Cardiac Pharmacology

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Outline

- Diuretics (VM)
- Inotropic Agents (JL)
- Anti-Hypertensives (JL)
- Anti-Arrhythmics (VM)
- Pulmonary vasodilators (JL)
- Anticoagulation (JL)
- Sedation/Pain (VM)
- Gastrointestinal (VM)

Diuretics

- FUROSEMIDE
- TORSEMIDE
- HYDROCHLOROTHIAZIDE
- SPIRONOLACTONE

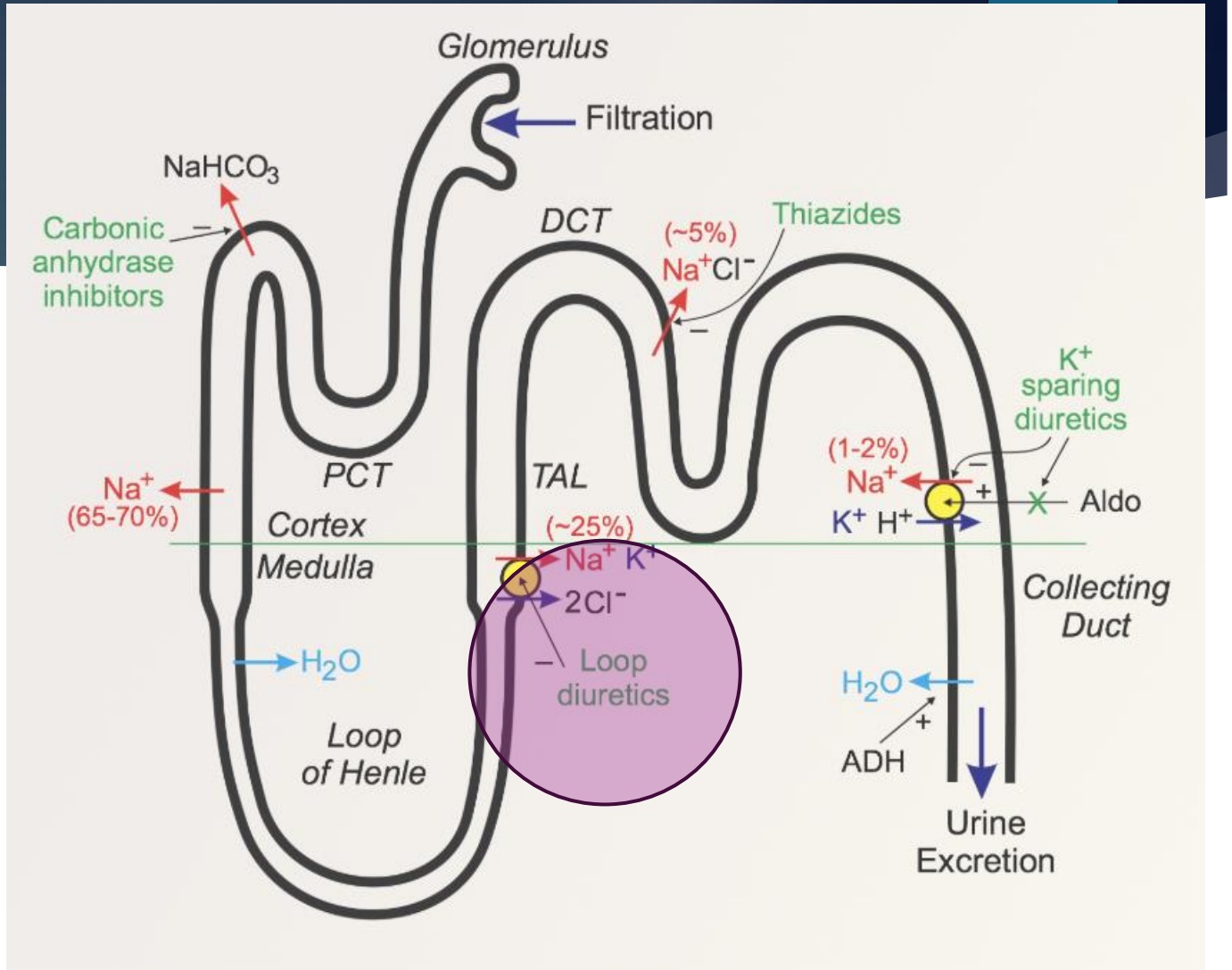
Case

- 11 year old girl with acute on chronic heart failure related to severe MR.
- Orthopnea, emesis, 5.2 kg weight gain since last
- Afebrile, pitting edema, hyponatremia

- **Approach to decongestion? What's your diuretic plan?**

Loop Diuretics - Pharmacology

- Inhibit the Na/K/Cl co-transporter in the thick ascending limb
- Leads to increase in distal tubular Na concentration → increased water reabsorption
- Powerful diuretics as the TAL reabsorbs ~25% of the sodium



https://cvpharmacology.com/diuretic/diuretics

Furosemide

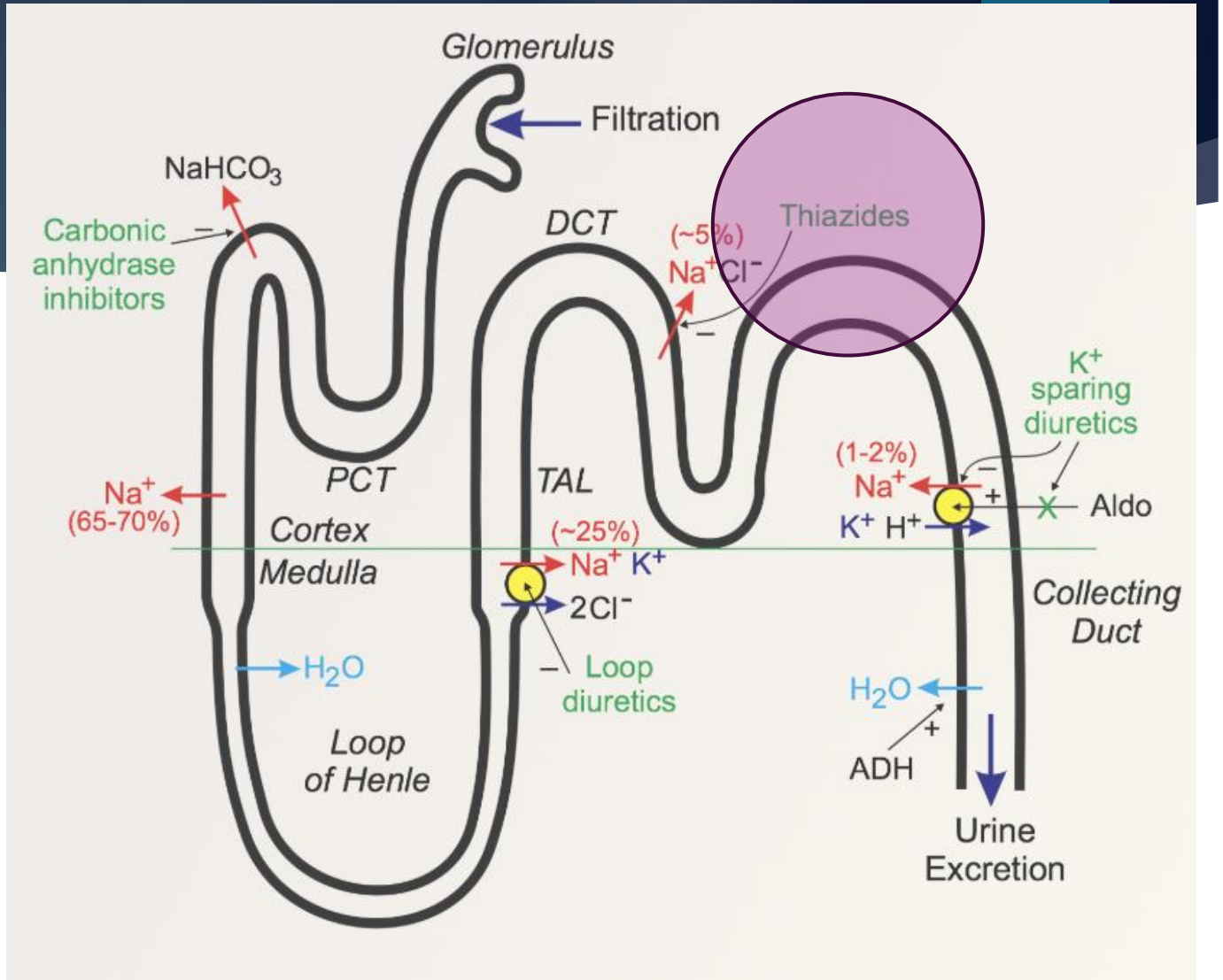
When to use	• Edema • Effusions
Standard Dosing	• PO: 1 - 2 mg/kg/dose Q6 to 24hrs; max 6 mg/kg/dose (acute) or day (chronic) • Intermittent IV: 0.5 - 2mg/kg/dose Q6 to 12hrs, max 6 mg/kg/dose • Continuous IV: 0.05 - 0.4mg/kg/hr, up to usual adult dosing range 10 - 40mg/hr
Side Effects	• Electrolyte loss: hypokalemia, hypomagnesemia, & hypocalcemia • Tinnitus up to hearing loss • Acute kidney injury due to fluid loss • Hypersensitivity reactions
Considerations	• Monitor and replete electrolytes • Tolerance

Torsemide

When to use	• Edema • Effusions
Standard Dosing	• Adult: Initial: 10 to 20 mg once daily; double the dose as needed (rather than administer the same dose more frequently) until diuresis occurs • Max effective single dose: 50 to 100 mg; max recommended total daily dose: 200 mg in 2 divided doses to minimize risk of ototoxicity
Side Effects	• Electrolyte loss: hypokalemia, hypomagnesemia, & hypocalcemia • Tinnitus up to hearing loss • Acute kidney injury due to fluid loss (less risk of AKI as compared with furosemide) • Hypersensitivity reactions
Considerations	• Approximate oral dose equivalency (normal renal function): Torsemide 10 to 20 mg = bumetanide 1 mg = furosemide 40 mg • Better absorption than furosemide with decreased cardiac output

Thiazides

- Inhibit the Na/Cl transporter in the distal tubule
- Less effective than loop diuretics as the distal tubule only reabsorbs ~5% of Na



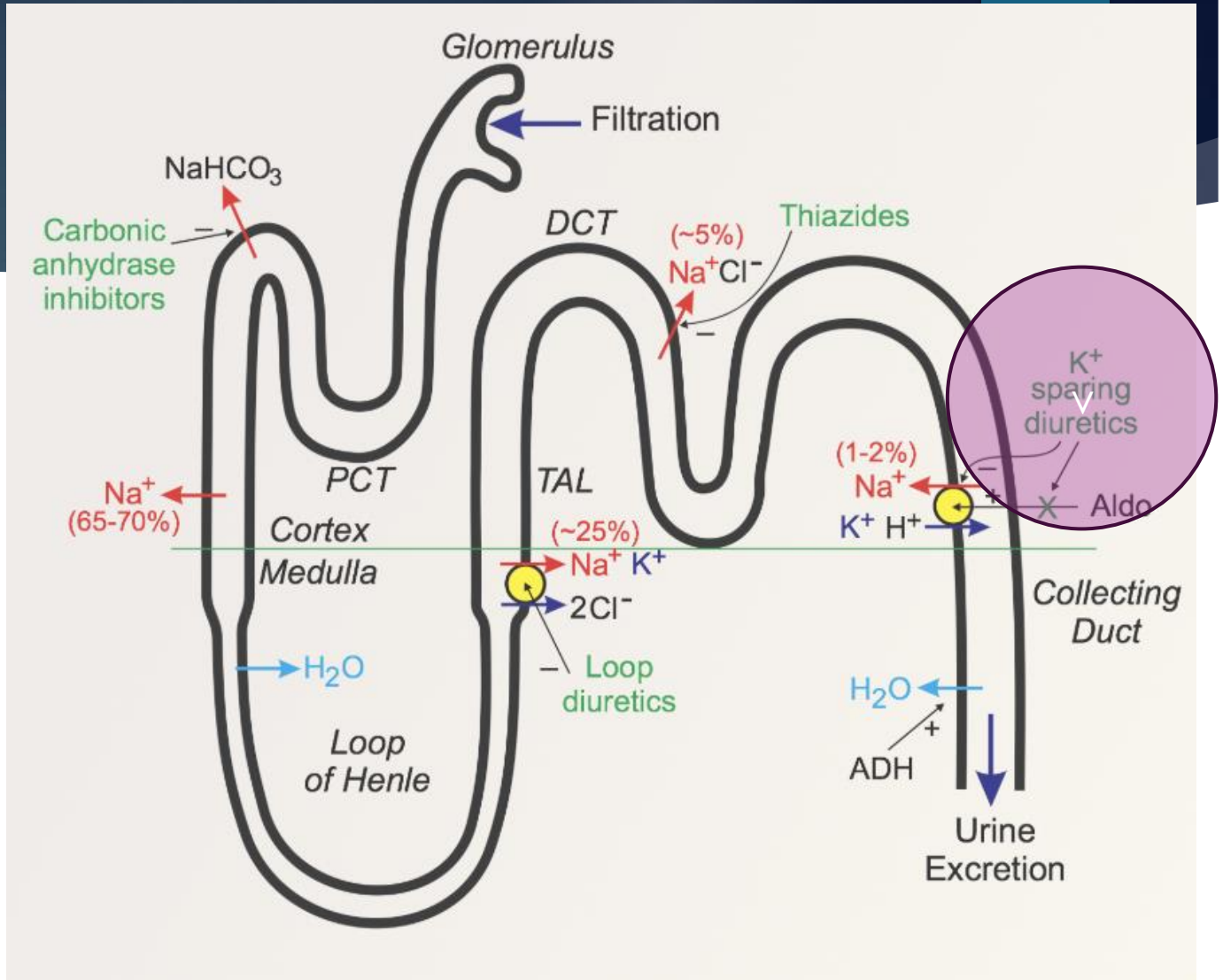
https://cvpharmacology.com/diuretic/diuretics

Hydrochlorothiazide

When to use	• Edema • Effusions
Standard Dosing (PO)	• Infants & Children < 2 yrs: 0.5-1 mg/kg/dose BID ; max daily dose 37.5mg/day • Children ≥ 2 yrs: 0.5 - 1 mg/kg/dose BID; max daily dose 100 mg/day • Adolescents: 0.5 - 1 mg/kg/dose BID; max daily dose 200 mg/day
Side Effects	• Electrolyte disturbances: hypokalemia, hypomagnesemia, hypercalcemia, & hyponatremia • Hyperuricemia and precipitate gout or gouty arthritis if susceptible • Acute transient myopia & acute angle-closure glaucoma
Considerations	• Don't use in patients with severe kidney disease or liver disease

K+ Sparing Diuretics

- Inhibit the actions of aldosterone at the distal end of the distal tubule
- More water and Na to pass into collecting duct and excreted in urine
- Less potassium and hydrogen are exchanged for sodium



https://cvpharmacology.com/diuretic/diuretics

Spironolactone

When to use	• Edema • Heart failure
Standard Dosing (PO)	• Initial: 1 to 3 mg/kg/day divided Q6 to 24 hours; titrate as needed • Max daily dose range: 4 to 6 mg/kg/day in divided doses Q6 to 12 hours not to exceed 400 mg/day
Side Effects	• Can cause hyperkalemia • Gynecomastia
General Information	• Monitor electrolytes and replace or make adjustments to dose as needed

Inotropic Agents

- ADRENALINE
- NORADRENALINE
- DOPAMINE
- DOBUTAMINE
- PHENYLEPHRINE
- MILRINONE

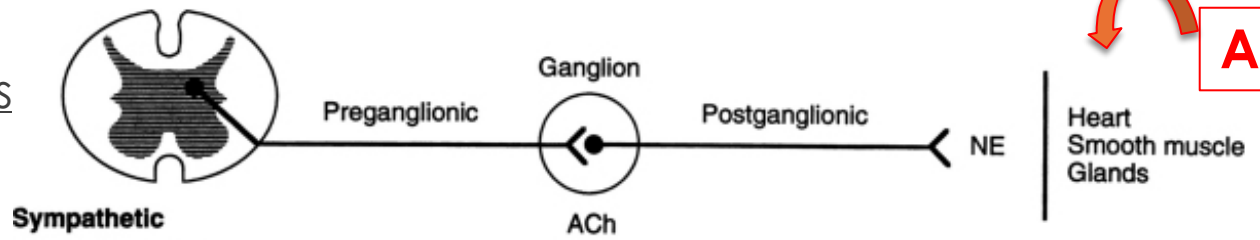
Case

- 6 year old boy s/p VSD closure with acute postoperative LV systolic dysfunction.
- Extubated, tachycardia, SVC saturation 52%, +1.2 L since OR

- **Benefit from inotropic support? If so, which agent?**

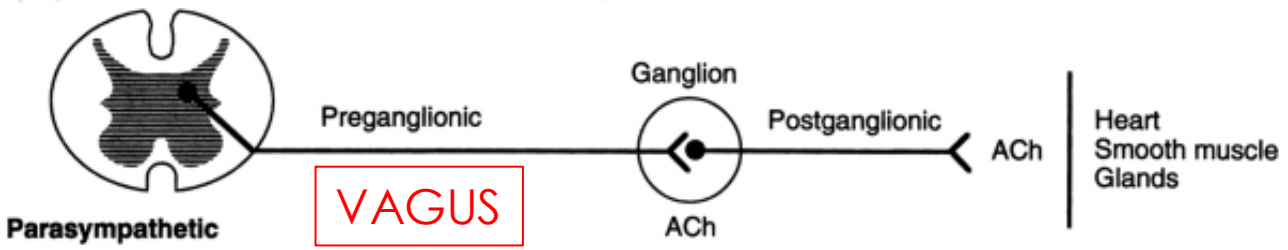
Autonomic Nervous System

- Sympathetic inputs



Adrenoreceptors (α_1+ β_1 + β_2)

- Parasympathetic inputs



Neurotransmitters:

- Acetylcholine (S+P)
- Norepinephrine (S)
- Epinephrine (S)
  -only from adrenals

Sympathetic Adrenoreceptors

- Classic ***Myocardial*** Receptor Subtypes:
  - **β_1** : majority of myocardial receptors (SA/AV nodes, myocytes)
    - Activation ▲ **inotropy and chronotropy**
  - **α_1**: 13-15% myocardial, vascular smooth muscle
    - Activation ▲ **inotropy**
  - **β_2** : < 5% myocardial, majority vascular smooth muscle, coronary circulation

Sympathetic Adrenoreceptors

- Classic ***Vasculature*** Receptor Subtypes:
  - α_1: Activation ▲ *vasoconstriction*
  - α_2 : complex negative feedback
    - Postganglionic stimulation→vasoconstriction
    - Central stimulation→decreased NE release from preganglionic nerve terminals…decreased sympathetic outflow (ie. precedex + clonidine)
  - β_2 : Activation ▲ *vasodilation*

Inotropic Agents

Vasoactive medication receptor activity and clinical effects

Drug	Receptor activity				Predominant clinical effects
	Alpha-1	Beta-1	Beta-2	Dopaminergic	
Phenylephrine	+++	0	0	0	SVR ↑ ↑, CO ↔/↑
Norepinephrine	+++	++	0	0	SVR ↑ ↑, CO ↔/↑
Epinephrine	+++	+++	++	0	CO ↑ ↑, SVR ↓ (low dose) SVR/↑ (higher dose)
Dopamine (mcg/kg/min)*					
0.5 to 2.	0	+	0	++	CO
5. to 10.	+	++	0	++	CO ↑, SVR ↑
10. to 20.	++	++	0	++	SVR ↑ ↑
Dobutamine	0/+	+++	++	0	CO ↑, SVR ↓
Isoproterenol	0	+++	+++	0	CO ↑, SVR ↓

+++: Very strong effect; ++: Moderate effect; +: Weak effect; 0: No effect.
* Doses between 2. and 5. mcg/kg/min have variable effects.

Adrenaline

When to use	• Hypotension – monitor BP frequently especially if titrating a continuous infusion • Ventricular dysfunction
Standard Dosing	• 0.01-0.1 mcg/kg/min but can be seen at higher doses in extreme cardiogenic shock • 0.02-0.04 mcg/kg/min is typical dose for ventricular systolic dysfunction • Code dose: 0.01 mg/kg (0.1 mg/mL concentration; max dose 1mg) IV push
Side Effects	• Hypertension • Tachycardia • Arrhythmias
Considerations	• Central IV access • Double check medication/dose - high risk for error • May need to decrease dose if the listed side effects are causing more harm than good

Noradrenaline

When to use	• Hypotension • Low SVR state/vasoplegia/septic shock
Standard Dosing	• 0.01-0.1 mcg/kg/min but can be seen at higher doses in extreme cardiogenic shock • Not used during codes
Side Effects	• Hypertension • Tachycardia • Arrhythmias
Considerations	• Central IV access • Double check medication/dose - high risk for error • Pure alpha-agonistMay need to decrease dose if the listed side effects are causing more harm than good

Dopamine

When to use	• Hypotension or shock that persists after adequate volume resuscitation
Standard Dosing	• 2-20 mcg/kg/min; titrate gradually by 5-10 mcg/kg/min until desired response is achieved
Side Effects	• Chest pain, ectopic beats, hypertension, tachycardia
Considerations	• Frequently used in decompensated heart failure and cardiogenic shock (with renal insufficiency)

Dobutamine

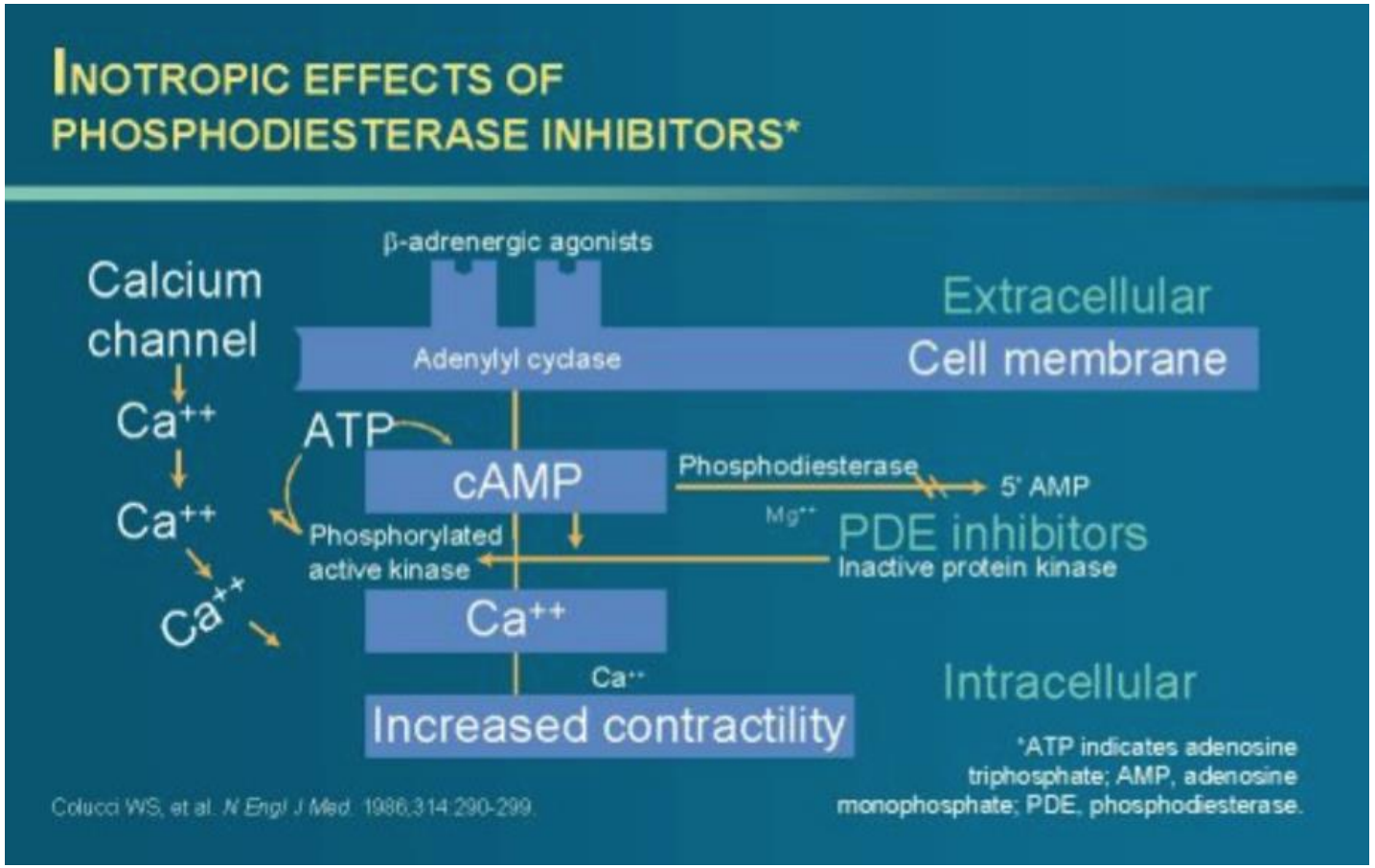
When to use	• Short-term management of cardiac decompensation due to decreased contractility
Standard Dosing	• 0.5-1 mcg/kg/min; titrate gradually every few minutes to achieve desired response
Side Effects	• Chest pain, tachycardia, hypertension, ventricular arrhythmias
Considerations	• Not commonly used in children in USA

Phenylephrine

When to use	• Profound hypotension or during hypercyanotic spells to increase pulmonary blood flow
Standard Dosing	• IV bolus- 5-20 mcg/kg/dose every 10-15 minutes as needed • Continuous infusion- 0.1-0.5 mcg/kg/min; titrate to desired response
Side Effects	• Hypertensive crisis, pulmonary edema, ischemia
Considerations	• Not commonly used outside of the operating theatre for children in the USA

Milrinone: Phosphodiesterase Inhibitor

- Alternative non-catecholaminergic agent
- Augments ***CONTRACTILITY*** via cardiomyocyte calcium processing pathway
- Also modulates systemic vascular resistance by inducing ***VASODILATION*** of vascular smooth muscle



Milrinone

When to use	• Decreased LV function • RV support • Low cardiac output after bypass surgery
Standard Dosing	• Normal starting dose 0.25mcg/kg/min • Range : 0.125mcg/kg/min – 1mcg/kg/min
Side Effects	• Hypotension when initating and changing the dose (long half-life for neonates/infants; renal insufficiency impacts clearance)
Considerations	• Half life is 4-6 hours • Onset of action is 5-15 minutes • Monitor blood pressure closely

Also consider these "inotropes"…

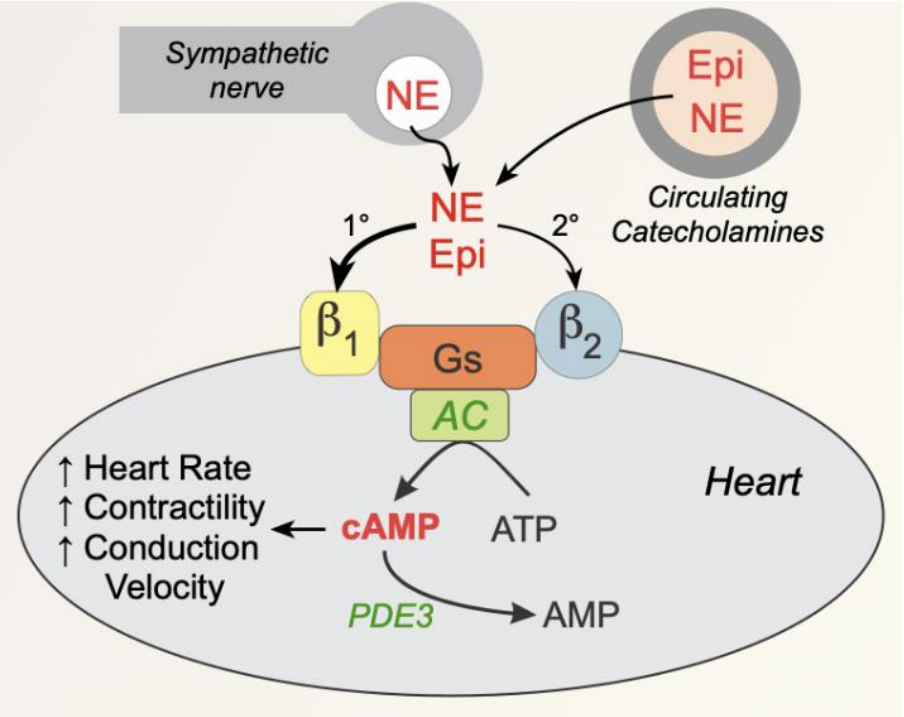
- ***Levosimendan***
  - Enhances myofilament sensitivity to calcium
  - Ino and vaso-dilator (+ATP-sensitive K+ channels)
  - "Compassionate" off-label use at TCH for decompensated heart failure
  - PK/PD in children
- ***Calcium chloride***
  - Bolus (20mg/kg) +/- infusion
  - Conflicting (little to none) data
- ***Hydrocortisone***
  - 1-2mg/kg load, then 0.5-1mg/kg Q6-8 hours (max 6 mg/kg/day for neonates/infants, unless true adrenal insufficiency)

Anti-Hypertensives

- METOPROLOL
- CAPTOPRIL
- LOSARTAN
- NITROPRUSSIDE
- NITROGLYCERINE

Beta-Blocker - Pharmacology

- Beta-blockers bind to beta-adrenoreceptors and block Epi and NorEpi from binding
- Beta receptors are coupled to Gs proteins, which activate adenylyl cyclase to form cAMP → increased intracellular Ca → increased contractility
- Beta blockers → decreased HR, contractility, conduction velocity



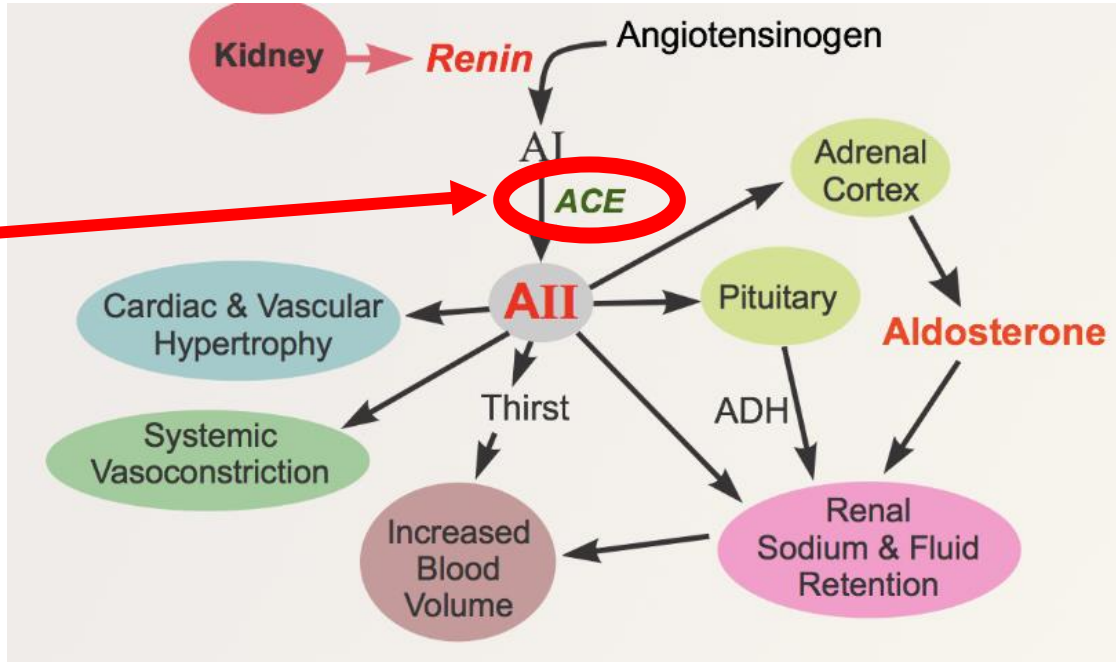
https://cvpharmacology.com/cardioinhibitory/beta-blockers

Metoprolol – Clinical Applications

When to use	• Hypertension • Heart Failure/MI
Standard Dosing (PO)	• Initial: 0.5 to 1 mg/kg/dose (max: 25 mg/dose) BID; adjust dose based on response; max daily dose: 6 mg/kg/day (not to exceed 200 mg/day)
Side Effects	• Bradycardia, hypotension, 1st degree HB (> 10% of the time), reduced exercise capacity • Hypoglycemia • Fatigue, sleep disturbances, insomnia
Considerations	• Don't give in incidence of severe sinus bradycardia, significant 1st degree HB (PR ≥ 0.24sec) • Should be gradually tapered off to avoid acute tachycardia, hypertension, &/or ischemia • Bronchospasm (selective beta-blockers like metoprolol have lower risk than non-cardioselective beta-blockers like propranolol, nadolol, timolol, carvedilol)

ACE Inhibitor - Pharmacology

- Angiotensin II is a vasoconstrictor that binds to AT1 receptors on smooth muscle
- ACEi cause vasodilation by inhibiting formation of angiotensin II
- ACE also leads to the breakdown of bradykinin (vasodilator); ACEi lead to increased bradykinin levels



https://cvpharmacology.com/vasodilator/ace

Captopril - Clinical Applications

When to use	• Hypertension/after-load reduction • Heart Failure/MI • Diabetic nephropathy
Standard Dosing (PO)	• Start slow and increase based on clinical effect • Infants: Initial: 0.05 to 0.2 mg/kg/dose Q6 to 24hrs; max daily dose: 6 mg/kg/day • Children: Initial: 0.3 to 0.5 mg/kg/dose Q8hrs; max daily dose: 6 mg/kg/day • Adolescents: Initial: 12.5 to 25 mg/dose Q8-12hrs; increase by 25 mg/dose weekly; Usual dose 150 mg/day
Side Effects	• Acute kidney injury • Dry cough (due to bradykinin) • Hyperkalemia • Skin rash • Rare, but serious: Angioedema or bone marrow suppression
Considerations	• Hypotension is most often observed in volume-depleted patients • Use with extreme caution in patients with aortic stenosis • Contraindicated in pregnancy

ARB - Pharmacology

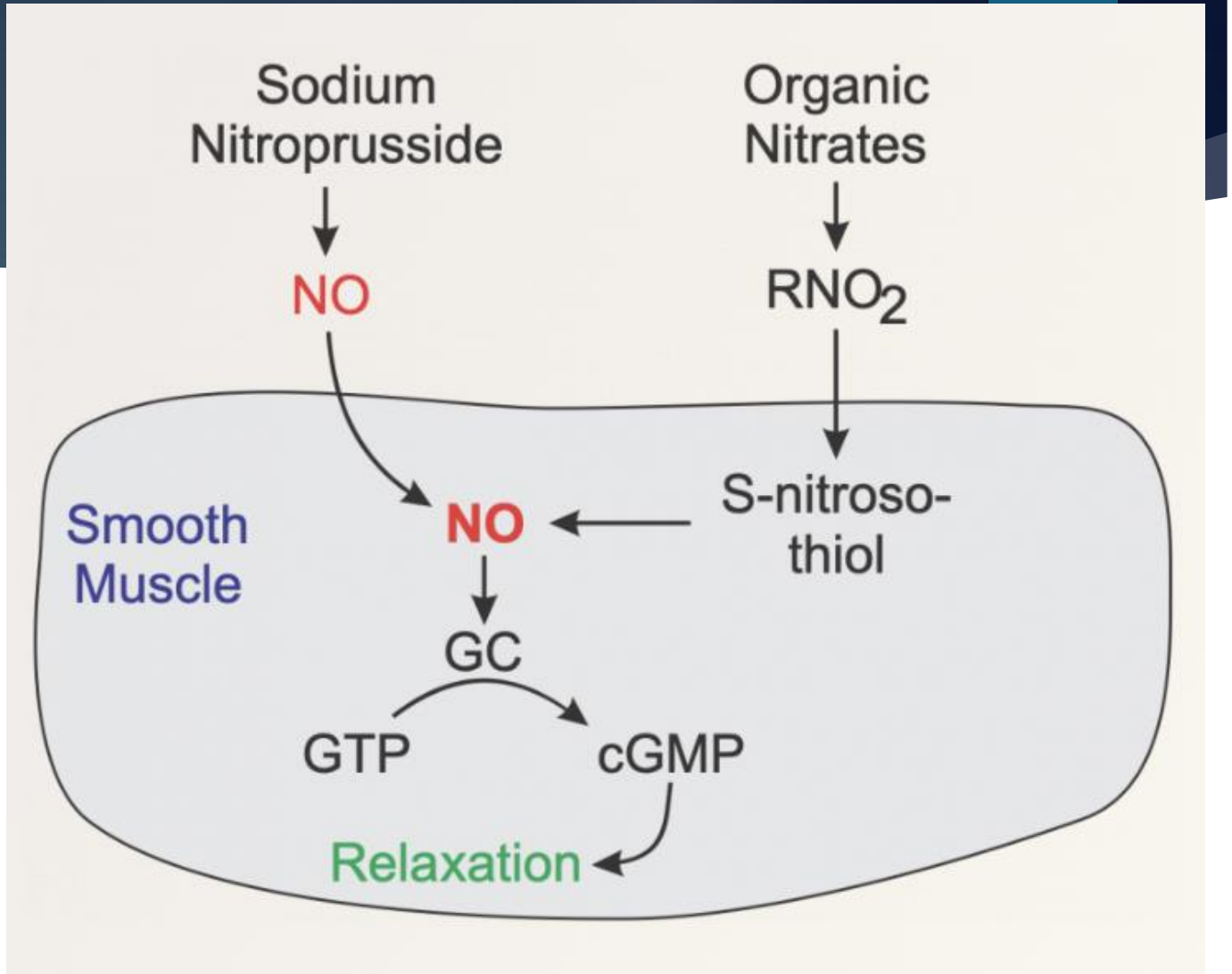
- Angiotensin II is a vasoconstrictor that binds to AT1 receptors on smooth muscle
- ARBs block AT1 receptors
- Receptors are coupled to Gq protein pathway that stimulates smooth muscle contraction
- Do not cause increase in bradykinin

Losartan – Clinical Applications

When to use	• Hypertension/after-load reduction • Heart Failure/MI
Standard Dosing (PO)	• Children >6 y.o.: Initial: 0.7mg/kg daily PO; max initial dose: 50 mg/day • >16 y.o.: Initial: 25-50 mg/day; increase doubling dose every 2-4 weeks, up to 100mg/day
Side Effects	• Acute kidney injury/UTI • Edema • Skin rash
Considerations	• Hypotension is most often observed in volume-depleted patients • Use with extreme caution in patients with aortic stenosis • Contraindicated in pregnancy

Nitrodilators - Pharmacology

- NO is produced by many cells in the body, primary vascular endothelial cells
- Several functions: vasodilator, anti-thrombotic, and anti-inflammatory
- NO activates guanylyl cyclase to form cGMP → inhibition of Ca entry into cells → smooth muscle relaxation



https://cvpharmacology.com/vasodilator/nitro

Nitroprusside – Clinical Applications

When to use	• Hypertension • Heart failure
Standard Dosing	• Starting dose: 0.3-0.5 mcg/kg/min • Titrate by: 0.3-0.5 mcg/kg/min q 5-15min • Max dose: 3-5 mcg/kg/min
Side Effects	• Headache and cutaneous flushing • Postural hypotension and reflex tachycardia • Cyanide toxicity (consider coadministration of sodium thiosulfate to help convert cyanide to less toxic thiocyanate)
Considerations	• Keep infusion syringe/bag away from light (wrap in aluminum foil or dark bag) - can cause discoloration and decomposition

Nitroglycerin

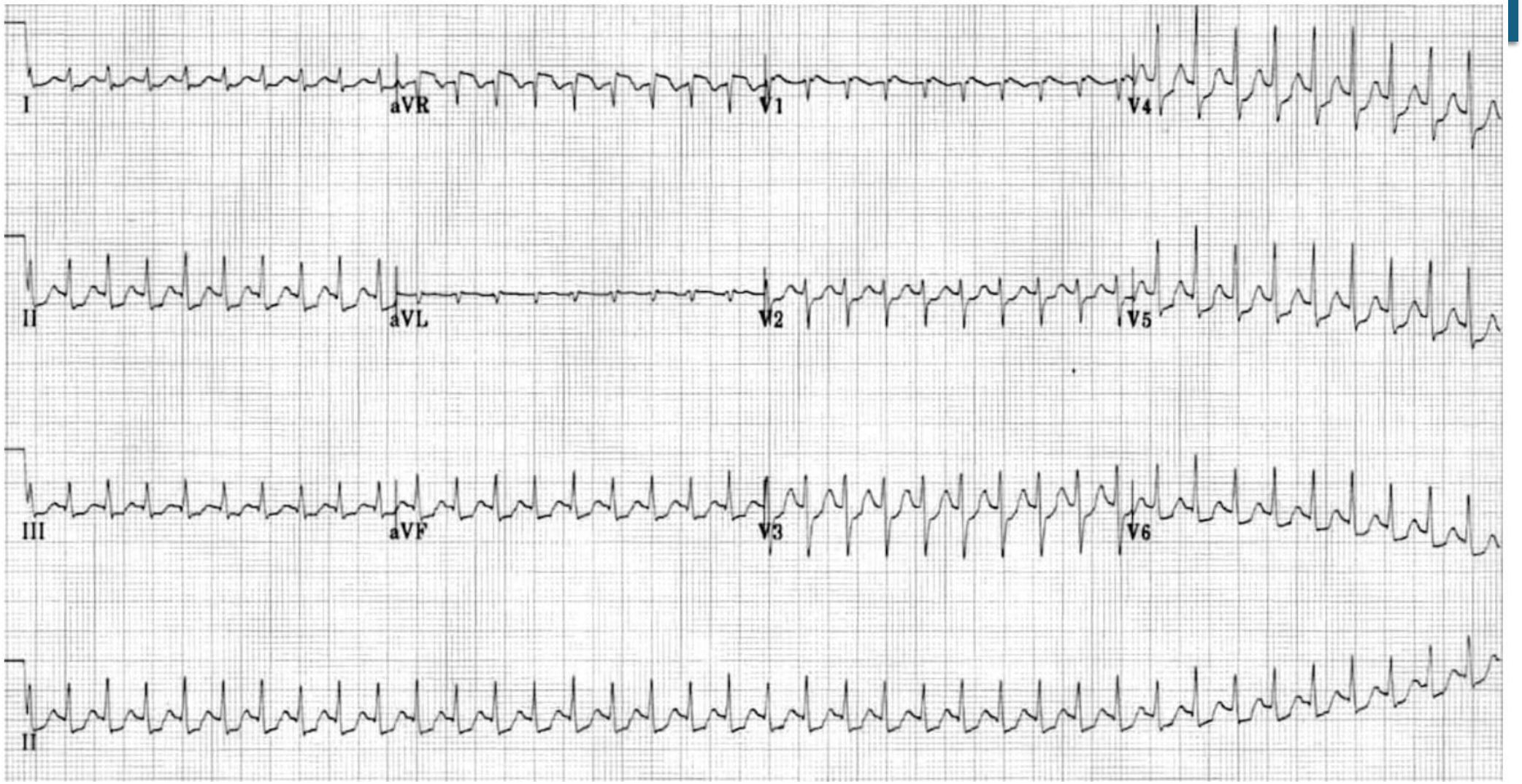
When to use	• Myocardial ischemia d/t poor coronary perfusion
Standard Dosing	• Starting dose: 0.25-0.5 mcg/kg/min • Range: 1-5 mcg/kg/min • Titrate every 15-20 minutes by 0.5-1mcg/kg/min
Side Effects	• Acute hypotension, EKG changes, tachycardia • Headache, dizziness, blurred vision
Considerations	• Onset and half life are immediate • Caution administration with other antihypertensives • Often utilized in OR but rarely used in pediatric post op recovery unless surgery was done on coronaries and there is remaining concern for stenosis/injury

Anti-Arrhythmics

- ADENOSINE
- DIGOXIN
- AMIODARONE
- LIDOCAINE

Case

- 9 year old boy with no past medical history presents with complaint of: ”I feel like my heart is racing”
- Afebrile, hydrated, review of systems otherwise negative
- EKG obtained



https://litfl.com/supraventricular-tachycardia-svt-ecg-library/

Adenosine - Pharmacology

- Naturally occurring purine nucleoside from ATP
- Adenosine binds to type 1 receptors, coupled with G proteins
- Activation leads to the opening of K^+ channels, hyperpolarizing the cell
- In the SA node, adenosine inhibits the pacemaker current and decreases the spontaneous firing rate
- Also inhibits L-type Ca^{+2} channels decreasing conduction velocity at the AV node

Adenosine – Clinical Applications

When to use	• SVT (AV reentry) when vagal maneuvers have failed • Diagnose atrial tachyarrhythmias by slowing HR
Standard Dosing	• **Initial dose: 0.1 mg/kg for pediatrics or 6 mg for adults** • **Repeat dose: 0.2 mg/kg for pediatrics or 12 mg for adults**
Side Effects	• Skin flushing, lightheadedness, nausea, sweating • Asystole
Considerations	• Very short half-life, rapid intracellular metabolism • Administer via RAPID IV PUSH followed immediately with a flush

Digoxin - Pharmacology

- Digitalis compounds are potent inhibitors of cellular Na^+/K^+-ATPase, which plays a role in membrane potential generation
- Digoxin increases intracellular Na+ → increased intracellular Ca+2 → more Ca+2 to bind Troponin-C → increase in contractility
- Increase vagal activity to heart, which decreases HR and conduction through AV node
- Half-life ~40 hours

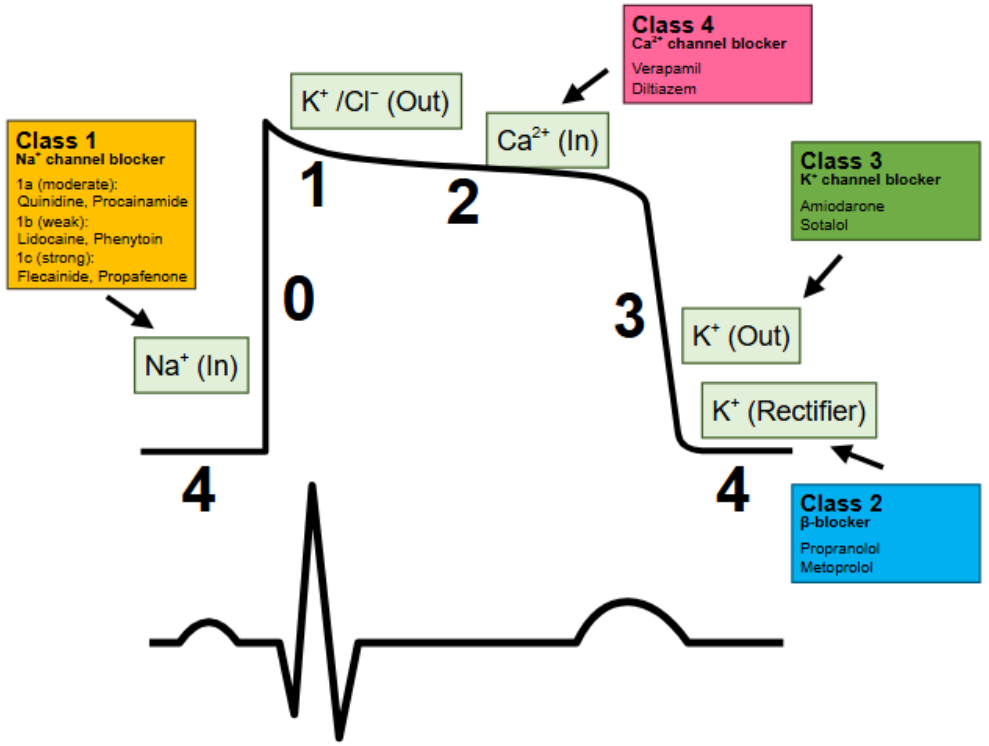
https://www.britannica.com/plant/foxglove

Digoxin – Clinical Applications

What is it used to treat?	• Slow ventricular rate in SVT • Atrial fibrillation
Standard Dosing	• Loading dose: 10-12 mcg/kg/dose IV q8h x3 doses OR 13-17mcg/kg/dose PO q8h x3 doses • Maintenance Dose: 5mcg/kg/dose BID PO
Side Effects	• Nausea/vomiting • Visual disturbances (“halos,” yellow or blurred vision) • Lethargy • Arrhythmias (all types of AV block, PVCs)
Considerations	• Never re-dose! • Monitor & correct electrolytes (HypoK+) • Contraindications: WPW, AV block, hypokalemia • Significant drug-drug interactions (quinidine)

Amiodarone - Pharmacology

- Class III anti-arrhythmic drug
- Primarily inhibits potassium currents that repolarize the heart during phase 3 of the cardiac action potential
- K+ channel blocking results in prolonged effective refractory period
- Leads to reduced myocyte excitability
- Prevents re-entry and ectopic foci
- Decreases sinus node automaticity, reduces AV node conduction velocity



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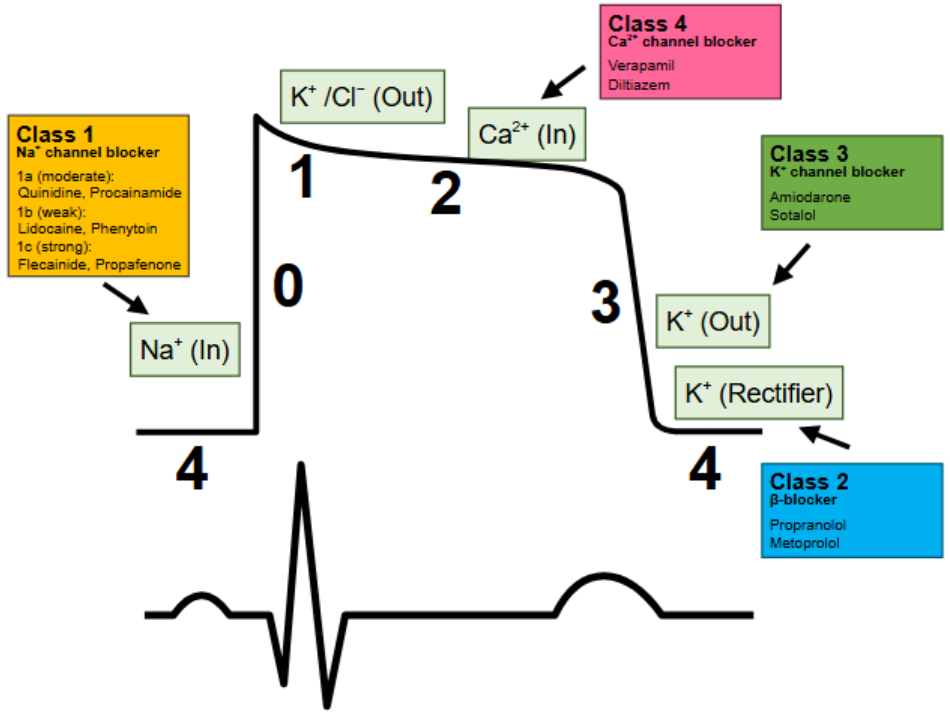
Amiodarone – Clinical Applications

When to use	• Life-threatening ventricular arrhythmias (VT, VF); also can be used for SVT
Standard Dosing	• IV (infusion): Loading dose: 5 mg/kg over 60 minutes; 10-20 mg/kg/day continuous infusion; • Oral: Loading dose: 10-20 mg/kg/day divided BID, then reduced to 5-7 mg/kg/d daily after 2 weeks
Side Effects	• Bradycardia, hypotension, hepatotoxicity, proarrhythmic effects, pulmonary toxicity, thyroid effects, prolonged QT
Monitoring/ considerations	• Obtain baseline thyroid studies, liver function tests, pulmonary function tests and then every 3-6 months for long-term use • Many drug-drug interactions

Lidocaine - Pharmacology

- Class I anti-arrhythmic
- Binds and blocks fast Na+ channels for rapid depolarization
- Decreases the slope of phase 0 → decrease in amplitude of the action potential → decrease in conduction velocity in non-nodal tissue
- Weakest of the class I (Na channel blockers)



https://www.ncbi.nlm.nih.gov/books/NBK557434/figure/article-20598.image.f2/

Lidocaine- Clinical Applications

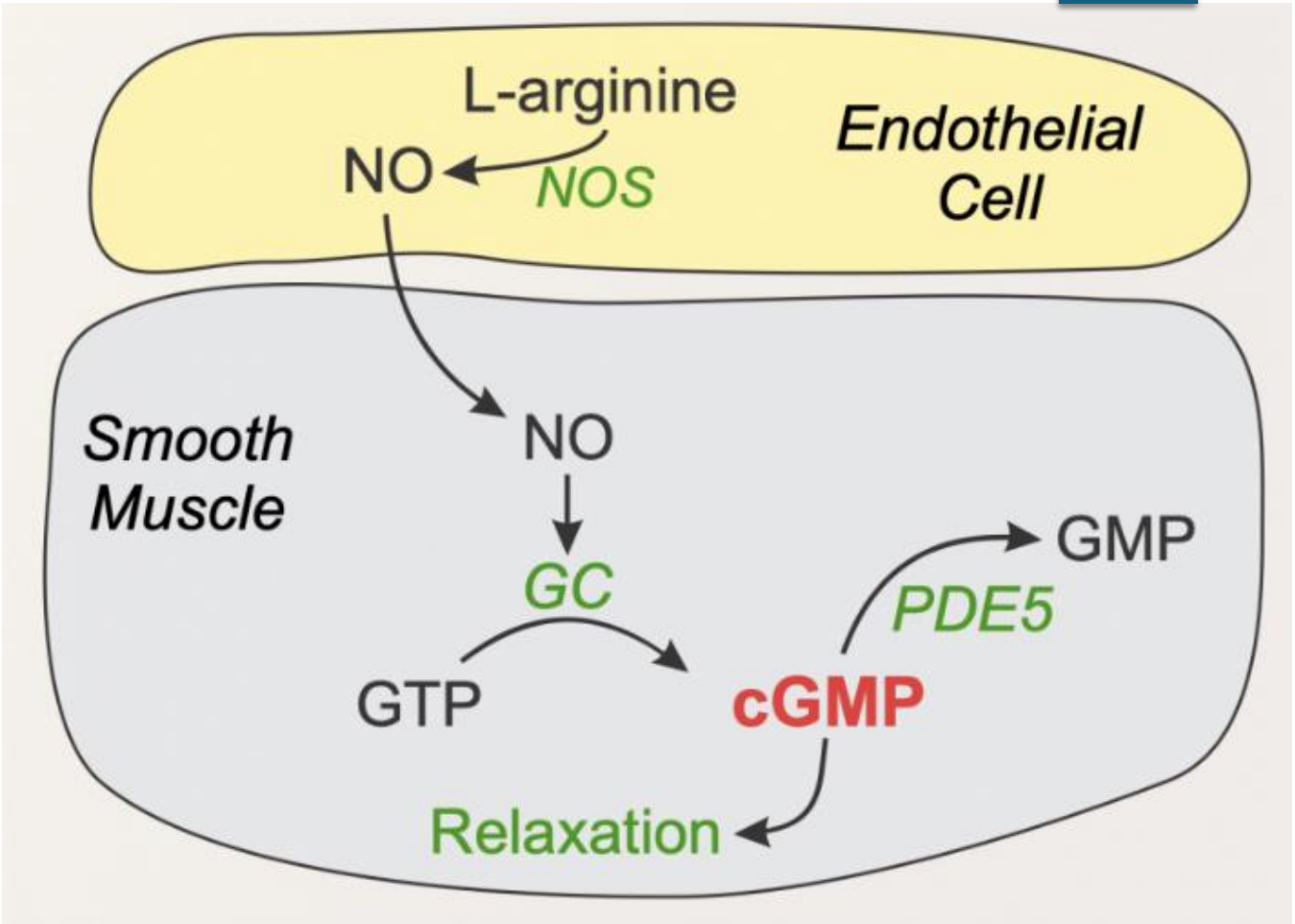
When to use	• Treatment of ventricular arrhythmias (VF, pulseless VT)
Standard Dosing	• 1 mg/kg/dose IV bolus • 20-50 mcg/kg/min continuous infusion IV
Side Effects	• Bradycardia, circulatory shock, hypotension, respiratory depression • Vomiting, nausea
Considerations	• Patients with liver failure increased risk of lidocaine toxicity • Can also be used as a local anesthetic, be mindful of dosing difference

Pulmonary Vasodilators

- SILDENAFIL
- TADALAFIL
- BOSENTAN

PDE-5 Inhibitors

- PDE-5 is an enzyme found in the vascular smooth muscle cells
- PDE5 breaks down cGMP in response to increased intracellular NO
- Inhibiting the action of this enzyme leads to increased cGMP → decreased intracellular Ca → smooth muscle relaxation



https://cvpharmacology.com/vasodilator/pdei

Sildenafil

When to use	• Treats pulmonary arterial hypertension (PAH)

Standard Dosing (PO)	• Infants: Initial: 0.25 mg/kg/dose Q6hrs or 0.5 mg/kg/dose Q8hrs; titrate as needed
	• Children and Adolescents <18 years:
	  • ≤20 kg: 10 mg three times daily.
	  • >20 to 45 kg: 20 mg three times daily.
	  • >45 kg: 20 mg three times daily; titrate as needed

Side Effects	• Flushing, headache • Hypotension • Diarrhea/upset stomach • Vision/hearing changes (vision color changes, blurred vision, photophobia, tinnitus, dizziness) • Priapism
Considerations	• Can be given TID rather than Q8hrs for ease of administration

Tadalafil

When to use	• Treats pulmonary arterial hypertension (PAH)
Standard Dosing (PO)	• Enteral: 1 mg/kg (max 40 mg) daily
Side Effects	• Flushing, headache, nausea, upset stomach • Vision/hearing changes (vision color changes, blurred vision, photophobia, tinnitus, dizziness) • Priapism • Back pain, limb pain, myalgia • Respiratory tract infection
Considerations	• Administered once daily, which helps with compliance

Endothelin Receptor Blocker

- Endothelin-1 (ET-1) is a 21 amino acid peptide that is produced by the vascular endothelium
- ET-1 is a potent vasoconstrictor
- ERBs block ET_A and ET_B receptors → block vasoconstrictor and cardiotonic effects → vasodilation

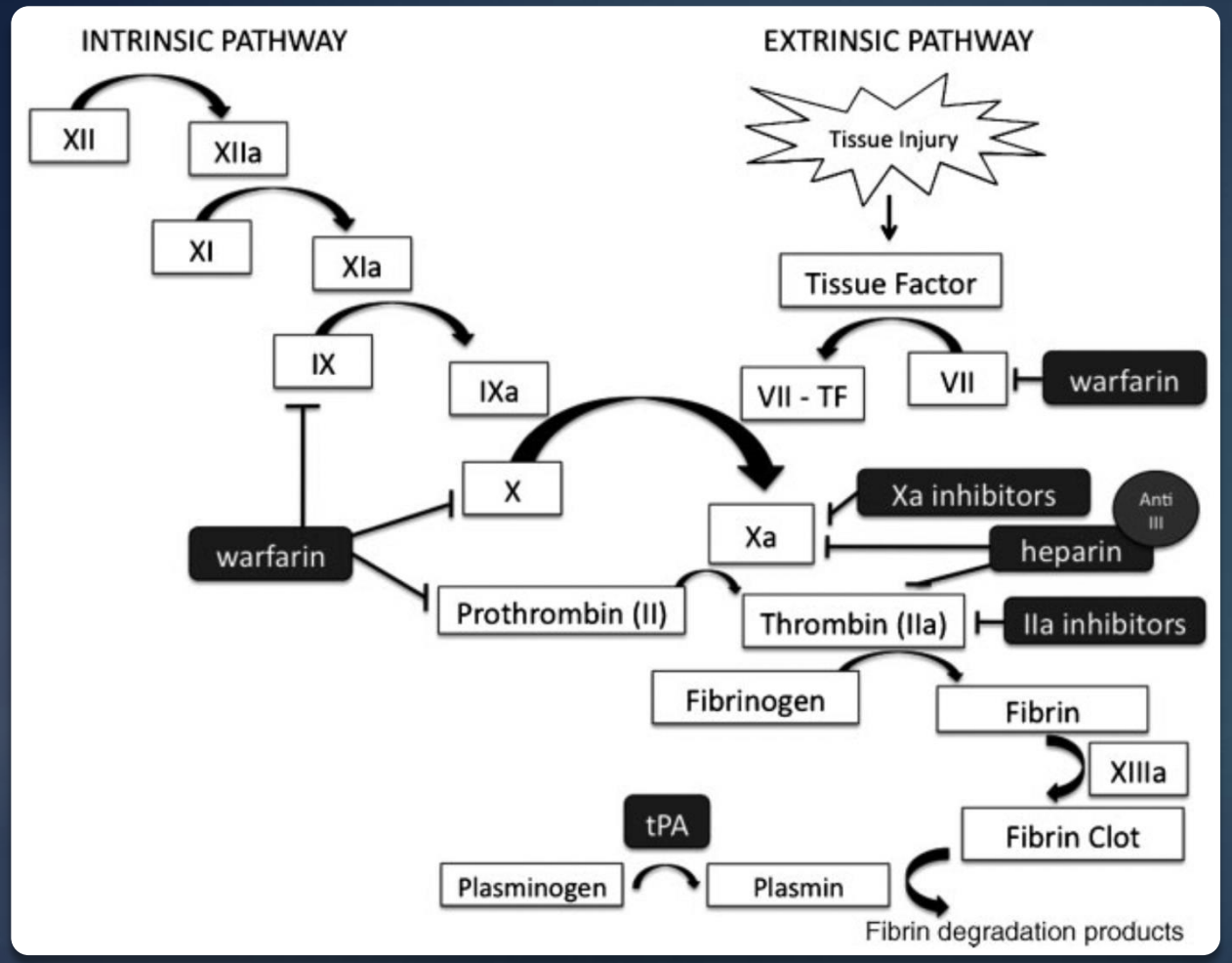
Bosentan

When to use	• Treatment of pulmonary arterial hypertension (PAH) in patients with idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR)
Standard Dosing (PO)	• Initial: 1mg/kg BID (max: 62.5 mg/dose) and continue for 3-7 days • Evaluate LFT's prior to titrating to target dose of 2 mg/kg BID (max: 125 mg/dose)
Side Effects	• Edema • Increased LFTs • Headache • Respiratory tract infection
Considerations	• Teratogenic – wear gloves when handling; pregnancy test for all females of child-bearing age prior to initiation and then monthly thereafter and 1 month after discontinuation. • Hepatotoxicity – monitor liver function tests (LFTs) prior to initiation, 1 week after initiating therapy or changing dose, and monthly

Anticoagulation

- HEPARIN
- ENOXAPARIN
- WARFARIN
- ASPIRIN
- CLOPIDOGREL

Coagulation Cascade



https://www.researchgate.net/figure/Elements-of-the-coagulation-cascade-with-anticoagulant-and-thrombolytic-medication_fig1_49729901

Heparin

What is it used to treat?	• Prevention of blood clot formation on artificial valves • Bridge to long-term anti-coagulation
Standard Dosing	• Starting dose: 20-28 units/kg/hr • Increase by 10-20% for goal coagulation results (PTT or Anti-X A)
Side Effects	• Bleeding either internal or external – think often about risk for stroke
Considerations	• Neuro checks! • Check coagulation labs 4 hours after a change and daily • No: rectal temps or hard bristle toothbrushes • Be cautious with: placing or removing IV lines, placing new feeding tubes or foleys

Enoxaparin

What is it used to treat?	• Treatment of arterial or venous thromboembolism, or mechanical valve prophylaxis • Prophylaxis in high-risk patients (history of central line-related thrombosis, post cardiac surgery, or pulmonary hypertension) • Venous Thromboembolism (VTE) prophylaxis
Standard Dosing (Sub-Q)	• Dosing titrated to targeted levels using anti-Xa levels • Treatment of thrombus: 1 mg/kg Q12hrs • Prophylaxis in high risk patients: 0.75 - 1 mg/kg Q12hrs
Side Effects	• Hemorrhage, Anemia • Heparin-induced thrombocytopenia (HIT) • Increased LFTs
Considerations	• Complete baseline lab work within 48 hours before starting; check CBC 5-7 days after initiation to ensure platelet count has not fallen • Draw anti-Xa level 4 hours after the 2nd or 3rd dose after initiation or dose change, then weekly if admitted, and monthly after discharge • Will need to hold at least 24 hours prior to surgery and/or transition to IV heparin

Warfarin

When to use	• Prophylaxis and treatment of thrombosis and thromboembolism • Prevent clot formation with mechanical valves
Standard Dosing	• Dose based on INR levels (therapeutic target 2-3; prophylaxis target 1.5-1.9); Draw daily INR until therapeutic
Side Effects	• Bleeding, hemorrhage, stroke • Decreased bone mineral density • Calciphylaxis
Considerations	• Strict lab monitoring required • Remain on alternate anticoagulation therapy until therapeutic INR achieved • Either avoid foods with high vitamin K, or maintain consistent diet (leafy greens), separate administration from feed/meal by 1 hour before and after

Anti-Platelet Agents

Aspirin:

- Cyclooxygenase-1 (COX-1) inhibitor
- Binds irreversibly to and modifies COX-2
- Blocks thromboxane A2 on platelets irreversibly → prevents platelet aggregation

Clopidogrel

- Irreversible inhibitor of platelet P2Y12 adenosine diphosphate receptor
- Prevents the downstream activation of the glycoprotein IIb/IIIa receptor → reduced platelet aggregation
- Inhibits for the life of the platelet (7-10 days)

Aspirin – Clinical Applications

When to use	• Prevent blood clots due to reducing platelet aggregation • Temporary pain relief
Standard Dosing (PO/PR)	• Antiplatelet effect: 1 to 5 mg/kg/dose once daily
Side Effects	• Dyspepsia, nausea • Minimal at low doses
Considerations	• Should be held ~5 days prior to invasive procedures and surgery • Can be given PR if PO administration is unsuccessful

Clopidogrel – Clinical Applications

When to use	• Prevent blood clots due to decreased platelet aggregation
Standard Dosing (PO)	• Infants & Children ≤ 24 months: 0.2 mg/kg/dose once daily • Children > 2 years and adolescents: 1mg/kg once daily, max 75 mg once daily
Side Effects	• Bleeding • Hypersensitivity reactions • Thrombotic thrombocytopenic purpura (TTP) – very rare
Considerations	• Should be held for ~5 days prior to invasive surgery or procedure

Pain/Sedation

- FENTANYL
- MORPHINE
- KETAMINE
- PROPOFOL
- PARACETAMOL
- IBUPROFEN

Opioids

- Pain modulators that decrease pain
- Opioid receptors (mu, delta, and kappa) are found on A delta and C fiber receptors)
- Activation of the receptors leads to preventing the release of glutamate
- Opioid receptors outside of the CNS is what leads to side effects
- **Morphine**: affinity for all 3 receptors, produces analgesic effect by binding mu receptor within the CNS and PNS
  - Inhibition of the nociceptive afferent neurons leads to reduction of nociceptive transmission
- **Fentanyl**: potent synthetic opioid, mu-selective receptor agonist

Fentanyl

When to use	• Post-procedural/operative pain • Intubated patients for <24hrs
Standard Dosing	• Intermittent: 0.5-2 mcg/kg • Continuous: 0.5-2 mcg/kg/hr • Higher doses typically seen with increased exposure/dependence
Side Effects	• Sedation • Respiratory depression • Reversal agent - Naloxone
Considerations	• Intermittent/PRN dose should be utilized for intubated patients • Should only be used in opioid tolerant patients if not intubated

Morphine

When to use	• Post-procedural/operative pain
Standard Dosing	• Pediatrics: 0.05-0.1mg/kg • Adults: 1-3 mg • Can give q 5 minutes until pain appropriately resolved • IV, PO, PR
Side Effects	• Respiratory depression, itching, nausea • Hypotension • CNS depression
Consideration	• Can administer to patients who are not intubated • Reversal agent - Naloxone • Watch for signs of withdrawal after ~5-7 days of continuous infusions; may require slow taper off

Ketamine - Pharmacology

- Nonbarbiturate dissociative anesthetic
- NMDA and glutamate receptor antagonist → raises glutamate levels in the brain
- Partial mu receptor agonist → sedation/comfort
- Metabolized primarily by CYP3A4
- Rapid onset of action with IV form; half-life 2 to 4 hours

Ketamine

When to use	• Acute pain; procedural sedation; induction and maintenance of general anesthesia
Standard Dosing	• Initial dose: 0.5-2 mg/kg • Infusion: 5-20 mcg/kg/min; titrate to effect
Side Effects	• Hypertension, tachycardia, hypertonia, hallucinations • Increased sialorrhea
Considerations	• Helpful anesthetic for patients with hemodynamic compromise • Spare opioids

Propofol - Pharmacology

- Mechanism poorly understood
- Thought to effect GABA mediated chloride channels in the brain
- Decreases dissociation of GABA from the receptor, which augments the inhibitory effects of GABA
- Rapid onset of action, within a minute
- Lipophilic → accumulates in peripheral tissue
- Bi-phasic half-life: initial ~40 minutes, terminal 4 to 7 hours

Propofol

When to use	• Induction and maintenance of general anesthesia; sedation of intubated and mechanically ventilated patients
Standard Dosing	• Sedation loading dose- 0.5-1 mg/kg/dose • Continuous infusion- 1-4 mg/kg/h
Side Effects	• Myocardial suppression, arrhythmias, Propofol-related infusion syndrome (PRIS)
Considerations	• Can cause a serious adverse reaction (PRIS) which manifests as dysrhythmia, widening of QRS complex, heart failure, hypotension and asystole. Risk is dose and duration related

Paracetamol - Pharmacology

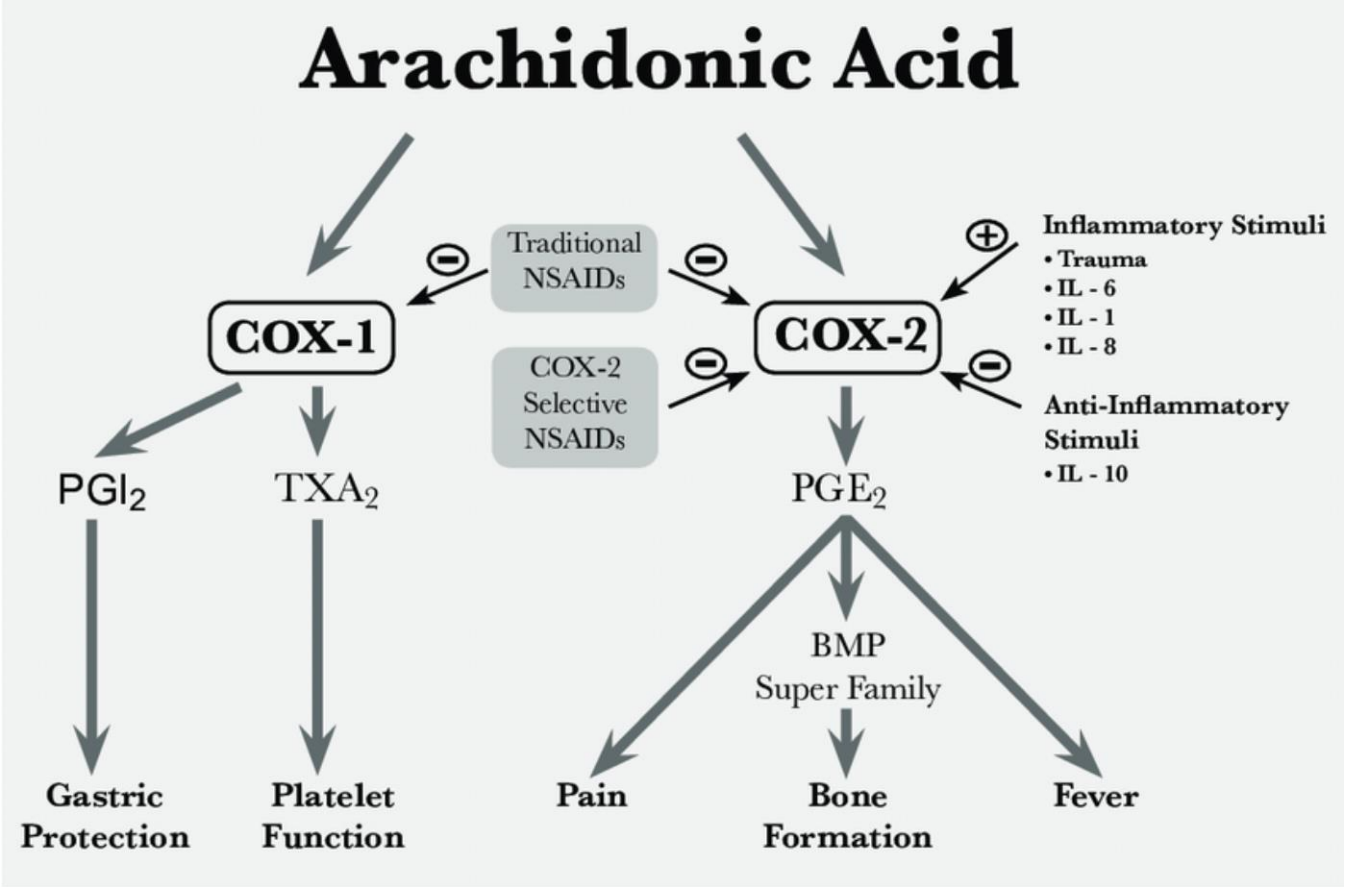
- Paracetamol is the active metabolite of phenacetin
- Mechanism of action not clearly understood
- Centrally active COX-1 and COX-2 inhibitor, but lacks peripheral anti-inflammatory effects
- Equivalent to aspirin as analgesic and anti-pyretic agent
- Peak onset of action within 30-60 minutes

Paracetamol

When to use	• Treat fever and pain
Standard Dosing	• PO: 10 to 15 mg/kg/dose every 4 to 6 hours PRN; do not exceed 5 doses in 24 hours; max daily dose: 75 mg/kg/day not to exceed 4,000 mg/day • IV: 7.5 to 15 mg/kg/dose every 6 hours; maximum daily dose: 60 mg/kg/day; max single dose: 15 mg/kg up to 750 mg; max daily dose: 75 mg/kg/day not to exceed 3,750 mg/day
Side Effects	• Nausea, vomiting, constipation • Liver Failure • Skin reactions, allergic reactions
Considerations	• After surgery, consider giving as soon as tolerating liquids (PO) or IV as adjunct to IV pain medications

NSAIDs

- COX is responsible for converting arachidonic acid into prostaglandin
- NSAIDs block the action of both COX1 and COX2
- COX-1: important role in GI tract, kidneys and platelets regulates blood flow to gastric mucosa and kidneys, platelet aggregation via TXA2 pathway
- COX-2: Induced in response to inflammatory stimuli, produces PGE that activates nociceptors



http://researchgate.net/figure/COX-1-and-COX-2-pathways_fig2_6690503

Ibuprofen

When to use	• Treat fever and pain
Standard Dosing	• PO: 5 to 10 mg/kg/dose (max dose: 600 mg/dose) every 6 to 8 hours as needed; maximum daily dose: 40 mg/kg/day
Side Effects	• Nausea, vomiting, dyspepsia • Kidney damage • Bleeding
Considerations	• After surgery, consider giving as soon as tolerating liquids PO as adjunct to IV pain medications • Careful with interactions with anticoagulants due to platelet effects

Gastrointestinal

- OMEPRAZOLE
- RANITIDINE

Gastrointestinal Agents

Proton-pump inhibitors:

- Parietal cells of the stomach contain H+/K+/ATPase which is the final step of acid secretion into the stomach
- PPIs block the action of the H+/K+/ATPase and lead to decreased acid secretion in the stomach
- Absorbed in the small intestine
- Few days required for full effect

H2 blockers:

- Gastrin stimulates histamine release from enterochromaffin like cells → histamine binds to the H2 receptors on parietal cells → gastric acid release
- H2 blockers reversibly bind to histamine receptors, blocking the binding of histamine, which leads to decreased gastric acid secretion
- Onset within 60 minutes, duration 4-10 hours

Omeprazole

When to use	• Treatment of GERD, heartburn, & H. pylori
Standard Dosing	• 5 kg to <10 kg: 5 mg once daily; 10 kg to <20 kg: 10 mg once daily; ≥20 kg: 20 mg once daily • 1-4 mg/kg/day; max daily dose: 40 mg/day
Side Effects	• Diarrhea • Hypomagnesemia; vitamin B12 deficiency • Bone fractures
Considerations	• Ideally used as a 14-day course • Potential drug interactions: clopidogrel – can diminish antiplatelet effect, • Delays clearance of some drugs: phenytoin, warfarin, diazepam

Ranitidine

When to use	• GERD, peptic ulcers, stress ulceration in critically ill patients
Standard Dosing	• Infants, Children, and Adolescents ≤ 16 yrs: 2 to 8 mg/kg/day divided twice daily; maximum daily dose: 300 mg/day • > 16 yrs: 150 mg once daily up to twice daily
Side Effects	• Nausea, vomiting, headache, dizziness, insomnia
Considerations	• No longer approved in United States due to NDMA (probable carcinogen)

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THANK YOU!