium excretion) and diuretic activity.
- Depresses sympathetic activity.
- Inhibits cardiac and vascular hypertrophy.

Examples of ACEI:

- Captopril is the prototype. It was discovered in 1970s, newer drugs with less side effects are now discovered
- Enalapril, Quinapril, Lisinopril, Benazepril, Fosonopril.

All of them have similar efficacy. But differ in toxicity.

Therapeutic Benefits of ACEI:

- Effective in high-rennin hypertension (which makes 20% of all hypertension cases), heart failure (HF) and ischemic heart disease (IHD).
- Do not increase HR; they don't work directly on the heart.
- Useful in diabetic nephropathy by dilating efferent arterioles thus reducing intraglomerular pressure and consequently protects against progressive glomerulosclerosis (glomerulosclerosis is a nephropathy that commonly occur in diabetics). It's now used as a prophylactic agent in diabetic patients even if the blood pressure isn't very high
- No need for a diuretic but a diuretic can be added. In contrast to vasodilators and CCBs where resistance can develop if not given along with diuretics.
- Can be combined with CCBs.
- Should not be combined with Beta blockers.
- No metabolic side effects, in contrast to Beta blockers and diuretics that can cause diabetes and hyperlipidemia.
- Contraindicated in pregnancy (teratogenic) and bilateral renal artery stenosis.

Side Effects of ACEI:

They are relatively safe drugs except for captopril.

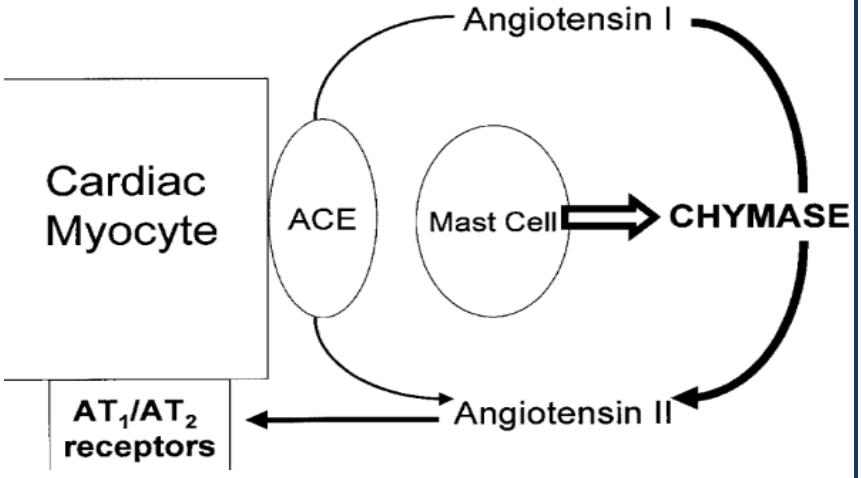
- Captopril is SH containing drug, so very toxic (bone marrow suppression, dysgeusia (change in taste sensation), proteinuria, allergic skin rash, fever). In general sulfhydryl containing drugs are toxic as they can bind many different enzymes and disrupt their actions.
- Hypotension (first dose phenomena) especially with renovascular hypertension. So these drugs are contraindicated in patients with this condition.
- K+ retention, especially in the presence of renal dysfunction or when combined with K+ sparing diuretics or ARBs.
- Cough, in 10% of patients, you might consider to change the preparation or even the whole class.
- Angioedema.

Chymase

Long-term treatment with ACE inhibitors is often associated with so-called "angiotensin escape" (resistance) characterized by the return of plasma angiotensin II concentration to pretreatment levels.

If ACE is inhibited then we shouldn't have high levels of angiotensin II? But we still find high levels of angiotensin II, so there must be some other site producing it. This place is the heart tissue.

This rebound generation of angiotensin II occurs through the action of the serine proteases such as *chymase* and *cathepsin G*. Chymase is an enzyme found in the heart. It can convert angiotensin I to angiotensin II.



- Vascular chymase has been implicated in the ACE-independent mechanism for local angiotensin II formation in human arteries.
- ACE-independent generation of angiotensin II plays a central role in the regulation of renal hemodynamics during the progression of diabetic nephropathy.

The physiologic importance of chymase is uncertain, because of the presence of natural protease inhibitors in the interstitial fluid which inhibit chymase-induced angiotensin II production. Therefore, the beneficial effects of ACE inhibitors on blood pressure usually persists.

Angiotensin II Receptor Blockers (AT-1)

AT-1 or ARBs (same thing different name) work directly on angiotensin receptors found on cell surfaces, resulting in more complete inhibition of angiotensin actions, with NO effects on bradykinins. In contrast to ACE inhibitors.

- May be only indicated when ACEI are intolerable. Simply because they very expensive.
- Most expensive, but fastest growing class of antihypertensive drugs.
- Free of side effects, especially cough, since they work inside the lungs, but ARBs work outside.
- May be better than ACEI in protection against stroke (due to activation of AT-2 receptor which facilitates collateral vessels and neuronal resistance).

Examples of ARBs:

- Losartan, Valsartan, Candesartan, Irbesartan, Eprosartan.
- Telmisartan (it has additional peroxisome proliferator-activated receptor PPR-γ agonist activity).

Renin Enzyme Inhibitors

Aliskiren:

- The first in this group.
- Not widely used, other better studied medications are typically recommended due to concerns of higher side effects and less evidence of benefit.

Sympatholytics or Adrenergic Blockers

- Alpha Adrenergic Antagonists, alpha receptors found in blood vessels causes vasoconstriction, so by giving alpha antagonists we prevent this and the vessels stay dilated and blood pressure goes down.
  - Non selective antagonists
  - Alpha1-selective antagonists
- Beta adrenergic blockers
- Adrenergic neuron blockers
- Ganglionic blockers

There are two types of alpha receptors. Alpha1 are present in the postsynaptic membrane, alpha2 are in presynaptic membrane. Alpha2 receptors inhibit NE release from the vesicles, thus, inhibiting alpha2 receptors alone will increase blood pressure. Inhibiting alpha1 receptors alone will decrease the blood pressure, while inhibiting both causes tachycardia and increase contractility.

Non selective Alpha-Adrenergic Antagonist

- They block both α1 and α2 receptors, causing reflex tachycardia and increased contractility.
- Blockade of α2-presynaptic receptors leads to augmented release of NE leading to tachycardia and increased contractility of the heart.
- Used only for pheochromocytoma (a tumor of the adrenal medulla which secretes epinephrine and norepinephrine in large amount, causing hypertension and increasing HR and CO). Therefore, we need a drug that works on both alpha1 and alpha2 receptors.
- EXTRA: in pheochromocytoma we initially give alpha blocker to control the hypertension (even though it causes further increase in HR & CO), then later we give the patient beta blockers to control the heart rate and cardiac output.

Examples:

- Phentolamine
- Phenoxybenzamine

α1-selective Alpha-Adrenergic Antagonists

- These drugs are selective, meaning they favor α1 rather than α2 (α1 > α2). However, they are not **specific** only for α1.
- α1 blockers will lower the BP but will not cause tachycardia.
- First-dose phenomenon, similar to ACE inhibitors, a sudden drop in blood pressure that might lead to fainting and tachycardia.
- All are free of metabolic effects, but can cause drowsiness, diarrhea, postural hypotension, tachycardia, and tolerance **due to fluid retention**. Similar to short-acting vasodilators.
- Effective in moderate hypertension as well as benign prostatic hypertrophy.

Examples:

- Prazosin, Terazosin, Doxazosin.

Non selective Beta Adrenergic Blockers

They work on beta receptors which are mainly present in heart.

Antihypertensive Mechanisms:

- Decrease HR, SV, and consequently cardiac output (CO).
- Central action in the **vasomotor center**, since many of them can cross the blood brain barrier (Beta Blockers can cross the BBB).
- Decrease rennin release↓ & Inhibit NE release↓.

There are 30 different preparations found in the market including:

- Propranolol, which is lipophilic, is a prototype of these of drugs and is the oldest and most widely used nonselective β-adrenoblocker (discovered in 1957).
- Timolol: Lipophilic
- Nadolol: Long acting
- Pindolol: intrinsic sympathomimetic activity (ISA)
- Acebutolol: ISA
- Esmolol: β1 selective, and has a short half life
- Metoprolol: β1 selective
- Atenolol: β1 selective
- Betaxolol: β1 selective
- Bisoprolol: β1 selective

Intrinsic sympathomimetic activity: being able to stimulate β-adrenergic receptors (agonist effect) and to oppose the stimulating effects of catecholamines (antagonist effect) in a competitive way.

Therapeutic Effectiveness:

- Effect is not immediate
- Useful in high-rennin hypertension (they inhibit renin release).
- Monotherapy or combination with vasodilators or ACEIs.
- Hyperkinetic hearts- to calm the heart.
- Used in other cardiovascular conditions, such as ischemic heart disease (IHD) and cardiac arrhythmias.
- Ineffective in blacks, maybe due to genetic predisposition.
- Doesn't cause postural hypotension (in contrast to vasodilators, CCBs, and diuretics).

Side Effects:

- Bronchospasm, especially with the non-selective blockers, because beta2 receptors are found in the lungs and bronchi.
- Heart failure, beta receptors normally stimulate the heart muscle, so blocking these receptors can reduce the activity of the heart. That's why they are not advisable in elderly patients.
  In general, beta blockers are contraindicated in patients with heart problems.
- CNS effects like fatigue, depression, impotence ...etc.
- Impair lipid and glucose metabolism, therefore not used for treatment of hypertensive diabetics.
- Mask hypoglycemia, normally during hypoglycemia sympathetic nervous system gets activated to warn the body, producing severe hunger, increased blood pressure, and increased heart rate. Additionally, you know that beta receptors, in the liver, stimulate gluconeogenesis and glycogenolysis to elevate glucose blood levels. But, if beta receptors are blocked, the body will go into severe hypoglycemia without even noticing.
- Claudication- pain caused by too little blood flow to your leg or arm, due to blockade of beta receptors.

Norepinephrine will overly activate alpha receptors causing vasoconstriction of peripheral blood vessels, usually in upper and lower limbs leading to cold extremities, cold and cyanotic nose and ear lobes, especially in winter.

- Withdrawal syndrome due to up-regulation of these receptors. This might happen upon sudden stop of using beta blockers.
  Over-activity of sympathetic systems happens which leads to stimulation of the heart, and increase in blood pressure to levels above that of pretreatment. So beta blockers should be stopped gradually over a two to three days.

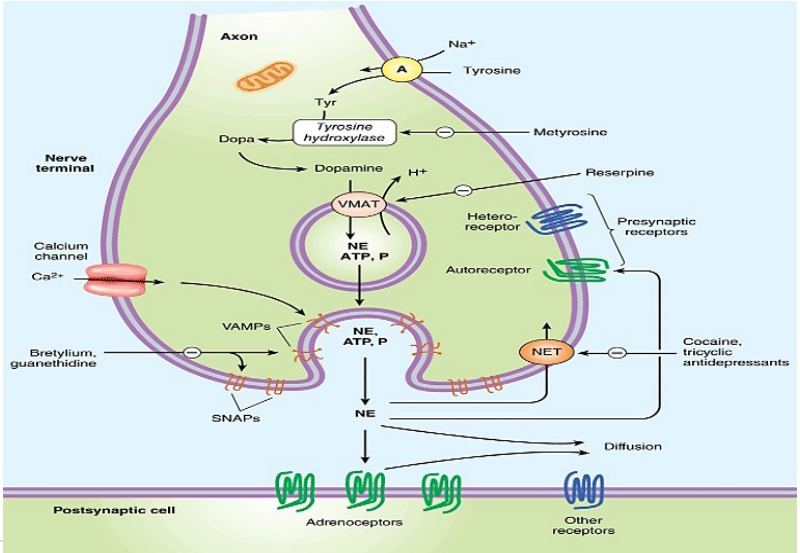
Vasodilating Beta-Adrenergic Blockers

- Labetalol:
  - It's a beta antagonist, alpha1 antagonist (weak alpha1 blocking activity only 20% of those on beta receptors) & beta2 partial agonist - keep in mind that beta2 receptors cause vasodilation- .
  - Useful for pheochromocytoma and emergencies.
- Carvedilol: beta and alpha1 (10% of those on beta receptors) antagonist.
- Esmolol:
  - Beta1 selective, rapidly metabolized (short half-life)
  - Used by continuous IV infusion.

- Nebivolol:
  - Beta1 selective.
  - Nitric oxide potentiating vasodilatory effect.

Adrenergic Neuron Blockers

- Adrenergic neuron blocking agents act at the sympathetic nerve terminals to prevent the **release** of transmitter substance, rather than at the effector cell to inhibit the association of the transmitter with its receptors.
- They're generally hydrophilic.
- They are uptaken by **uptake 1**.
- Blocks NE release.
  These agents displace NE from intracellular vesicles, then, the free NE inside the cell will be metabolized by mono-amine oxidase (MAO).



Therefore, they cause the depletion of NE from peripheral nerve endings.

Examples:

- Guanethidine, Bethanedine, Debrisoquin, Guanadrel.

Reserpine:

- It's an adrenergic neuron blocking agents derived from the plant Rauwolfia alkaloid.
- *Lipophilic.*
- Binds to the sympathetic intracellular vesicles, and prevents DA (dopamine) uptake into these vesicles.
- Amines are metabolized by MAO.
- It depletes NE, 5HT (serotonin), ACTH, and DA.
- **Old** fashioned, **slow** onset and offset, and very **cheap**.
- It can cause depression and suicide (it can cross the BBB, since it's lipophilic), and has possible carcinogenic effect.

Ganglionic Blockers

- They work directly on the autonomic ganglions
- Blocks transmission in both sympathetic & parasympathetic systems.
- They act immediately and are very efficacious.
- The effect of ganglionic blockers can be rapidly reversed, thus, they're used for short term control of BP (e.g. intraoperatively and in emergencies). I.E. if you stop the drug, the effect terminates immediately due to their **short** duration of action.
- They have **many** side-effects.

Examples:

- Trimethaphan
- Pentolinium
- Mecamylamine

The table below shows the side effects of ganglionic blockers.

Notice the involvement of many organs that are controlled by ANS.

Organ	Predominate system	Results
Cardiovascular system heart veins arterioles	 Parasympathetic Sympathetic Sympathetic	 Tachycardia Vasodilation Dilation
Eye Iris, Ciliary muscles	 Parasympathetic Parasympathetic	 Mydriasis Cycloplegia

GI tract	Parasympathetic	Relaxation (constipation)
Urinary bladder	Parasympathetic	Urinary retention
Salivary glands	Parasympathetic	Dry mouth
Sweat glands	Sympathetic	Anhidrosis

Centrally Acting Antihypertensive Drugs

These drugs work directly on the brain specifically in the vasomotor center, there, we have both alpha and beta receptors but their effect is reversed; meaning that alpha receptors activation decreases BP while Beta receptor activation increases BP.

The vasomotor center constitutes of the following nuclei:

1. Nucleus Tractus Solitarius
2. Nucleus Ambiguss
3. Rostral Ventral Medulla.

The vasomotor center controls both the sympathetic and parasympathetic systems.

Common Properties of these drugs:

- Cross BBB.
- Reduce **pre**ganglionic sympathetic activity.
- Orthostasis is unusual, due to **preservation of peripheral sympathetic activity**.
- CNS side effects.

Examples of these drugs include:

- Propranolol (Beta blocker).
- Reserpine (acts on sympathetic nerve terminals).
- a-Methyl Dopa.

a-Methyl Dopa:

- An old drug, that's thought to act as a pseudo-transmitter (by being converted into a-methyl-norepinephrine), which works peripherally. Now, it's proved to have central alpha agonist activity.
- a-MD (alpha methyl-dopa) is converted into a-MDA (alpha methyl-dopamine) which is then converted to a-MNE (alpha methyl-norepinephrine).
- It lowers BP but doesn't affect CO or renal blood flow.
- It can cause lactation and positive *Coomb's* test.
- Safe in pregnancy (drug of choice for treatment of eclampsia or preeclampsia- a pregnancy complication characterized by high blood pressure and signs of damage to another organ system- and for treatment of hypertension in pregnancy).

Clonidine:

- Imidazoline derivative, tried initially as a nasal decongestant (local effect).
- Central alpha agonist (lowering blood pressure).
- I.V administration of clonidine would have biphasic effect; initially, it acts peripherally causing **vasoconstriction** of blood vessels which further raises the blood pressure (that's why clonidine I.V. administration is contraindicated), then central actions begin (lowering BP).
- Given **orally**, so that the initial vasoconstrictive effect would be reduced, by slower absorption from the GI.
- Also available as transdermal patch (extended activity for about 7 days).

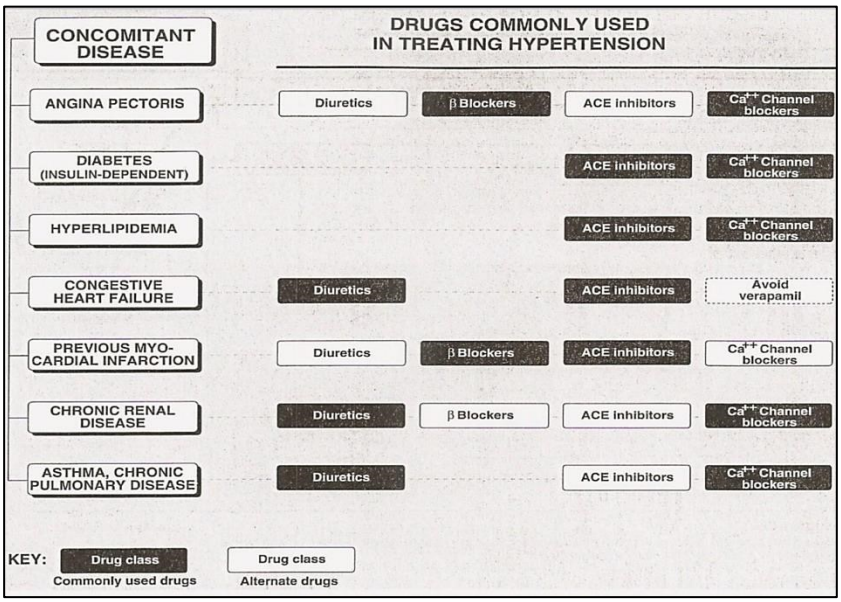
Causes of Resistant Hypertension

Resistant hypertension means that it doesn't respond to drugs. The causes include:

- Improper BP measurement
- "White coat hypertension" (we don't measure BP in clinic directly; rather, we wait a little bit to avoid it).
- Non-compliance to the prescribed drugs
- Psychological stresses
- Secondary hypertension (to a tumor like pheochromocytoma)
- Sleep disorders
- Volume overload
- Pseudo-tolerance to drugs
- Excess sodium intake
- Volume retention from kidney disease
- Inadequate diuretic therapy
- Inadequate doses
- Inappropriate combinations
- NSAID, cyclooxygenase 2 inhibitors (e.g. Aspirin, Ibuprofen, and Voltaren)
- Cocaine, amphetamines, anorectics, and other illicit drugs
- Sympathomimetic drugs
- Oral contraceptives
- Corticosteroids
- Cyclosporine
- Erythropoietin
- Licorice عِرق السوس (including some chewing tobacco).
- Excess alcohol intake

→ A summary for some drugs and their other indications besides treating hypertension.

- The drugs in black are commonly used drugs.
- The drugs in white are alternative drugs.



Good luck