LEARNING OBJECTIVES

- Know how each drug class works in the body
- Understand the place in therapy for each class of medications (first choice vs 2nd or 3rd choice)
- Know major/most common adverse effects
- See “things you should know” and additional questions in the lecture
- Understand which hypertension reduction strategy is being utilized with each medication
- Understand the benefits of TLCs in the treatment of hypertension
HYPERTENSION OVERVIEW

Hypertension is sustained elevated systolic blood pressure, diastolic blood pressure, or both.

• 1 in 3 adults have hypertension, many who have hypertension DO NOT KNOW it
• Most is essential
• Secondary is hypertension of a specific cause
  • Tumors, kidney disorders, pregnancy, Cushing's syndrome, and medications

• BLOOD PRESSURE (MEAN ARTERIAL PRESSURE) = CARDIAC OUTPUT X PVR

• CARDIAC OUTPUT = STROKE VOLUME X HEART RATE

• The silent killer
HOW DO YOU KNOW WHEN YOU HAVE HYPERTENSION?

Risk factors (Hypertension)

- Family history
- Race
- Variations in vasculature
- Stress
- Obesity
- Diet high in fat or sodium
- Smoking
- Hormonal birth control
- Sedentary lifestyle
- Aging

Risk factors: (Cardiovascular disease)

- Hypertension
- Cigarette smoking
- Obesity
- Physical inactivity
- Dyslipidemia
- Diabetes
- Microalbuminuria
- GFR < 60 mls/min
- Age - > 55 for men, > 65 for women
- Family history of premature cardiovascular disease
WHEN DO YOU TREAT HYPERTENSION?

JNC 7

Age 65 years & older = Same as age under 50 years
Age less than 50 years = < 140/90
Diabetes or CKD = < 130/90
Non black = Start with thiazide diuretic, consider ACEI, ARB, CCB, or BB
Black = CCB or thiazide diuretic

JNC 8

Age 60 years & older = < 150/90
Age 30-59 = < 140/90
Non black = ACEI, ARB, thiazide diuretic, or CCB
Black = CCB or thiazide diuretic
# Therapeutic Lifestyle Changes

<table>
<thead>
<tr>
<th>Modification</th>
<th>Recommendation</th>
<th>Avg. SBP Reduction Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>Maintain normal body weight (body mass index 18.5–24.9 kg/m²).</td>
<td>5–20 mmHg/10 kg</td>
</tr>
<tr>
<td>DASH eating plan</td>
<td>Adopt a diet rich in fruits, vegetables, and lowfat dairy products with reduced content of saturated and total fat.</td>
<td>8–14 mmHg</td>
</tr>
<tr>
<td>Dietary sodium reduction</td>
<td>Reduce dietary sodium intake to ≤100 mmol per day (2.4 g sodium or 6 g sodium chloride).</td>
<td>2–8 mmHg</td>
</tr>
<tr>
<td>Aerobic physical activity</td>
<td>Regular aerobic physical activity (e.g., brisk walking) at least 30 minutes per day, most days of the week.</td>
<td>4–9 mmHg</td>
</tr>
<tr>
<td>Moderation of alcohol</td>
<td>Men: limit to ≤2 drinks* per day. Women and lighter weight persons: limit to ≤1 drink* per day.</td>
<td>2–4 mmHg</td>
</tr>
</tbody>
</table>

* -- Alcohol consumption.
TREATING HYPERTENSION

- Set point (elevated)
  - Baroreceptors & renin-angiotensin system
  - MOST drugs do not reset

How do you tackle BP?

BLOOD PRESSURE

- BLOOD VOLUME
- PVR
- CARDIAC OUTPUT
DIURETICS

What is a diuretic?
- Any substance that increases the production of urine and increases the excretion of water and salt in the urine

What is anuria?
- When the kidney does not produce urine

What is enuresis?
- Urination at night, involuntary

What is oliguria?
- Production of only small amounts of urine
KIDNEY OVERVIEW — THIAZIDE DIURETICS

Filtrate composition:
- H₂O
- NaCl
- HCO₃⁻
- H⁺
- Urea
- Glucose
- Amino acids
- Some drugs

Reabsorption ➔
Secretion ➝

Blood ➔ Bowman’s capsule ➔ Proximal tubule ➔ Cortex ➔ Medulla ➔ Loop of Henle ➔ Distal tubule ➔ Collecting duct ➔ Urine (to renal pelvis)
KIDNEY OVERVIEW – THIAZIDE DIURETICS

Filtrate composition:
- $\text{H}_2\text{O}$
- NaCl
- $\text{HCO}_3^-$
- $\text{H}^+$
- Urea
- Glucose
- Amino acids
- Some drugs

Reabsorption →
Secretion ←
THIAZIDE DIURETICS

Hydrochlorothiazide, chlorthalidone, indapamide, metolazone, chlorothiazide

MOA – increased excretion of sodium, water, potassium, and hydrogen ions due to the inhibition of the sodium/chloride cotransporter in the DCT

Place in therapy – One of several first line treatments in hypertension

Adverse effects – hypokalemia, orthostatic hypotension, dehydration, elevated lipids, elevated uric acid, GI upset, sun sensitivity (sulfa)

Drug – drug – Use with caution in patients also taking Digoxin

Dosing – Doses greater than 25-50 mg daily do not generally experience lower blood pressure but do experience greater adverse effects

Initially blood volume decrease leads to decrease in BP – After 6-8 weeks, blood volume is restored but PVR declines. Perhaps due to lower sodium concentrations leading to the softening of the vasculature

Sulfa drug – Watch out for allergies/protect yourself from the sun
KIDNEY OVERVIEW — LOOP DIURETICS
UNDER NORMAL CIRCUMSTANCES

Lumen:
• The stuff here gets excreted in the urine

Interstitial:
• The stuff here gets reabsorbed back into the body

Epithelial cell of the kidney tubule (TAS of henle)
KIDNEY OVERVIEW — LOOP DIURETICS WITH MEDICATION

Lumen:
- The stuff here gets excreted in the urine

Interstitium:
- The stuff here gets reabsorbed back into the body

Epithelial cell of the kidney tubule (ASL of henle)

Mg^{++}

Ca^{++}

\[ \text{Na}^+ \quad \text{K}^+ \quad 2\text{Cl}^- \]

\[ \text{Na}^+ / \text{K}^+ \text{ATPase} \]

\[ \text{Sympporter} \]

\[ \text{Ca}^{++} \]
LOOP DIURETICS

**Furosemide**, bumetanide, torsemide, ethacrynic acid

**MOA** - Inhibits reabsorption of sodium and chloride in the ascending loop of Henle and distal renal tubule, interfering with the chloride-binding cotransport system, thus causing increased excretion of water, sodium, chloride, magnesium, and calcium

**Place in therapy** – Not first line therapy in HTN, however, very important to HF and conditions with marked edema

**Adverse effects** – Decrease in electrolytes (Na, K, Ca, Mg), ototoxicity, hyperuricemia

**Caution**: The use of furosemide with aminoglycoside antibiotics (ototoxicity)

**Sulfa drug** – Watch out for allergies/protect yourself from the sun

**Monitor** – Electrolyte balance when co-administered with digoxin
KIDNEY OVERVIEW — POTASSIUM SPARING

Filtrate composition:
- H₂O
- NaCl
- HCO₃⁻
- H⁺
- Urea
- Glucose
- Amino acids
- Some drugs

Reabsorption →
Secretion ↔

Blood

Bowman’s capsule

Proximal tubule
- Nutrients
- NaCl
- H₂O
- HCO₃⁻
- Some drugs and poisons

Distal tubule
- NaCl
- HCO₃⁻
- H₂O
- H⁺

Cortex

Medulla

Loop of Henle
- NaCl
- H₂O
- Urea

Collecting duct

Urine (to renal pelvis)
KIDNEY OVERVIEW — POTASSIUM SPARING DIURETICS

Lumen:
- The stuff here gets excreted in the urine

Interstitial:
- The stuff here gets reabsorbed back into the body

Epithelial cell of the kidney tubule
CORTICAL COLLECTING/DCT

- Na/K ATPase
- Na⁰⁺/K⁺ ATPase
- ENaC
- MR

Saving K

ALDOSTERONE

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POTASSIUM SPARING/ALDOSTERONE ANTAGONISTS

Aldosterone antagonists – Spironolactone & eplerenone

Potassium sparing – triamterene & amiloride

MOA – Antagonist at the mineralocorticoid receptor to reduce action of ENaC and Na/K ATPase pump or inhibition of the ENaC channel

Place in therapy – Add on therapy for HTN or correction for electrolyte imbalance with the use of other medications (loop/thiazide diuretics), also utilized in heart failure

Adverse effects – Hyperkalemia, gynecomastia (aldosterone antagonists), kidney stones

Caution – Should not be used as monotherapy in the treatment of HTN
THINGS YOU SHOULD KNOW

At which area of the kidney tubule do each of the diuretics discussed have its primary MOA?

Which diuretic causes which electrolyte imbalance?

If diuretics cause increase in urination, when might you tell your patient to take this medicine? AM/PM????
WHICH OF THE FOLLOWING GROUPS DO NOT CONTAIN “SULFA” DRUGS?

A. Loop diuretics  
B. Thiazide diuretics  
C. Potassium Sparing diuretics
ALPHA RECEPTOR ANTAGONISTS

**Clonidine:** Inhibition of vasomotor center through alpha 2 receptor agonist actions

**Methyldopa:** Binds to alpha 2 receptors in the vasopressor center of the brain to decrease the outflow of NE
ALPHA-RECEPTOR ANTAGONISTS

Clonidine, methyldopa, guanfacine

MOA – Reduction of sympathetic outflow to decrease beta 1 stimulation (decrease HR and contractility) or decrease stimulation of alpha 1 receptors (vasodilate vasculature of digestive tract and prostate gland) ultimately leading to a decrease in blood pressure.

Place in therapy – Clonidine, mild to moderate HTN / Methyldopa, moderate to severe HTN or HTN of pregnancy

Adverse effects – Central ADRs, drowsiness, constipation, headaches, impotency, anxiety…..

Guanfacine – NOT TO BE CONFUSED WITH GUAIFENACIN

Clonidine – Also used for migraine prophylaxis, nicotine and opioid withdrawal, and others

Taper to avoid hypertensive crisis
**BETA-RECEPTOR ANTAGONISTS (BETA BLOCKERS)**

- **B1 Receptor**
  - Decreased HR
  - Decreased conduction AV node
  - Decreased force of contraction

**DECREASED CARDIAC OUTPUT**

- **B2 Receptors**
  - Lungs
    - Contraction of bronchial smooth muscle
  - Liver
    - Decreased glucose production
  - Vascular smooth muscle
    - Vasoconstriction of arteries to skeletal muscle and liver

**Vascular smooth muscle**
NON-SELECTIVE BETA BLOCKERS

**Propranolol**, nadolol, timolol

MOA - Competitively blocks response to beta$_1$ and beta$_2$ adrenergic stimulation which results in decreases in heart rate, myocardial contractility, blood pressure, and myocardial oxygen demand.

Place in therapy – No longer considered first line therapy option for HTN, however may still be used, used often in rate control.

Adverse effects – Bradycardia, drowsiness, confusion, diarrhea, constipation, thrombocytopenia, bronchoconstriction

Monitoring – Co-administration with other cardiac/BP mediations, check blood pressure and heart rate. Watch for masking effects of hypoglycemia.

Taper when discontinuing over 2 weeks to avoid acute tachycardia, hypertension, and/or ischemia.

Also used for migraine prophylaxis and other indications
SELECTIVE BETA BLOCKERS

Atenolol, metoprolol, esmolol, bisoprolol

MOA - Competitively blocks beta_1 receptors, with little or no effect on beta_2 receptors. Does not exhibit any membrane stabilizing or intrinsic sympathomimetic activity

Place in therapy - No longer considered first line therapy option for HTN, however may still be used, used often in rate control – same as propranolol

Adverse effects – Bradycardia, dizziness, fatigue, depression, diarrhea, rash

Monitoring - Monitor blood pressure and heart rate. Assess for swelling/dysrhythmia and postural hypotension. Taper dosage slowly when discontinuing. Report abdominal pain, unusual bleeding or bruising, or changes in color of urine or stool. Advise patients with diabetes to monitor glucose levels closely; beta-blockers may alter glucose tolerance.

Advantage over non-selective agents for patients with comorbid asthma, DM, PVD
BETA BLOCKERS WITH ISA

Labetolol, acebutolol, pindolol

- Intrinsic sympathomimetic activity

Can partial activate the SNS, clinical benefit not found. However, danger in use with patients who are post MI. May be helpful in patients where beta blockers are indication but with a pulse less than 60 bpm.
BETA BLOCKERS ARE ONLY USED FOR REDUCING HYPERTENSION.

A. True
B. False
WHICH GROUP OF BETA BLOCKERS WOULD NOT BE USED FOR MIGRAINE PREVENTION?

A. Cardioselective beta blockers
B. Non-selective beta blockers
QUESTIONS
**CALCIUM CHANNEL BLOCKERS**

Dihydropyridines

End in “dipine”

Work primarily on PVR — vasodilation

Substrate for CYP3A4

Non-dihydropyridines

No naming scheme

Work primarily on heart rate/contraction

Major CYP3A4 inhibitors
CALCIUM CHANNEL BLOCKERS — CARDIAC MYOCYTE (CONTRACTILITY)

Ca ++ (+123)
Na+ (+67)
K+ (-92)

Stage 4
Stage 0
Stage 1
Stage 2
Stage 3

mV

Stage 4
Stage 0
Stage 1
Stage 2
Stage 3
CALCIUM CHANNEL BLOCKERS — CARDIAC MYOCYTE (CONTRACTILITY)

Ca ++ (+123)
Na+ (+67)
K+ (-92)

Stage 4
Stage 3
Stage 2
Stage 1
Stage 0

mV

Stage 1
Stage 2
Stage 3
CALCIUM CHANNEL BLOCKERS — PACEMAKER CELLS (HEART RATE)

Ca ++ (+123)
Na+ (+67)
K+ (-92)

Stage 4
Stage 0
Stage 3

mV
CALCIUM CHANNEL BLOCKERS — PACEMAKER CELLS (HEART RATE)

Ca ++ (+123)
Na+ (+67)
K+ (-92)

Stage 4
Stage 0
Stage 3

mV
**DIHYDROPYRIDINE CCBS**

*Amlopidine, felodipine, nicardipine*

**MOA** – Works primarily on the arterial smooth muscle to vasodilate and reduce PVR (most smooth muscle selective)

Place in therapy – First line therapy in hypertension of all races. However, evidence shows increased efficacy in black population, vasospastic (Prinzmetal’s) angina – less desirable for angina due to reflex tachycardia (increase oxygen demand to heart muscle)

Adverse effects – Reflex tachycardia, peripheral edema, male sexual dysfunction

Monitoring – Blood pressure and heart rate, weight gain (edema)

Caution – Should not be used in patients with arrhythmias, metabolized by CYP3A4 avoid concurrent use with inhibitors or inducers of this enzyme, taper upon d/c
NON-DIHYDROPYRIDINE CCBS

Diltiazem

MOA – Works in the cardiac tissue but to a lesser extent as compared to verapamil, also works in the arteries but to a lesser extent as compared to DHP

Place in therapy – Rate control in afib and vasospastic angina

Adverse effects – Edema, headache, AV block, heart failure, and GI upset, may cause reflex tachycardia (lesser extent)

Monitoring – Blood pressure and heart rate, edema

Major CYP3A4 enzyme inhibitor, use with caution in patients with heart failure

Taper upon d/c

Verapamil

MOA – Primary site of action in the cardiac tissue to decrease the rate and contractility of the heart, less systemic vasodilation

Place in therapy - Rate control in afib and vasospastic angina

Adverse effects – Constipation, gingival hyperplasia, AV block, hypotension, peripheral edema

Monitoring – blood pressure and heart rate

Major CYP3A4 enzyme inhibitor, use with caution in patients with heart failure

Contraindicated-with BB use

Taper upon d/c
WHICH TYPE OF CALCIUM CHANNEL BLOCKER IS MORE LIKELY TO CAUSE EDEMA?

A. Dihydropyridine
B. Non-dihydropyridine
RENIN-ANGIOTENSIN ALDOSTERONE SYSTEM (RAAS) UNDER NORMAL CIRCUMSTANCES

Endothelial cells too
ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS

Benazepril, captopril, enalapril (at), fosinopril, lisinopril, quinapril, *naming scheme*

MOA – Block the conversion of angiotensin I to angiotensin II by inhibiting angiotensin converting enzyme

Place in therapy – First line therapy for the treatment of hypertension, valued for kidney protective effects – especially for HTN in a diabetic patient, heart failure

Adverse effects – hypotension, dry cough, angioedema, hyperkalemia, acute renal failure, headache, diarrhea

Duration of action: All 24 hours except for captopril and enalaprilat (IV)

Monitoring – Blood pressure, serum potassium, serum creatinine

Caution – In use with other medications that may increase potassium (K-sparing diuretics, BB, NSAIDS, K supplements)

Cl – In pregnancy, fetal hypotension, renal failure, malformations, and deaths & renal artery stenosis

***Can change blood pressure set point
ACE INHIBITOR - ADRS

- Increased bradykinin
  - Decreased BP through the activation of bradykinin system
  - Increase in pro-inflammatory reactions
    - Dry cough
    - Angioedema
ANGIOTENSIN RECEPTOR BLOCKERS (ARBS)

Losartan, valsartan, candesartan, irbesartan, olmesartan

MOA – Block angiotensin II receptors, blocks vasoconstriction action of angiotensin II, decreases aldosterone release

Place in therapy – Used in the treatment of hypertension, especially when a patient cannot tolerate ACEI (cough/angioedema), heart failure

Adverse effects – Hypotension, angioedema, renal failure with dehydration, headache, muscle pain, dizziness

Monitoring – Blood pressure, serum creatinine, serum potassium

Caution – In use with other medications that may increase potassium (K-sparing diuretics, BB, NSAIDS, K supplements)

Cl – In pregnancy, fetal hypotension, renal failure, malformations, and deaths & renal artery stenosis
PATIENTS WHO EXPERIENCE __________________ SHOULD DISCONTINUE THEIR RAS INHIBITOR.

Cough
Angioedema
Hypokalemia
HONORABLE MENTION

Aliskirin
Hydralazine
Sodium nitroprusside
ALISKIREN

MOA – Direct renin inhibitor

Place in therapy – Not considered first line therapy in the treatment of hypertension

Adverse effects – Hypotension, hyperkalemia, renal impairment, skin rash, diarrhea, cough

Monitoring – Blood pressure, serum potassium, serum creatinine, BUN

CI – Not to be combined with ACEI or ARB

Caution – Co-administration with an ACEI, ARB, or NSAID (including COX-2 inhibitors) may increase risk of developing acute renal failure, May be metabolized to some extent by CYP3A4

Avoid use in pregnancy
HYDRALAZINE

MOA – Arterial vasodilator

Place in therapy – Moderate to severe hypertension and in combinations with other medications

Adverse effects – Headache, nausea, diarrhea, edema, reflex tachycardia, facial flush, angina

Monitoring – Blood pressure (sitting to standing) & heart rate

Combinations – May work well with diuretic as hydralazine can cause sodium and water retention, combat tolerance
SODIUM NITROPRUSSIDE

MOA – Release nitric oxide to dilate veins as well as arteries

Place in therapy – Hypertensive emergency

Adverse effects – Cyanide accumulation, metabolic acidosis, arrhythmias, hypotension, methemoglobinemia

Monitoring – Blood pressure every 30 seconds when the infusion if started then every 5 minutes to check for severe hypotension, cyanide toxicity (dilated pupils, pink color, shallow respirations), thiocyanate toxicity (tinnitus, blurred vision, delirium)
WHICH OF THE FOLLOWING IS/ARE AN ALPHA 2 AGONIST?

A. Aliskirin
B. Clonidine
C. Hydralazine
D. Nitrates
E. Both c and D
F. All of the above
QUESTIONS