Antihypertensives

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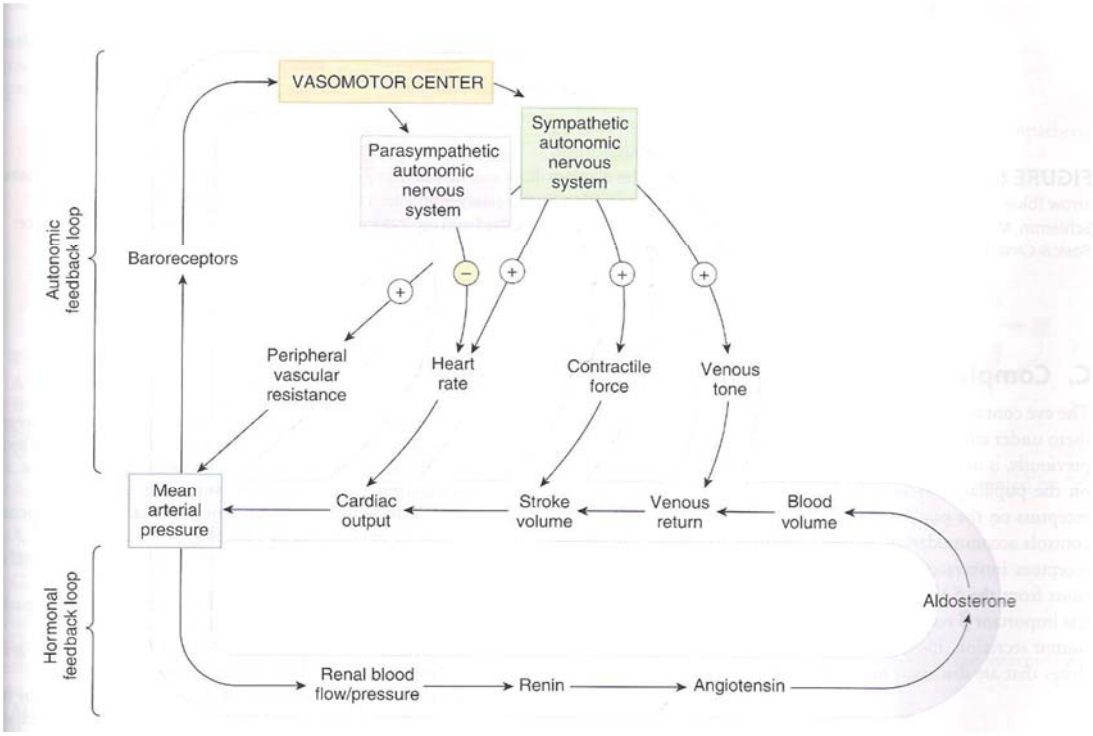
Hypertension

Table 13-48. **Classification of blood pressure levels of the British Hypertension Society**

Category	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
Blood pressure		
Optimal	< 120 and	< 80
Normal	120-129 and/or	< 85
High normal*	130-139 and/or	85-89
Hypertension		
Grade 1 (mild)	140-159 and/or	90-99
Grade 2 (moderate)	160-179 and/or	100-109
Grade 3 (severe)	≥ 180	≥ 109
Isolated systolic hypertension		
Grade 1	140-149	< 90
Grade 2	≥ 160	< 90

* Equivalent to pre-hypertension.
The European Societies of Hypertension and Cardiology Guidelines 2007 are based on clinical blood pressure and not values for ambulatory blood pressure measurement. Threshold blood pressure levels for the diagnosis of hypertension using self/home monitoring are greater than 135/85 mmHg. For ambulatory monitoring, 24-hour values are greater than 125/80 mmHg. If systolic blood pressure and diastolic blood pressure fall into different categories, the higher value should be taken for classification.

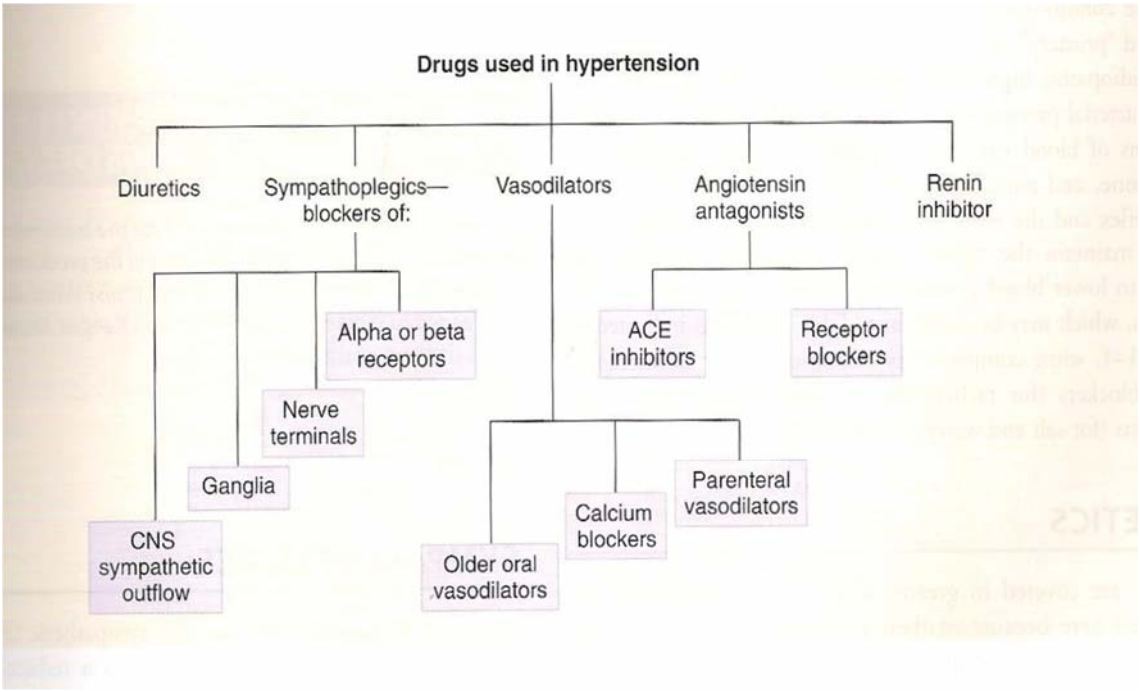
Vasomotor Centre



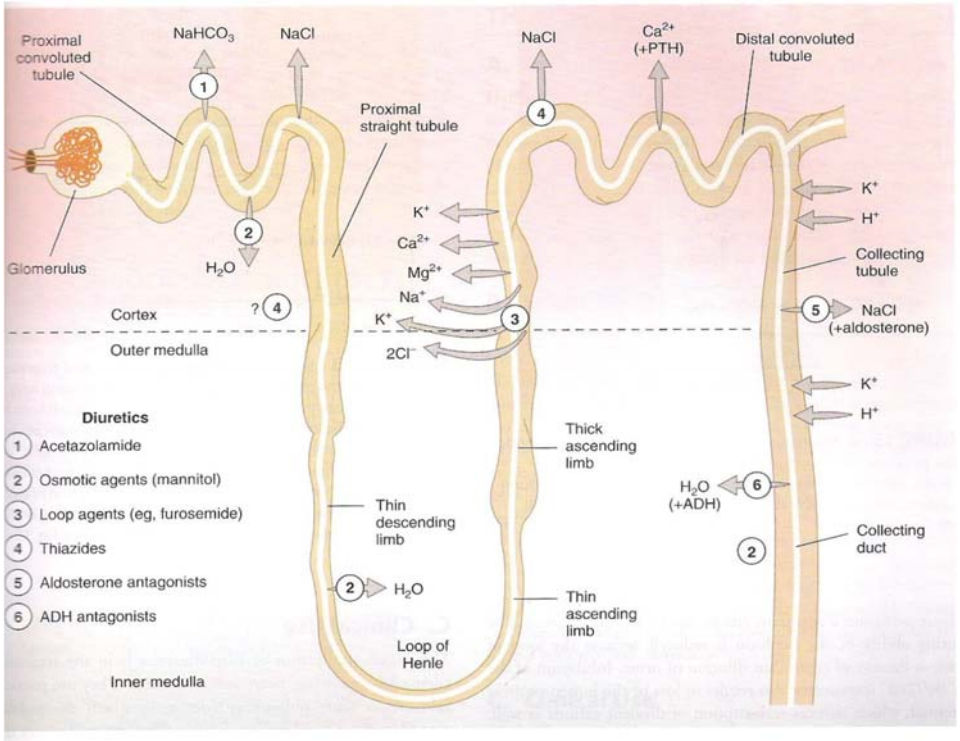
Mechanisms of ↓ Bp

- Reduced cardiac output
- Increased vagus nerve activity
- Decreased central sympathetic outflow
- Reduced angiotensin II levels

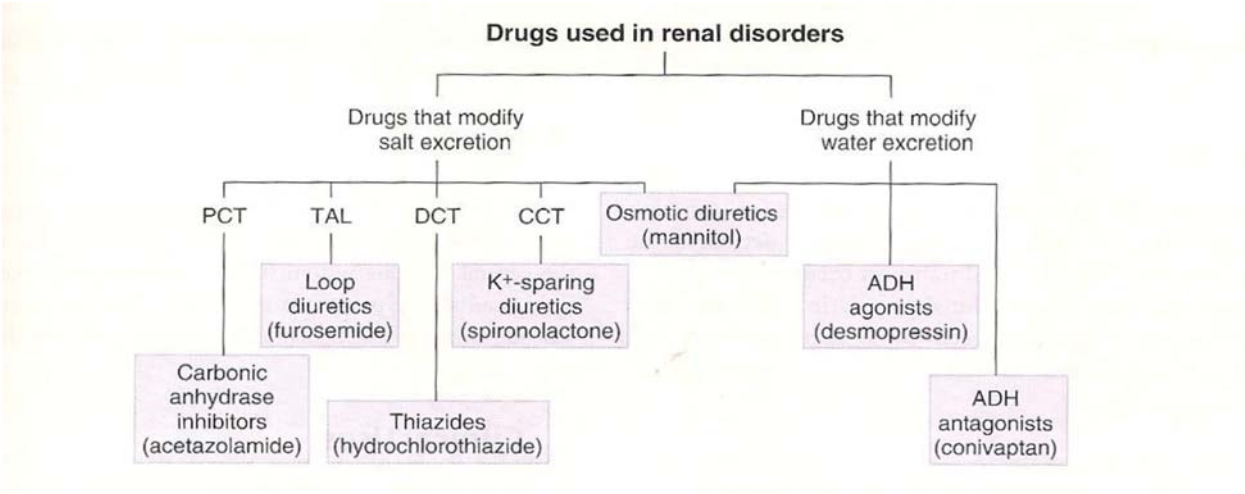
Antihypertensives



Diuretics



Antihypertensives



Diuretics

- ***Classification***
  - Thiazides (eg,Hydrochlorothiazide)
  - Thiazide-like (eg, Indapamide)
- ***Mechanism of Action***
  - Block Na/Cl transporter in distal convoluted tubule
- ***Clinical Applications***
  - First-line therapy for mild to moderate hypertension, especially in black patients and the elderly
- ***Pharmacokinetics***
  - Oral Duration: 8–12 h
- ***Toxicities, Interactions***
  - Hypokalemia, hyperglycemia, hyperuricemia (may precipitate gout), hyperlipidemia

Diuretics

- ***Classification***
  - Loop diuretics(eg, furosemide)
- ***Mechanism of Action***
  - Block Na/K/2Cl transporter in thick ascending limb
- ***Clinical Applications***
  - Hypertension, heart failure, oedema, hypercalcaemia
- ***Pharmacokinetics***
  - Oral, parenteral Duration: 2–3 h
- ***Toxicities, Interactions***
  - Hypokalemia, hypovolemia, ototoxicity

Diuretics

- ***Classification***
  - Potassium-sparing diuretics(eg, Spironolactone, eplerenone, Amiloride)
- ***Mechanism of Action***
  - Inhibitors of cytoplasmic aldosterone receptor in cortical collecting ducts; reduce K^+ excretion (Spironolactone & Eplerenone)
  - Inhibitor of ENaC epithelial sodium channels in cortical collecting duct, reduces Na^+ reabsorption and K^+ excretion(Amilioride)
- ***Clinical Applications***
  - Hypertension, heart failure, oedema in cirrhosis
  - To reduce the loss of potassium when they are used with thiazides(Amiloride)
  - Amiloride, an epithelial sodium-channel blocker, is reportedly more effective than spironolactone as therapy in blacks who have resistance to treatment.
- ***Pharmacokinetics***
  - Oral Duration: 24–36, 48 h (Spironolactone & eplerenone)
  - Oral Duration: 10–12 h(Amiloride)
- ***Toxicities, Interactions***
  - Hyperkalemia; gynecomastia (spironolactone only)

Vasodilators

- Oral vasodilators
  - Calcium channel blockers
  - Hydralazine
  - Minoxidil
- Parenteral vasodilators
  - Nitroprusside
  - Dihydralazine

Calcium Channel Blockers

- ***Classification***
  - **Dihydropyridine** (eg, Amlodipine, nifedipine)
  - **Non-dihydropyridine**(eg, Verapamil, Ditiazem)
- ***Mechanism of Action***
  - L-type calcium channel blockers; combine moderate vascular effect with strong cardiac effect
- ***Clinical Applications***
  - Dihydropyridines have greater vasodilator than cardio depressant effect therefore used in hypertension more.
  - Non-dihydropyridines have prominent depressant effects on the nodes and can therefore be used to treat supraventricular arrhythmias.
- ***Pharmacokinetics***
  - Oral, parenteral Durations: 6–8 h
- ***Toxicities, Interactions***
  - Excessive cardiac depression; constipation

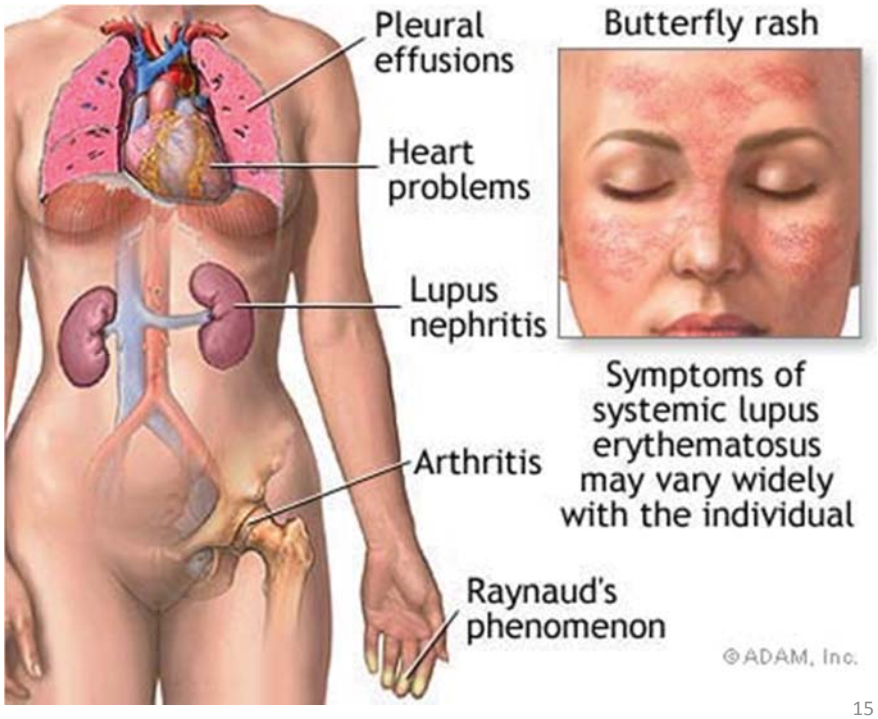
Minoxidil

- ***Mechanism of Action***
  - Prodrug, sulfate metabolite opens K^+ channels, causes arteriolar smooth muscle hyperpolarization and vasodilation
- ***Clinical Applications***
  - Severe hypertension; male-pattern baldness
- ***Pharmacokinetics***
  - Oral, topical Duration: 6–8 h
- ***Toxicities, Interactions***
  - Marked tachycardia(beta blockers often combined to counteract tachycardia), salt and water retention; hirsutism

Hydralazine

- ***Mechanism of Action***
  - Causes release of nitric acid (NO) by endothelial cells causes arteriolar dilation
  - Does not dilate veins
- ***Clinical Applications***
  - Hypertension (also used in; heart failure in combination with isosorbide dinitrate)
- ***Pharmacokinetics***
  - Oral Duration: 6–8 h
- ***Toxicities, Interactions***
  - Tachycardia(beta blockers often co-prescribed), salt and water retention, lupus-like syndrome

Systemic Lupus Erythematosus



Sodium Nitroprusside

- ***Mechanism of Action***
  - Releases nitric acid from drug molecule.
- ***Clinical Applications***
  - Hypertensive emergencies; cardiac decompensation
- ***Pharmacokinetics***
  - Parenteral only Duration: minutes; requires constant infusion
- ***Toxicities, Interactions***
  - Excessive hypotension; prolonged infusion may cause thiocyanate and cyanide toxicity

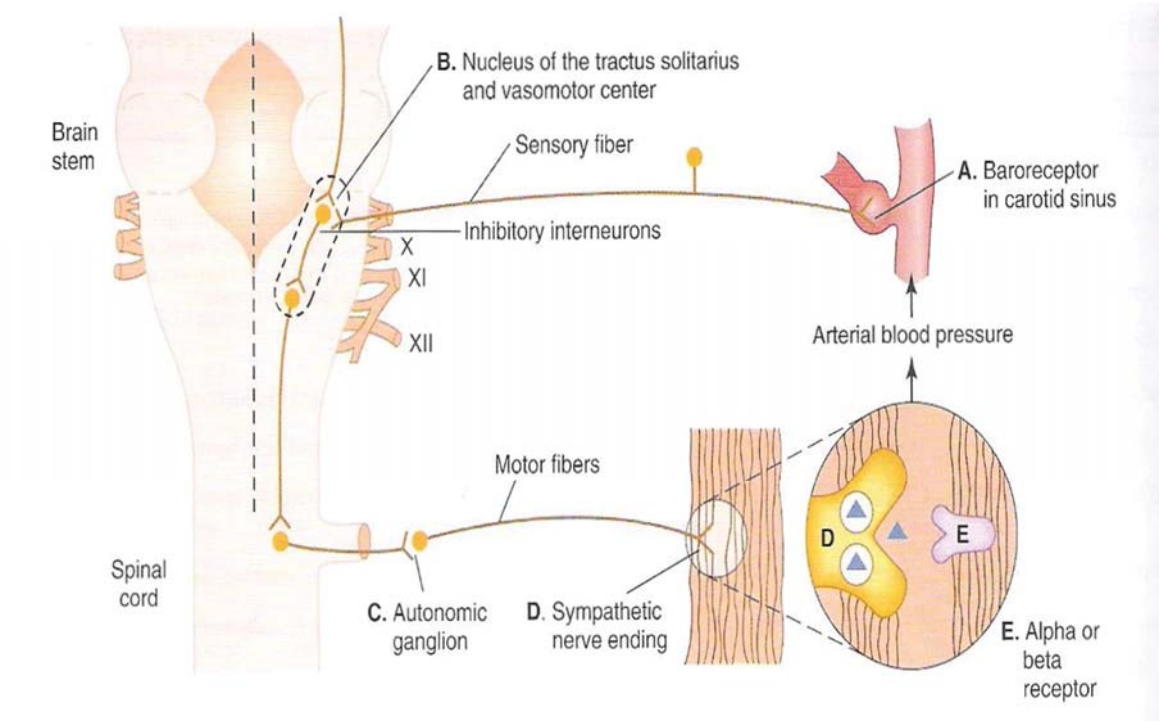
Angiotensin antagonists

- Angiotensin Converting Enzyme Inhibitors
  - ***Subtypes***
    - Class I: Captopril-like (eg, captopril)
    - Class II: Prodrugs (eg, Enalapril, Perindopril, Ramipril)
    - Class III: Water-soluble(eg, Lisinopril)
  - ***Mechanism of Action***
    - ACE inhibitor; reduces angiotensin II synthesis
  - ***Clinical Applications***
    - Hypertension, diabetic renal disease, heart failure
  - ***Pharmacokinetics***
    - Oral Half-life: 2.2 h but large doses provide duration of 12 h
  - ***Toxicities, Interactions***
    - Hyperkalemia; teratogen; cough, angioedema, acute renal failure (particularly in patients with bilateral renal artery stenosis or stenosis of the renal artery of a solitary kidney) CONTRAINDICATED

Angiotensin antagonists

- Angiotensin II receptor blockers (ARBs)
  - **Examples**
    - Losartan, Valsartan,Candesartan,Irbesartan,Telmisartan
  - ***Mechanism of Action***
    - Blocks AT_1 receptors
  - ***Clinical Applications***
    - Hypertension. ACEi intolerant patients due to intractable cough or who develop angioedema.
  - ***Pharmacokinetics***
    - Oral Duration: 6–8 h
  - ***Toxicities, Interactions***
    - Hyperkalemia; teratogen

Sympathoplegics



Sympathoplegics

- Centrally acting
  - Clonidine
  - Moxonidine
  - Methyldopa
  - Reserpine
- Alpha blockers
  - Prazosin
- Beta blockers
  - Propranolol
- Alpha + Beta blockers
  - Labetalol
  - Carvedilol

Clonidine

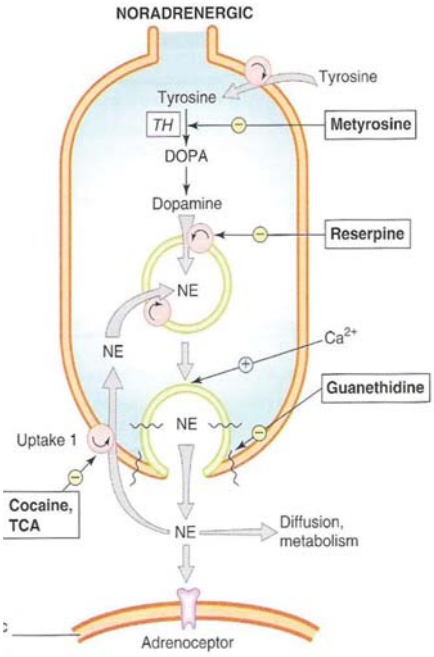
- ***Mechanism of Action***
  - Agonist at α_2 receptors; in CNS this results in decreased sympathetic nervous system outflow
- ***Clinical Applications***
  - Hypertension
- ***Pharmacokinetics***
  - Oral and transdermal Oral duration: 2–3 days; 1 week transdermal
- ***Toxicities, Interactions***
  - Sedation, danger of severe rebound hypertension if suddenly stopped, orthostatic hypotension, dry mouth

Methyldopa

- ***Mechanism of Action***
  - Prodrug converted to methylnorepinephrine in CNS, with result like clonidine
- ***Clinical Applications***
  - Hypertension especially in pregnancy
- ***Pharmacokinetics***
  - Oral Duration: 12–24 h
- ***Toxicities, Interactions***
  - Sedation, induces haemolytic antibodies

Reserpine

- Blocks transport of biogenic amines, noradrenaline, dopamine, and serotonin from the cytoplasm into storage vesicles
- Slow onset and long duration of action 5 days.
- Side effects- sedation; severe psychiatric depression (high doses)



Beta Blockers

- ↓ the central aortic systolic pressure less than calcium channel blockers and angiotensin converting enzyme inhibitors
- May precipitate new diabetes, especially when used with diuretics
- May worsen asthma
- Lipid-soluble beta blockers, especially **propranolo**l, but also **metoprolol** and **labetalol**, enter the central nervous system and may cause mental depression and vivid dreams.
- **Atenolol**, **nadolo**l and **sotalol** are least lipid soluble, and thus cause fewer central nervous system side effects.

Beta-adrenergic blocking agents

DRUG	RECEPTOR SPECFICITY	THERAPEUTIC USES
Propranolol	β_1, β_2	Hypertension Migraine Hyperthyroidism Angina pectoris Myocardial infarction
Nadolol	β_1, β_2	Hypertension
Timolol	β_1, β_2	Glaucoma, hypertension
Acebutolol[1] *Atenolol* *Esmolol* *Metoprolol*	β_1	Hypertension
Nebivolol	β_1, NO ↑	Hypertension
Pindolol[1]	β_1, β_2	Hypertension
Carvedilol *Labetalol*	$\alpha_1, \beta_1, \beta_2$	Hypertension Congestive heart failure

Alpha Blockers

- Block alpha $_1$ and alpha $_2$ receptors.
- Vasodilatations takes place
- 4th line antihypertensives
- Orthostatic hypotension – prazosin

Alpha+beta blockers

- ***Examples*** (Labetalol, Carvedilol)
- ***Mechanism of Action***
  - Four isomers; 2 bind and block both α and β receptors
- ***Clinical Applications***
  - Hypertension, hypertensive emergencies (IV)
- ***Pharmacokinetics***
  - Oral and IV Duration: 5 h
- ***Toxicities, Interactions***
  - Excessive β blockade: bronchospasm (can be fatal in asthmatics), atrioventricular block, heart failure; CNS sedation, lethargy, sleep disturbances

Antihypertensives

- 3 classes of antihypertensive agents for the management of persons without compelling indications- 1st line drugs
  - Diuretics (thiazide-like and thiazide)
  - Angiotensin-converting enzyme inhibitors (ACE-Is)
  - Calcium channel blockers (CCBs)
- The others
  - Angiotensin-receptor blockers
  - Aldosterone-receptor antagonists
  - Beta blockers
  - Direct acting vasodilators
  - Drugs that alter sympathetic nervous system

Antihypertensives with concomitant diseases

Any drug that lowers BP unless absolutely contraindicated (Table VII), will confer protection against target-organ damage. However, the following classes of drugs have additional protective properties in the case of the listed associated clinical conditions/target-organ damage.

Compelling indications	Drug class
Angina	Beta-blocker OR CCB (rate lowering preferred)[69]
Prior myocardial infarct	Beta-blocker AND ACE-I (ARB if ACE-I intolerant).[70,71] Verapamil if beta-blockers contraindicated. If heart failure, see below
Heart failure	ACE-I (ARB if ACE-I intolerant) AND certain beta-blockers[72,73] AND aldosterone antagonist[74,75] For combination ARB and ACE-I see ref.[76] Loop diuretics for volume overload
Left ventricular hypertrophy (confirmed by ECG)	ARB (preferred)[60] OR ACE-I
Stroke: secondary prevention	Low-dose thiazide-like diuretic and ACE-I[67] or ARB[68]
Diabetes type 1 or 2 with or without evidence of microalbuminuria or proteinuria	ACE-I OR ARB[57,62-66,77,78] – usually in combination with a diuretic
Chronic kidney disease	ACE-I OR ARB – usually in combination with a diuretic
Isolated systolic hypertension	Low-dose thiazide or thiazide-like diuretic OR long-acting CCB[79,80]

Hypertensive emergency

Table XI. Intravenous and oral drugs for hypertensive emergency*

Drug	Dose	Indications and precautions	Effect on BP
Intravenous			
Nitroglycerine (glyceryl trinitrate)	5 - 10 µg/min	Especially useful for myocardial ischaemia	BP lowering occurs in 2 - 5 min
Dihydralazine	10 mg every 10 - 15 min until either BP is controlled or a maximum of 50 mg given	Avoid in patients with myocardial ischaemia	BP lowering occurs in 10 min
Sodium nitroprusside	0.25 - 10 µg/kg/min diluted in 5% dextrose and adjust dose as necessary	Admission to ICU An intra-arterial BP line is desirable	BP control is immediate
Labetalol	2 mg/min to a total dose of 1 - 2 mg/kg	Use where emergency caused by phaeochromocytoma caution in acute pulmonary oedema	
Furosemide	40 - 80 mg	Acts only for 6 hours Potentiates all of the above drugs	
Oral (use only if IV drugs are not available)			
Nifedipine (long-acting only)	Long-acting CCBs must be used to prevent rapid and dangerous BP reduction Check dosage according to CCB brand used	Preferred in black persons	
Captopril	6.25 mg as a test dose Increase to 25 mg if BP lowering is not obtained in 15 - 30 min	Other rapidly acting ACE-I may be used starting with a low test dose DO NOT USE if bilateral renal artery stenosis is suspected DO NOT USE if pregnancy is suspected	BP lowering in 15 - 30 min

* For treatment of hypertensive emergency in pregnancy see section 9.3.

New Treatments and New Targets

- ***Example*** (Aliskiren)
- ***Mechanism of Action***
  - Renin inhibitor; reduces angiotensin I synthesis
- ***Clinical Applications***
  - Hypertension
  - Can be combined with other antihypertensives , such as diuretics, ACEi, ARBs, and CCBs.
- ***Pharmacokinetics***
  - Oral Duration: 12 h
- ***Toxicities, Interactions***
  - Angioedema, renal impairment
  - Can be combined with other antihypertensives , such as diuretics, ACEi, ARBs, and CCBs.

In Summary

- 1st three drugs given
  - Diuretics
  - ACEi /ARBs
  - CCBs
- 4th drug
  - α blocker
  - β blocker
  - Aldosterone antagonist
  - Centrally acting drugs
  - Direct vasodilators