

Drug Treatment of Hypertension

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Definition: Systolic BP \geq 140 mm Hg
 or Diastolic BP \geq 90 mm Hg

- Diagnosis is based on multiple (≥ 3) measurements, on different days
- For patients having diabetes or chronic kidney disease (high-risk group), diagnosis of hypertension is made with BP \geq 130/80 mmHg

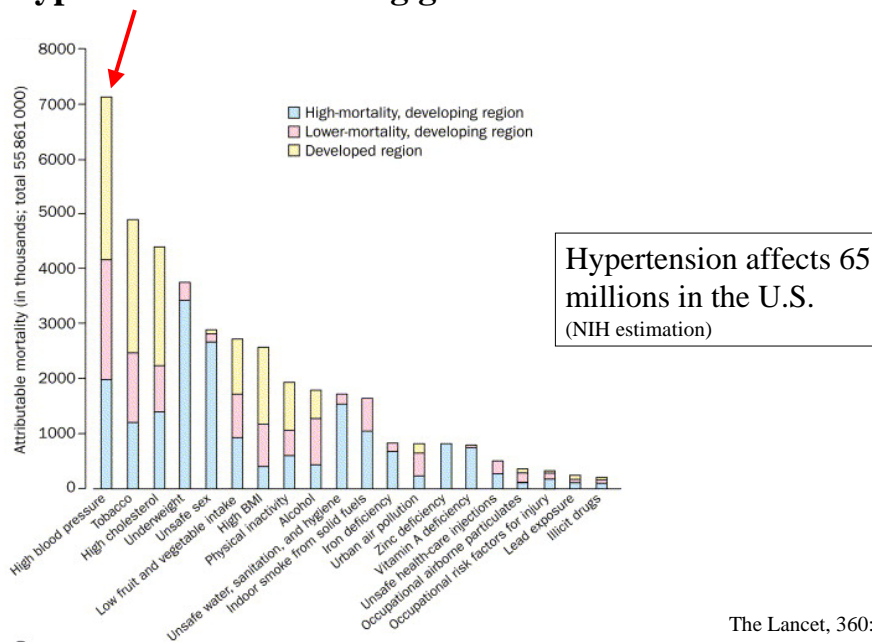
Classification and management of BP for adults

Category	Systolic	Diastolic	Lifestyle modification	Initial drug therapy
Normal	< 120	and < 80	Encourage	Not needed
Pre-hypertension	120-139	or 80-89	Yes	No, or treat Compelling indications
Stage 1 hypertension	140-159	or 90-99	Yes	Diuretic, ACEI, ARB, β -blocker, CCB, Combination; + compelling indications
Stage 2 hypertension	≥ 160	or ≥ 100	Yes	Two-drug combo (diuretic and ACEI, or ARB or β -blocker or CCB); Also treat compelling indications

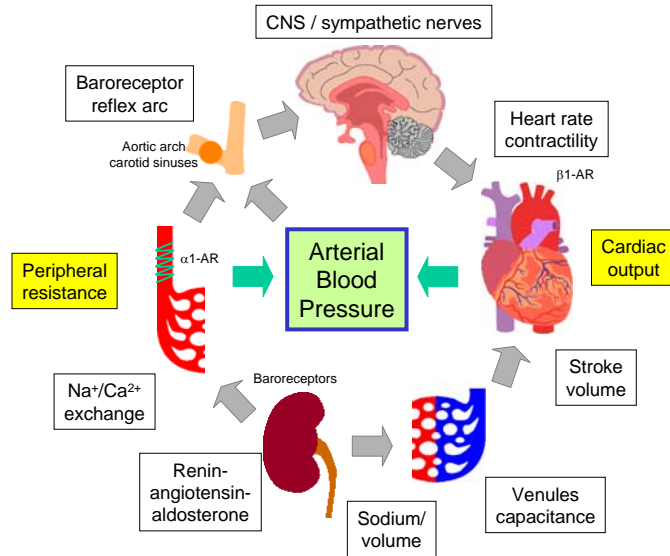
Based on 7th Report of the Joint National Committee on Detection, Evaluation, and Treatment of High BP (JNC 7)

Diuretic here means thiazide-type; ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; β -blocker, β -adrenergic receptor blocker; CCB, calcium channel blocker

Hypertension is a leading global risk factor for mortality



$$BP = CO \times PVR$$



$$BP = CO \times PVR$$

and

$$MAP = CO \times TPR$$

$$MAP = \text{Mean Arterial Pressure} = (SBP - DBP) / 3 + DBP$$

CO = Cardiac Output

TPR = Total Peripheral Resistance

Factors affecting drug treatment of hypertension:

- Accuracy of diagnosis; severity of hypertension
- Etiology: Primary (essential hypertension) vs. secondary (10-15% patients)
e.g., pheochromocytoma, renal artery constriction, Cushing's syndrome
- Pre-existing risk factors and medical conditions (smoking, hyperlipidemia, diabetes, congestive heart failure, asthma, current medications...)
- Individualization (age, gender, ethnicity); patient compliance
- Single drug (monotherapy) vs. multiple drug (polypharmacy)

Mechanism-based classification of AHDs

Diuretics:

Thiazide - *Hydrochlorothiazide*

Loop - *furosemide, torsemide, ethacrynic acid*

Potassium-sparing - *amiloride, spironolactone, triamterene*

Sympathoplegic agents:

Adrenergic synthesis / release blockers - *reserpine, granethidine*

Central α -adrenergic agonists – *α -methyldopa, clonidine*

α -blockers - *prazosin, terazosin, doxazosin*

β -blockers - *propranolol, nadolol, timolol, metoprolol, acebutolol, penbutolol, pindolol*

Ganglion blocker - *Trimethaphan*

Direct vasodilators: *hydralazine, minoxidil, sodium nitroprusside, diazoxide*

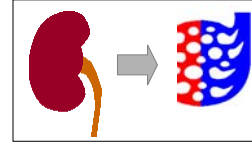
Calcium channel blockers: *nifedipine, amlodipine, felodipine, diltiazem, verapamil*

AT-II antagonists & ACE inhibitors:

ACE inhibitors – *captopril, enalapril, enalaprilat, lisinopril, benazepril*

AT-II receptor antagonists - *losartan*

I. DIURETICS



First-line drug for hypertension. Relatively safe and effective. Suitable for older adults. Can be given orally. Use alone or with other antihypertensive agents. Low cost and mostly available in 3rd world countries.

Mechanism of action:

Diuretics lower BP by depleting body sodium stores. Full effects take 2 steps: (1) initial reduction of total blood volume and hence cardiac output; peripheral vascular resistance may increase; (2) when CO returns to normal (takes 6-8 weeks), PVR declines.

Therapeutic use:

Thiazide diuretics, such as **hydrochlorothiazide**, act on distal convoluted tubule and inhibit $\text{Na}^+\text{-Cl}^-$ symport. Can counteract the Na^+ and H_2O retention effect of direct vasodilators such as hydralazine and therefore are beneficial for combined use.

Particularly useful for elderly patients, but not effective when kidney function is inadequate.

Thiazides reduce blood K^+ and Mg^{2+} levels, and induce hypokalemia. It retains Ca^{2+} and decreases urine Ca^{2+} content. It is necessary to monitor serum K^+ level in patients with cardiac arrhythmias and when digitalis is in use.

Loop diuretics, including [furosemide](#), [torsemide](#), and [ethacrynic acid](#), are more powerful than thiazides. They are often used for treatment of severe hypertension when direct vasodilators are administered and Na⁺ and H₂O retention becomes a problem. Can be used in patients not responding to thiazides. Increase urine Ca²⁺ content.

K-sparing diuretics include [triamterene](#), [amiloride](#) (both are Na⁺ channel inhibitors), and [spironolactone](#) (aldosterone antagonist). Used for treating hypertension in patients given *digitalis*. Also enhance the natriuretic effects of other diuretics (e.g., thiazides) and counteract the K⁺ depleting effect of these diuretics.

Adverse effects and toxicity:

- (1) Depletion of K⁺ (except K⁺-sparing diuretics), leading to hypokalemia.
- (2) Increase uric acid concentration and precipitate gout.
- (3) Increase serum lipid concentrations. Diuretics are not used for treating hypertension in patients with hyperlipidemia or diabetes.
- (4) Gynecomastia with [spironolactone](#).

II. SYMPATHOPLEGIC AGENTS

Centrally acting (on vasomotor center):
 α -methyldopa, clonidine, guanabenz, guanfacine
acting as α_2 agonists



Blocking synthesis and/or release of NE:
reserpine, guanethidine, granadrel
Blocking β -adrenoceptors:
propranolol, metoprolol, labetalol, etc.



Blocking sympathetic ganglia:
trimethaphan



Blocking α_1 -adrenoceptors in vessels:
prazosin, doxazosin, tetrazosin

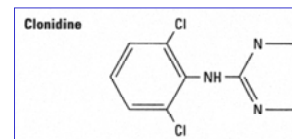
Blocking renin release:
propranolol and other β -blockers



Centrally-acting adrenergic drugs:

Clonidine

A 2-imidazoline derivative that reduces sympathetic and increases parasympathetic tone, leading to BP lowering and bradycardia.



Mechanism of action: Clonidine binds α_2 -AR with higher affinity than α_1 -AR. The α_2 -agonistic activity contributes to its BP lowering effect due to negative feedback at the presynaptic neurons. When given i.v., clonidine induces a brief rise of BP, which is followed by prolonged hypotension.

In addition, clonidine is thought to bind imidazoline receptors (IR) that have not been fully characterized at molecular level.

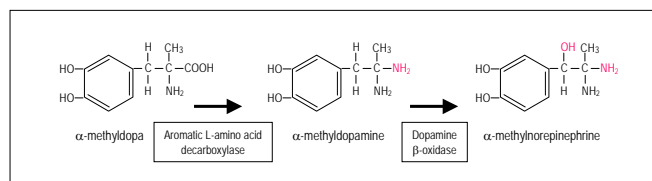
Similar drugs: guanabenz and guanfacine

Therapeutic use: Clonidine reduces CO due to decreased heart rate and relaxation of capacitance vessels. Used for treatment of mild to moderate hypertension, often together with diuretics. Because it decreases renal vascular resistance, it maintains renal blood flow and glomerular filtration and therefore can be used in patients with renal diseases. Clonidine is lipid-soluble and enters brain readily. Half-life is about 8-12 h.

Adverse effects and toxicity: Sedation, dry mouth. Clonidine also causes Na⁺ and H₂O retention. Abrupt withdrawal may induce hypertensive crisis. Do not give to patients who are at risk of mental depression, or are taking tricyclic antidepressants.

α -methyldopa

α -methyldopa is a prodrug. It enters into adrenergic neurons and is converted by two enzymes to α -methylnorepinephrine, which has the antihypertensive effect.



Mechanism of action: The metabolite, α -methylnorepinephrine, is stored in neurosecretory vesicle in place of NE. When released, α -methyl-NE is a potent α -AR agonist and in PNS is a vasoconstrictor. Its CNS effect is mediated by α_2 -AR, resulting in reduced adrenergic outflow from the CNS and an overall reduced total peripheral resistance.

Therapeutic use: This drug does not alter most of the cardiovascular reflexes. Cardiac output and blood flow to vital organs are maintained. It reduces renal vascular resistance and can be used in patients with renal insufficiency. Given orally; effect reaches max. in 4-6 h and continues to 24 h. Not used as first drug in monotherapy, but effective when used with diuretics.

Adverse effects and toxicity: Sedation, lassitude, nightmares, lactation (due to inhibition of dopaminergic neuron in hypothalamus). Long-term use may cause development of autoantibodies against Rh locus and give positive Coomb's test.

Antihypertensive agents that act on PNS

1. Beta blockers

Mechanism of action: (1) Reduce cardiac output; (2) inhibit renin release, AT-II and aldosterone production, and lower peripheral resistance; (3) may decrease adrenergic outflow from the CNS.

Therapeutic use: Recommended as **first-line** antihypertensive agents. Combined use with diuretics are common. More effective in treating hypertension in white than in black patients, and in young patients than elderly (due to high occurrence of chronic lung and heart diseases in the elderly). Especially useful in treating hypertension with preexisting conditions such as previous myocardia infarction, angina pectoris, migraine headache.

Propranolol: Prototype β -blocker; antagonizes β_1 and β_2 AR. It inhibits renin production (due to β_1 -antagonistic activity) and is used in patients with high renin level. It causes no prominent postural hypotension in mild to moderate hypertension patients.

Metoprolol: Much less β_2 -antagonistic than propranolol, thus can be used in patients who also suffer from asthma, diabetes, or peripheral vascular disease.

Nadolol, carteolol, atenolol, betaxolol, bisoprolol: Slower metabolism and longer half-life for these drugs. They can be administered once daily. The underlined are β_1 -selective antagonists.

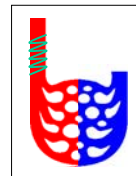
Pindolol, acebutolol, penbutolol: Antagonistic effect is combined with partial agonistic effect on β_2 -AR. Particularly useful for patients with cardiac failure, bradyarrhythmias, or peripheral vascular disease.

Labetalol, carvedilol: These are given as racemic mixture of isomeric compounds. Major advantage is combined α and β blockers and therefore these are more powerful drugs. Labetalol also has some β_2 -agonistic effect. Labetalol is used for treating hypertensive emergencies (injection) or hypertension resulting from pheochromocytoma. Carvedilol can be used in patients with congestive heart failure.

Adverse effects and toxicity:

- (1) Withdrawal syndrome (nervousness, tachycardia, angina, BP increase).
- (2) Reduced myocardial reserve and peripheral vascular insufficiency; exacerbates asthma, diabetes.
- (3) Increased plasma triglycerides and decreased HDL cholesterol (propranolol).
- (4) CNS effects: lassitude, mental depression, insomnia, nightmares.
- (5) GI effects: diarrhea, constipation, nausea, vomiting.

2. Alpha-1 blockers



Prazosin, tetrazosin, doxazosin (all second-line drugs)

Mechanism of action: Competitive antagonists for α_1 -AR. Blocking α_1 -AR leads to relaxation of both arterial and venous smooth muscles and thereby reduce PVR.

Non-selective alpha blockers: Phentolamine and phenoxybenzamine, for treatment of hypertensive emergencies resulting from pheochromocytoma

Therapeutic use: These agents are indirect vasodilators, and are used for treating patients who have not responded to initial antihypertensive therapy. Combined use with propranolol or diuretics may produce additive effects. Long-term use is not likely to cause significant changes in cardiac output and renal blood flow. Thus tachycardia and increased renin release do not occur. No adverse effect on serum lipids and other cardiac risk factors.

Adverse effects and toxicity:

(1) For prazosin, tetrazosin, doxazosin: Reflex tachycardia and first-dose syncope are common. Concomitant use with a β -blocker may be necessary.

(2) For phentolamine, increased cardiac stimulation (by blocking α_2 -AR negative feedback) can cause severe tachycardia, arrhythmias, and myocardial ischemia.

For phenoxybenzamine, postural hypotension may occur. CNS symptoms, such as fatigue, sedation and nausea, are also seen in patients using phenoxybenzamine.

3. Ganglion-blocking agents.

Not currently used clinically because of toxicity.

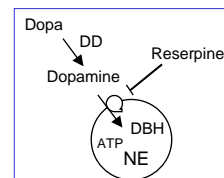
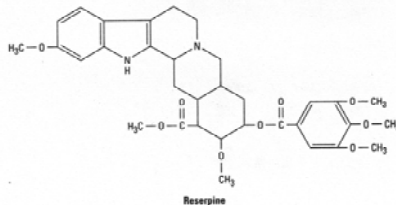
Trimethaphan: It competitively blocks nicotinic cholinergic receptors on postganglionic neurons, in both sympathetic and parasympathetic ganglia. The antihypertensive effect is due to pooling of blood in capacitance vessels. Antihypertensive effect is rapid, but excessive hypotension may occur.

Adverse effects: (1) sympathoplegia (excessive orthostatic hypotension, sexual dysfunction); (2) parasympathoplegia (constipation, urinary retention, dry mouth, precipitation of glaucoma, etc.)

4. Agents that block adrenergic neurotransmitter synthesis and/or release.

-- Reserpine, guanethidine

Reserpine



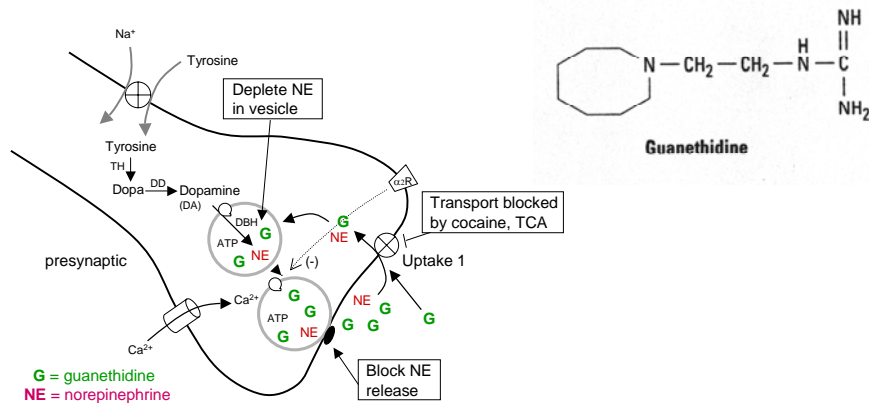
Mechanism of action: Interferes with the Mg^{2+} and ATP-dependent uptake of biogenic amines, thereby depleting NE, dopamine, and serotonin. The effect is universal and irreversible. Reserpine acts both centrally and in the periphery. It decreases both CO and PVR.

Therapeutic use: Reserpine is effective but has significant adverse effects. It is a 3rd line ADHD. The drug is inexpensive, and the effect stays long even after the drug disappears from circulation. Effective when used at low dose (0.05 mg), in combination with diuretics.

Adverse effect and toxicity: Enters brain easily and can produce sedation, mental depression, Parkinson's like symptom. Reserpine should not be given to patients with mental depression or peptic ulcer (for stimulating gastric acid secretion).

Guanethidine and guanadrel

Mechanism of action: (1) Inhibition of NE release from sympathetic nerve ending. (2) gradual depletion of NE stores in the nerve ending. Guanethidine enters cell through uptake 1, which also recaptures NE. Cocaine and tricyclic antidepressant block uptake 1 and reduce the effect of guanethidine.



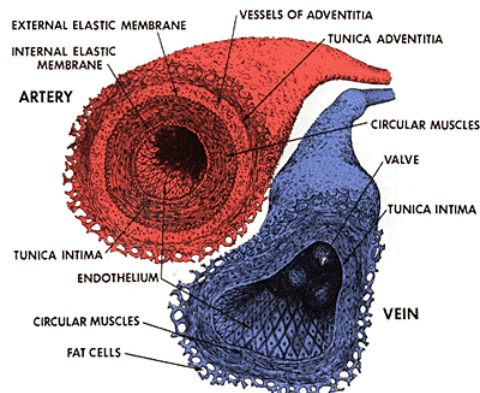
Therapeutic use: Guanethidine reduces CO due to bradycardia and relaxation of capacitance vessels. Long-term use leads to reduced PVR. Clinically used for outpatient treatment of severe hypertension. Guanethidine is highly basic and cannot enter brain. Therefore there is no CNS adverse effects seen in many other antihypertensive agents.

Adverse effects and toxicity:

- (1) Sodium and water retention are often seen.
- (2) Postural hypotension and decreased blood flow to heart and brain.
- (3) Delayed ejaculation in men. Increased GI motility and diarrhea.
- (4) Supersensitivity of effector cells (smooth muscle) occurs following long-term use, reminiscent of surgical sympathectomy. Therefore it cannot be used with some over-the-counter cold medicine that contain sympathomimetic agent. Not suitable for patients with pheochromocytoma.
- (5) Not to be used together with drugs that act on Uptake 1, such as TCA.

Direct vasodilators

Mechanism of action: These agents relax smooth muscle of arterioles and some also work on veins. They stabilize membrane potential at resting level by opening K^+ channel (hydralazine, minoxidil, diazoxide), or increase cellular cyclic GMP level which leads to smooth muscle relaxation (sodium nitroprusside).



Therapeutic use: The side effects of these AHDs restrict their use in outpatient treatment. They are effective for difficult to control BP.

Hydralazine dilates arteries and arterioles. It is used together with a diuretic and a β -blocker, for treatment of moderately severe hypertension. Single-use causes reflex tachycardia and sodium retention.

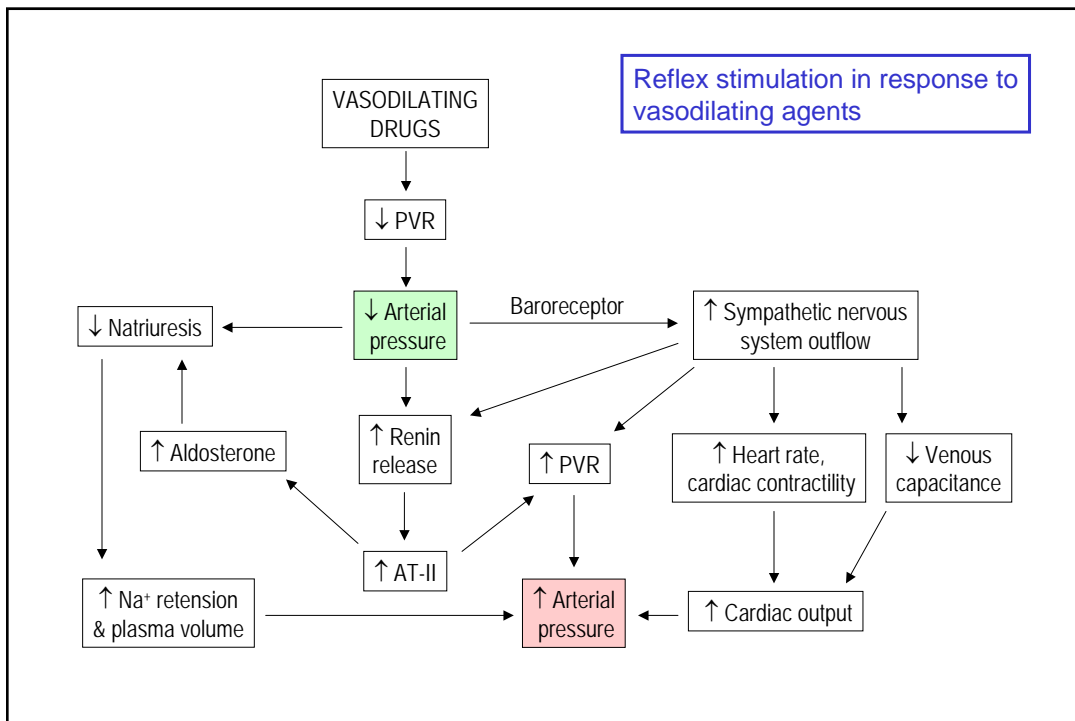
Minoxidil is also used together with a diuretic and a β -blocker, for treatment of severe or malignant hypertension.

Diazoxide is used (i.v.) for treating hypertensive emergency. A β -blocker is used together to minimize reflex activation of the heart.

Sodium nitroprusside is another drug for hypertensive emergency. It dilates both arteries and veins. Effect takes place immediately (i.v.) but does not last long (1-2 minutes). Thus continuous infusion is required.

Adverse effects and toxicity:

- Reflex tachycardia, sodium retention, and for nitroprusside, cyanide ion production.
- Minoxidil causes excessive growth of body hair (hypertrichosis) if used for more than 4 weeks. This effect has been used for treating male pattern baldness (Rogaine®).



A list of AHDs for treatment of hypertensive emergencies

(DBP > 120 mmHg, potentially life-threatening, seen in pheochromocytoma crisis, eclampsia, cocaine overdose, clonidine withdrawal, etc.)

Nitroprusside, IV, rapid action (within seconds), short lasting (a few minutes), requires continuous IV infusion. May cause thiocyanate toxicity. Avoid use in renal failure and pregnancy.

Diazoxide, IV, action takes 1-5 min, lasts 4-12 hrs. May cause hyperglycemia, sodium retention, tachycardia. Avoid use in angina pectoris, MI, pulmonary edema, intracranial hemorrhage.

Enalaprilat, IV, action seen in 15 min, max in 1-4 hrs, lasts 6-12 hrs. May cause hyperkalemia. Do not use in pregnancy, renal failure in patients with bilateral renal artery stenosis.

Hydralazine, IV (action in 10-30 min) or IM (action in 20-40 min), lasts 2-6 hrs. May cause angina, tachycardia, headache. Do not use in angina pectoris, MI, aortic dissection.

Others: Labetalol, nicardipine, nitroglycerin, trimethaphan, phentolamine.

Calcium channel blockers (CCBs)

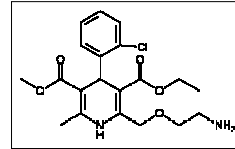
- Considered as a different class of vasodilators that are used in treatment of angina and hypertension.
- Mechanism of action is based on the role of calcium in maintaining smooth muscle tone and in the contraction of myocardium. Blocking the entry of calcium through cell surface L-type channels relaxes smooth muscle cells. Selective blocks arteriole smooth muscle cells is most desirable for reduction of PVR.
- There are dihydropyridine CCBs and non-dihydropyridine CCBs in treating hypertension. These are alternative drugs for initial treatment of hypertension in patients who cannot take β -blockers (e.g. due to angina + bronchospastic disease).

Diphenylalkylamines – **Verapamil**, is less selective on the type of calcium channels and have effects on both arteriole and cardiac SMC.

Benzothiazepines -- **Diltiazem**, has similar function but less adverse effect than verapamil.

Dihydropyridines – DHPCCBs are an expanding class of CCBs that include **amlodipine, nifedipine, felodipine, isradipine, nicardipine, and nisoldipine**. They have higher affinity for vascular calcium channels than for cardiac calcium channels.

- One of these DHPCCBs, **amlodipine**, is clinically used together with **benazepril**, an ACE inhibitor, under the commercial name of Lotrel®.

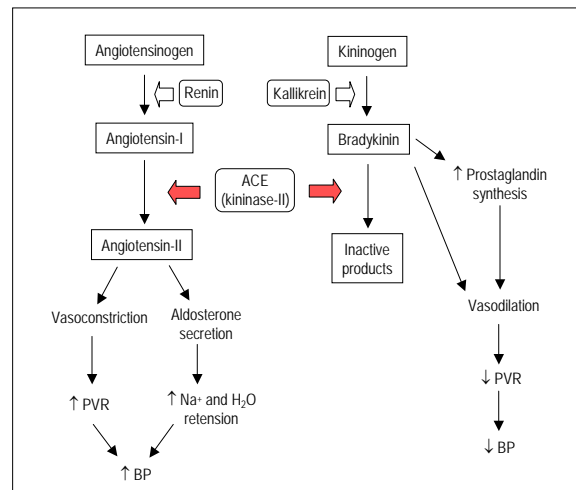


Amlodipine (Norvasc®)

Adverse effects and toxicity:

- Dizziness, headache and constipation are common.
- Verapamil should not be used in congestive heart failure patients due to its negative inotropic effect. Use with caution in patients with conductive disturbances involving SA or AV node.

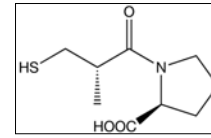
ACE inhibitors and angiotensin receptor antagonists:



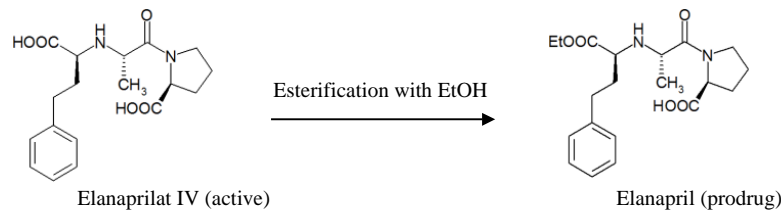
ACE = angiotensin-converting enzyme

ACE inhibitors: Captopril, enalapril, enalaprilat, lisinopril, benazepril, fosinopril, moexipril, quinapril and ramipril

Mechanism of action: Captopril and other ACE inhibitors are competitive inhibitors of ACE, mimicking the structure of its substrate. **Captopril, enalaprilat** and **lisinopril** are active molecules. Others listed above are prodrugs that need to be converted to active metabolites (di-acids) for functions. ACE inhibitors (1) directly block the formation of AT-II; (2) at the same time increase bradykinin level. The net results are reduced vasoconstriction, reduced sodium and water retention, and increased vasodilation (through bradykinin).



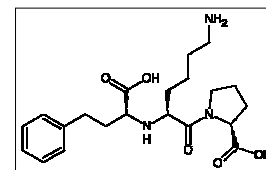
Captopril



Enalaprilat IV (active)

Enalapril (prodrug)

- **Lisinopril**, a lysine-analog of enalapril, has several properties that other ACE inhibitors do not have. **Lisinopril** is hydrophilic, does not go through liver metabolism and is active (not a prodrug), has good tissue penetration and long half-life (12 hrs), and is excreted unchanged in the urine. **Lisinopril** is used commonly in the clinic under the commercial names of Zestril® and Prinivil®.



Lisinopril

Therapeutic use: **First-line alternatives**, when diuretics or β -blockers are either ineffective or contraindicated. Most effective in white and young hypertensive patients, or when used together with diuretics. ACE inhibitors are more effective in patients with higher renin level. Commonly used in patients with left ventricular dysfunction (myocardial infarction, chronic congestive heart failure), and also in patients with type I diabetes with renal damage.

Adverse effects and toxicity: In hypovolemic patients, severe hypotension may occur after initial doses. Fetotoxic and should not be used in pregnant women. Other adverse effects: Angioedema, dry cough, rashes, altered taste, and proteinuria, and hyperkalemia (especially when used with K⁺-sparing diuretics).

Angiotensin-II receptor antagonists. **Losartan** (FDA approval in 1995) and **valsartan** are non-peptide antagonists of AT-II receptor. Other non-peptide antagonists of this class include candesartan, irbesartan, telmisartan (Micardis®), eprosartan, zolasartan and valsartan (Diovan®).

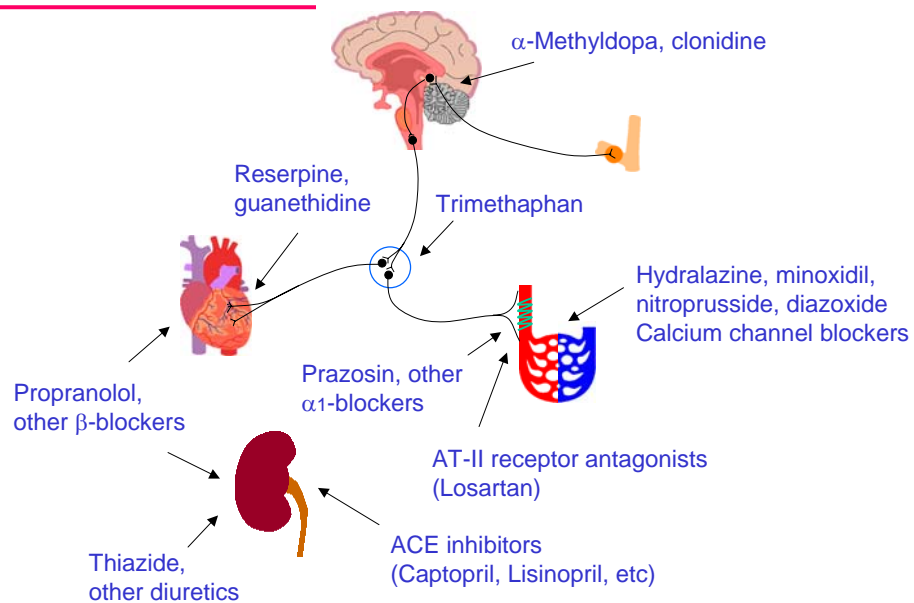
These are products of rational drug design. Some of these are in various stages of clinical development. **Saralasin** is a peptide analog and competitive inhibitor of AT-II receptor, but is orally ineffective and requires continuous intravenous infusion. Saralasin also has partial agonist activity, and is not currently used for hypertension treatment.

Mechanism of action: Competitive inhibition of AT-II receptor (Type 1), thereby (1) inhibiting the vasoconstrictor effect of AT-II; (2) prevent the release of aldosterone. Effect is more specific on AT-II action, and less or none on bradykinin production or metabolism.

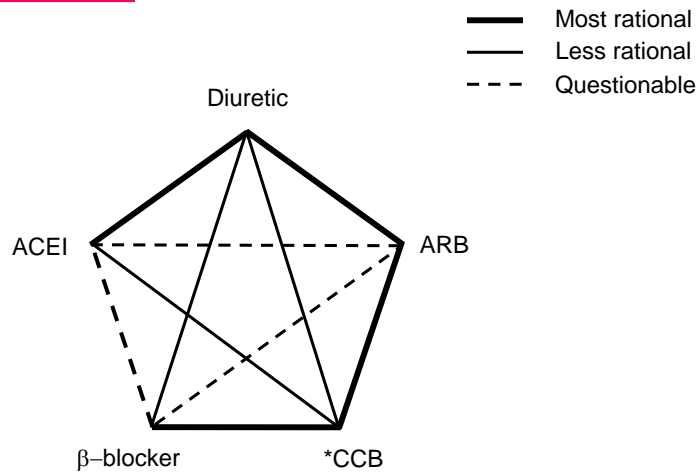
Therapeutic use: Clinical use is similar to ACE inhibitors. **Losartan** has the advantage of not causing dry cough and angioedema, which are side effects of ACE inhibitors through their bradykinin-increasing action.

Adverse effects and toxicity: Similar to those of ACE inhibitors. AT-II antagonists are also fetotoxic and should not be used for treating hypertension in pregnant women.

SUMMARY - Mechanisms



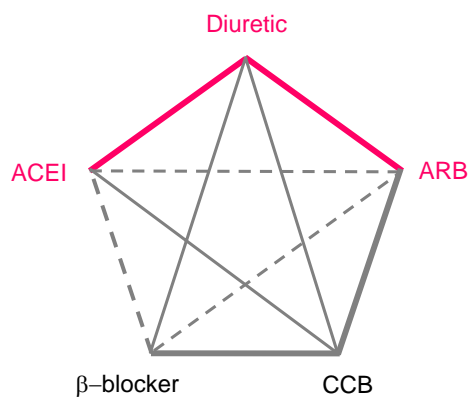
Combined use of AHDs



* Only DHPCCB + β -blocker to be used together

J. Hypertens. 21:1011-53, 2003

An example of combined use of AHDs:



Diuretics lowers BP by reducing sodium and water retention, and reducing PVR. Lowering of BP stimulates renin release. The released renin can trigger the renin – angiotensin – aldosterone pathway, thus compensate for the BP lowering effect.

ACEI and ARB can block this effect of renin by blocking ACE and AngIIIR1 respectively. Thus, the combined use of a diuretic + ACEI or a diuretic + ARB can produce additive effect in lowering BP.