Antihypertensive Agents

	Definition	Treatment	Nonpharmacologic Trx	BP Variability	Classification	
Hypertension	A common, incurable, persistent, but usually asymptomatic disease whose treatment provides no immediate or obvious benefit	Associated with: -**40%** reduction in stroke incidence -**25%** reduction in myocardial infarction. -**50%** reduction in HF. ↑**BP**: ↑organ damage & cardiovascular morbidity	-Weight reduction -Diet rich in potassium and calcium and sodium reduction. -Dietary Approaches (DASH) → effect like single drug therapy -Physical activity	- "**White Coat**" or isolated office hypertension (abnormal in the clinic) -**Masked** hypertension, normal at the clinic -**Morning surge** of BP. -**During Sleep**: Two possibilities: 1.Non dipping: during sleep BP usually drops, but in this case it doesn't 2.Extreme dipping	<120/80 120-135/80-89 ≥140/90 140-159/90-99 ≥160/100	**Normal** **Abnormal** **Hyper-tension** **Stage 1** **Stage 2**
Goal of therapy: maximal protection against cardiovascular consequences with minimal bother → stroke, coronary, and renal complications increase when BP is vigorously lowered						

Drug	MOA	Uses	Side Effects	Notes
	Diuretics (Saluretics)			
General View	▫**Early Effects (3-4 days):** -Diuresis lowers blood volume and cardiac output -Mainly affects the systolic BP (will drop) ▫**Late Effects (3-4 weeks):** -↓ Na+ & Cl- in blood vessels → lowers vessel contractility (even with low doses)	-Widely recommended as first-line therapy, especially in the elderly, the obese, and black patients -Better at reducing coronary heart disease, HF, stroke, and mortality	▫Metabolic side effects (in high doses): -Diabetes -Hypercholesteremia -Hyperuricemia ▫Increase plasma renin (will cause **hypertension** → tolerance)	-Inexpensive -Combine well with others -All have same efficacy in lowering BP, although not same diuretic activity
Thiazide diuretics: ▫**Hydro-chlorothiazide** ▫**Chlorthalidone** ▫**Bendrofluazide** ▫**Indapamide**		-Effective in mild and moderate hypertension with normal renal and heart function		-Most commonly used -**Chlorthalidone** is long acting -**Indapamide** "Natrilex" is vasodilating and lipid **neutral** (also induces **regression** of LVH)
Loop Diuretics: ▫**Furosemide** ▫**Torsemide**		-Needed in severe hypertension, in renal insufficiency, and in heart failure or cirrhosis *(Thiazide not **effective**)*	-Torsemide is free of metabolic side effects - Very potent, causes severe diuresis (not preferred by patients)	-Furosemide is short acting → not ideal

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Potassium-sparing diuretics: ▫**Spironolactone** ▫**Eplerenone** ▫**Ameloride** ▫**Nov-Triamteren**	-Inhibit the action of aldosterone → reduces Na+ & Cl- but prevents K+ levels from getting low	-Useful in heart failure, renal insufficiency and cirrhosis → these drugs antagonize aldosterone, which is elevated in those diseases (secondary hyperaldosteronism).		
Vasodilators				
General View	-Work **directly** on arterial blood vessels, or veins -Action is not antagonized by known blockers		-**Reduce** peripheral resistance → will elicit compensatory mechanisms through activation of baroreceptors→ causes increased sympathetic outflow + decreased renal sodium excretion → will eventually lead to **increased pressure** → leading to tolerance, resistance, or pseudo-resistance	-Other drugs have vasodilator activities but aren't classified as vasodilators because they don't act directly on blood vessels -Drugs are combined with vasodilators to **avoid** the problem of tolerance
Hydralazine	-**Arterial** dilator, works by release of NO	-Used in heart failure, combined with isosorbide dinitrate (a vendilator)	-Tachyphylaxis (tolerance or peusdo-resistance): activates baroreceptor reflex * Combined with a ß-blocker to prevent this -Drug-induced lupus syndrome	-Oldest vasodilator -Metabolized by acetylation -Replaced by Ca^{+2} channel blockers
Diazoxide	-Potent **arterial** dilator, works by opening potassium channels	-Used in emergencies by rapid I.V. bolus injection	-Causes excessive hypotension	-Thiazide derivative, but not a diuretic -Rapidly bound to albumin -Onset 10-30 seconds -Duration 2-4 hours -Does not require constant monitoring
Sodium Nitroprusside	-Relaxes both **arterial and venous** smooth muscle, works by release of NO.	-Useful in emergencies, surgery, heart failure, malignant hypertension. This is because it's a short acting drug and has a fast onset of action	-No excessive reflex increase in cardiac output (might increase C.O. if there is failure)	-Cyanide-containing molecule -Short half-life -Drug is light sensitive

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Sodium Nitroprusside (Cont.)			-Can elevate thiocyanate levels and disturb acid-base balance: weakness, nausea, tinnitus, flushing, lactic acidosis and anoxia	-Action is immediate, requires constant monitoring in ICU
Minoxidil	-K+ channel-opener: increases efflux leading to hyperpolarization (Prolonged arterial relaxation)	-For severe intractable hypertension, or renal insufficiency, usually in combination with a diuretic and β blocker (not commonly used) -Causes hypertrichosis (vasodilation of hair follicles) → useful for baldness	-Pericarditis: one of the reasons why it's not used for treating hypertension	- Superior to hydralazine
Fenoldopam	-D1 agonist, which results in vasodilation renal vessel dilation, natriuresis	- Used by continuous infusion in emergencies or postoperatively		Rapidly metabolized, short acting
Calcium Channel Blockers				
Ca-Channel Blockers – **Nifedipine (dihydro-pyridine)**	A potent vasodilator: reduces PVR (---) → baroreceptor reflex → indirectly increases heart rate (+++) → which increases cardiac output (++)	-Indicated for: angina, hypertension and Raynaud's phenomena	-Hypotension Headache, dizziness -Flushing, especially with short acting agents -Peripheral edema -NO metabolic disturbances	-Effective in the elderly -Equally effective in black and nonblack patients - Primarily act to reduce peripheral vascular resistance, aided by at least an initial diuretic effect, especially with the short-acting DHPs -More effective than others in protection against stroke.
Diltiazem (benzo-thiazepine)	Not as potent as Nifedipine: reduce PVR (--) but don't cause a baroreceptor reflex so they **decrease** HR & CO **-Diltiazem** → HR (-), CO (-) **-Verapamil** → HR (--), CO (--)	-Indicated for: angina, hypertension and Raynaud's phenomena		
Verapamil (phenylalkylamine)		-Angina, hypertension, arrythmias, migraine		
Angiotensin - Converting Enzyme Inhibitors (ACEI)				
General View	-Inhibit ACE in the lungs -Inhibit kinin metabolism -Inhibit cardiac and vascular hypertrophy (depress sympathetic activity)	- Vasodilation (arterial & venous): ↓arterial & venous pressure ↓ ventricular afterload and preload -Decrease blood volume: natriuretic & diuretic		-Long-term treatment is often associated with Angiotensin Escape: A rebound generation of angiotensin II by the action of chymase and cathepsin G

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Drug	MOA	Uses	Side Effects	Notes
Captopril (Prototype)	Angiotensin - Converting Enzyme Inhibitor (ACEI)	-Effective in high-rennin hypertension (20%), HF and Ischemic Heart Disease. -Useful in **diabetic nephropathy** by dilating efferent arterioles thus reducing intraglomerular pressure and consequently protects against progressive glomerulosclerosis	-Contraindicated in pregnancy and bilateral renal artery stenosis -Captopril is SH containing drug → very toxic (bone marrow suppression, dysgeusia, proteinuria, allergic skin rash, fever) -Hypotension (First Dose Phenomena) especially with renovascular hypertension -K+ retention, especially in the presence of renal dysfunction or when combined with K+ sparing diuretics or ARBs -Cough (10% of patients) -Angioedema	-Other examples: Enalapril, Quinapril, Lisinopril, Benazepril & Fosonopril -All are similarly effective but might differ in toxicity -No need for a diuretic but a diuretic can be added -Can be combined with CCB -Should not be combined with Beta blockers -Do not increase HR -No metabolic effects
Chymase	-A serine protease responsible for the rebound generation of angiotensin II caused by ACEI (has been implicated in 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
Angiotensin II Receptor Blockers (AT-1)				
Losartan **Valsartan** **Candesartan** **Irbesartan** **Telmisartan** **Eprosartan**	-Blocks Angiotensin II receptors: result in more complete inhibition of angiotensin actions, with no effects on bradykinins -Telmisartan has additional peroxisome proliferator- activated receptor "PPR "-γ agonist activity	-May be only indicated when ACEI are intolerable -May be better than ACEI in protection against stroke (activation of AT-2 receptor facilitates collateral vessels and neuronal resistance)	- Free of side effects, especially cough	-Most expensive, but fastest growing class of antihypertensive drugs

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Renin Enzyme Inhibitors				
Aliskiren	Inhibits renin enzyme			- The first in the group -Other better studied medications are typically recommended due to concerns of higher side effects and less evidence of benefit
Non-Selective α-Adrenergic Antagonists				
Phentolamine **Phenoxy-benzamine**	Block both α1 and α2 receptors, so cause reflex tachycardia and increased contractility	-Used only for pheochromocytoma	-Blockade of α 2-presynaptic receptors leads to augmented release of NE leading to tachycardia and increased contractility of the heart	
α1 -Selective Adrenergic Antagonists				
Prazosin **Terazocin** **Doxazosin**	Selective (α 1 > α 2) blockers will lower the BP but will not cause tachycardia	-Effective in moderate hypertension as well as benign prostatic hypertrophy	-Hypotension (First - Dose Phenomenon) -All are free of metabolic effects, but can cause drowsiness, diarrhea, postural hypotension, tachycardia, and tolerance due to fluid retention	
Beta Adrenergic Blockers				
General View	-Decrease HR, SV, and consequently C.O. -Decrease Rennin Release -Central Action in the vasomotor center. -Inhibit NE release	-Useful in high - rennin hypertension -Combination or monotherapy -Hyperkinetic hearts -Used in other cardiovascular conditions Ineffective in blacks	- Bronchospasm: with non-selective -Heart Failure -CNS: fatigue, depression impotence -Impair lipid & glucose metabolism -Mask hypoglycemia -Claudication, due to α receptor overactivity -Withdrawal Syndrome	-30 preparations: refer to slide 60 if you want to memorize them -Prototype: propranolol -Effect not immediate -No postural hypotension

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Vasodilating ß-Blockers	Labetalol	α1 (20% of β) antagonist & β2 partial agonist	-Useful for pheochromocytoma and emergencies		
	Carvedilol	– β, α1 (10% of β) antagonist.			
	Esmolol	β1 selective	– Used by continuous IV infusion.		Rapidly metabolized
	Nebivolol	β1 selective and nitric oxide-potentiating vasodilatory effect			
Adrenergic Neuron Blockers					
▫Guanethidine ▫Bethanedine ▫Debrisoquin ▫Guanadrel		Displace NE from vesicles → Block NE release → Cause depletion of NE			-Hydrophilic -Termination of action: uptake 1
Reserpine (Rauwolfia Alkaloids)		- Binds to the sympathetic vesicles → Prevents DA uptake into vesicles - Amines are metabolized by MAO - Depletes: NE, 5HT, ACTH, DA			-Lipophilic -Old fashioned, slow onset and offset, very cheap.
▫Trimethaphan ▫Pentolinium ▫Mecamylamine		- Block transmission in both sympathetic & parasympathetic systems	- Effect rapidly reversed, so used for short term control of BP, e.g. intraoperatively or emergency	-Many side effects	- Act immediately and are very efficacious
Centrally Acting Antihypertensive Drugs					
General View		-Reduce preganglionic sympathetic activity - α Receptor activation decreases BP - β Receptor activation increases BP		-CNS side effects -Orthostasis is unusual, due to preservation of peripheral sympathetic activity	
Propranolol Reserpine					

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Drug	MOA	Uses	Side Effects	Notes
α- Methyl Dopa	-Central α agonist -Metabolized to alpha-methylnorepinephrine (-α MD- → α MDA → α MNE) -Lowers BP but not CO or renal blood flow		- Can cause lactation and positive Coomb's test -Safe in pregnancy	- Old drug, thought to work by forming a pseudo transmitter which works peripherally
Clonidine	-Central α agonist	- I.V: Biphasic Effect: peripheral then central actions -Oral -Transdermal Patch (7 days)		- Imidazoline derivative, tried initially as a nasal decongestant

Causes of Resistant Hypertension	
-Improper BP measurement. -"White Coat Hypertension" -Noncompliance. -Psychological stresses, secondary hypertension, sleep disorders -Volume overload and pseudotolerance -Excess sodium intake -Volume retention from kidney disease -Inadequate diuretic therapy -Inadequate doses -Inappropriate combinations	-NSAID; cyclooxygenase 2 inhibitors -Cocaine, amphetamines, other illicit drugs. -Sympathomimetics, e.g. decongestants, anorectics - Oral contraceptives -Corticosteroids -Cyclosporine -Erythropoietin -Licorice (including some chewing tobacco) -Excess alcohol intake

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