The BIG PICTURE

BP = CO x PVR

ANTIHYPERTENSIVES
- target either CO or PVR
- Two goals:
  1. Reduce sign (↓ bp)
  2. Prevent target organ damage
     - Heart: MI
     - Brain: stroke
     - Kidneys: renal failure

- Peripheral vasoconstriction

- HR
- Contractility
- Na+ & H2O conc.

1. Sympatholytics
   - CNS-acting sympatholegics (methyldopa, clonidine)
   - Adrenergic neuron blockers (guanethidine, reserpine)
   - α-blockers (-zosi)
   - β-blockers (-lol)

2. Ca2+ channel blockers
   - Dihydropyridines (-dipine)
   - Nondihydropyridines (verapamil, diltiazem)

3. Diuretics
   - Thiazides, loop, K+ sparing

4. RAS cascade inhibitors
   - ACE inhibitors (-pril)
   - ARBs (-sartan)
   - Direct renin inhibitors

5. Direct-acting vasodilators
   - (hydralazine, minoxidil)

Classes of drugs

All classes act on PVR
**CNS-ACTING SYMPATHOPLEGICS**

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  Sympathetic brain signals
- Doesn’t affect baroreceptor reflex (no orthostatic hypotension)

**Methyldopa** → α-methylNE → crosses BBB → (+) α-adrenoreceptors (sympatholytic) → ↓PVR

**Clonidine**
- Agonist of α-adrenoreceptors in medulla: ↓symp tone, ↑parasymp tone → ↓BP, ↓HR
- Similar effects: guanzbenz, guanfacine
- SE: xerostomia, sedation, sudden withdrawal causes rebound sympathetic activity

**ADRENERGIC NEURON BLOCKERS**

- Suppress firing of adrenergic nerves on blood vessels (knocks out vasoconstriction)
- Effects: vasodilation, impaired baroreceptor reflex (caution with orthostatic hypotension)
- Rarely used today: many SE and drug interactions

**Ganethidin**
- Taken into vesicles, replaces NE → no NE release at synapse → ↓symp action → vasodilation

**Reserpine**
- Blocks NE, DA, & 5-HT uptake into vesicles → ↓NE release at synapse → ↓symp action → vasodilation

**α-BLOCKERS**

- Act on vasculature (↓PVR) by blocking sympathetic impulses
- Selective α1 blockers: ↓symp action → dilation of vessels → ↓arterial pressure
  - Less reflex tachycardia than nonselectives
  - Some problems with orthostatic hypotension
- *-zosin: prazosin, terazosin, doxazosin

- Nonselective α blockers: blocks both α1 & α2 receptors
  - No longer used to treat hypertension but available
  - Phentolamine: blocking α2 causes tachycardia
  - Phenoxybenzamine: covalently binds to α receptors, longer duration of action

**β-BLOCKERS**

- Act on heart (↓CO), block renin production (↓bp), peripheral vasodilation
- Compelling indications: good for pts who had MI or have high coronary risk
- SE: bradycardia, ↓contractility (problem for CHF), bronchoconstriction (problem for respiratory disorders), CNS (sedation, insomnia, depression), hypoglycemic episodes in diabetics (Sx may be masked)
- Nonselective: affect other organs besides heart
  - Propranolol, naldolol, carteolol
- Selective:
  - Metoprolol, atenolol, betaxolol, bisoprolol, esmolol (iv only)
- With ISA: intrinsic sympathomimetic activity
  - Both β2 agonists and β1 antagonists: β2 agonist> β1 antagonist activity
  - Pindolol, acebutolol, penbutolol
  - ↓PVR
  - Good for pts with bradyarrhythmias and peripheral vascular disease
  - Bad for pts with angina
- With α-NE-blocking activity
  - Selective α- and β- antagonist activity
  - Block α: vasodilation
  - Labetalol, carvedilol
CALCIUM CHANNEL BLOCKERS (CCBs)

Overview
- Treats: arrhythmias, angina, hypertension
- Inhibit Ca\(^{2+}\) influx into cardiac/vascular smooth muscles \(\rightarrow\) ↓PVR
- Potent vasodilators
- Sensitivity: arterioles > veins

Dihydropyridines
- Prevents: calmodulin kinase activation, myosin phosphorylation, contraction
- Greater effect: vasculature > heart
- -dipine: nifedipine, amlodipine, felodipine, etc.
- Less cardiac depressant activity: may ↑HR and cause tachycardia due to reflex symp activity

Non-dihydropyridines
- Prevents: actin & myosin interaction
- Induces: bradycardia, ↓contractility, ↓AV conduction
- Greater effect: heart > vasculature
- Verapamil, diltiazem
- Negative ionotropic effect: cardiac depression (verapamil>diltiazem)
- ↓HR \(\rightarrow\) ↓CO (less likely to cause tachycardia)

Adverse effects
- Cardiac depression: bradycardia, AV block, cardiac arrest, CHF, risk of MI
- Other: dizziness, constipation, peripheral edema, flushing, nausea
**K+ SPARING DIURETICS**

Where: early distal tubule, collecting duct

How: avoid K+ depletion

Who: aldosterone antagonists (spironolactone, eplerenone); block sodium channel directly (amiloride, triamterene)

Caution: hyperkalemia, gynecomastia, hypochloremic acidosis

↓ K+ ↑ uric acid  ↑ glucose  ↓ lipids

**THIAZIDE DIURETICS**

Where: late distal tubule, collecting duct

How: inhibit Na+/Cl- cotransporter, enhances Ca2+ reabsorption

Acute action: diuresis ↓ blood volume, ↓ CO, ↑ PVR (from ↑ Na+)

Chronic action: CO normal, ↓ PVR (from ↓ Na+)

Who: end in “-thiazide,” e.g. HCTZ, chlorothiazide

Most frequently prescribed diuretic/antihypertensive

Lower doses have same effect as high doses; don’t push it

Caution: hypokalemia (<3 problems), hyperuricemia (gout), hyperglycemia, hyperlipidemia

↓ K+ ↑ uric acid  ↑ glucose  ↓ lipids

**CARBONIC ANHYDRASE INHIBITORS**

Where: proximal tubule

How: block CA → ↓ HCO₃ → ↓ H₂O

HCO₃ excreted in urine → alkaline urine → acidosis

Weak; effects diminish because ↓ HCO₃ enhances Na+ reabsorption

Who: acetazolamide (diamox)

Not used much, but led to thiazides

**LOOP DIURETICS**

Where: loop of Henle, thick ascending limb

How: inhibit NKCC2 transporter

Enhance K+ & Mg²⁺ excretion (bad for <3)

Who: end in “-amide,” e.g. furosemide, bumetamide; also ethacrynic acid

Potent, used to treat severe hypertension

Caution: hypokalemia (alkalosis), hyperuricemia (gout), hypomagnesemia, ototoxicity

↓ K+ ↑ uric acid  ↓ Mg²⁺
ACE inhibitors
- Inhibits ACE: angiotensin I \(\rightarrow\) angiotensin II
- \(↓\) Angiotensin II (circulating vasoconstrictor) = \(↓\) afterload, \(↓\) PVR
- Prevents mitogenic effect of angiotensin II on heart: prevents heart remodeling
- Prevents bradykinin, a vasodilator, from being degraded (but causes SE: cough, edema, bronchospasm)
- \(↓\) Aldosterone = \(↑\) Na\(^+\) and H\(_2\)O excretion = \(↓\) blood volume
- Incomplete inhibition since there are other sources of angiotensin II
- Results: \(↓\) PVR, no change in CO or HR, no reflex tachycardia
- Compelling indications: useful for treating pts with MI, CHF (with HCTZ), CKD, stroke (with HCTZ), diabetes
- SE: hypotension after initial dose, ARF, hyperkalemia, dry cough, angioedema
- Drug interactions: aspirin & NSAIDS may diminish response (due to \(↓\) prostaglandins)
- Contraindicated in pregnancy: 2\(^{nd}\) & 3\(^{rd}\) trimesters
- \(-\)pril: captopril, lisinopril, enalapril, etc.

ARBs
- Blocks angiotensin II type 1 from binding to its receptor \(\rightarrow\) \(↓\) PVR
- Inhibits aldosterone secretion
- Does not affect bradykinin (i.e. cough not a SE)
- Clinical effects similar to ACE inhibitors
- Compelling indications: useful for treating pts with CKD or diabetes
- SE: same as ACEI except dry cough and angioedema
- \(-\)sartan: losartan, valsartan, olmesartan, irbesartan, telmisartan, etc.

Direct renin inhibitors (DRI)
- Binds to binding pocket of renin \(\rightarrow\) inhibits enzyme activity of renin
- Renin converts angiotensinogen \(\rightarrow\) angiotensin I
- Result: \(↓\) angiotensin I, \(↓\) angiotensin II, \(↓\) aldosterone
- Aliskiren (Tekturna): also as combo therapy with HCTZ
VASODILATORS

Dilates arterioles → no effect on veins!

Hydralazine
• Used in combo: tachyphalaxis develops if monotherapy
• SE: may provoke angina

Minoxidil
• Metabolite opens K⁺ channels in smooth muscle membranes → suppresses contraction
• Topical: Rogaine for hair growth
• SE: angina, headache, sweating, hirsutism

Parenteral: sodium nitroprusside, diazoxide, fenolopam (SE: tachycardia, angina)
Classification of BP:

- **Systolic**: use rule of 20’s (<=120 normal, <=140 pre, <=160 stage 1, >160 stage 2)
- **Diastolic**: use rule of 10’s (<=80 normal, <=90 pre, <=100 stage 1, >100 stage 2)
- Systolic BP is a better indicator than diastolic
- If one is higher and the other ok, still hypertension; always use the higher to classify
- **Diagnosis**: use rule of 2’s: avg of 2 readings taken at 2 visits after initial screening

**Ultimate goal**: reduce morbidity & mortality

**Major risk factors**: smoking, drinking, family hx, diet, obesity (BMI>30), exercise, dyslipidemia, diabetes, GFR<60, men>55y/o, women>65y/o)

**Thiazide diuretics**: always first line therapy if no other indications