DISCLOSURES

None of the planners or presenters of this session have disclosed any conflict or commercial interest
OBJECTIVES

- TO GAIN AN UNDERSTANDING OF THE SITE OF ACTION AND PHARMACOLOGIC RESPONSE OF CARDIOVASCULAR DRUGS
- TO DISCUSS THE MEDICATION REGIMES UTILIZED BY PATIENTS FOR CARDIOVASCULAR DISEASE STATES
- TO REVIEW PHARMACOLOGIC CLASSES OF CARDIOVASCULAR DRUGS AND CHARACTERISTICS OF INDIVIDUAL AGENTS
1. “WHAT DO YOU WANT FROM ME?”

CV active drug and friends

- NP: We want you to take care of our patients with
  - HTN-- HF--AFIB--CAD-- ACS--& MORE

- CV: My friends and I can
  - Diurese — Vasodilate— Vasoconstrict— Slow the HR— Affect Platelets & Coag— and a whole bunch more
YOUR PATIENTS

- Hypertention
- Diuresis
- Vasodilation
- Decrease heart rate
YOUR PATIENTS
Diagnosis-Pathophysiology-Target

- HTN
  - Diuresis - Vasodilation - Alter heart characteristics

- Heart Failure
  - Diuresis - regulate BP -
  - Prevention of morbidity / mortality

- AFIB
  - Regulation of heart rate / rhythm
  - Prevention of thrombosis

- Each pathology has treatment goals
NP: How?

CV: How about this idea? ---we can match a patient and their problem with one of us that hits the receptor that affects the change you want

And try to avoid problems along the way
MAJOR CLASSES TO CONSIDER

- DIURETICS
- ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACE-I) & ANGIOTENSIN RECEPTOR BLOCKERS (ARB)
- BETA BLOCKERS
- CALCIUM CHANNEL BLOCKERS (CCB)
- ANTIPLATELET AND ANTICOAGULATION DRUGS
- DIGOXIN
- NITRATES
MANY OTHER CLASSES

- Beta Adrenergic Agonists
- Alpha Receptor Blockers
- Lipid Lowering Agents
- Vasopressors
- Others
DIURETICS

- HTN  HF
- Concept - site of activity determines efficacy*
  - Proximal Convoluted Tubule
  - Loop of Henle
  - Distal Convoluted Tubule
  - Last segment of DCT
DIURETICS

- PCT - Carbonic Anhydrase Inhibitors = weak diuretic d/t predominant effect on NaHCO3
- Loop Of Henle - loop diuretics = potent
  - furosemide* - torsemide* -
  - bumetanide* -ethacrynic acid
- * sulfonamide based - possible allergic cross reaction - most likely predisposition to Ax’s
LOOP DIURETICS

- In equipotent doses - no significant differences
- All have dose response curve
  - Minimum rate of drug excretion (delivery to site of action) to induce diuresis
  - Plateau dose producing little or no additional diuresis (may increase ADR)
LOOP DIURETICS

- Refractory Edema - three major factors
  - High sodium intake
  - Decreased diuretic secretion into tubular lumen
    - Reduced renal perfusion in HF patients & cirrhosis (vasoconstriction)
    - Hypoalbuminemia in nephrotic syndrome (loop diuretics are highly protein bound)
  - Increased sodium reabsorption at other renal sites
    - Add diuretic with different site of action
LOOP DIURETICS

- Continuous vs Bolus dosing
  - Rationale - continuous - maintenance of effective rate of drug excretion over time
  - Similar efficacy
  - If bolus fails, continuous will fail
  - Less ototoxicity with continuous
Thiazide Diuretics

- Site of action - start of DCT
- Moderate diuresis but usually effective (BP) due to longer duration of action vs loop diuretic (in patients with normal renal function)
- Multiple MOA? As U/O subsides over time
- Complimentary action when used with loop
  - Discuss timing of doses & route of administration
THIAZIDE DIURETICS

- CHARACTERISTICS
  - Hydrochlorothiazide
    - Oral - Limited when GFR < 20ml/min
  - Chlorothiazide
    - Only thiazide available as IV
  - Chlorthalidone - thiazide-like
    - Mean T1/2 40-50 hours
THIAZIDE DIURETICS

- **Metolazone - thiazide-like**
  - Possibly effective with GFR <20ml/min
  - Multiple sites of action
  - T 1/2 5-20 hours

- **Thiazide ADR**
  - Hypokalemia - Hyperuricemia
  - Hyperglycemia - Hypertriglyceridemia
  - Hypercalcemia *Loop = Hypocalcemia
POTASSIUM SPARING DIURETICS

- **CONCERN:** Increased Na delivery to distal segment of DCT stimulates the aldosterone sensitive pump and renin-angiotensin-aldosterone system leading to increased K and hydrogen ion excretion (possible metabolic alkalosis)

- Spironolactone /Eplerenone
  - Aldosterone Antagonists leading to K sparing
  - Reduction of renal and cardiac fibrosis (remodeling) - use: HF
Angiotensin Converting Enzyme Inhibitors
Angiotensin Receptor Blockers

- Renin-Angiotensin-Aldosterone System Basics
  - Triggers of Renin Secretion
    - Renal hypo-perfusion (hypotension or volume depletion)
    - Increased sympathetic activity
  - Renin acts on angiotensinogen
    - angiotensin I
    - angiotensin II (via ACE) which attaches to AT receptors
ACE-I and ARB
Angiotensin II

- **Major systemic effects:**
  - Vasoconstriction - binding to AT1 and AT2 (not well defined)
  - NaCl and H2O reabsorption - direct effect on renal tubule
  - Increased secretion of aldosterone
    - Na and H2O retention
    - Interstitial fibrosis via increased collagen deposition in the extracellular matrix of heart tissue
ACE-I

- Major result of inhibiting ACE = less production of angiotensin II

- Additional mechanisms
  - ACE is a kininase - inhibiting ACE ➔ ↑ Bradykinin = vasodilation (and probably cough)
  - Reduced sympathetic activity unknown mechanism
  - Increased prostaglandin synthesis - vasodilation
  - Possible angioedema connection
Angiotensin Receptor Blockers

- Blocks angiotensin II receptors
  - Angiotensin II, kinins and prostaglandins not affected so....
  - No cough, very limited angioedema
  - Same clinical effects as ACE-I
ACE-I and ARB

- Class effects
  - Reduced pre-load, afterload, sympathetic activity, cardiac remodeling, hyperkalemia,
- More similarities than differences
  - Treat to goal rather than drug
- Starting doses - start low d/t hypotension and renal effect
- Target doses if reachable
- Caution: BILATERAL renal artery stenosis
COMBINED ACE-I & ARB THERAPY?

- Original thought: Makes Sense
  - Feedback production of angiotensin II
  - Alternative pathways to produce angiotensin II
  - ACE-I may reduce the ARB induced rise in ang II

- Current thought:
  - Not recommended due to ↑ ADR’s
  - Progression of non-diabetic CKD- possible benefit
BETA BLOCKERS
(Beta-adrenergic Antagonists)

- Binding of Norepinephrine and Epinephrine
- BETA 1 Receptors
  - Primary location - heart
  - ↑ HR, Contractility, AV Conduction, ↓ AV node refractoriness
- BETA 2 Receptors
  - Primary locations - bronchial and vascular smooth muscle, heart
BETA BLOCKERS
(Beta-adrenergic Antagonists)

- Concepts:
  - Selectivity
    - Selective preferentially blocks beta 1 - atenolol, bisoprolol, metoprolol
    - Non-selective blocks beta 1 and beta 2 - carvedilol, labetalol, propranolol, sotalol
    - Selectivity is a relative property that can be lost especially at higher doses
  - Up and Down Regulation of Receptors
BETA BLOCKERS

CONCEPTS:

- Intrinsic Sympathomimetic Activity (ISA)
  - Slight to moderate activation of beta receptor while preventing normal and enhanced SA - labetalol
- Alpha 1 receptor blockade -vasodilation- carvedilol, labetalol
- Membrane Stabilizing Ability - similar to sodium channel blockers (Vaughan Williams Class II antiarrhythmics) - propranolol, metoprolol
- Sotalol has independent Class III antiarrhythmic activity
BETA BLOCKERS

- Excretion
  - Renal - atenolol, nadolol, sotalol
  - Hepatic - labetalol, metoprolol

- Diabetes
  - Beta blockers can mask hypoglycemia sx of tremor, tachycardia and palpitation - NOT sweating
  - Delay in recovery time - catecholamine mediated compensation
BETA BLOCKERS

- Additional mechanisms of action?
  - Inhibition of renin release
  - Reduced risk of plaque rupture
  - Anti-remodeling effects

- Concern for HF
  - Only metoprolol succinate, carvedilol & bisoprolol have been studied for M&M benefits
  - Initial dosing can ↑ sx of HF - bradycardia, hypotension, also bronchospasm, PVD exacerbation
BETA BLOCKER DOSING

- Initial Dosing
  - Start low
- Titration Dosing
  - To effect
  - Towards target dose
- Target Dosing
  - Maximum dose tolerated up to target
CALCIUM CHANNEL BLOCKERS

- Bind to L-type calcium channels on vascular smooth muscle, cardiac myocytes and cardiac nodal tissue (sinoatrial & atrioventricular nodes)
  - Vascular SM relaxation = vasodilation
  - ↓ Myocardial force generation = (-) inotropy
  - ↓ Heart rate = (-) chronotropy
  - ↓ Conduction velocity = (-) dromotropy
- Useful in HTN Angina Arrhythmias
CALCIUM CHANNEL BLOCKERS

- Two ? Three? Classes
  - Dihydropyridines (-ipines) -nifedipine, amlodipine, felodipine, isradipine, nicardipine, nimodipine
    - High vascular selectivity (arterial)
    - Can lead to reflex tachycardia and ↑ inotropy and may offset reduction in myocardial O2 demand
  - Second generation (amlodipine, felodipine etc) have little or no (-) inotropic effects - can treat HTN in systolic heart failure (not first line choice)
DIHYDROPYRIDINES

CCB

- Long acting dihydropyridines have reduced reflex responses - amlodipine, nifedipine ER
- ADR’s flushing, headache, hypotension, edema and reflex tachycardia
- Short acting nifedipine : Increased mortality via various mechanisms - reserved for tocolytic
- Nimodipine - used for the improvement of neurologic outcome by reducing the incidence and severity of ischemic deficits in SAH
CCB
NON-DIHYDROPYRIDINES

- Phenylalkylamine - Verapamil
  - Relatively selective for myocardium - ( - ) effect on AV conduction and SA node --less vasodilation
  - Angina, coronary vasospasm, SVT

- Benzothiazepine - Diltiazem
  - Both cardiac depressant - ( - ) effect on AV conduction and SA node and vasodilator activity between verapamil and dihydropyridines
NON-DIHYROPYRIDINES
ADVERSE DRUG REACTIONS

- Excessive bradycardia, AV Node block, depressed contractility
- Excessive constipation - verapamil
- May augment the effects of beta blockade - depressed cardiac electrical and mechanical activity
ANTIPLATELET & ANTICOAGULATION

- **GOALS**: prevention or treatment of clots (DVT/PE/CVA)
- Activated platelets secrete:
  - Thromboxane A2, adenosine diphosphate (ADP), serotonin, prostaglandins, and more
- Activated platelets bind to fibrinogen via glycoprotein (GP) IIb/IIIa receptor
ANTIPLATELET AGENTS

- Aspirin
  - Irreversibly acetylates and inactivates Cyclo-oxygenase (COX) for the life of the platelet
  - COX mediates the biosynthesis of prostaglandin, thromboxanes (TxA2)
  - ASA effect = platelet aggregation
  - ASA non-response - up to 40% of patients?
    - Poor compliance, inadequate dose, PLT turnover, up regulation of non-platelet pathways of TxA2 production
ANTIPLATELET AGENTS
Adenosine diphosphate Purigenic 2Y12 Receptor Inhibitors (ADP P2Y12)

- Thienopyridines
  - Clopidigrel -Plavix® - irreversible binding
    - Prodrug requiring 2 step activation P450 CYP Enz
    - Loss of CYP 2C19 function is common (genetic)
    - Meds can inhibit enzyme (PPI’s)
    - 600mg LD - 2 hour peak platelet inhibition
    - 300mg LD - 6 hour peak platelet inhibition
ANTIPLATELET AGENTS
Adenosine diphosphate Purigenic 2Y12 Receptor Inhibitors (ADP P2Y12)

- Prasugrel - Effient® - irreversible binding
  - Prodrug - 1 P450 CYP step to active metabolite
  - 60mg LD = 50% inhibition at 1 hr and 80% at 2hrs
  - 10mg/day MD = approx. 70% inhibition
  - Caution in pt >75yrs, < 60kg, Hx stroke/TIA
ANTIPLATELETS AGENTS
CYCLOPENTYLTRIAZOLOPYRIMIDINE

- Ticagrelor - Brilinta® - reversible inhibition
  - 180mg LD - 41% inhibition at 0.5hr, 70-88% at 2 hrs, 87-89% at 2-8 hours
  - ASA dose must be < 100mg to avoid ADR
  - Multiple drug interactions - CYP 3A4
ANTICOAGULATION
Inhibit thrombin generation

- Vitamin K antagonists - Warfarin
  - Blocks Vit K synthesis of clotting factors II, VII, IX, X and proteins C & S (anticoagulants)
  - Biochemical paradox - anticoagulant and potential thrombogenic effect
  - Peak effect approx. 36-72 hours post dose
  - Genetic polymorphism - estimated that up to 30% of dose variation results from genetic variants of Vit K epoxide reductase or CYP 2C9*2, CYP2C9*3
WARFARIN

- Many days to full anticoagulation due to different $T\frac{1}{2}$ of various clotting factors
  - Factor VII $T\frac{1}{2}$ approx. 4-6 hours
  - Factor II $T\frac{1}{2}$ approx. 3 days
  - Usual within 7 days, factors II, IX & X are 10-35% of normal at therapeutic INR
  - Various bridge therapy with parenteral drugs
  - Discuss dosing strategies - risk factors - age, DM, malignancy, A or C ETOH, hepatic disease,
Dabigatran etexilate - Pradaxa®
- Prodrug - rapid conversion to active - not CYP P450
- Onset 1 hour - 2 hours with food - 3-7% bioavailable - if capsule open bioavailability increases by 75%
- BID dosing adjusted for renal function
- T½ 12-17 hours
- Reversal with Praxbind® - idarucizumab
  - Binds to dabigatran with a higher affinity than dabigatran has affinity for thrombin
Rivaroxaban - Xarelto®

- Selective inhibition for Factor Xa - reduces thrombin burst
- Gastric absorption - caution with feeding tube - max concentration in 2-4 hours
- Highly protein bound (92-95%)
- T½ 5-12 hours - metabolized by CYP 3A4 & 2J2
- Renal dosing as well as dosed by indication - stroke prevention vs post TKR vs post THR
DIGOXIN
ORAL INOTROPE

- Inhibition of Na+/K+-ATPase ion transport system
  - \(\rightarrow\) accumulation of intracellular Ca++ which binds to troponin-C \(\rightarrow\) increased contractility (inotropy)

- Increases vagal activity to the heart
  - \(\rightarrow\) reduced sinoatrial firing rate = (-)chronotropy and reduces conduction velocity of impulses through the AV node = (-) dromotropy

- May decrease sympathetic tone by: increase in CO, normalization of pathologic baroreflex response,
DIGOXIN

- Used in the treatment of mild to moderate heart failure and to control the ventricular response rate in patients with atrial fibrillation
- T½ approx. 40 hours - need for digitalization with multiple approaches
- Caution due to narrow therapeutic index
- If toxicity occurs may need Digibind d/t T½
DIGOXIN

- Renal dosing and drug interactions with drugs influencing renal function
- Hypokalemia - ↑ dig binding to Na+K+-ATPase
- Hypercalcemia - ↑ risk of dig induced arrhythmias
- Hypomagnesemia - sensitizes heart to dig induced arrhythmias
DIGOXIN
ADVERSE DRUG REACTIONS

- Cardiac arrhythmias - atrial tachycardia, atrioventricular block
- Warning/Caution in hypokalemic, atrioventricular block or Wolff-Parkinson-White syndrome patients
- Lean elderly are more susceptible to toxicity d/t reduced renal function and because muscle Na+/K+ -ATPase acts as a binding reservoir
- Improves HF symptoms but not mortality
VASODILATORS
Nitrodilators

- 2 types
  - Those that release Nitric Oxide spontaneously - sodium nitroprusside
  - Those that form NO via enzymatic process - organic nitrates - nitroglycerin, isosorbide mono & dinitrate

- NO via decreasing intracellular calcium concentrations and activating K+ channels causes smooth muscle relaxation
Sodium Nitroprusside

- Dilates arteries more than veins
- Rapid onset and short half life (2 minutes)
- Only available as IV prep - continuous infusion
- Hypertensive emergencies and severe heart failure
- > 2mcg/kg/min yields cyanide and thiocyanate
- Caution in hepatic and renal pts (CY tox)
NITRODILATORS
ORGANIC NITRATES

- Can dilate veins and arteries, vein predominate
- Reduces venous pressure, ventricular preload which enhances the oxygen supply/demand ratio
- Tachyphylaxis - use lowest possible dose and nitrate free periods
- Uses HTN*, angina, heart failure, MI
  - * NTG and Na Nitroprusside for acute hypertensive emergencies
NITRODILATORS
ORGANIC NITRATES

- Nitroglycerin
  - SL avoids 1\textsuperscript{st} pass hepatic metabolism
  - Fast acting - lasts approx 30 minutes
  - Available in transdermal patches -
- Isosorbide dinitrate / mononitrate
  - Longer onset and duration than NTG
  - Only mononitrate avoids 1\textsuperscript{st} pass hepatic metabolism
- Direct acting vasodilator - hydralazine
  - Primarily affects arterial vessels so coupled w/nitrate
ADDITIONAL CARDIOVASCULAR CLASSES

- Beta Adrenergic Agonists
  - Cardiac stimulation - ↑HR, contractility, conduction velocity: Smooth muscle tissues - systemic vasodilation
  - Bronchial smooth muscle - relaxation
  - Hepatic tissue - glycogenolysis
  - Pancreatic -release of glucagon
  - Kidneys -stimulate renin release
ADDITIONAL CARDIOVASCULAR CLASSES

- Beta Adrenergic Agonists
  - Various receptor selectivity - Beta 1, Beta 2, Alpha 1, Alpha 2
  - Epinephrine, Norepinephrine, Dopamine, Dobutamine, Isoproterenol
  - Uses include anaphylactic, septic and cardiogenic shock, cardiac arrest, severe hypotension, acute heart failure, bradycardia, atrioventricular block
ADDITIONAL CARDIOVASCULAR CLASSES

- Alpha Adrenergic Antagonists - Alpha 1 Blockers
  - Cause vasodilation by blocking binding of norepinephrine to smooth muscle receptors
  - Prazosin, Terazosin, Doxazosin
  - Caution: Orthostatic hypotension

- Alpha Adrenergic Agonists
  - Alpha 1 - vasoconstriction - phenylephrine, oxymetazoline, tetrahydralazine
  - Alpha 2 - inhibit release of NE, vasodilation, - clonidine
ADDITIONAL CARDIOVASCULAR CLASSES

- Lipid lowering therapy
  - Statins
  - PCSK9-abs - Proprotein Convertase subtilisin kexin 9 antibodies

- Endothelin Receptor Antagonists
  - Produce vasodilation
  - Bosentan - non specific ETa & ETb receptors
  - Ambrisentan - specific ETa receptor
  - Used for pulmonary hypertension
NEW CARDIOVASCULAR MEDICATIONS

- Prostacyclin receptor agonist
  - Selexipag - Uptravi®
    - Reduce pulmonary vascular resistance, increase cardiac index and inhibit platelet aggregation

- Neprilysin Inhibitor
  - Sacubitril / valsartan - Entresto®
    - Increases the levels of natriuretic peptides, bradykinin and andremedullin leading to vasodilation, natriuresis and counteracting cardiac remodeling (neurohormonal)
NEW CARDIOVASCULAR MEDICATIONS

- Ivabradine - Corlanor®
  - HCN channel / If current inhibitor
    - Mixed Na+/K+ channel - pacemaker current
    - No effect on cardiac contractility or ventricular repolarization
  - Used in HF pts with ↑ HR