Autonomic System

Autonomic Nervous System

- The autonomic nervous system (ANS) is the part of the nervous system that controls **involuntary** body functions—things your body does automatically without you thinking about them
- Heart rate
- Blood pressure
- Breathing (partially)
- Digestion
- Temperature control
- Sweating
- Pupil size
- Urination

Sympathetic (Fight or Flight)

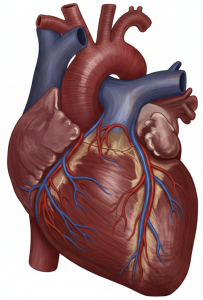
- Prepares the body for action, stress, or emergencies
- Norepinephrine, epinephrine is released
- Examples of effects:
  - Increases heart rate
  - Raises blood pressure
  - Dilates pupils
  - Slows digestion
  - Releases glucose for energy

Parasympathetic Nervous System (Rest and Digest)

- Handles normal body activities during rest and recovery
- Acetylcholine is released
- Examples of effects:
  - Slows heart rate
  - Enhances digestion
  - Constricts pupils
  - Promotes urination and bowel movement

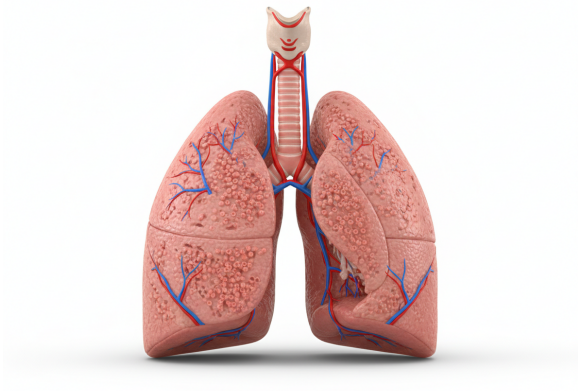
Comparison

- **Overall Purpose**
  - Sympathetic: Fight or flight
  - Parasympathetic: Rest and digest
- **Primary Neurotransmitters/Hormones**
  - Sympathetic: norepinephrine at most target organs; epinephrine and norepinephrine released from adrenal medulla
  - Parasympathetic: Acetylcholine at ganglia and target organs
- **Heart**
  - Sympathetic: Increases heart rate and contractility
  - Parasympathetic: Decreases heart rate



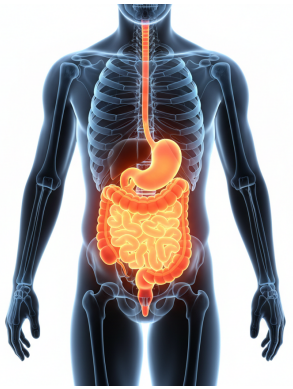
Comparison

- **Lungs**
  - Sympathetic: Dilates bronchi (opens airways)
  - Parasympathetic: Constricts bronchi



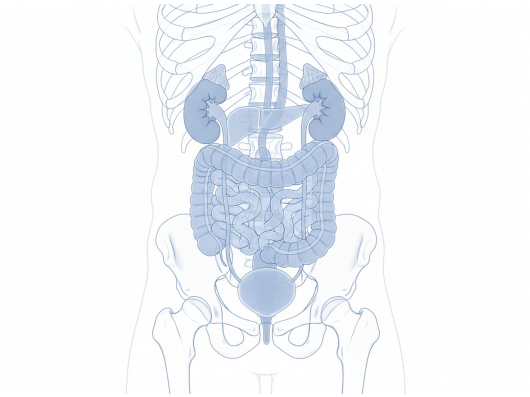
- **Eyes**
  - Sympathetic: Dilates pupils
  - Parasympathetic: Constricts pupils

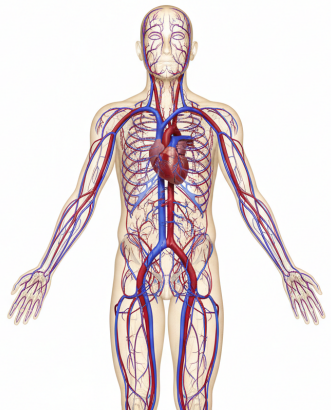
- **GI Tract**
  - Sympathetic: Slows digestion and reduces GI motility
  - Parasympathetic: Stimulates digestion and increases GI motility



Comparison

- **Bladder**
  - Sympathetic: Relaxes bladder (retention)
  - Parasympathetic: Contracts bladder (urination)
- **Sweat Glands**
  - Sympathetic: Increases sweating (uses acetylcholine at sweat glands—an exception)
  - Parasympathetic: Minimal effect
- **Blood Vessels**
  - Sympathetic: Constricts most vessels
    - Dilates vessels to skeletal muscle
  - Parasympathetic: Little effect on vascular tone





Enteric Nervous System

- Sometimes called the “brain of the gut.”
- Controls GI motility, secretion, and blood flow.
- Can function even without direct input from the brain.

Drug Targets Within The Sympathetic and Parasympathetic System

- Raise or lower blood pressure
- Treat asthma (e.g., albuterol)
- Treat urinary retention or overactive bladder
- Affect heart rate
- Dry secretions
- Manage GI motility

Cholinergic Agonists (Acts Like Acetylcholine)

- Methacholine
  - Restricts breathing – used in asthma diagnosis
- Pilocarpine
  - Used for treating glaucoma, helps dry mouth
- Bethanechol
  - Used for urinary retention
- Adverse effects: diarrhea, nausea, abdominal cramping, bradycardia, hypotension, urinary frequency, increased secretions, miosis (pupils constricting)
- Acetylcholinesterase inhibitors – similar effects; will cover in central nervous system medications

Cholinergic Actions

- **S** – Sweating *(sometimes included)*
- **L** – Lacrimation
- **U** – Urination
- **D** – Diarrhea
- **G** – Gastrointestinal cramping
- **E** – Emesis
- **B** – Bradycardia
- **L** – Lacrimation
- **U** – Urination
- **B** – Bronchoconstriction
- **S** – Salivation

Anticholinergic Actions (Blocking acetylcholine)

- Dry mouth
- Blurred vision, dry eyes
- Constipation
- Urinary retention
- Confusion, delirium, or memory impairment (especially in older adults)
- Sedation
- Tachycardia (increased heart rate)
- Decreased sweating (can increase risk of heat intolerance)
- Pupil dilation (mydriasis)
- Worsening of glaucoma (especially narrow-angle glaucoma)

Anticholinergic Agents and Indications

- Respiratory
  - COPD – ipratropium, tiotropium for bronchodilation
  - Asthma (adjunct) – ipratropium in acute exacerbations
- Gastrointestinal
  - Irritable bowel syndrome with cramping – dicyclomine, hyoscyamine
  - Peptic ulcer disease (historically) – reduced acid secretion
  - Motion sickness and nausea – scopolamine patch
- Genitourinary
  - Overactive bladder or urge incontinence – oxybutynin, tolterodine, solifenacin
  - Neurogenic bladder – reduces bladder spasms

Anticholinergic Agents and Indications

- Neurologic
  - Parkinson disease – benztropine, trihexyphenidyl for tremor
  - Drug-induced extrapyramidal symptoms (EPS) – dystonia from antipsychotics
- Ophthalmic
  - Uveitis – atropine or cyclopentolate to dilate pupil and prevent synechiae
  - Eye examinations – cycloplegics for pupil dilation
- Cardiac
  - Bradycardia – atropine increases heart rate by reducing vagal tone
- Secretions control
  - Palliative care – glycopyrrolate or scopolamine for terminal secretions
  - Pre-anesthesia – reduces salivation and airway secretions

Anticholinergic Acronym

- **A – Anti-sludge effects** *(Dry mouth, dry eyes, dry skin)*
  B – Blurred vision
  C – Constipation
  D – Dizziness / Delirium / Dementia
  E – Elevated heart rate *(Tachycardia)*
  F – Frequent urinary retention
- “HOT as a hare, DRY as a bone, MAD as a hatter, BLIND as a bat”
- “Can't See, Can't Pee, Can't Spit, Can't Sh*t”

Cardiovascular

Hypertension Pearls

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Complications/Risks

- MI
- Stroke
- Kidney
- Vision
- Heart Failure
- Aneurysm

Setting Goals

- American Heart Association and American College of Cardiology
- Elevated systolic – 120-129 (do not begin pharmacotherapy, lifestyle interventions; exercise, DASH diet, etc.)
- JNC-8 cutoffs were 140/90 and 150/90 for elderly without higher risk disease states
- New updates lower threshold for pharmacotherapy in higher risk populations

Stage 1 Hypertension 130-139 or 80-89

- Medication therapy for high risk patients (Goal <130/80)
  - CV event
  - Diabetes
  - CKD
  - Risk stratification
    - If greater than 10% ASCVD 10 year risk
    - http://www.cvriskcalculator.com/

Stage 1 Hypertension 130-139 or 80-89

- Lifestyle modification for low risk patients
  - DASH Diet
  - Reduced sodium intake
  - Alcohol reduction
  - Weight Loss
  - Physical Activity
  - Smoking Cessation
  - Reduce caffeine and other BP increasing medications
  - Stress reduction

Clinical Factors

- Age/life expectancy
- Falls
- Hypotension history
- Drug induced hypertension
- Medical causes of hypertension

Drug Induced Hypertension

- NSAIDs
- Stimulants
- Corticosteroids
- Estrogen
- SNRI’s
- ESA’s

Medical Induced Hypertension

- Sleep apnea
- Thyroid
- Adrenal gland problems
- Illicit drug use/addiction
  - Opioid withdrawal

Hypertension Medications

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ACE Inhibitors

- ACE Inhibitors: benazepril (Lotensin), captopril (Capoten), enalapril (Vasotec), fosinopril (Monopril), **lisinopril** (Prinivil, Zestril), moexipril (Univasc), perindopril (Aceon), quinapril (Accupril), ramipril (Altace)
  - Mechanism of Action: Inhibits angiotensin converting enzyme which results in less angiotensin 2 which is a potent vasoconstrictor
- Common Side Effects
  - **C** – Cough
    R – Renal impairment
    A – Angioedema
    P – Pressure drop (Hypotension)
    H – Hyperkalemia

Clinical Pearls

- ACE inhibitors can exacerbate CKD, but can also help be renal protective
- Lisinopril most commonly used
- Classic medication cause of angioedema (extremely rare)
- Avoid ACE/ARB combo

Compelling Indications

- Diabetes
- Stroke
- CAD
- CKD
- CHF

Angiotensin Receptor Blockers

- ARBs: azilsartan (Edarbi), candesartan (Atacand), eprosartan (Teveten), irbesartan (Avapro), telmisartan (Micardis), valsartan (Diovan), **losartan** (Cozaar), olmesartan (Benicar)
  - Mechanism of Action: Blocks angiotensin receptors which prevents angiotensin 2 from activating vasoconstriction
  - Do NOT use with ACE Inhibitors (overlapping mechanism of action, increased risk for adverse effects)

ARB Clinical Pearls

- Think ACE minus the cough
  - Hyperkalemia
  - Kidney function
  - Angioedema
  - Similar compelling indications

Thiazide Diuretics

- Thiazide and thiazide-like diuretics: chlorthalidone (Hygroton), **hydrochlorothiazide** (Hydrodiuril, Microzide), indapamide (Lozol), metolazone (Zaroxolyn)
  - Mechanism of Action: Blocks sodium reabsorption in the distal convoluted tubule of the kidney which leads to an increase in diuresis
  - Major compelling indications (CHF or edema, stroke reduction)

Thiazide Diuretics

- Memorable Side Effects
  - “HERFED”
  - Hypokalemia/Hyperglycemia
  - Elevated uric acid (gout flare)
  - Renal impairment (rise in creatinine)
  - Frequent urination
  - Erectile dysfunction
  - Dehydration

Calcium Channel Blockers

- Mechanism of Action: Inhibition of calcium channels which prevents ion transfer and relaxes smooth muscle like blood vessels
- Dihydropyridines: **Amlodipine** (Norvasc), nifedipine (Procardia, Adalat), felodipine (Plendil), Isradipine (Dynacirc), nicardipine (Cardene), Nimodipine (Nymalize)
  - Compelling indications: Raynaud's, angina, headache prophylaxis
  - Edema, orthostasis (ALL meds that lower blood pressure can cause orthostasis)
  - Nifedipine often used in pregnancy
  - Minimal to no impact on heart rate
  - One of the first line agents in patients without a compelling indication

Calcium Channel Blockers

- Non-Dihydropyridines: Verapamil (Verelan), Diltiazem (Cardizem, Taztia)
  - Act on heart and vessels
  - Can be used for rate control in atrial fibrillation
  - Monitor pulse
  - Watch for interactions via CYP3A4 inhibition
  - Edema, constipation major side effects
  - Dihydropyridines (i.e. amlodipine) are typically preferred over non-dihydropyridines in patients without compelling indications

Aldosterone Antagonists

- **Spironolactone** (Aldactone), Eplerenone (Inspra)
  - Heart failure compelling indication with mortality benefit
  - Should be used in NYHA Class II-IV with ejection fraction of 35% or less
- Hyperkalemia
- Gynecomastia
- Avoid eGFR <30 ml/min, K+ >5
- 100mg spironolactone/40 mg furosemide
- Might see used in refractory hypertension cases where patients aren’t responding to more common medications (ACE, CCB, etc.)

Beta-Blockers

- Beta-blockers: acebutolol (Sectral), atenolol (Tenormin), betaxolol (Kerlone), bisoprolol (Zebeta, Ziac), carteolol (Cartrol), carvedilol (Coreg), labetalol (Normodyne, Trandate), **metoprolol** (Lopressor, Toprol-XL), nadolol (Corgard), nebivolol (Bystolic), penbutolol (Levatol), pindolol (Visken), propranolol (Inderal), sotalol (Betapace), timolol (Blocadren)
  - Mechanism of Action: Inhibition of beta-1 receptors causes cardiac slowing and blood pressure lowering; beta-2 inhibition can lead to closing of the airways and difficulty breathing
  - Avoid abruptly stopping moderate to high doses unless very serious adverse effect
  - Side effects
    - Sedation/fatigue
    - Low pulse
    - Increase asthma exacerbation risk or block beta-2 agonists effectively, more of an issue with non-selective
    - Mask hypoglycemia (most should still sweat) – non-selective beta-blocker usually higher concern
    - Exacerbate erectile dysfunction

Beta-Blockers

- Selectivity is important
- Metoprolol and atenolol are classic beta-1 selective agents
- Propranolol, nadolol are classic non-selective agents (beta-1 and beta-2 activity)
- Carvedilol and labetalol have some alpha activity
- Compelling Indications: Angina, CHF (stable), Post MI, Atrial fibrillation

Beta-Blockers

- Propranolol often used in:
  - Migraine
  - Esophageal Varices (portal hypertension associated with cirrhosis)
  - Essential Tremor
- Labetalol
  - Safest in pregnancy
- Sotalol
  - Used for arrhythmias only

Central Acting Agents

- Central Acting Alpha-2 agonists: **clonidine** (Catapres), methyldopa (Aldomet), guanfacine (Tenex)
  - Mechanism of Action: Stimulation of alpha-2 receptors in the CNS reduces sympathetic outflow and reduces vascular resistance and heart rate
  - Not first line for hypertension
    - Methyldopa may be used in pregnancy
  - Drowsiness, dizziness, dry mouth (avoid in elderly if possible)
  - May see used for psych disorders occasionally (ADHD etc.)
  - Clonidine is used for opioid withdrawal symptom management
  - Rebound hypertension troublesome if stopped abruptly

Vasodilators

- Direct Acting Vasodilators: **Hydralazine** (Apresoline), minoxidil (Loniten)
  - Mechanism of Action: Not well understood; exerts a relaxation effect on vessels causing vasodilation and lowering of blood pressure
  - Hydralazine can exacerbate/contribute to Lupus type symptoms
  - Hydralazine is dosed frequently which can be a pain for adherence
  - Minoxidil used for hair loss (alopecia) – Rogaine is common brand name
  - May see hydralazine/nitrate combination in heart failure for patients of African descent as ACE/ARBs may not be as effective

Nitrates

- Nitrates: Isosorbide mononitrate (Imdur), isosorbide dinitrate (Dilatrate), nitroglycerin (Nitroquick)
  - Mechanism of Action: Direct acting vasodilation by nitric oxide which causes smooth muscle relaxation and reduction in blood pressure
  - Primarily used in the management of angina
  - Nitro sublingual for acute angina attack (other dosage forms, but they are expensive (i.e. spray)
    - Dose every 5 minutes and dial 911 if chest pain is not improving; maximum of 3 doses
  - Long acting nitrates (Imdur) used in the prevention of angina
  - Nitrate tolerance can begin to develop in 8-12 hours, so nitrate free period is ideal
  - Patch formulation (Nitro-Dur) – on for 12 hours, off for 12 hours
  - Avoid combination with PDE-5 inhibitors for erectile dysfunction (I.e. sildenafil)

Alpha Blockers

- Non-selective alpha-blockers: Doxazosin (Cardura), Prazosin (Minipress), Terazosin (Hytrin)
  - Mechanism of Action: Blocks alpha receptors causing smooth muscle relaxation, vasodilation and opening of the ureter
  - Not first line for hypertension (see BPH for medication discussion)
  - Often dosed at night to minimize orthostasis/fall risk
  - Risk of floppy iris syndrome for those undergoing eye surgery

Antiplatelet Agents

Aspirin (Ecotrin)

- Mechanism in cardioprophylaxis – irreversibly inhibits COX-1 which reduces thromboxane A2 and leads to platelet inhibition
- Also used in acute treatment/emergency situation
- Low dose (“Baby”) 81 mg once daily is ok in majority of situations
- Higher dose (325 mg daily) may be used in clinical judgement scenarios where patients have had events despite low dose and GI/bleed risk remains low

Aspirin

- Reye's syndrome can occur with aspirin use but is extremely rare
  - Typically only associated with use of aspirin following or during a viral infection – risk is significantly increased in children
  - Low doses used in ACS and older patients are unlikely to cause any issues
  - Characterized by nausea, CNS changes, and in severe cases, seizures, brain, and liver damage

P2Y12 Inhibitors

Ticagrelor (Brilinta)

- Mechanism - inhibits adenosine diphosphate by binding to P2Y12 receptor (on platelets) which inhibits platelet aggregation
- Bleed risk
- Can increase uric acid
- Boxed warning for reduced effectiveness when patients are using aspirin doses greater than 100 mg
- 3A4 major pathway for metabolism – drug interaction risk
- Twice daily dosing is a downside compared to clopidogrel/prasugrel
- False negative results may occur when trying to diagnose heparin induced thrombocytopenia

Prasugrel (Effient)

- Mechanism - inhibits adenosine diphosphate by binding to P2Y12 receptor which inhibits platelet aggregation
- Main side effect is bleed risk; higher risk in very elderly and low weight patients
- Boxed warning in patients 75 or older
- Avoid in patients with active bleeding or a history of TIA/stroke
- More potent P2Y12 blocking effects versus clopidogrel
- Possibly reduce dose in patients 60kg or less (5 mg)
- Normal maintenance is 10 mg
- Thrombotic thrombocytopenic purpura (rare)
- Avoids 2C19 pathway (different from clopidogrel)

Clopidogrel (Plavix)

- Mechanism - inhibits adenosine diphosphate by binding to P2Y12 receptor which inhibits platelet aggregation
- Used in combination with aspirin or alternative for those who can't tolerate aspirin
- Typically for at least 12 months following stenting
  - May be shorter for high risk bleeding complications
  - May be longer if multiple MI's or MI that happened while patient was on aspirin alone, based upon clinical judgement
- Prodrug
  - CYP2C19 converts to active form
  - Rapid metabolizers may be at higher risk of bleed
  - Poor metabolizers may have risk of non-response or increased risk of clot formation/MI (boxed warning) – recommend another P2Y12 inhibitor
  - Omeprazole can inhibit CYP2C19 – clinical impact still debated/controversial

Atrial Fibrillation

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Symptoms of Atrial Fibrillation

- General fatigue
- Rapid and irregular heartbeat
- Fluttering or “thumping” in the chest
- Dizziness
- Shortness of breath and anxiety
- Weakness
- Faintness or confusion
- Fatigue when exercising

Controlling Rate

- Beta-blockers
- Calcium Channel Blockers
- Digoxin

Clinical Medication Pearls

- Beta-blockers
  - Usually first line
  - Generally avoid non-selective unless compelling indication
  - Metoprolol is the most common agent
- Calcium Channel Blockers
  - Non-dihydropyridines (diltiazem, verapamil)
  - Heart failure risk
- Generally target a heart rate less than 80 beats per minute
- Monitor blood pressure to avoid hypotension

Calcium Channel Blockers

- Non-Dihydropyridines: Verapamil (Verelan), Diltiazem (Cardizem, Taztia)
  - Act on heart and vessels
  - Can be used for rate control in atrial fibrillation
  - Monitor pulse
  - Watch for interactions via CYP3A4 inhibition
  - Edema, constipation major side effects
  - Dihydropyridines (i.e. amlodipine) are typically preferred over non-dihydropyridines in patients without compelling indications

Digoxin (Lanoxin)

- Mechanism of action – inhibits Na+/K+ ATPase which can increase contractility and affect cardiac pacemaker cells
- Used for rate control and may be an alternative to Beta-blocker/CCB in the event of a patient who already has low blood pressure
- Target goal concentration generally higher for atrial fibrillation versus CHF - around 0.8-1.2 (versus 0.5 to 0.8 for CHF)
- Signs of toxicity – weight loss, poor appetite, GI upset, low pulse, central nervous system changes, vision disturbances (blurred or yellow vision)
  - May appear when level is 1.5-2.0 or higher
- Can accumulate with worsening kidney function
- Can cause arrhythmias; low potassium or low magnesium levels can potentially increase this risk
- Amiodarone can increase digoxin levels

Rhythm Control

- Used if rate control fails, patients have intolerable symptoms, or in patients who may be intolerant to rate control medications
- Amiodarone (Cordarone)
  - Mechanism of action – Class 3 antiarrhythmic that prolongs phase 3 of the heart's action potential by inhibiting potassium and sodium channels
  - Extremely long half-life; effects can linger a long time following discontinuation
  - Also be on the lookout for drug interactions being complicated by this long half life
    - 3A4 interactions
      - Warfarin, phenytoin etc.
    - QTc prolongation risk with other antiarrhythmics, quinolones, macrolides, antipsychotics, citalopram, ondansetron, etc.
  - Monitor thyroid function (hypothyroid more common than hyperthyroid)
  - Can cause pulmonary fibrosis, monitor lung function throughout therapy
  - Boxed warning for liver toxicity – LFT monitoring important

Anticoagulation

- Cha2ds2Vasc
  - Score of 2 or greater indicates that anticoagulation should be used to prevent stroke due to atrial fibrillation
  - Anticoagulation is going to be indicated for most patients especially if they are of older age (i.e. greater than 65) and have no contraindications to therapy
  - Score of less than 2 and aspirin can be utilized
    - CHF +1
    - Hypertension +1
    - Age >65 +1, >75 +2
    - Diabetes +1
    - Sex: Female +1
    - Vascular disease +1
    - Stroke/TIA +2
  - As Cha2ds2Vasc score goes up, so does the risk of clot; for example;
    - Cha2ds2Vasc of 2 = 2.2% risk of thromboembolism/yr
    - Cha2ds2Vasc of 5 = 6.7% risk of thromboembolism/yr

Direct Oral Anticoagulants (DOACs)

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DOACs

- Mechanism of action: Inhibits action of factor 10a, which plays a vital role in the coagulation cascade
- Drug interactions
- Less monitoring
  - Is that good or bad?
- When might you not choose them
  - Patient stability
  - Prosthetic valves
  - Cost/insurance coverage
  - Provider comfort/preference

Apixaban (Eliquis)

- Apixaban
  - Twice daily
  - Possible dose adjustments based upon age, creatinine, weight
  - DVT Treatment 10 mg BID for 7 days then 5 mg BID
  - Afib – 5 mg BID
  - 2 of 3; age ≥ 80, body weight <60, or creatinine ≥ 1.5; reduce dose to 2.5 BID
  - Post op prophylaxis – 2.5 BID
  - Specific dose adjustments for 3A4 and P-glycoprotein inhibitors like clarithromycin, ketoconazole, itraconazole, ritonavir
  - Reversal - coagulation factor Xa [recombinant], inactivated-zhzo
  - Preferred DOAC in severe renal impairment (warfarin alternative) - ACC

Rivaroxaban (Xarelto)

- Rivaroxaban
  - Once daily
  - 3A4/P-glycoprotein interactions possible
  - <30mls/min avoid use
  - DVT – 15 mg BID for 21 days followed by 20 mg daily
  - DVT prophylaxis – 10 mg daily; up to 35 days
  - Afib – 20 mg daily
  - May have to reduce dose in elderly with CrCl between 30-50 mls/min
  - Reversal - coagulation factor Xa [recombinant], inactivated-zhzo

Edoxaban (Savaysa)

- Edoxaban
  - >95 mls/min boxed warning (stroke)
  - Once daily
  - Creatinine clearance 15-50 mls/min – dose reduction (30 mg daily)
  - Usual dosing = 60 mg daily
  - Reduced dose with 3A4/P-glycoprotein inhibitors
  - Avoid in very obese/low weight extremes

Dabigatran (Pradaxa)

- Direct Thrombin Inhibitor
- GI bleed risk >75 y/o
- Reversal agent available
- Dose adjustment in CKD
- Twice daily

Warfarin

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Warfarin Common Indications

- Atrial Fibrillation (2-3)
- DVT/PE (2-3)
- Prosthetic Mechanical Mitral Valve
  - 2.5-3.5
- Lower goals
  - High bleed risk
  - High fall risk

Warfarin - Pharmacokinetics

- Metabolized by
  - S-warfarin: CYP 2C9 (potent)
    - Metronidazole, fluconazole, Bactrim
  - R-warfarin: CYP 1A2, 2C19, 3A4
- Inducers can cause treatment failure
  - Carbamazepine, St. John’s Wort
- Bound to albumin
- Half-life = 36-42 hours

Warfarin – Adverse Effects

- Bleeding
- Purple Toe Syndrome
  - Don’t load warfarin
  - Painful purple lesions on toes and sides of feet

Warfarin –
How long does it take to work?

- Half-life of clotting factors
  - II - 60 hrs (prothrombin)
  - VII - 6 hrs
  - IX - 24 hrs
  - X - 40 hrs (reduction of II and X = prolongation of PT)

- Half-life of anticoagulants
  - Protein C 6 hrs
  - Protein S 72-96 hrs

Causes of INR Variation

- Adherence
- Diet
- Drug Interaction
- Changes in Disease States
  - Liver
  - CHF
  - Fever

Dose Adjustments

- Goal INR 2-3
- 10-15% adjustments (based on total weekly dose)
- Aggressiveness based upon INR
- Hold doses for INR greater than 4 in most circumstances
- INR of 5+, may want to recheck

Vitamin K

- Elevated INR and bleeding
- INR greater than 9
- Not going to work instantly
- Transfusion for acute, severe blood loss
- INR 5-9, no bleeding
  - May give vitamin K, don’t have to

Heparin Type Medications

Enoxaparin

- Enoxaparin (Lovenox)
  - Mechanism of action: primarily inhibits factor 10a; less thrombin (factor 2a) inhibition compared to unfractionated heparin
  - Injection is the big downside
  - DVT Prophylaxis
    - Usually 40 mg daily or possibly 30 mg BID (twice daily injection is a downside)
    - CrCl less than 30 – 30 mg daily
  - Treatment
    - 1 mg/kg/dose (twice daily)
    - OR 1.5 mg/kg/day once daily

Enoxaparin

- Careful in patients who have a history of heparin induced thrombocytopenia (HIT)
- Rarely may contribute to hyperkalemia
- Bleed risk is most common adverse effect
- If bridging to warfarin, discontinue when INR hits target range (usually 2-3)
- Converting to and from DOACs/NOACs – simply take one in place in the other at the time it is standardly given
- Derived from pork (porcine) – Jews and Muslims typically avoid pork products, so may need other options
- Low molecular weight heparins are generally preferred in pregnancy when anticoagulation is necessary

Heparin

- Mechanism of action: Binds antithrombin 3 and enhances rate of inactivation of factor 2a and 10a leading to a blood thinning effect
- Unpredictable kinetics
- Monitoring of activated Partial Thromboplastin Time (aPTT) and/or anti-10a levels may be monitored to assess dosing
- Treatment dosing is typically done IV
  - May see subQ used for prophylaxis
- Can be used in renal failure
- Protamine is antidote to heparin (approximately - 1 mg to 100 units of heparin)
- Fish allergy co-reaction risk
- Pork (porcine derived product-as well as enoxaparin)
- Hyperkalemia, osteoporosis (long term use only)

Heparin Induced Thrombocytopenia

- Heparin Induced Thrombocytopenia (HIT)
  - Type 1 – mild drop in platelets that happens quickly after starting the medication
  - Type 2 – big drop in platelets (usually >50%), usually more delayed onset
    - When people refer to HIT, Type 2 is normally what they are talking about as it is much more concerning clinically
    - Immune type reaction
    - Paradoxical reaction: Despite drop in platelets, patients are at risk of blood clots
    - Less risk with enoxaparin, but you would not transition a patient to this if they had confirmed Type 2 HIT

Congestive Heart Failure

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CHF Characteristics

- Inability to effectively pump blood
- Elevated BNP (or pro-BNP)
- SOB, cough
- Fatigue, weakness
- Edema
- HFrEF

Staging

- New York Heart Association Classification – Patient Symptoms
  - Class – 1 Asymptomatic
  - Class – 2 Become winded with exertion
  - Class – 3 Trouble with regular activities
  - Class – 4 Most severe, symptoms even at rest
- ACC/AHA Classification
  - Class – A – At risk for heart failure but no evidence of heart disease or symptoms of heart failure
  - Class – B – Evidence of structural disease, but no signs and symptoms of heart failure
  - Class – C – Structural heart disease with symptoms of heart failure
  - Class – D – Refractory heart failure not responsive to treatments

Medications Frequently Used in CHF

- Four Classes for Guideline Directed Medical Therapy (GDMT) in HFrEF – RAAS system medications (Entresto, ACE, ARB), SGLT-2 Inhibitors, beta-blockers, and mineralocorticoid inhibitors
- Quadruple Therapy
  - ARNI (or ACEI/ARB)
  - Beta-blockers
  - SGLT2 Inhibitors
  - MRAs
- Diuretics
  - Loops
  - Thiazide Like

ARNI – Angiotensin receptor – Neprilysin inhibitor

- ARNI – Angiotensin receptor – Neprilysin inhibitor (sacubitril/valsartan) - Entresto
  - ACC guidelines: Preferred first line therapy over ACE or ARB alone
  - Morbidity/mortality reduction
  - Indicated in NYHA class 2-4
  - Evidence of greater benefit in specific subsets, but cost is a downside to use

ARNI – Angiotensin receptor – Neprilysin inhibitor (sacubitril/valsartan)

- Neprilysin breaks down atrial and brain natriuretic peptide (ultimately leads to lower blood pressure and increase in fluid loss)
- More hypotension than ACE/ARB (<100 mm Hg SBP avoid)
- Avoid with hx of angioedema
- 36 hour washout period when switching from ACEI
  - Enalapril 10 mg or valsartan 160 mg or higher – may start higher dose (49/51 mg)
    - 24/26 mg BID naïve titrate to target of 97/103 mg of sacubitril/valsartan

Beta-blockers/ACE Inhibitors

- See Hypertension for more clinical breakdown
- Generally try to push the dose
  - Not that easy in the elderly
  - Falls
  - Weakness
  - Kidney function
- Carvedilol, metoprolol succinate, and bisoprolol are most commonly used in CHF (proven mortality benefit)

SGLT-2 inhibitors

- Dapagliflozin, empagliflozin, sotagliflozin
- Benefit in HFrEF even in patients without diabetes
- In diabetes patients who need blood sugar lowering, it makes sense to start an SGLT-2 inhibitor in patients who have heart failure
- HFpEF – SGLT2i (2a recommendation) with MRAs, ARBs and ARNI (2b)
  - LVEF 50% or greater
- See diabetes for more monitoring/adverse effects information

Aldosterone Antagonists

- Spironolactone, Eplerenone
  - Competitively inhibits aldosterone at the mineralocorticoid receptor. This reduces sodium and water reabsorption while decreasing potassium and hydrogen excretion. Net loss of sodium and water; potassium increases
  - Heart failure compelling indication with mortality benefit
  - Should be used in NYHA Class II-IV with ejection fraction of 35% or less
- Hyperkalemia
- Gynecomastia
- Avoid eGFR <30 ml/min, K+ >5
- 100mg spironolactone/40 mg furosemide

Loop Diuretics

- Furosemide (Lasix), torsemide (Demadex), bumetanide (Bumex), ethacrynic acid (Edecrin)
- Mechanism – Inhibits reabsorption of sodium and chloride in the ascending loop of Henle and therefore causes fluid loss (natriuresis)
- Can dramatically reduce electrolytes
  - Potassium, magnesium, calcium, sodium
- Risk of dehydration (inadequate perfusion of the kidney due to reduction of intravascular fluid)
- Monitor kidney function and electrolytes
- Frequent urination
- Ototoxicity risk (rare)

Thiazide Like Diuretics

- Metolazone (Zaroxolyn) most often used for fluid loss promotion
- MOA: Inhibits sodium and chloride reabsorption in the distal convoluted tubule of the nephron
- Possibly better efficacy in patients with reduced kidney function versus hydrochlorothiazide
- May only need to be given periodically (i.e. once or twice per week) in combo with loop diuretic
- Kidney function, electrolyte monitoring incredibly important especially when used in combo with loops and/or potassium sparing diuretics
- If on loop diuretic, some may recommend giving Metolazone 30-60 minutes before the furosemide
- Known for elevating uric acid and contributing to gout

Digoxin in CHF

- Increased mortality at higher levels
- Target 0.5-0.8
- Monitor closely
  - Changing renal function
  - Symptoms of toxicity

Classic Drugs that Exacerbate CHF

- NSAIDs
  - Sodium retention
  - Also risk of Kidney damage with ACE/Diuretics on board
- CCB’s
  - Increase edema
- TZD’s
  - Pioglitazone
- Pregabalin
- Cilostazol

Critical Monitoring

- SOB, respiratory rate
- Lung sounds
- Oxygen saturation
- BP, HR
- Daily weights (fluid retention)
- Water/urine - Intake/output
- Labs: BNP, electrolytes (potassium, sodium, magnesium), renal function (creatinine/BUN)

Hyperlipidemia

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Cholesterol Basics

- High levels of cholesterol, particularly LDL is associated with heart disease
- Cholesterol deposits form in vessels
- Deposits can break loose and clog in vessels – heart attack/stroke happens
- Asymptomatic

Hyperlipidemia Basics

- LDL is primary focus for statin medications
  - Shift back toward target goals
- Triglycerides – primary target >500
  - Fibrates
  - Niacin

ACC/AHA Risk Calculator – Primary Prevention

- Provides 10 year risk as well as if aspirin is recommended
- Factors
  - Age
  - Gender
  - Race
  - Cholesterol/HDL (doesn't use LDL in calculator, but if >190 recommend likely starting statin)
  - Blood Pressure (level plus if on medication)
  - Diabetes
  - Smoking
- Primary prevention 5-10% risk – clinical gray area

Target Goal of LDL <70 is Back

- Very high risk cardiovascular patients
  - Previous MI, ischemic stroke, etc.
- High intensity statin
- Ezetimibe likely to be first step after that to get patients to goal
  - Does have some cardiovascular outcomes data
- PCSK-9 inhibitors

Table 1. Statin Therapy

Intensity	Definition	Dosage
Low	Daily dose lowers LDL-C by <30%, on average	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg
Moderate	Daily dose lowers LDL-C by approximately 30% to <50%, on average	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg bid Pitavastatin 2-4 mg
High	Daily dose lowers LDL-C by approximately ≥50%, on average	Atorvastatin 40-80 mg Rosuvastatin 20-40 mg

C: cholesterol; XL: extended-release.
Source: Reference 1.

Statins

- Atorvastatin (Lipitor), rosuvastatin (Crestor), simvastatin (Zocor), pravastatin (Pravachol), lovastatin (Mevacor)
- Mechanism of action: Inhibition of HMG-CoA reductase which is the rate limiting step in the production of cholesterol
- Myopathy risk
- Rhabdomyolysis (rare, but severe)
  - Elevated CPK
  - Risk of renal failure
  - Fibrates can increase risk

Clinical Pearls

- Rosuvastatin/Atorvastatin for high intensity
- Generally avoid simvastatin if not on/hasn’t tried others
  - CYP3A4 interactions (amlodipine, amiodarone, diltiazem, etc.)
- Rosuvastatin
  - Most potent LDL lowering, less strict on interaction with gemfibrozil
- Atorvastatin
  - Covers moderate/high intensity nicely
  - Does have some 3A4 interaction potential
- Lovastatin
  - 3A4 potential

Alternative Options – High Risk Patients

- Rechallenge with statin is recommended
- Ezetimibe, PCSK-9, or bempedoic acid may be added to statin therapy for further LDL lowering
- Target LDL<70 mg/dL
- Target LDL <55 mg/dL for highest risk patients
  - Recurrent MI
  - Recent MI
  - Diabetes
  - Bypass
  - Significant PAD

Alternative Options

- Bempedoic acid (Nexletol)
  - Mechanism of Action: Adenosine triphosphate-citrate lyase (ACL) inhibitor
  - Add-on therapy for those needing further LDL reduction
  - Caution with gout patients (hyperuricemia), tendon rupture risk
  - Avoid using with over 20 mg of simvastatin or 40 mg of pravastatin
- Ezetimibe (Zetia)
  - Mechanism of Action: inhibits gut absorption of cholesterol via impacting Niemann-Pick C1-Like1 transporter (NPC1L1)
  - Can be added to statin to try to get to target goal in highest risk patients (typical LDL goal of <70)
  - Usually pretty well tolerated; GI and possible myopathy are side effects

PCSK9 Inhibitors

- Alirocumab (Praluent), Evolocumab (Repatha)
- Mechanism of Action: PCSK9 destroys LDL receptors in the liver; by inhibiting this protein, it allows LDL receptors to do their job and to remove circulating LDL from the blood stream
- Humanized monoclonal antibodies
  - Advantageous in high risk patients (i.e. secondary prevention) who don’t respond to statins alone or to those intolerant to other therapies
  - Both are injections every 2-4 weeks, expensive
  - Side effects: Injection site reactions, fatigue
- Low to no muscle toxicity compared to statins

Triglycerides

- Fibrates
  - Mechanism of Action: Activates lipoprotein lipase and reduces apoprotein C-3 production which leads to breaking down of fat/triglyceride rich particles
  - Fenofibrate (TriCor, Lofibra, Triglide), gemfibrozil (Lopid)
  - GI Side effects
  - Gemfibrozil tends to have a higher risk of rhabdomyolysis than fenofibrate
  - Use fenofibrate if possible when patient is already receiving a statin
  - First line agent if the patient is at lower CV risk and has elevated TGs