ANTIHYPERTENSIVE DRUGS – Target is <135/85 BP				
Class	**Drugs/Dose**	**Uses/MOA**	**ADME**	**ADRs/CI**
Angiotensin-converting enzyme **(ACE) inhibitors** **"-PRILS"**	**Ramipril (P) 2.5-20mg PO daily** (or 10mg PO BID in HF/difficult HTN) **Perindopril 2-8mg PO daily** Captopril, Enalapril (P), **Ramipril (P),** Lisinopril, Benazepril HCl, Fosinopril (P) Cilazapril, **Perindopril,** Quinapril, Trandolapril **MoA Summary:** -block ACE: ↓ATII, ↓ VC effects of AT-II, and ↓aldosterone -blocks breakdown of bradykinin (potent VD) -hypotensive action = ACE inhib and bradykinin buildup	• **Inhibits AT converting enzyme (ACE) in lungs (mainly) +** kidneys prevent conversion from ATI to ATII = lower BP through suppression of renin-angiotensin (block RAAS systemic) • **ATII =** powerful VC – mostly binds AT1 (VC, ↑ aldos) vs AT2 (VD) 1) acts on AT1 R in sm mscl → IP3 → release Ca+ in store house (SR) → MLCK → add P to myosin → actin/myosin slide over each other = contraction = ↑ **TPR** **2) releases aldosterone** = act on MR → stim AIP → make ↑ Na+ channels = ↑ Na+ re-absorbed → ↑ H2O retention = ↑blood volume = ↑ SV =↑ BP **3) Acts on Pituitary → ADH (prevent loss of H2O): vasopressin** = ↓ cAMP = ↑ H2O channels (aquaporin II → to plasma membrane) → facilitate reabs of H2O = prevents water from being loss because gets reabsorbed **4) Fibrosis (thickening of BV wall) = causes hypertrophy** ***NONE ACE PATHWAY: AT I → ATII via ATII escape (e.g. chymase, cathepsin) – during HF**	• Various T ½ - all doses OD except Captopril (b/c of short T ½) given 2-3/daily • Elimination varies: Captopril = renal Fosinopril = renal/biliary Ramipril = renal/fecal • When block ACE = ↑bradykinin b/c doesn't break down = VD • **Other uses:** MI, HF, left ventricular dysfn, chronic kidney disease	• Hypotension after initial doses in pt who are hypovolemic or on salt restricted diets (synergistic effect) • **SEs: dry persistent cough*** (↑ bradykinin/↑PGE2), light-headedness/dizzy, fatigue, headache, hypotension, N/V, dysgeusia, renal dysfn, hyperk+, rash • **ADR**: ***hyperkalemia*** ↓ aldosterone, = blocking ACE = Na+ not being reabsorbed + K+ not being lost/secreted ***Angioedema*** (v rare, <1%) ***caution**: ↑ risk in blacks ***Hypotension:*** after initial doses inpatients on Na+ restricted diets or diuretics • **CI: pregnancy** (risk of fetal hypotension, malformation or death – RAAS for formation of BVs =↓ angiogenesis = ↓ gas exchange), **hx of angioedema (2* to ACE-I- don't put back on ACE-I), hypersensitivity, bilateral renal artery stenosis** • **Caution:** not rx for ***black*** people b/c potential reduced efficacy and angioedema is 2-4x higher) • ***careful with K+ sparring diuretics/ K+ supplements/cotrimoxazole = hyperkalemia, Lithium ↑ Li, NSAIDs (renal dysfn/ ↑ BP)**
Angiotensin II receptor antagonist (ARBs) **"-SARTANS"**	**Losartan** 25-100mg PO daily **Valsartan** 80-320mg PO daily **Candesartan (P):** 8-32mg PO OD **Telmisartan** 40-80mg PO daily Eprosartan, Olmesartan, Irbesartan	• Competitive antagonist of AT II at AT1 R - Block action of ATII • No effect on bradykinin metabolism – less effective VD but can ↑vasorelaxant AT2 R activity • Candasartan> Losartan (potency) • Recommended if ACE inhibitors not tolerated • **Effect:** ↓ TPR and BP		• **SEs:** hypotension, hyperkalemia, light headedness, dizzy, fatigue, headache, N/V, dysgeusia, renal dysfn, rash (no dry cough like ACEI) • **CI: pregnancy, bilateral renal artery stenosis, hypersensitivity** • *Combination of ACE inhibitor + ARB = NOT rx b/c renal dysfn and hyperkalemia
[B-blockers] **B-adreno R Antagonist** **"-LOL"** Selective A-M N-Selec: N-T Except Carb/Lab	**Cardio non-selective:** • **Carvedilol: 6.25-25mg PO BID** • **Labetalol: 100-400mg PO BID** • Propranolol, Timolol, Nadolol, **More CNS effects b/c cross BBB (more lipophilic)** **Cardio selective b blockers:** • **Metoprolol: 12.5-100mg PO BID** • **Bisoprolol: 2.5-10mg PO OD** • Atenolol, Esmolol	• **All BB: Not recommended first line for patients ≥ 60 years without compelling indication** [high risk of stroke, no reduction in mortality, inferior vs others, diuretics more effective] OR in **asthmatics** (COPD ok) • Blocks B and a1 = more B blocking [3:1] – more potent anti-HTN • **Intrinsic symp activity (ISA):** acebutolol/pindolol = partial B-agonist activity: less negative effects on HR, glucose, lipids and resp • **Blocks both B1 and B2 R** (↓CO),↓ renin release (↓ATII levels = ↓Na+ reabsorption), ↓NE overflow at sympathetic nerve ending = ↓vascular resistance = ↓sympathetic outflow from CNS • Selective for B1 at lower doses at high does block both B1 and B2 • **Mixed:** both nonspecific and specific: Labetolol, Carvedilol = ↓BP = ↓CO and ↓VR (possess both B blocker and partial agonist (symp activity)	• **Metoprolol** (short T½ , CYP2D6) **Drug Intx:** • **Amiodarone** = bradycardia • **Non-DHP CCB**= bradycardia, hypotension • **Digoxin** = bradycardia • **NSAIDs** = HTN • **Insulin** = inhib hypoglycemic response	• **CI: severe asthmatic** (risk of bronchoconstriction – b/c B2 in lungs = relax but if block will constrict) – selective may be safe in mild-mod in rare circumstances **≥60y:** exercise intolerance, fatigue, **2* or 3* heart block, Decompensated HF, Severe PAD** – b/c VC in periphery, **Pheochromocytoma** (without a1 blocker) , **Hypersensitivity** • **SEs: fatigue**, dizzy, insomnia, vivid dreams, depression, decreased libido, cold extremities, masking response w hypoglycemia, **↓HDL, ↑ TG, bradycardia, ↓exercise capacity (↓HR), hypotension**, heart block (rare), bronchospasm, impotence • ***need to taper off due d/c rebound HTN over 1-2 wks** • **Avoid acebutalol/pindolol:** stable angina and post MI patients (ISA)
Ca+ antagonists (CCBs) **[VDs]**	• **Verapamil [Non-DHP]** • **Diltiazem [Non-DHP]:** 30-60mg PO tid 120-360mg ER PO daily **DHP** • **Amlodipine:** 2.5-10mg PO daily [long T ½: 1-2days] • **Felodipine** [T ½ :25 hr], **Nifedipine [**Short T ½:7 hr], **Nimodipine**	• **Primary action of heart:** cardiac cells [contractility and impulse conduction (↓ HR)] and increase O2 supply in coronary arteries • **Primary action on conducting tissue**: AP of SA and AV node is dependent on Ca+ → Ca+ channel blockade slows the gen of AP at the SA node = slows conduction of APs thru the AV node • **CI: HRrEF** b/c reduce force of contraction • **Primary action arterioles:** only ↑ arterial diameter (NOT venous d) even tho L-type Ca+ channel exists in both • **Decreased peripheral vascular resistance primarily** and no effect on HR but may increase through reflex tachycardiac **Mech**: acts on voltage dep Ca+ channel to block entry of Ca+ into cardiac and smooth muscle *L-type predom in cardiac & sm mscle ↑ **time that Ca+ ch are closed** • **Effects:** block flux of Ca+ ions into sm msl + heart = **relax arteries = VD*** ↓ TPR, contractility BP ↓ afterload NOT preload		• **SEs (related to VD): flushing (DHP),** headaches, dizzy, peripheral edema (DHP- amlodipine), **reflex tachycardia (DHP),** rash (diltiazem) • **Peripheral edema** b/c only arteries dilated and not venules = ↑ capillary pressure and permeability expels fluid into surround tissue • **Verapamil & Diltiazem:** more cardiac depressant effect: arrhythmias, **bradycardia, heart block** ***caution w/ B-blocker /CHF** • **Nicardipine** d/c b/c MI safety • **CI:** severe hypotension (SBP<90), recent MI with pulmonary edema, HFrEF (except amlodipine), 2*/3* heart block or sick sinus syndrome (non-DHP), hypersensitivity • **Drug Intx: BB (non DHP):** bradycardia, hypotension **CYP3A4 inhib**= ↑ CCB level. **CYP3A4 subs =** ↑ CYP3A4 sub level **CYP3A4 inducers =** ↓ CCB level **Digoxin =** bradycardia, ↑ digoxin **Amiodarone =** Bradycardia. **NSAIDs =** HTN

Diuretics **Thiazide** **Thiazide like**	**Short Acting:** benzothiazide **HCTZ:** 12.5-25mg PO Chlorothiazide **Long Acting:** Indapamide, Metolazone, **Chlorthalidone:** 12.5-25mg PO OD **Long > Short**	• Glaucoma, Edema (CHF),tx of renal stones (hypercalcemia) = ↑ Ca+ reabsorption = less Ca available to stone formation , ***Mild-moderate hypertension*** • **ALL have same MoA:** ↓blood volume b/c peeing = ↓preload = ↓amt of fluid entering heart (↓EDV) = ↓stretch on heart = ↓SV = ↓CO =↓ BP • 1) Block Na+ absorption in **DISTAL tubule** ***(only 4.5%, not main fn) – inhibit Na+/Cl- co-transporter in distal tubule*** • 2) Lose Na+ = Lose H2O = ↓ fluid volume = ↓EDV =↓ SV = ↓BP b/c of ↓BP = **Baroreceptor STOP** firing = sympathetic activity = ↑ SVR + ↑ CO to try to bring ↑ BP to normal = vasoconstriction = but loss of fluid volume > ↑ peripheral resistance = net effect: ↓BP *but over months+: thiazide diuretics affect peripheral resistance ↓ > fluid volume = affects vascular resistance b/c have direct affected on smooth muscle (relax/VD) by: ***NO*** (↑ cGMP in sm msc), ***PGI2*** (↑cAMP), ***EDH*** (sm mscl release EDHF = loss of K+ = hyperpolarize = decrease Ca+ from outside thru LType Channel = less Ca+ coming = less sliding = vasodilation)	• **Hypokalemia tx**: increase K+ diet (fresh fruits like banana, cantaloupe and veggies (beans/potato's), K+ salts, K+ sparing diuretics (if serum K+<3mmol/L) • **Drug Intx:** **Digoxin**: ↑ digoxin, (hypoK+, hypoMg) **Lithium:** ↑ Li **NSAIDs**: renal dysfn **CCsteroids**: hypokalemia	• **CI:** anuria, **gout**, hypoNa+, **severe sulfa allergy,** hypersensitivity, lactation • Excess pharmacological effect (↓BV, dehydration) • **Hyperglycemia** (↓release of insulin) ***caution w/ diabetics** (b/c cause K+ loss = less insulin) • **Hyperlipidemia** (return to normal with prolonged use) – b/c lower insulin secretion -> insulin inhibits HSL (which breaks down TGs in to FA) → FA can go to liver and form TG in liver • **Hypokalemia [↓K+]:** block Na/Cl cotransporter in distal tube → more Na+ on outside vs inside K+ higher inside vs outside- in collecting duct only Na+ channels = but Na comes w/ Cl => lumen becomes -ive b/c of Cl => K+ leaves cell = lost in lumen **Cause:** neuro (drowsy, irritb, confs), neurmomusc (loss of sens, msc weak), cariac (arryth,) • **Gout:** Uric acid also secreted OAT = transports thiazide and uric acid – competing = uric acid builds up • **Electrolyte disturbances: ↓ K+, ↓ Na+, ↓Mg, ↑ Ca+, hyperglycemia, hyperuricemia**
Diuretics **K+ Sparing Diuretics** **Never given alone**	**Spironolactone: 25-50mg PO OD** Eplerenone* (*more selective for MR = less SEs) (Aldosterone Antagonists) ***given w/ loop or thiazide to prevent hypokalemia**	• K+ sparing diuretics: not given to block reabsorption • Act on collecting duct (only 4.5% reabsorption Na+) **– they are only given to prevent loss of K+** • **MoA: want to prevent hypokalemia: aldosterone antagonist in collecting duct: aldosterone = AIP = promotes Na+ reabsorption = causes loss of K+**	Used in: • CHF b/c aldosterone↑ • Hypokalemia • Combined w/ other diuretics to prevent K+ loss	• **Gynecomastia** • Impotence • Males: ↓libido • Females: Deepening voice and menstrual irregularities • Hyperkalemia: lethargy, confusion, muscle cramps, arrhythmias
	Triamterene, Amiloride (non-aldosterone antagonists)	• Act on late distal tubule and collecting duct (poor efficacy) • Inhibits the entry of Na+ from tubule lumen side = prevent Na+ from being reabsorbed and prevent K+ loss • Na+ channel blockers	Useful in edema, combined w/diuretic to prevent K+ loss, few SEs	
Loop Diuretic	Furosemide	Acts on the loop of Henle → reabsorption at distal tubule only have 4.5% reabsorption capacity of Na+		

a-AdrenoR Antagonist [A1 R blockers]	• **Prazosin** • **Doxasoin** • **For mild-moderate HTN** • ↓LDL-C (5-10%)	• **A1-AdrenoR predom a receptor located on vascular sm mscl – selective to postsynaptic a1 adrenoceptors** • **Prevents:** Sympathetic outflow causes release of NE → bind to a1 R → IP3 → Ca+ intracellular = activates calmodulin → MLCK → myosin/actin contraction **Mech:** • 1) act at post-synaptic R = arteriole (have more VD here) & venous sm msc dilation 2) ↓TPR and ↓ arterial pressure 3) ↓BP = preventing catecholamine-induced VC (confined to vascular sm msc)*catecholamine can still activate presynaptic a2 R = inhibit NE release	• Toxicities mild/infrequent • ***Postural hypotension*** (within 90 mins – seen in 50% of pts) * limits agents, should be started with low doses, pt take QHS or reclining → over t pt develop tolerance • Doxazosin = newer, more gradual onset or action (less postural HTN to occur)	• **a-AdrenoR Antagonist** [A1 R blockers]
Direct renin inhibitors	• **Aliskiren**	• **Mech:** direct renin inhibitor → blocks proteolytic activity of renin: binds directly to catalytic site of renin and prevents angiotensinogen to ATI **Inhibits ATI = inhibits ATII (b/c cant covert)** **= ↓ renin, ATI, ATII, aldosterone, no effect on bradykinin**	• Neutralizes the FB loop effects – may offer benefits with ACE or ARBs = no clinical benefits	• **SEs:** Hypotension, Hyperkalemia (similar to ARBs) • **CI:** pregnancy
Arteriolar Vasodilators	• **Minoxidil**	• ***must be used w/ diuretic or BBlocker (b/c reflex tachycardia)** • **Mech:** acts on ATP K+ channel (antagonizes action of intracellular ATP → opens K+ channel → hyperpolariz→ ↓entry of Ca+ → relaxation of sm msc • **Effects:** ↓TPR, BP	• Very long duration of action (72 hrs) • Used in SEVERE HTN resistant to other agents	• **Hypertrichosis** (abnormal growth of hair) → Rogaine (used for tx of male baldness – applied directly to scalp) • Need to be used w/ diuretic or BBlocker due to reflex tachycardia = baroreceptors activated when BP falls = HR and contraction changes
	• **Hydralazine**	• **Mech:** Direct acting VD, ***selective for arterial resistance vessel***, acts on sm muscle of BV (arteries) → produce VD → NO → opening of K+ channel • **Effects:** ↓TPR, BP • **VDs: secretes NO → ↑ cGMP** = ↓ Ca+ entry directly → opens K+ channels → sequester Ca+ intracellular by ER = ↓ Ca+ intracell = ↓ MLCK activity = inhibit myosin P = smooth msc relaxation **PG → cAMP → IP3**	• Not general used as sole drug for tx of LT HTN (b/c short T ½) • ***Used w/ B-blocker / diuretic = combine to reduce reflex response**	• May ↑ CO (stim sympath NS) + ↑ renin (fluid retention) = limit effectiv b/c of active of baroR reflex • Reversible lupus like syndrome (arthritis, fever) • May cause myocardial ischemia • Reflex tachycardia • **CI:** HTN pt with CAD
CNS acting anti-HTN **declined use*	• **Clonidine**	• **Mech:** Act mainly via CNS action (brain stem) → stimulates a2-receptors in brain = ↓sympathetic outflow + ↓ BP & May also supress renin release **Effect**: ↓TPR, HR, CO and BP	• Short acting drug <8hrs • Usually given BID • ↓NE transmission = super sensitivity of a1 and b1 R in BV and heart	• Drowsiness (in early tx), dry mouth (may be severe), constipation, fluid retention (w/ diuretic)
	• **Methyldopa**	• **Mech:** v complex, central effects: converted to methylNE (stored in neurosecretory vesicle of adrenergic neurons substituting for NE – depletes NE stores) → prevent NE causing BV to contract Stimulated a2 R in brain = ↓sympathetic outflow; may cause direct VD • **Effect**: ↓TPR, CO and BP	• Used in mod-severe HTN	• Drowsiness, fluid retention (effective when given w/ diuretic), hemolytic anemia (20% pts)