

Cardiovascular Boot Camp

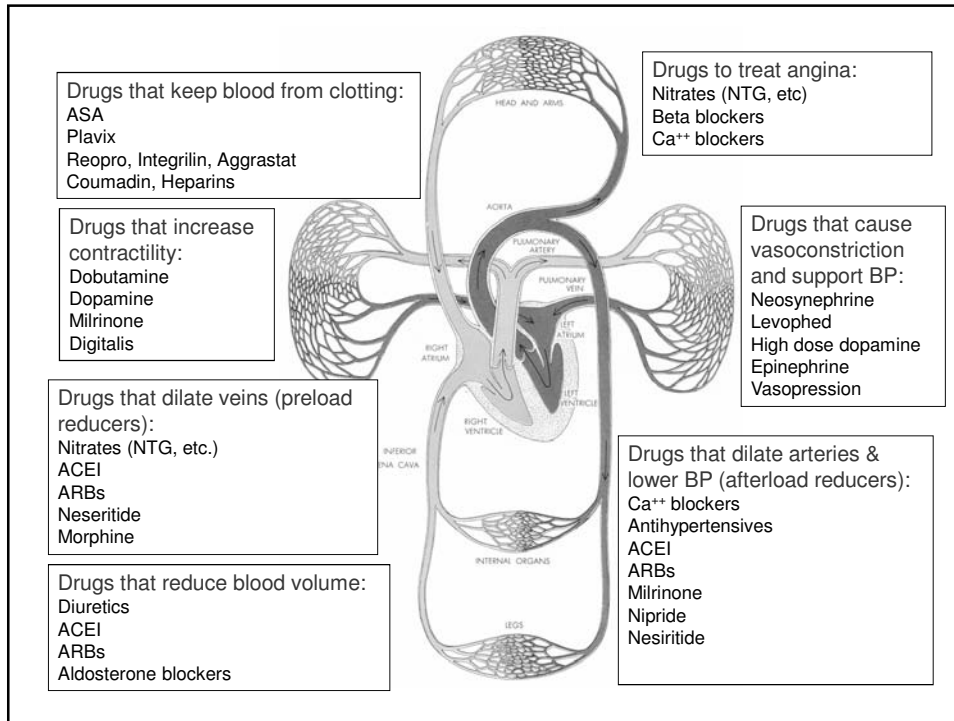
Basic Training Day 4: Principles of CV Pharmacology



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Types of Cardiovascular Drugs

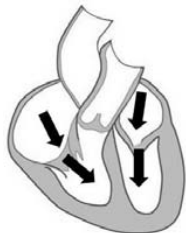
- Antiarrhythmics
- Beta Blockers
- Calcium Channel Blockers
- Nitrates
- Diuretics
- Anticoagulants
- Platelet Inhibitors
- ACE Inhibitors
- ARBs
- SARAs
- Anti-lipid Agents
- Vasoactive Drugs
- Antihypertensives
- Thrombolytics
- Inotropes



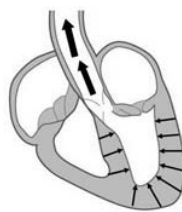
Determinants of Cardiac Output

$$CO = HR \times SV$$

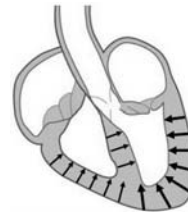
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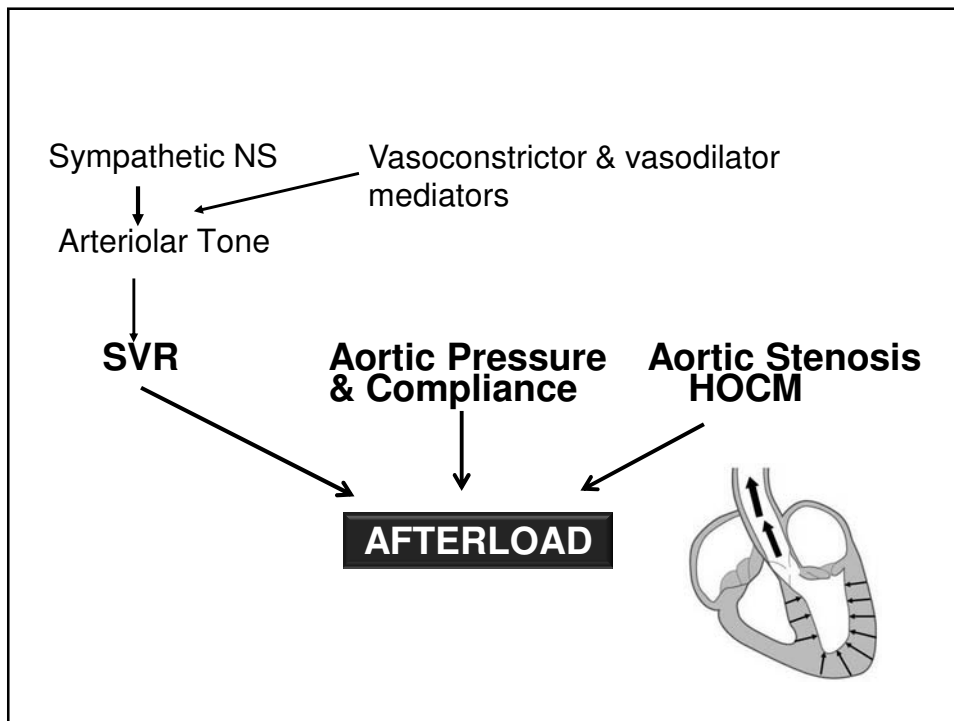
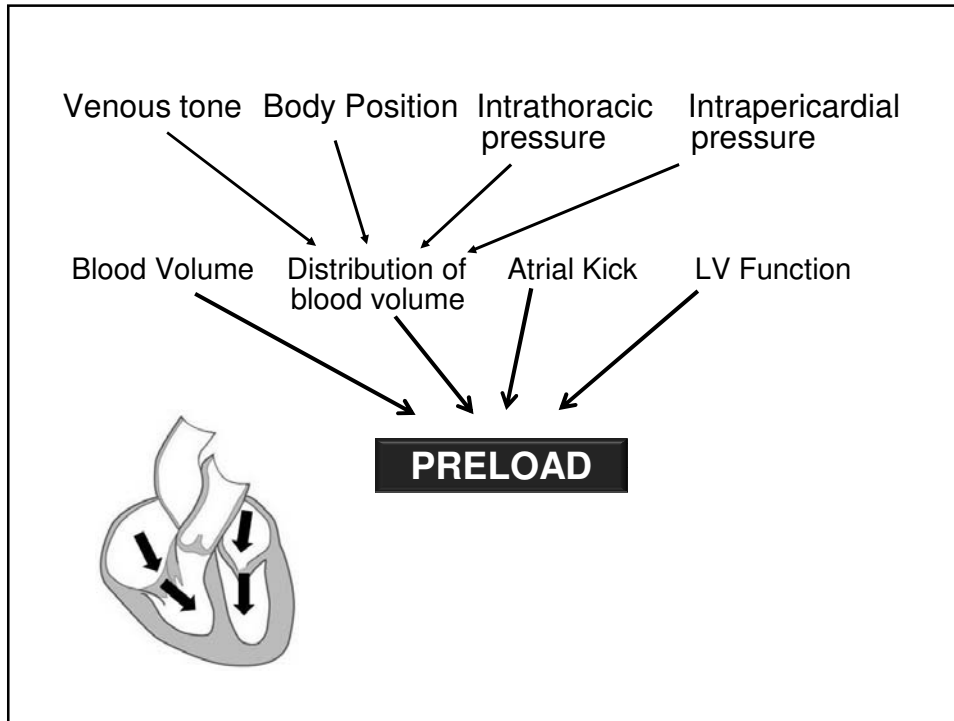


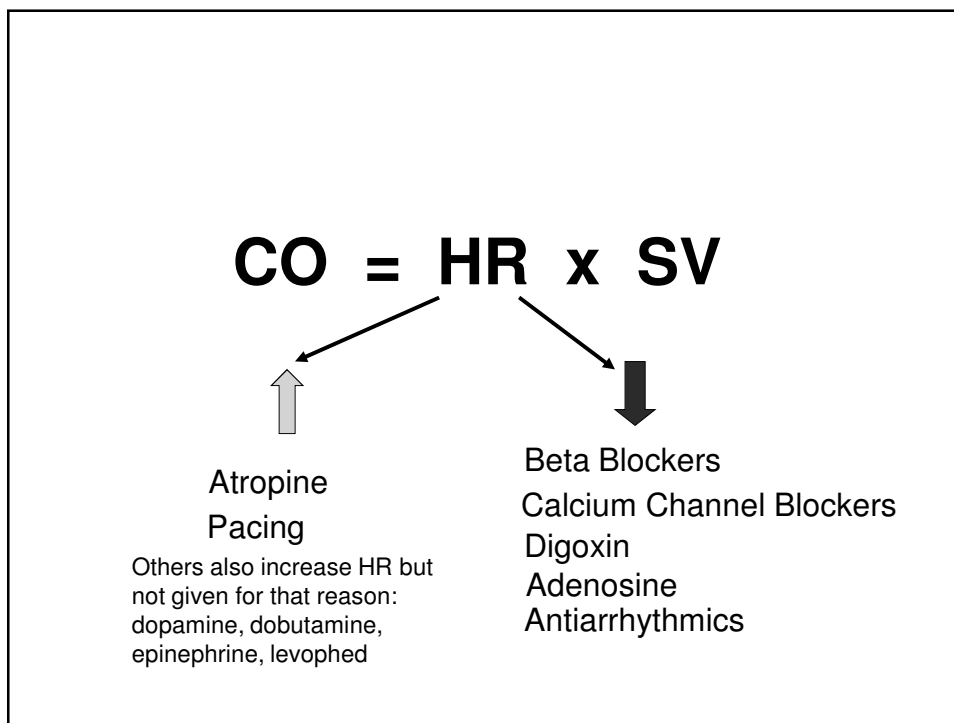
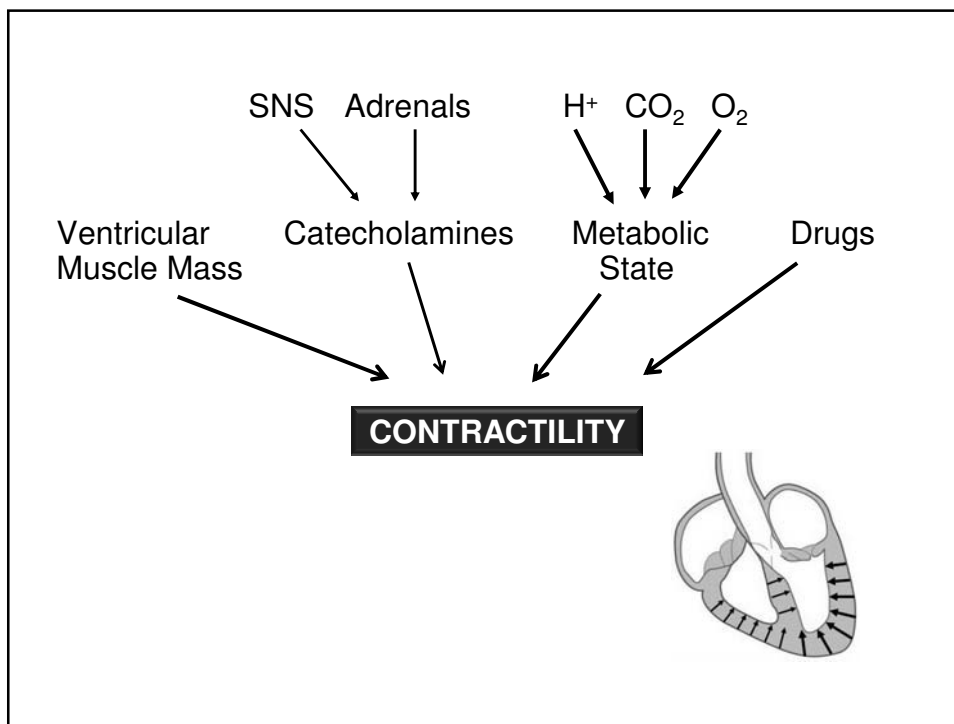
Afterload



Contractility







$$CO = HR \times SV$$

Preload

↑
Fluids
Blood Products
Volume Expanders

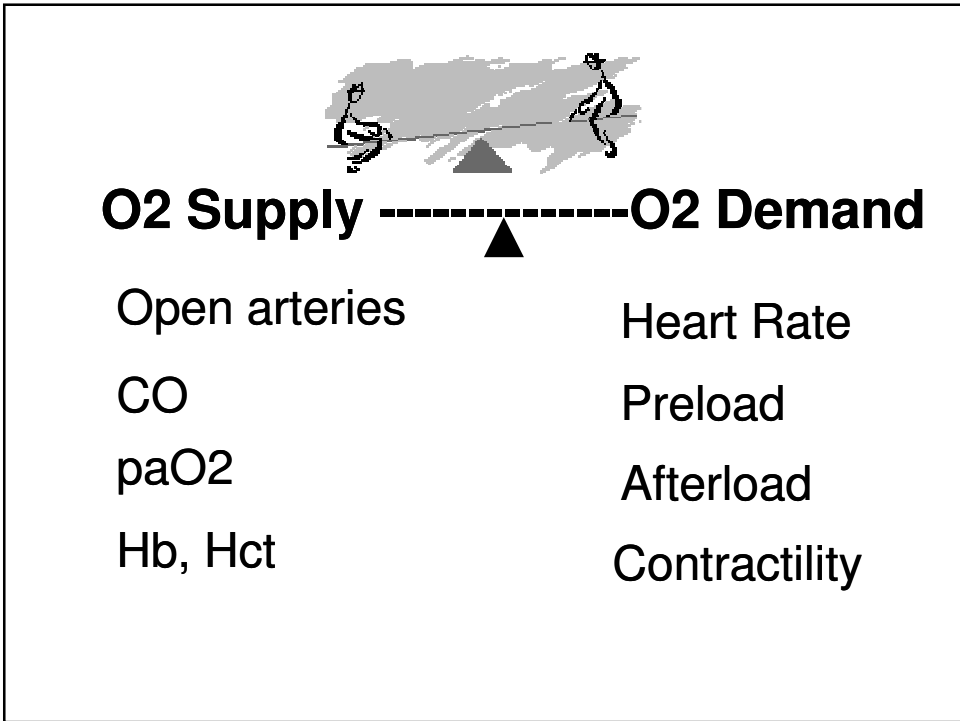
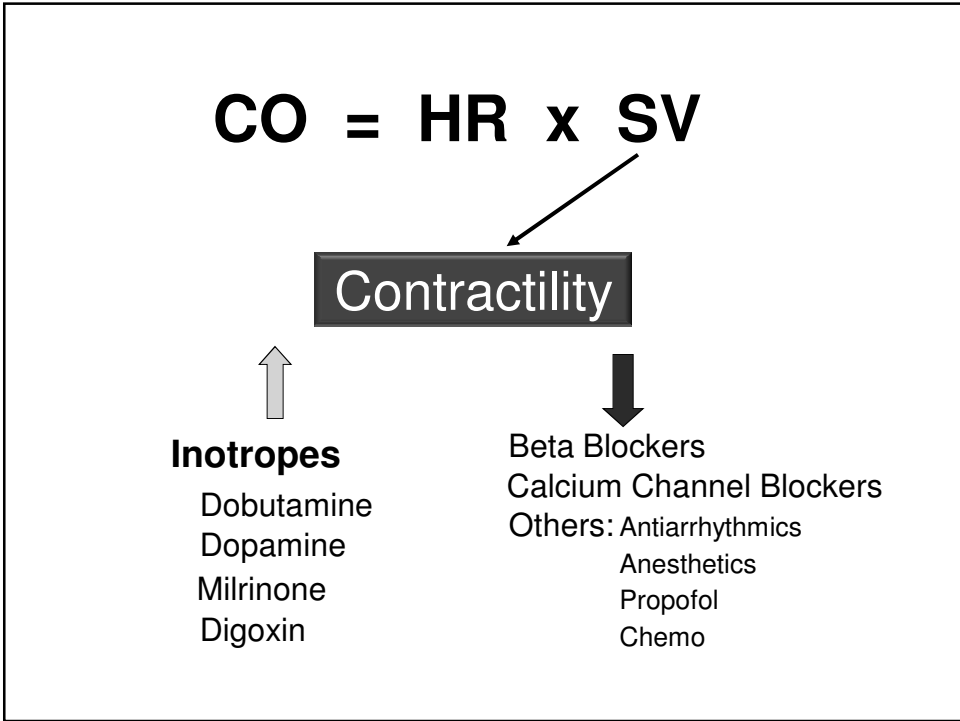
↓
Diuretics
Venous Dilators (NTG)
ACE Inhibitors
ARBs
Aldosterone Blockers
Nesiritide (Natrecor)
Morphine

$$CO = HR \times SV$$

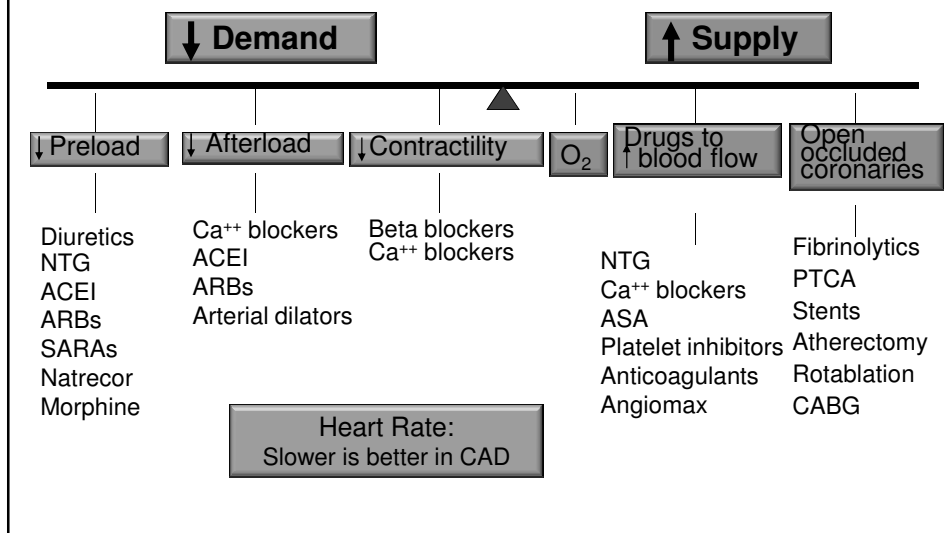
Afterload

↓
Arterial Dilators
Nitroprusside
Milrinone
Ca⁺⁺ blockers
Antihypertensives
ACEI, ARBs
Nesiritide

↑
Vasopressors
Levophed
Dopamine (high dose)
Epinephrine
Neo-synephrine
Vasopressin



Balancing O2 Supply & Demand



Drug Therapy to Increase BP

$$\uparrow BP = \uparrow CO \times \uparrow SVR$$

Drugs to ↑ CO

- Volume
- Inotropes
 - Dobutamine
 - Dopamine
 - Milrinone

Drugs to ↑ SVR

- Vasopressors
 - Levophed
 - Neosynephrine
 - Vasopressin
 - Epinephrine
 - Dopamine

Drug Therapy to Decrease BP

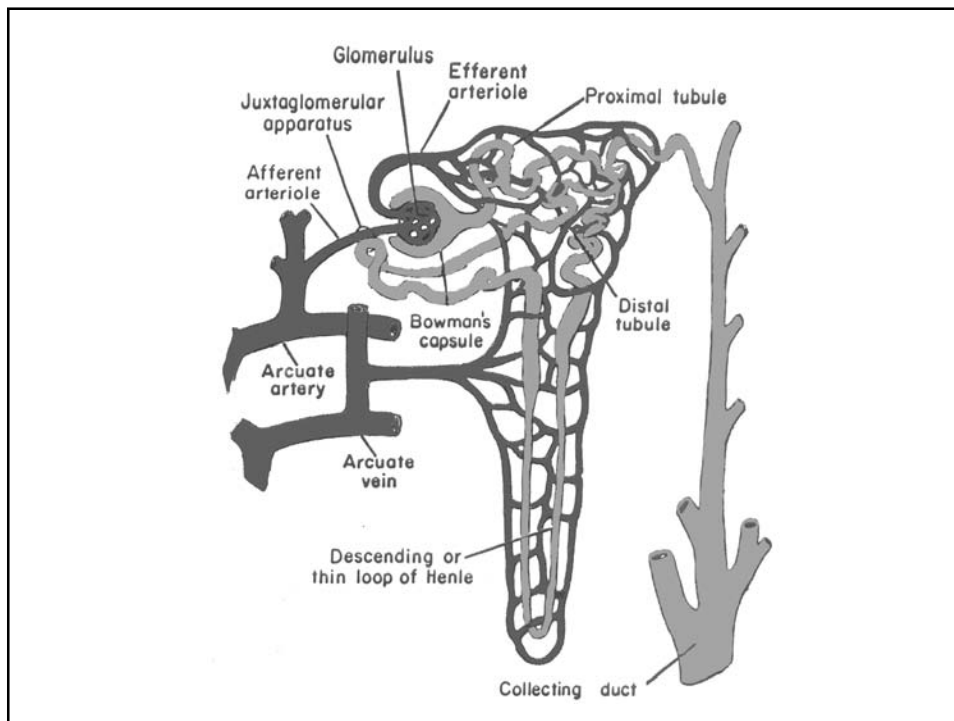
$$\downarrow BP = \downarrow CO \times \downarrow SVR$$

Drugs to \downarrow CO

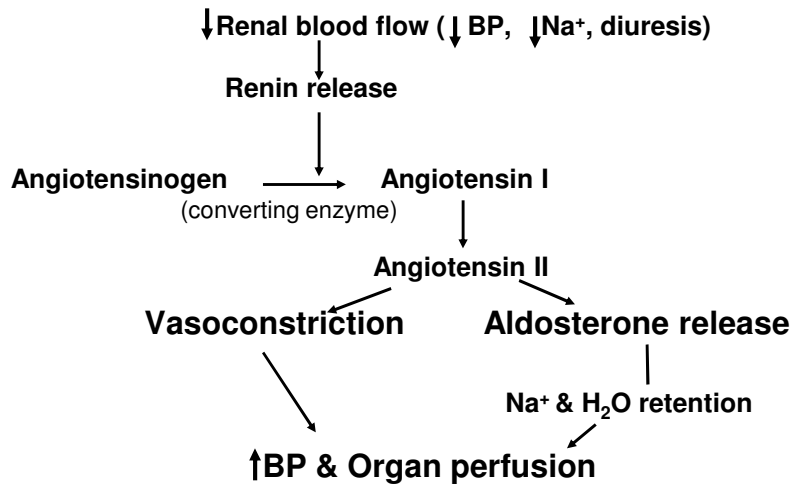
- Diuretics
- Beta Blockers (“olols”)
- Calcium Channel Blockers

Drugs to \downarrow SVR

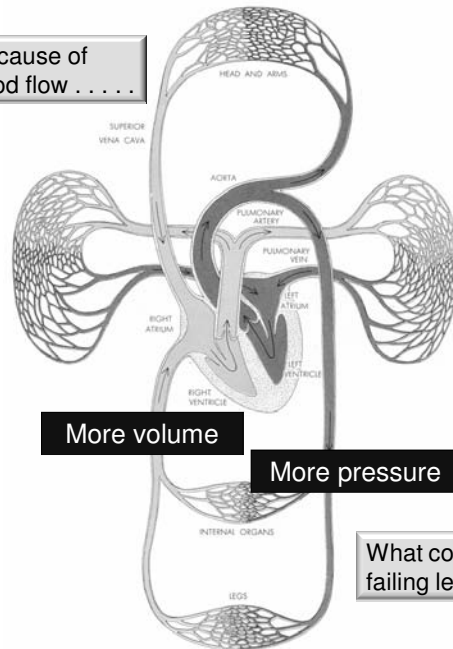
- Peripheral Alpha Blockers (prazosin, terazosin, regitine etc)
- Direct Arterial Dilators (hydralazine, minoxidil)
- ACEI (“prils”), ARBs (“sartans”)
- PDE inhibitors (milrinone)
- Calcium Channel Blockers (“pines”: amlodipine, felodipine, etc)
- \uparrow nitric oxide in vascular tissue (nitroprusside, nitrates)
- Centrally Acting Agents (clonidine, guanabenz, guanfacine)



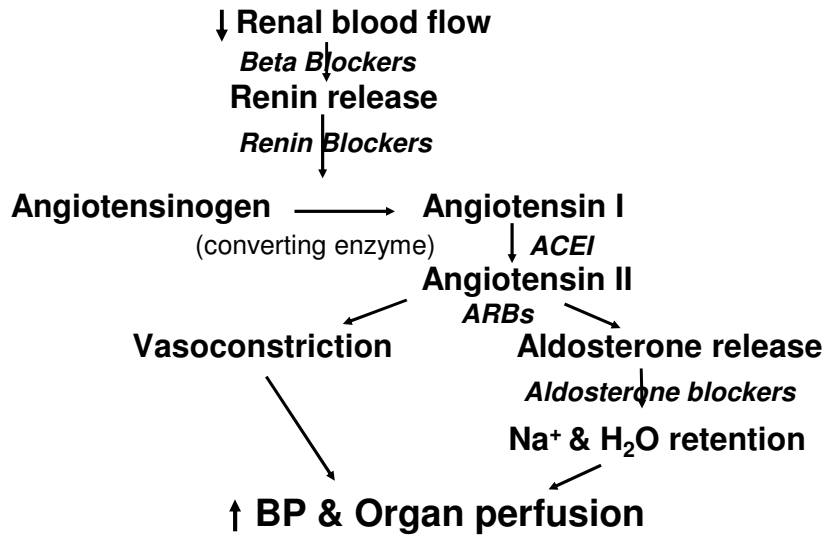
Renin-Angiotensin-Aldosterone System



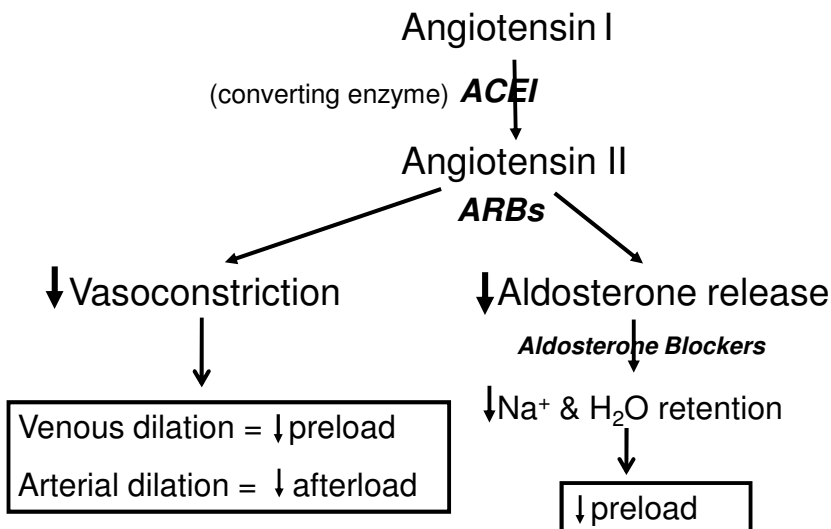
If LV failure is the cause of reduced renal blood flow



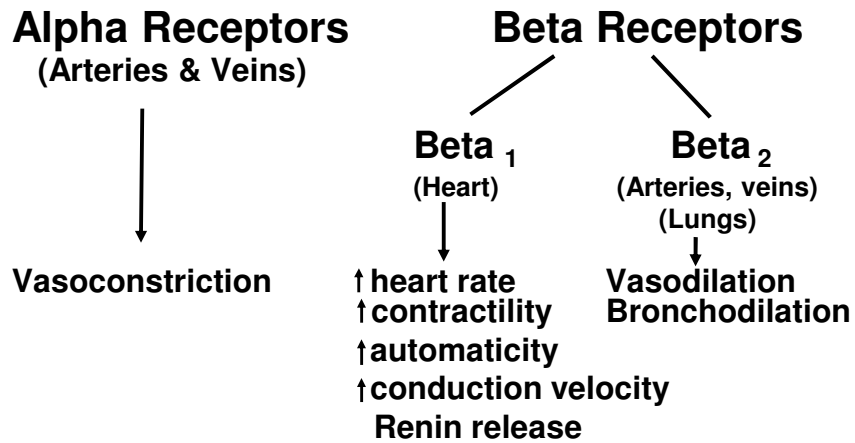
Renin-Angiotensin-Aldosterone System



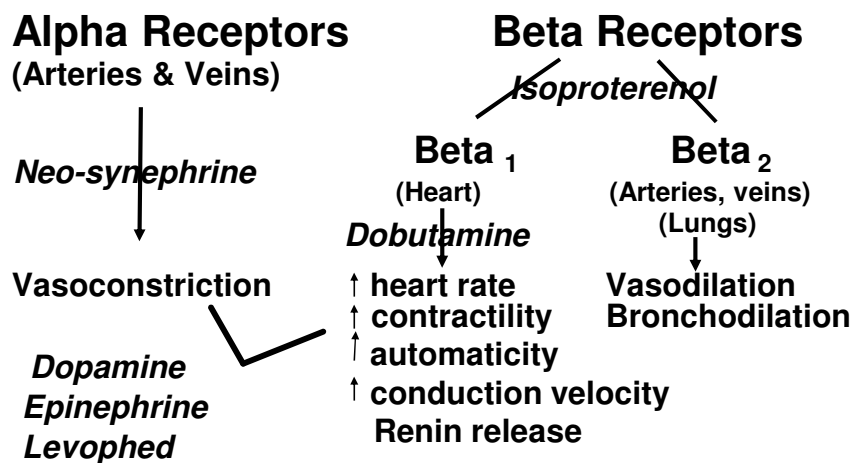
Hemodynamic Effects of ACEI & ARBS



Cardiovascular Effects of SNS

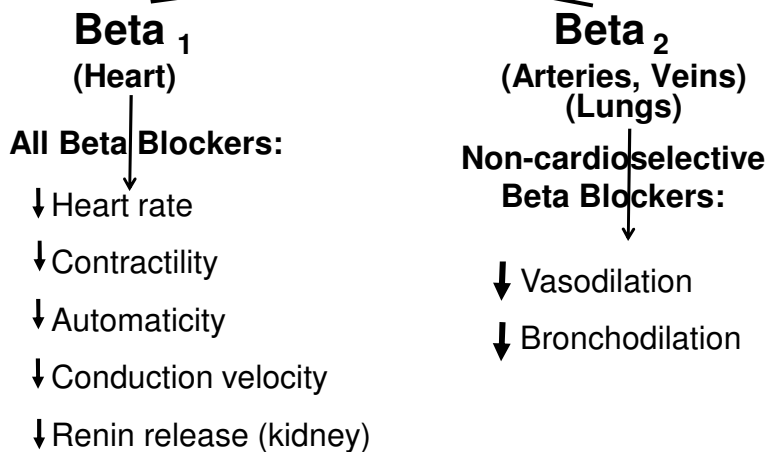


Sympathomimetic Drugs



Effects of Beta Blockers

Beta Receptors



Clinical Use of Beta Blockers

Use	Mechanism of Action
Hypertension	↓ heart rate = ↓ CO = ↓ BP ↓ contractility = ↓ CO = ↓ BP ↓ renin release in kidney = ↓ angiotensin II formation $BP = CO \times SVR$
Classic Angina	↓ O ₂ demand by ↓ HR, ↓ contractility, ↓ BP ↑ O ₂ supply by ↓ HR which ↑ diastolic filling and coronary perfusion time
Acute MI MI Follow-up	↓ automaticity in ventricle so ↓ risk of VF early in MI Preserves ischemic myocardium by ↓ O ₂ demands
Arrhythmias	↓ automaticity so ↓ VT, VF ↓ AV conduction to slow ventricular rate in A Fib or flutter, may terminate PSVT
Hypertrophic Cardiomyopathy	↓ contractility so reduces outflow tract obstruction ↓ HR allows longer diastolic filling time, more blood in ventricle decreases outflow tract obstruction
Migraines	Inhibits β mediated vasodilation in cerebral vessels

Beta Blockers

- **Nonselective: Block both Beta₁ & Beta₂**
Propranolol (Inderol) Nadolol (Corgard)
Timolol (Blocadren) Sotalol (Sotacor)
Penbutolol (Levitol) Oxprenolol (Trasicor)
- **Cardioselective: Block Beta₁**
Acebutolol (Sectral) Atenolol (Tenormin)
Metoprolol (Lopressor) Esmolol (Brevebloc)
Bisoprolol (Zebeta) Nebivolol (Bystolic)
- **Combined Alpha & Beta Blocking:**
Labetalol (Trandate, Normodyne)
Carvedilol (Coreg)

Effects of Ca⁺⁺ on Heart & Blood Vessels

- Depolarization of SA node and AV node cells (“slow current” calcium dependent cells)
- Facilitates contraction of heart and smooth muscle layer of blood vessels
 - Facilitates actin-myosin interaction in muscle)



Effects of Ca⁺⁺ Channel Blockers

- **Heart:**
 - ↓ **heart rate** (except Nifedipine-like agents)
 - ↓ **AV conduction velocity**
 - ↓ **contractility**
- **Blood Vessels:**
 - Coronary vasodilation** (prevent vasospasm)
 - Peripheral vasodilation** (afterload reduction)

Clinical Uses of Ca⁺⁺ Channel Blockers

Use	Mechanism of Action
Angina: Coronary Spasm Classic Angina	Prevents vasoconstriction by decreasing amount of Ca ⁺⁺ available for contraction. Coronary vasodilation increases collateral blood flow. ↓MVO ₂ by ↓HR, ↓contractility, ↓afterload
Hypertension	BP = CO x SVR ↓CO by ↓contractility, ↓SVR by vasodilation
Arrhythmias: SVT	Slows AV conduction so ↓ventricular response to atrial fib & flutter. Can terminate AV nodal active arrhythmias.
Hypertrophic Cardiomyopathy	↓ contractility lessens outflow tract obstruction. ↓HR allows longer diastolic filling time, more blood in ventricle keeps outflow tract open

Ca⁺⁺ Channel Blockers

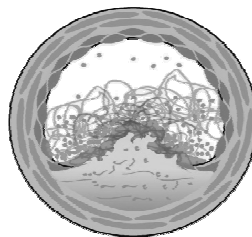
- **Heart Rate Lowering:**
 - Verapamil (Calan) – most depression of contractility
 - Diltiazem (Cardizem)
- **Dihydropyridines** (potent vasodilators, little or no depression of contractility)
 - Nifedipine (Procardia, Adalat) – short acting, comes in sustained release form for longer action
 - Felodipine (Plendil)
 - Isradipine (DynaCirc)
 - Nicardipine (Cardene)
 - Nisoldipine (Sular)
 - Amlodipine (Norvasc) – long acting, no cardiac depression, safest one in HF

Longer acting, little cardiac depression

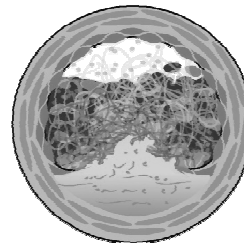
Antiplatelet Drugs



Plaque rupture

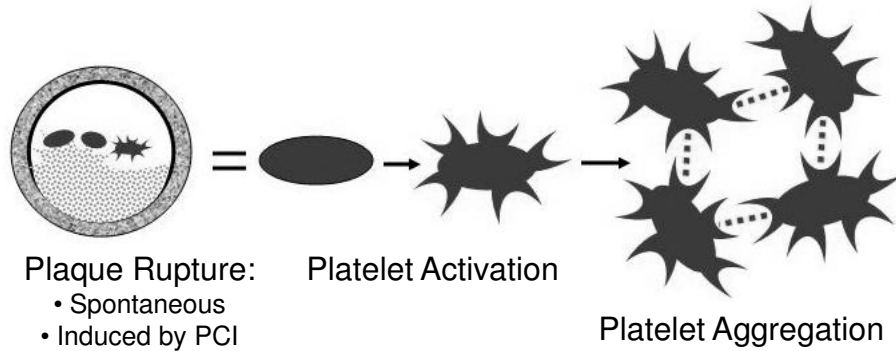


Platelet activation & aggregation

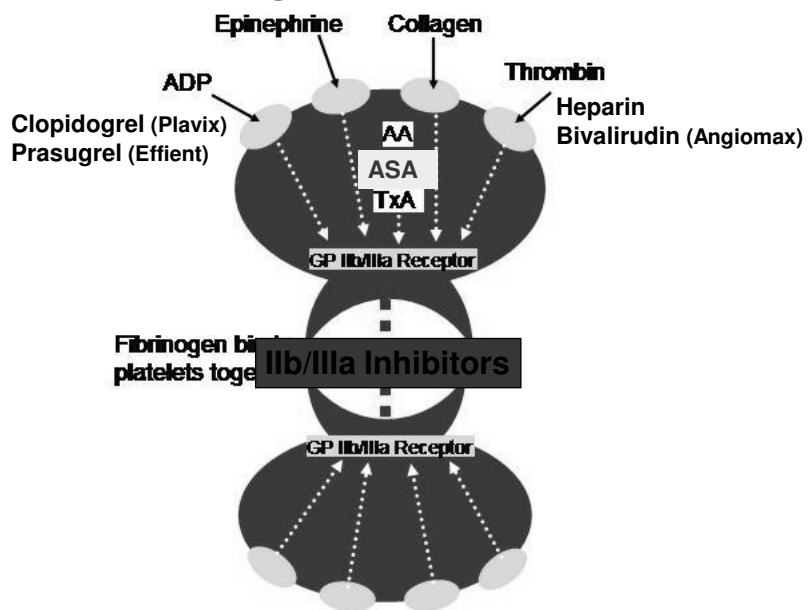


Thrombus formation

Pathogenesis of ACS

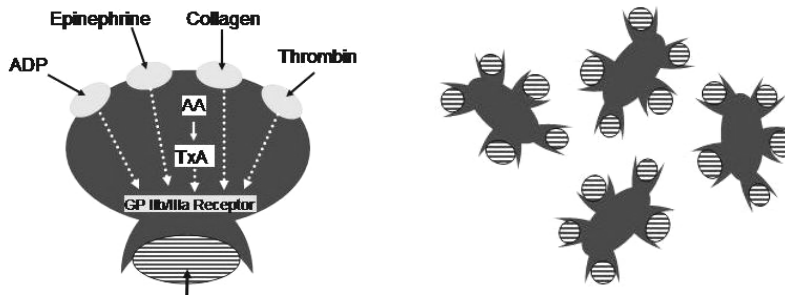


Drug Site of Action

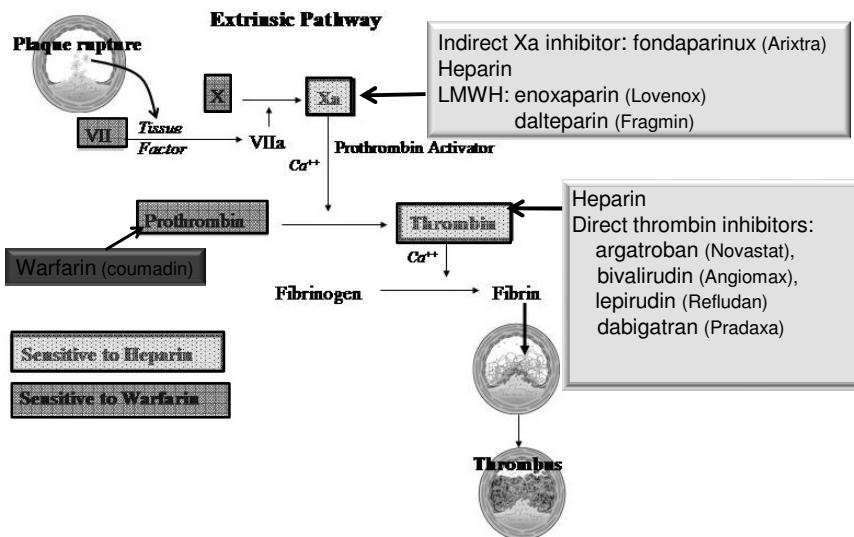


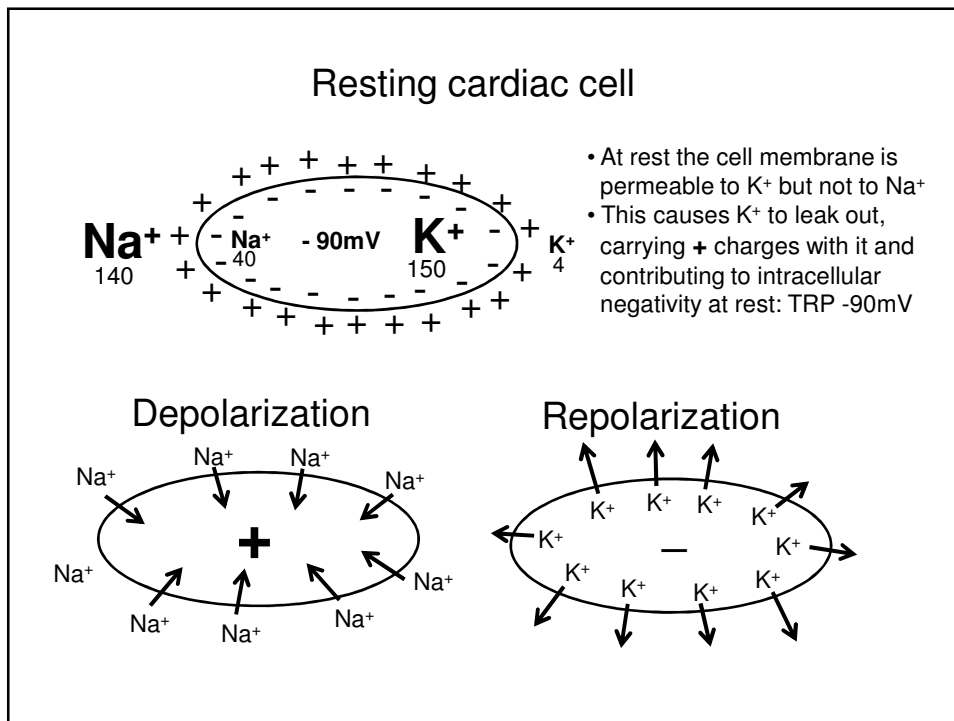
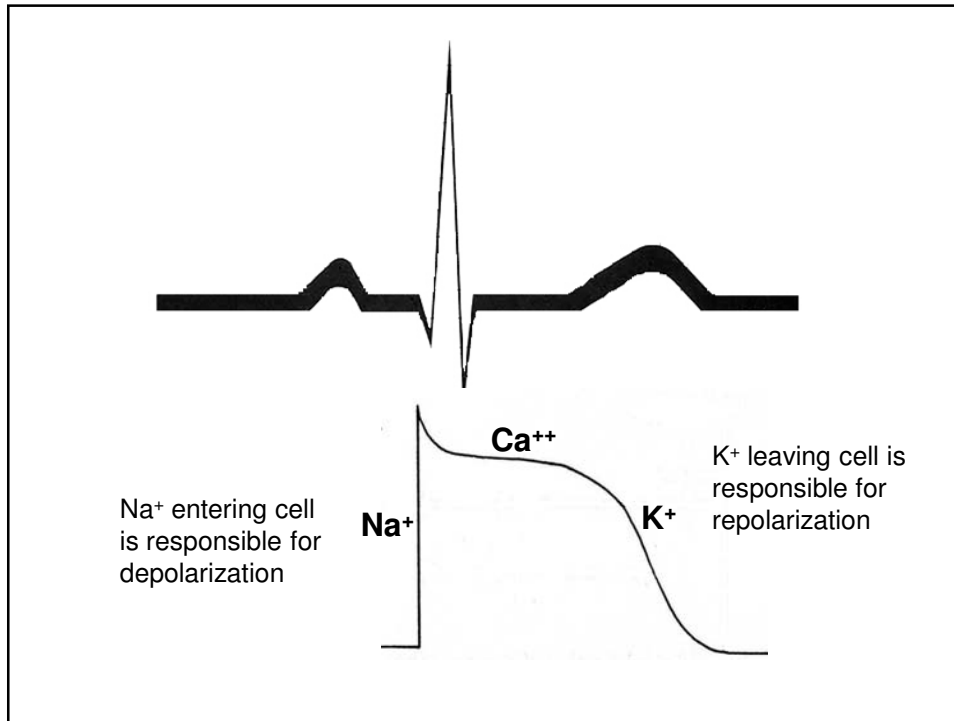
IIb-IIIa Inhibitors

- Reopro
- Integrilin (eptifibatide)
- Aggrastat (tirofiban)

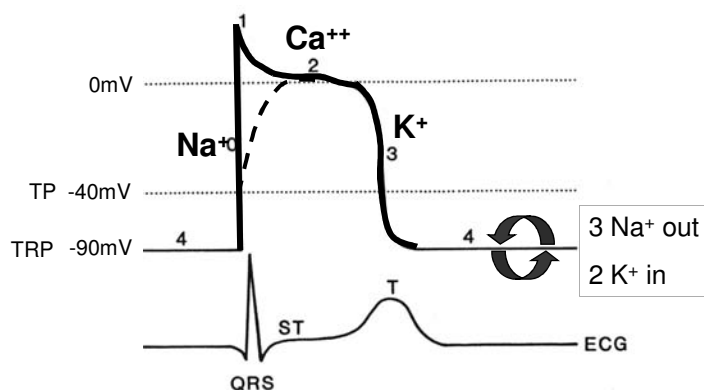


Anticoagulants



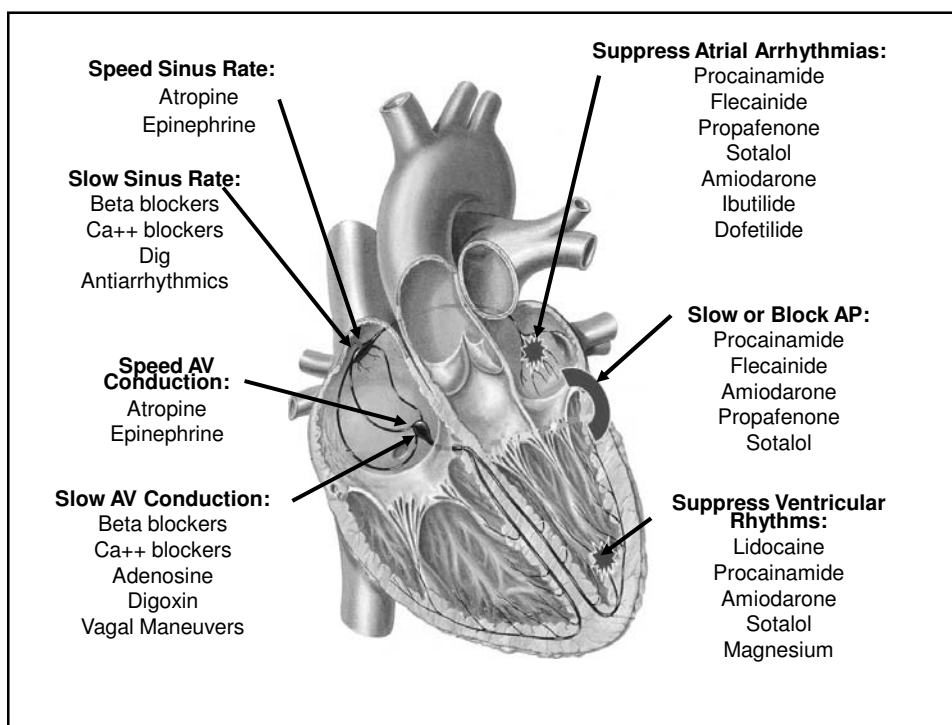


Cardiac Action Potential



	Class	Examples
Na ⁺ channel blockers	IA	Quinidine Procainamide (Pronestyl) Disopyramide (Norpace)
	IB	Lidocaine Mexilitine Tocainide
	IC	Propafenone (Rhythmol) Flecainide (Tambocor)
	II	Beta blockers ("olols")
	III	Amiodarone Dronedarone Ibutilide (Corvert) Sotalol Dofetilide (Tycosin)
	D	Calcium channel blockers: Verapamil, Diltiazem

Class	Action	ECG Effect
IA	Sodium channel blockade Prolong repolarization time Slow conduction velocity Suppress automaticity	↑QRS ↑QT
IB	Sodium channel blockade Accelerate repolarization	↓QT
IC	Sodium channel blockade Marked slowing of conduction No effect on repolarization	↑↑QRS
II	Beta blockade	↓HR ↑PR
III	Potassium channel blockade Prolong repolarization time	↑QT
IV	Calcium channel blockade	↓HR ↑PR



Drug Therapy for Dyslipidemias

Drug	Examples	Effects
Bile Acid Binding Resins	Cholestyramine Cholestipol, Colesevelam	Lower LDL 15-30% Slight increase HDL No change in TG
Nicotinic Acid	Niacin Niacin XR	Lower LDL 10-25% Raise HDL 15-35% Lower TG 25-30%
HMG-CoA Reductase Inhibitors (statins)	Atorvastatin, Fluvastatin Lovastatin, Pravastatin Rosuvastatin, Simvastatin	Lower LDL 20-60% Lower TG 10-33% Raise HDL 5-10%
Fibric Acid Derivatives	Gemfibrozil Fenofibrate	Lower LDL 5-20% Lower TG 35-50% Raise HDL 15-33%
Intestinal Absorption Inhibitors	Ezetimibe (Zetia)	Lower LDL 18% No change in HDL May increase TG

Drug Therapy in Heart Failure

- **Diuretics**
 - Loops preferred
 - Thiazides
 - K⁺ sparing
- **Arterial Dilators**
 - Nitroprusside
 - Milrinone
 - ACEI
 - ARBs
- **Venous Dilators**
 - NTG
 - ACEI
 - ARBs
 - Nesiritide
- **Inotropes**
 - Dobutamine
 - Dopamine
 - Milrinone
 - Digoxin
- **Beta Blockers**
 - Carvedilol
 - Metoprolol
 - Bisoprolol
- Morphine

Drug Therapy for Hypertension

- Thiazide diuretics (chlorthalidone, HCTZ)
- ACE Inhibitors / ARBs
- Calcium blockers
- Beta blockers

The amount of blood pressure reduction is the major determinant of reduction in cardiovascular risk, not the choice of antihypertensive drug.

Make it Stop!!



Cardiovascular Boot Camp

Basic Training Day 4: Principles of CV Pharmacology



Cardiovascular Pharmacology: Specific Agents

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A Closer Look at Pharmacological Agents

Let's Clear Up Some Terminology

- Vasopressors
 - Term given to any medication in any class that is used to increase left ventricular afterload (systemic vascular resistance)
- Inotropes
 - Term given to any medication in any class that is used to increase myocardial contractility

Sympathomimetics

These drugs are used to:

- ✓ Increase afterload
- ✓ Increase contractility
- ✓ Increase HR

✓ We often refer to these drugs as inotropes or vasopressors depending on why we are giving them.

Sympathetic Nervous System Adrenergic Receptors and Effects

Alpha Receptors (Alpha_1)

Located in Vessels

Vasoconstriction of most vessels especially the arterioles

• β_1 Receptors

- Located in the heart
- Increases heart rate (chronotropic)
- Increases conductivity (dromotropic)
- Increase contractility (inotropic)
- Increase automaticity
- Increase conduction velocity

Sympathetic Nervous System Adrenergic Receptors and Effects

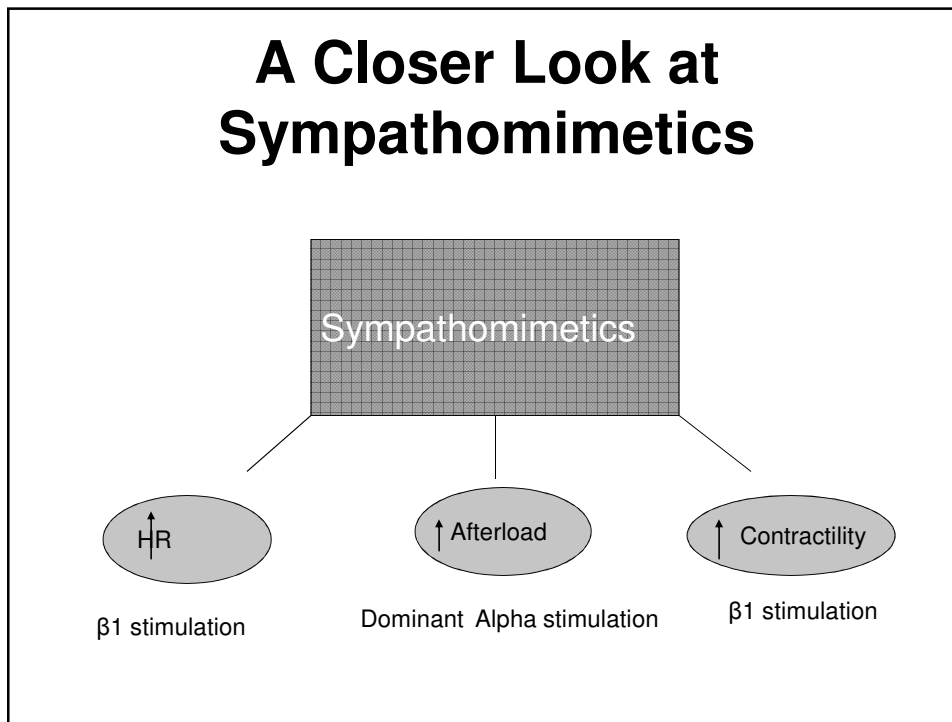
• β_2 Receptors

- Located in bronchial and vascular smooth muscle
- Causes bronchial dilatation
- Causes arterial vasodilatation to skeletal muscle
- ***Causes renin release and therefore activation of the RAAS***

• Dopaminergic Receptors (D_1)

- Located in renal and mesenteric artery bed
- Dilation of renal and mesenteric arteries

A Closer Look at Sympathomimetics



A Closer Look at Sympathomimetics

- Sympathomimetics that increase heart rate (β_1 receptors)
 - Dopamine
 - Epinephrine
 - Isuprel (no longer used except with cardiac transplants)
- Sympathomimetics that increase afterload (vasopressors) (α_1 receptors)
 - Dopamine
 - Norepinephrine (Levophed)
 - Phenylephrine (Neo-Synephrine)
 - Epinephrine
- Consider when you might NEED to increase afterload since increasing afterload is very costly to the myocardium in oxygen demand !

A Closer Look at Sympathomimetics

- Sympathomimetics that increase contractility (inotropes) (β_1 receptors)

Used primarily as inotrope

– Epinephrine

– Dobutamine

Used primarily as vasopressor but has inotropic properties when used

– Dopamine

– Norepinephrine

Epinephrine

Endogenous catecholamine

What receptors are stimulated:	β_1 and β_2 Alpha receptors
What are the resultant actions:	Increase contractility (+inotrope) β_1 Increase heart rate (+chronotrope) β_1 Bronchodilation β_2 Selective vasoconstriction (alpha) – not coronary or cerebral vessels
When and why do we use:	ACLS first line drug for cardiac standstill; V-fib; pulseless electrical activity Hypotension or profound bradycardia Anaphylactic Shock
What are special nursing considerations:	Onset instant Peak 20 minutes 1mg every 3-5 minutes during cardiac standstill IV Infusion: 1mcg/min Range 2-10mcg/min

Dobutamine

Synthetic Compound

What receptors are stimulated:	Primarily β_1 Some α_1 receptor stimulation Modest β_2 stimulation (more β_2 than α_1)
What are the resultant actions:	Increase contractility (+ inotrope) (β_1) Increase AV node conduction Modest vasodilation
When and why do we use:	Used as an inotrope (resultant preload reduction) with modest afterload reduction (ACC / AHA Guidelines for Heart Failure*)
What are special nursing considerations:	Onset 1 to 2 minutes; Peak 10 minutes Half-life 2 minutes Note: Blood pressure response is variable; β_2 causes vasodilatation; β_1 increases cardiac output and may increase BP

Dopamine

Mimics endogenous dopamine;
metabolic precursor of
norepinephrine and epinephrine

What receptors are stimulated:	Dopaminergic at low doses (0.5-2.0 mcg/kg/min) β_1 also at moderate doses (2.0-10.0 mcg/kg/min) Pure alpha stimulation at high doses > 10mcg/kg/min
What are the resultant actions:	Increase GFR at low doses Increase contractility at moderate doses (greater effects on contractility than heart rate) Vasoconstriction (alpha) at high doses
When and why do we use:	Refractory hypotension / shock * Not indicated for routine treatment or prevention of acute renal failure
What are special nursing considerations:	Onset 1-2 minutes; Peak 10 minutes Maximal effects @20/mcg/kg/min Large IV line or central line; Regitine (alpha blocker) for infiltrate

Norepinephrine

Endogenous precursor
of epinephrine

What receptors are stimulated:	Primarily alpha stimulation Some β_1 (In lower doses β_1 can be more dominant)
What are the resultant actions:	Potent vasoconstrictor (increased afterload) Some increased contractility (+inotrope)
When and why do we use:	Refractory hypotension / shock (used as a vasopressor but will have inotropic properties)
What are special nursing considerations:	Onset: rapid; very short half-life Duration 1-2 minutes (BP checks q2 minutes while titrating) Large IV line or central line Regitine (alpha blocker) for infiltrate

Phenylephrine

Synthetic compound

What receptors are stimulated:	Direct effect: Dominant alpha stimulation No substantial β_1 effect at therapeutic doses Indirect effect: Releases norepinephrine
What are the resultant actions:	Vasoconstriction (increased afterload)
When and why do we use:	As a vasopressor for unresponsive hypotension
What are special nursing considerations:	Pressor effect occurs almost immediately Persists for 10 to 15 minutes

Remember!!

- Titrate up based on onset of action
- Wean based on duration of action
- Link physiological properties of drug to patient condition

Non Sympathomimetic Vasopressor

Arginine Vasopressin (ADH)

- Vasoconstrictive effects
 - Allowing for regional vasodilation
- Antidiuretic hormone effects
- Restoration of catecholamine sensitivity

- Use in refractory shock
 - Also consider methylene blue
 - Also consider adrenal insufficiency as cause
- Low dose exogenous
 - 0.04 units / min
 - Non titrateable drug

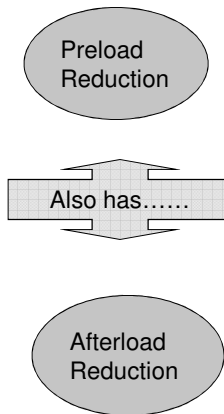
Not a sympathomimetic

**Non Sympathomimetic
Inotropes**

Phosphodiesterase Inhibitors

Used as an
Inotrope

BUT



Phosphodiesterase Inhibitors

- New generation: Milrinone (Primacor)
- Creates + inotropic effect by increasing availability of calcium
 - Inhibits the degradation of cyclic AMP which is indirectly responsible for increasing the influx of calcium through the calcium channel
- Smooth muscle relaxant (venous and arterial vasodilator)
- Indications:
 - Refractory heart failure (in combination with dobutamine)
 - Left ventricular failure in MI
 - Patients waiting transplant
- Side Effects:
 - Ventricular arrhythmias, thrombocytopenia (new generation less)
- Nursing Considerations:
 - Onset IV: Immediate
 - Peak: 10 minutes

Venous and Arterial Vasodilators

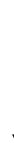
A Closer Look at Venous Versus Arterial Vasodilators

Venous Vasodilators



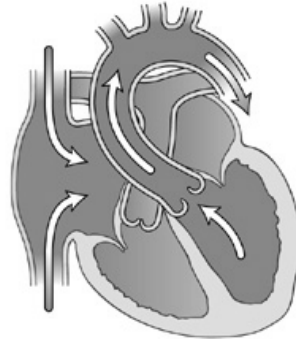
Decrease Preload

Arterial Vasodilators



Decrease Afterload

- Preload reduction:
- Decreased pulmonary venous congestion
 - Decreased ventricular wall stress
 - Increased diastolic coronary blood flow
 - Improved myocardial oxygen delivery



- Afterload reduction:
- Reduction in ventricular wall stress
 - Increased coronary blood flow
 - Enhanced oxygen delivery and utilization
 - Improved systolic contractile function
 - Reduction in mitral regurgitation



A Closer Look at Venous Versus Arterial Vasodilators

- Some medications do both
- Some depend on dose
 - ✦ Nesiritide
 - ✦ NTG
 - ✦ Nipride
 - ✦ CA Channel blockers
 - ✦ PDE Inhibitors
 - ✦ ACE Inhibitors
 - ✦ Other Vasodilators

Nesiritide (Natreacor)

- Recombinant form of human B type natriuretic peptide (BNP)
- BNP is a naturally occurring cardiac neurohormone secreted by the heart in the body's response to heart failure
- BNP allows the heart to participate in the regulation of vascular tone and extracellular volume status
- The BNP system and the renin-angiotensin system counteract each other in heart failure
- BNP levels are elevated in heart failure

Nesiritide (Natreacor)

- Balanced arterial and venous vasodilatation
 - Causes rapid reduction in right and left sided ventricular filling pressures (preload reduction)
 - Reduces afterload
- Indicated for acutely decompensated heart failure patients who have dyspnea at rest

Nesiritide (Natreacor)

- Patient must have systolic BP > 90 mmHg
- PAOP should be estimated to be \geq 20 mmHg
- Given by IV bolus and maintenance infusion (bolus to be taken from reconstituted IV bag and not from vial)
 - 2mcg/kg
- Infusion is usually 24-48 hours
 - 0.01mcg/kg/min

Monitor BP closely during administration.

Nitroglycerin

- Mixed venous and arterial vasodilator
 - Dosage < 1mcg/kg/min = venous vasodilator
 - Dosage > 1mcg/kg/min = arterial and venous vasodilator
 - Sublingual tablets provide high enough dosage to dilate arteries and veins
 - Rules for taking SL NTG
 - Nitrate tolerance can be avoided by providing nitrate free interval preferably during night time hours
 - NTG Paste – predominantly venous dilator
 - Decreases activity of Heparin

Nitroglycerin

- Uses: Acute MI, unstable angina, CHF
- Side Effects: H/A, Hypotension, flushing
- Nursing Considerations:
 - Contraindicated with Sildenafil like drugs (24 hours)
 - Caution (all venous vasodilators) with:
 - Hypertrophic cardiomyopathy, aortic stenosis, right ventricular MI
 - Do not give if
 - Systolic BP < 90 mm Hg or \leq 30 mm Hg below baseline
 - Bradycardia < 50 BPM
 - Tachycardia > 100 BPM (in absence of clinical HF)
 - Right ventricular infarct
 - Treat H/A with pain meds and decrease dose
 - Onset IV: 1-2 minutes
 - Duration: 3-5 minutes

Nipride

- Mixed venous and arterial dilator (primarily arterial)
- Decreases SVR, BP, PVR, PAOP, RAP
- Uses:
 - Hypertensive crisis
 - CHF
 - Acute Mitral Regurgitation
 - Other Indications for Afterload Reduction
- Side Effects:
 - Hypotension
 - Thiocyanate toxicity: tinnitus, blurred vision, delirium, seizures, muscle twitching, absent reflexes, dilated pupils [several days – high doses]
- Nursing Considerations:
 - Onset: 1-2 minutes
 - Duration: 1-10 minutes
 - Monitor BP carefully- arterial line encouraged
 - Light sensitive

Non ACE Inhibitor Arterial Vasodilators

- All non ACE Inhibitor (or ARB) vasodilators are potent stimulators of the renin angiotensin system
 - Thus side effects include increased intravascular volume and progressive edema
- Direct Smooth Muscle Relaxants
 - Examples: Hydralazine, Minoxidil
- Alpha₁ Adrenergic Blockers
 - Examples: Prazosin, Terazosin, Doxazosin
- Central anti-adrenergics
 - Examples: Clonidine, Methyldopa
- Peripheral anti-adrenergics
 - Examples: Reserpine, Guanethidine
- “INE” Calcium Channel Blockers
 - Nifedipine, isradipine, amlodipine, felodipine, mimodipine

Acute Conditions Requiring Vasodilator Therapy

- Vasodilators can be life saving in conditions which require immediate afterload reduction or reduction of systemic blood pressure
 - Severe acute mitral regurgitation (papillary muscle rupture) (inferior / posterior MI)
 - Ventricular septal rupture (anterior MI)
 - Severe acute aortic insufficiency
 - Hypertensive emergency
 - Aortic dissection



Shifting Gears!

Common Oral Medications to
Optimize Cardiac Performance in
Chronic Disease Management

Digoxin

- Inhibits the Na^+ and K^+ membrane pump
- ▼
- Increase in intracellular Na^+
- ▼
- Enhances the Na^+ and Ca^{++} exchange
- ▼
- Leads to ▲ in intracellular Ca^{++}
- ▼
- ▲ inotropic activity

Digoxin

- Increases vagal activity
- Digoxin decreases conduction velocity through the AV node (sympathetic stimulation easily overrides the inhibitory effects of digoxin on AV node conduction)
- The conduction velocity increases in the atria, but decreases in the AV node.
- Automaticity is also increased, in the atria, AV node, Purkinje fibers and ventricles.
 - Calcium channel blockers are replacing digoxin as agent for rate control in atrial arrhythmias
 - Digoxin no better than placebo in converting atrial fib to SR
- Digoxin decreases sympathetic outflow and decreases renin production
 - Beneficial in heart failure

Digoxin

- Indications
 - HF
 - Atrial arrhythmias (older indication)
 - Still an option when BP is a concern
- Contraindication / cautions
 - Acute MI
 - Ventricular arrhythmias, HB, Sick Sinus Syndrome
 - Obstructive Hypertrophic Cardiomyopathy
 - Electrolyte abnormalities (decreased K⁺, Ca⁺⁺ and Mg⁺⁺)

Digoxin

- Has a narrow therapeutic range
- Toxicity may occur at therapeutic levels
- Lower doses now routinely used 0.125 mg daily
- Amiodorone increases serum digoxin concentration (digoxin doses must be reduced if starting amiodarone)
- Multiple other medication interactions
- Dialysis is not effective with digoxin toxicity because of high tissue binding of digoxin

More About Digoxin Toxicity

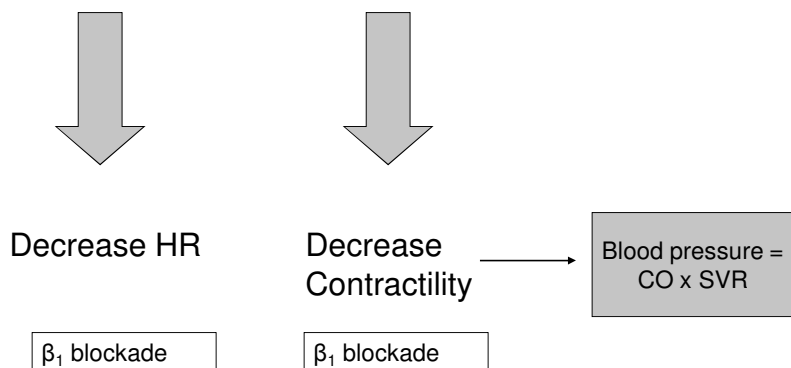
- EKG Changes with Toxicity
 - Increased automaticity with with impaired conduction is common (example: PAT with AV Block)
- Other Signs and Symptoms of Toxicity
 - N & V, HA, Confusion
 - Visual disturbances: halos, change in color perception



Beta Blockers

“lol” medications

A Closer Look at Beta Blockers



Cardiovascular Indications for Beta Blockers

- Hypertension
- Angina
- AMI
- Post Infarction
- Supraventricular arrhythmias
- Ventricular arrhythmias
- Aortic Dissection
- Hypertrophic cardiomyopathy (actually increase C.O.)
- Mitral valve prolapse
- Prolonged QT syndrome
- Heart failure
- Digitalis induced ventricular arrhythmias

Betablockers prevent reflex tachycardia associated with other vasodilators

A Closer Look at Beta Blockers

Common Cardiac Indications

- Angina: Used with angina to decrease myocardial oxygen demand and increases diastolic filling time
- Acute Coronary Syndrome: Decreases ventricular arrhythmias short term and ventricular remodeling long term
 - Mortality benefit
- HF: Decrease contractility, however, now indicated in HF because they block the neurohormonal response of the SNS
 - Decrease ventricular remodeling
 - Mortality benefit
 - Avoid in acute decompensated HF

Beta Blockers

- **Nonselective: Block both Beta₁ and Beta₂**

- Propranolol (Inderal)
- Timolol (Blocadren)
- Nandolol (Corgard)
- Sotalol (Betapace)
- Carvedilol (Coreg)
 - ✦ also alpha blockade
 - ✦ Intrinsic sympathetic activity – causing stimulation of B₁ and slight increase of HR
 - Net effect less drop in HR

- **Cardio selective: Block Beta₁**

- Acebutolol (Sectral)
- Metoprolol (Lopressor)
- Atenolol (Tenormin)
- Esmolol (Breviblock)
- Bisoprolol (Z Beta)
- Nebivolol (Bystol)
 - (also nitric oxide vasodilatory properties)

Beta Blockers Recommended by Disease State

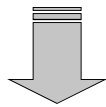
- **Post MI**
 - Atenolol
 - Carvedilol
 - Metoprolol
 - Propranolol
 - Timololol
- **Heart Failure**
 - Bisoprolol
 - Carvedilol
 - Metoprolol

Beta Blockers Considerations in AMI

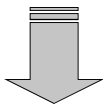
- Oral Beta Blockers
 - Within 24 hours
- IV Beta Blockers
 - Reasonable in patients who are hypertensive
 - May be harmful in patients with high risk for cardiogenic shock
- Contraindications
 - Signs of HF
 - Low cardiac output state
 - Increased risk for cardiogenic shock
 - Relative contraindications
 - PR > .24 seconds
 - 2nd or 3rd degree block
 - Active asthma
 - Reactive airway disease

Calcium Channel Blockers

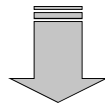
A Closer Look at Calcium Channel Blockers



Decrease
HR



Decrease
Contractility



Decrease
Afterload

Not all calcium channel blockers are created equal:
therefore not all calcium channel blockers have the
same actions

A Closer Look at Calcium Channel Blockers

- Three potential effects of Calcium Channel Blockers
 - Cardiac Muscle Contractility
 - Blocks inward flow of calcium in Phase II of action potential and decreases force of contraction
 - Cardiac Conduction
 - Depresses automaticity and velocity and decreases HR
 - Vascular Smooth Muscle Relaxant
 - Coronary artery dilatation and increases blood flow to coronary arteries (except nifedipine)

A Closer Look at Calcium Channel Blockers

	Verapamil	Dihydropyridines	Diltiazem
Heart Rate	▼▼	▲	▼
AV Nodal Conduction	▼▼	-----	▼
Contractility	▼▼	▼	▼
Arterial Vasodilatation	▲▲	▲▲▲	▲

Calcium Channel Blockers: Indications

- Atrial Fibrillation / Flutter and PSV
 - Diltiazem and Verapamil
- Treatment of angina in combination with beta blockers and nitrates
 - Diltiazem and Verapamil with Nitrates
 - “ines” with Beta Blockers
- Hypertension (decreases SVR)
 - “ines”
- Adjunct treatment for diastolic not systolic heart failure
- Hypertrophic cardiomyopathy (verapamil)
- Prevention of coronary spasm for patients undergoing PCI

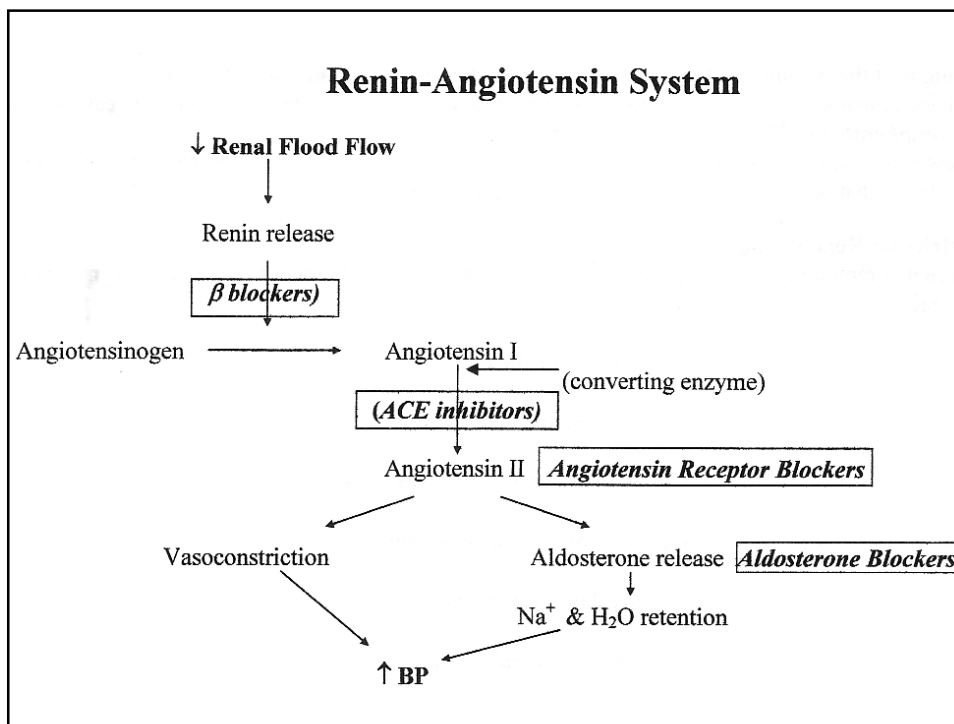
A Closer Look at “Ine” Calcium Channel Blockers

- Newer Dihydropyridines Calcium Channel Blockers
 - Amlodipine (Norvasc)
 - Effects vascular smooth muscle with minimal to no effect on heart rate or conductivity
 - Good decrease in total peripheral vascular resistance
 - Directly dilates coronary arteries (nitric oxide release)

Amlodipine in Heart Failure

Caution with Nifedipine

ACE Inhibitors and Angiotensin II Receptor Blockers



A Closer Look at ACE Inhibitors

- ACE Inhibitors impact afterload and preload because they block the vasoconstrictive effects of angiotensin II
 - Very important in reducing workload of left ventricle in systolic dysfunction
- ACE Inhibitors additionally assist with preload reduction by blocking the effects of aldosterone release

A Closer Look at ACE Inhibitors & Angiotensin II Receptor Blockers

- Angiotensin-converting enzyme inhibitors (“pril” medications)
 - Captopril (Capoten), Enalapril (Vasotec), Lisinopril (Zestril), Quinapril (Accupril), Ramipril (altace), Benazepril (Lotensin), Fosinopril (Monopril)
- Angiotensin II Receptor Blockers (“sartan” medications)
 - Losartan (Cozaar), Irbesartan (Avapro), Candesartan (Aticand), Valsartan (Diovan)

A Closer Look at ACE Inhibitors

- The effects of blocking the Renin Angiotensin Aldosterone system are complex:
 - Overall cardioprotective and vasculoprotective effect
 - Improved balance of myocardial oxygen supply and demand by decreasing left ventricular preload and afterload
 - Reduction of left ventricular mass in LV hypertrophy
 - Can decrease the progression rate of kidney failure especially in insulin dependent diabetics
 - Kinins and Prostaglandins

A Closer Look at ACE Inhibitors

- Influences bradykinin and can produce cough
- Cough is side effect in 10-20% of patients
- Need to assure cough is not sign of worsening heart failure
- Patient may need changed to ARB

Absolute Contraindication!
Oral Angioedema

A Closer Look at ACE Inhibitors

- Can cause a temporary rise in creatinine in patients with low cardiac output
- Can cause acute renal failure in patients with bilateral renal artery stenosis
 - Dilating efferent glomerular arterioles which result in decreased glomerular filtration with no improvement in afferent arterioles
- Renal function
 - Evaluated prior to and 1-2 weeks after initiation of ACE inhibitors in high risk patients
- If acute kidney injury develops from ACE – I, then hydralazine in combination with isosorbide dinitrate should be used
 - Combination achieves venous and arterial vasodilation

Aldosterone Antagonists

Clinical Effects of Aldosterone

- Promotes retention of sodium
- Promoted loss of potassium and magnesium
- Potentiates catecholamines
- Inhibits the parasympathetic nervous system
- Decreases arterial compliance
- Promotes direct remodeling
- Has prothrombotic properties
- Causes vascular inflammation and injury

Spironolactone (Aldactone)

- Non selective aldosterone blocker
 - Blocks aldosterone and androgen; stimulates progesterone

Major side effect: gynecomastia, sexual dysfunction and menstrual problems due to non selectivity

- Side effect of hyperkalemia when used with ACE Inhibitor or ARB
- Mortality reduction

Eplerenone (Inspra)

- Selective aldosterone receptor antagonist

Eliminates most gynecomastia and sexual side effects associated with aldactone

- Side effect of hyperkalemia when used with ACE Inhibitor or ARB
- Indicated in MI with LV Dsyfunction
 - Prevent progression of heart failure
 - Prevent sudden cardiac death
 - Prevent recurrent MI

Newer / Future Agents

- Direct Renin Inhibitors
 - Aliskiren (Tekturna)
 - Currently used as antihypertensive
- Vasopressin 2 Antagonists
 - Vasopressin 1 (vascular)
 - Vasopressin 2 (renal collecting ducts)
 - Vasopressin 3 (pituitary)
 - Tolvaptan – in addition to standard IV therapy in acute decompensated HF
- Adenosine A1 Receptor Antagonists
 - Investigational
 - Enhances response to diuretics

Antiarrhythmic Medications Effecting the Action Potential

- **Class I** – Fast sodium channel blockers
 - IA: Quinidine, Procainamide, Disopyramide
 - IB: Lidocaine, Mexiletine
 - IC: Flecainide, Propafenone
- **Class III** – Potassium channel blockers
 - Amiodarone, Ibutilide, Dofetilide, Sotalol
- **Class IV** – Calcium channel blockers
 - Verapamil, Diltiazem



Class II ???

Class III Antiarrhythmics

Action Potential	Inhibits potassium ion fluxes during phase II and III of the action potential
Actions	Directly on myocardium to delay repolarization (prolongs QT); prolongs effective refractory period in all cardiac tissue; By definition act only on repolarization phase and should not impact conduction
Cautions	Proarrhythmic Effects (amiodarone less) Prolongs QT interval
Uses	Drug dependent
Drugs	Amiodarone (Pacerone, Cordorone) Ibutilide (Corvert) – pure class III Dofetilide (Tikosyn) – pure class III Sotalol (Betapace)

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Class III Antiarrhythmics

Amiodarone (ARREST Trial)	<p>Approved for life threatening refractory ventricular arrhythmias; considered before lidocaine in pulseless VT or V fib; considered ahead of lidocaine for stable VT with impaired cardiac function; expanded to atrial and ventricular arrhythmias, conversion and maintenance of atrial fib</p> <p>Slows conduction in accessory pathways</p> <p>Originally marketed as anti-anginal (potent vasodilator)</p> <p>Relaxes smooth and cardiac muscle, reduces afterload and preload (well tolerated in heart failure and cardiomyopathy)</p> <p>Proarrhythmias less frequent</p> <p>Is also a weak sodium channel blocker, also has effects similar to class II and IV, also has anticholinergic properties</p>
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Amiodarone Dosing

- Life-threatening ventricular arrhythmias
 - Rapid loading infusion 150 mg administered at a rate of 15 mg/minute (over 10 minutes); initial infusion rate should not exceed 30 mg/minute
 - The slow loading phase is 360 mg at a rate of 1 mg/minute (over 6 hours)
 - First maintenance phase of the infusion is 540 mg at a rate of 0.5 mg/minute (over 18 hours).
 - After the first 24 hours, maintenance infusion rate of 0.5 mg/minute should be continued; the rate of the maintenance infusion may be increased to achieve effective arrhythmia suppression.
 - In the event of breakthrough episodes supplemental infusions of 150 mg administered at a rate of 15 mg/minute (over 10 minutes) may be given.
- For cardiac arrest secondary to pulseless ventricular tachycardia or ventricular fibrillation
 - Initial adult loading dose is 300 mg (diluted in 20–30 mL of a compatible IV solution) given as a single dose, rapid IV

More on Amiodarone

- Nursing Considerations
 - Peripheral IV concentration not to exceed 2mg/ml
 - Oral administration / GI symptoms
 - Severe adverse reactions
 - ✦ Potentially lethal interstitial pneumonitis
 - ✦ CXR q 3 -6 mos
 - Less common in lower doses;
 - Thyroid dysfunction is also a side effect
 - by weight amiodarone is 37% iodine
 - Toxic side effects increase with length of use and dose

New Antiarrhythmic

- Dronedarone (Multaq)
 - Rejected by FDA 2006
 - Decision by April 30 2009
 - Decreases hospitalizations in atrial fib
 - Paroxysmal or persistent atrial fibrillation
 - Safer alternative to amiodarone in terms of extra cardiac SE
 - Contraindicated in decompensated HF

Class III Antiarrhythmics

Ibutilide (Corvert)	Indicated for rapid conversion of atrial fib or flutter to sinus rhythm; IV use only; also facilitated cardioversion (Don't convert atrial fib or flutter of duration without anticoagulation) Rather than blocking outward potassium currents – promotes influx of sodium through slow inward sodium channel
Dofetilide (Tykosit)	More "pure" class III agent Conversion to and maintenance of SR in A fib and flutter Reserved for very symptomatic patients, monitored 3 days in hospital Widens the QT; cannot be given with many other drugs (prolong QT or inhibit metabolism or elimination); no negative inotropic effects, neutral effect on mortality from arrhythmias post MI and in in HF, can be used in this population to prevent worsening HF from atrial fib

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Class III Antiarrhythmics

<p>Sotalol (Betapace^R) (Betapace^{AF})</p>	<p>Used in atrial arrhythmias and life threatening ventricular arrhythmias Indicated for stable monomorphic VT or Polymorphic VT with normal QT in ACLS protocol Non selective beta blocking agent with class III properties Significant class III effects are only seen at doses \geq 160 mg Proarrhythmic potential (prolonged QT) More effective in preventing reoccurring arrhythmias than several other drugs</p>
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Drugs Used to Alter Clotting

- Fibrinolytics
- Anticoagulants
- Antiplatelets

Anticoagulants

- Unfractionated Heparin
- Low Molecular Weight Heparin
- Direct Thrombin Inhibitors
- Factor Xa Inhibitors
- Warfarin (Coumadin)

A Closer Look at Heparin

- Prevents conversion of prothrombin to thrombin by binding to antithrombin III
- Antithrombin III naturally inhibits thrombin; when heparin binds with it the inhibition is increased 1000 times
- Neutralizes the clotting capabilities of thrombin
- Works in the intrinsic and common pathway
- Also Inhibits platelets (thrombin is most potent platelet stimulator)
- Anticoagulation is almost instant
- $\frac{1}{2}$ life relatively short
- Antidote: Protamine 1 mg per 100 units

More About Heparin

- aPTT (activated partial thromboplastin time) is used to monitor effectiveness and safety
- Goal is aPTT 1.5 Xs the control
- Weight based heparin dosing reaches goal 90% of time compared to 77% with standard therapy
- Baseline aPTT, PT/INR, platelets and CBC
- Increased bleeding can occur with renal failure
 - Heparin has dual clearance mechanism but greater effect on platelet function than LMWH

Complications of Heparin

- Bleeding
- Mild thrombocytopenia
 - Mild thrombocytopenia occurs in 10-20% of patients
- Severe thrombocytopenia occurs in 1-2% of patients
 - Platelet aggregation resulting in venous or arterial thrombosis
 - Determining patients at risk is unpredictable
 - Generally occurs 10-14 days after initiation of heparin
 - DC heparin if platelets fall below 100,000
 - Severe thrombocytopenia is due to an immune response (HIT)
 - ✦ No additional heparin including line flushes

A Closer Look at Low Molecular Weight Heparin

- **Low Molecular Weight Heparin (Lovenox)**
 - Enoxaparin, dalteparin, tinzaparin, and nadroparin
 - **Smaller in size**
 - Antithrombin by inhibiting factor Xa
 - Causes less inactivation of thrombin and less inhibition of platelets and less bleeding than standard heparin
 - Does not significantly influence bleeding time
 - Anti Xa levels can be drawn 4 hours after SQ dose
 - Renal failure results in increased risk of bleeding because LMWH is renally cleared
 - Special dosing for chronic renal insufficiency with enoxaparin

Benefit of Low Molecular Weight Heparin over Unfractionated Heparin

- More predictable anticoagulant response
- Lower incidence of heparin induced thrombocytopenia
- Lower incidence of osteoporosis
- No need to monitor APTT
- Less platelet activation
- Can be self administered with Sub – Q administration
- ½ life 4-6 hours
- Protamine reverses 60% of drug effect

Administration of Enoxaparin

- Full length of 27 gauge $\frac{1}{2}$ needle (prepackaged) should be injected
- Skin fold held until needle withdrawn
- Use anterolateral or posterolateral walls of abdomen
- Rotate sites frequently
- Do not massage site
- Prevention of DVT
 - 30 mg BID or 40 mg daily
 - 40 mg daily in most situations
- Venous thrombosis / DVT
 - 1 mg/kg BID or 1.5 mg/kg daily depending of specific circumstances
- Unstable Angina / NSTEMI (or as adjunct in STEMI)
 - 1 mg/kg BID
 - IV dosing can be used in STEMI
- Embolism with Atrial Fib
 - 1 mg/kg BID
- *Dosing adjustments are required in several renal impairment*

Direct Thrombin Inhibitor

- Indicated for patients with HITTS
- Approved in Non STEMI guidelines and for PCI
- Ability to inactivate fibrin bound thrombin
- Less binding to plasma proteins, therefore more reliable anticoagulation effect
- Examples
 - Lipirudin and desirudin (hirudin)
 - Argatroban
 - Bivalirudin* (angiomax)
 - Pradaxa (dabigatran)

Synthetic Factor Xa Inhibitor

- Fondaparinux (Arixtra)
 - Used for venous thromboembolism and PE
 - Approved for DVT prophylaxis in certain surgical patients
 - Recently approved and added to NonSTEMI Guidelines
 - Cannot be used as sole anticoagulant during PCI
- Neutralizes Factor Xa and interrupts the clotting cascade
- Does not inhibit thrombin
- No reported HIT
- Sub Q injection
- Once daily dosing (fixed dose can cover a range of body weights – lower dose for low body weight)
- Contraindicated in severe renal dysfunction
- No laboratory monitoring
- No antidote (Recombinant factor VIIa can help reverse anticoagulation effect)

A Closer Look at Warfarin

- Inhibits the synthesis of prothrombin.
- Acts indirectly through the liver by altering the synthesis of vitamin K dependent factors in the extrinsic pathway. The vitamin K dependent factors are left biologically inactive.
- It takes 4-5 days to reach a therapeutic level.
 - Can have initial transient hypercoagulable state
 - Must be overlapped with heparin

More About Warfarin

- PT (prothrombin time monitored to evaluate effectiveness and safety)
- PT – problems with standardization of anticoagulation intensity
- INR (International Normalized Ratio) – relates the patients PT to the intensity of actual coagulation.
- **Dosing**
 - Start with 5mg per day
 - Loading doses not recommended
 - PT / INR daily until therapeutic level reached
 - Dosage may need adjusted after 4-6 days due to individual sensitivity
 - PT / INR twice weekly for 2 weeks and weekly for two months
 - PT / INR every 4-6 weeks after dose stable

More About Warfarin

- Goal for INR of 2.0 – 3.0 is adequate in most situations
- INR of 2.5 – 3.5 is goal for mechanical prosthetic valves and prevention of recurrent MI
- Chronic condition require lifelong therapy
- Acute conditions (PE, DVT) usually require at least six months of therapy

Nursing Considerations with Warfarin

- Many many drugs interact with coumadin to alter PT
 - Amiodarone increases effect of warfarin
 - Antibiotics increase effect of warfarin
- Consistency in diet is important especially with known high vitamin K foods (green vegetables)
 - Foods high in Vit K decrease effect
- Patient compliance is critical
- Antidote: Vitamin K
 - May not be indicated INR 4.5-10
- Fresh frozen plasma if severe hemorrhage
- Recombinant factor VIIa is also an option for life threatening bleeding

Pradaxa (dabigatran)

- Approved October 2010 for prevention of stroke in nonvalvular atrial fibrillation
- Direct thrombin inhibitor
- Superior in preventing stroke
- 150 mg BID (CC <30 75 mg BID)
- Gastrointestinal bleeding
- Keep in original bottle (expires 60 days after open)
- Works for 13 hours so Q12 hours not BID
- D/C 1-2 days prior to surgery (3-45 for CC <50)

Antiplatelet Drugs

- GP IIb/ IIIa Inhibitors
- ADP Antagonists
 - Thienopyridines
- Thromboxane A₂ Inhibitor

A Closer Look at Antiplatelet Drugs: GP IIb/IIIa Inhibitors

- GP IIb/IIIa Inhibitors
 - **Eptifibatid (Integrelin)**
 - **Tirofiban (Aggrastat)**
 - **Abciximab (Repro)**
 - Inhibit the glycoprotein protein IIb/IIIa receptors which platelets and fibrinogen bind with to form the fibrin mesh

More about GP IIb / IIIa Inhibitors

- Glycoprotein 2b / 3a receptors are most abundant protein on the platelet surface. It is tightly packed on the platelet surface with about 80,000 receptors per platelet. Primary receptor for platelet aggregation.
- Fibrinogen links to these receptors and simultaneously binds receptors on two separate platelets. Platelet cross-linking occurs leading to platelet aggregation.

A Closer Look at ADP Inhibitors

- Adenosine Diphosphate (ADP) Inhibitors
 - Clopidogrel (Plavix)
 - Inhibit ADP which is released by platelets.
 - ADP enhances adhesiveness and aggregation of platelets by activating GPIIb/IIIa receptors.
 - Concern with Proton Pump Inhibitors
 - Resistance concern
 - D/C 5 days prior to surgery

Prasugrel (Effient)

- More effective in PCI with STEMI in preventing ischemic events than clopidogrel
- Same class
- Dosing differences from clopidogrel
- Tighter criteria for administration due to increased bleeding risk
- Not in those > 75 years
- Not in those < 60 KG
- Not in those with history of TIA
- D/C 7 days prior to surgery

A Closer Look at Aspirin

- ASA
 - Inhibits Thromboxane A₂ which is released with vascular injury. Platelet reactivity is diminished.
 - Also inhibits the endothelium's production of prostaglandin I₂ which decreases platelet aggregation and induces vasodilation.

Caution with Asthma

Aspirin

- 75 – 325 mg dosing
- 325 mg used after stent placement
- New recommendations for primary prevention
 - Men \geq 45
 - Women \geq 55

