Cardiovascular Pharmacology: From Physiology to Clinical Practice

PESI Health Care
Cardiac Essentials Conference

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CNEA / Key Choice
“I’m not telling you it is going to be easy, I’m telling you it is going to be worth it.”

~ Art Williams
Impacting Cardiac Output to Improve Myocardial Performance
The Heart as a Pump

**Goal:** Forward propulsion of blood to perfuse the body.

**Flow** is determined by:

\[ \sqrt{\text{Pressure}} \]
\[ \sqrt{\text{Resistance}} \]
\[ \sqrt{\text{Volume}} \]
FIGURE 4-1 Cardiovascular circuit.
Right Sided versus Left Sided System
Determinants of Myocardial Performance

- Stroke Volume
  - Preload
  - Afterload
  - Contractility
- Heart Rate
  - Synergy
  - Synchrony
Basic Hemodynamic Formula

Cardiac Output

Heart Rate X Stroke Volume

Preload  Afterload  Contractility

Same four components also determine myocardial oxygen demand
Definitions

- **Cardiac Output**: Volume of blood ejected by the ventricle each minute
  - Normal: 4-8 liters/minute

- **Cardiac Index**: Adjustment made for body size
  - Normal cardiac index: 2.5-4 liters/minute/m²

- **Stroke Volume**: Volume of blood ejected with each beat.
  - Normal 60-120 ml / beat
  - Systolic BP as non invasive indicator

- **Ejection Fraction**: Percent of blood ejected from the ventricle
  - Normal: 55% to 60%
Preload

- The ventricle is **preloaded** with blood at the end of diastole: Creates stretch on **myocardial muscles fibers**

- Determined by:
  - Volume of blood filling the ventricle at end of diastole
  - Greater the volume the greater the stretch (muscle fiber length)
    - Greater the stretch the greater the contraction
      - Greater the contraction the greater cardiac output

**TO A POINT**
Preload Assessment

**Right ventricular preload**
- Central venous pressure or right atrial pressure

**Noninvasive assessment**
- JVD
- Hepatojugular reflux
- Peripheral edema
- Weight

**Left ventricular preload**
- Pulmonary artery occlusive pressure (to reflect left atrial pressure)

**Noninvasive Assessment**
- Lungs sounds
- $S_3$
- Blood Pressure
- Urine Output

Right Side Effects the Left Side
Factors Influencing Preload

• Body Position
• Venous Tone
• Intrathoracic pressure
• Intrapericardial pressure
• Dysrhythmias
• Atrial Kick
• LV Function

• Circulating blood volume
  – Hypervolemia
  – Hypovolemia
  – Third spacing

• Size of Container
  – Sepsis
  – Anaphylaxis
  – Venous vasodilators
Afterload

• **After the ventricle is loaded:**
• **Pressure ventricle needs to overcome to eject blood volume**

• Blood pressure is major component of afterload but it does not equal afterload

• Other components
  – Valve compliance
  – Viscosity of blood
  – Arterial wall compliance
    • Aortic compliance
Afterload Assessment

- Left ventricle:
  - Systemic vascular resistance
  - Other components
    - Valve compliance
    - Viscosity of blood
    - Arterial wall compliance
      - Aortic compliance

- Right ventricle:
  - Pulmonary vascular resistance
Key Principles in Understanding Hemodynamic Assessment

• Vascular tone is affected by:
  – Large vessel compliance
  – Peripheral vascular resistance (smaller vessels)

• Vessel resistance changes more quickly than large vessel compliance

• Increased resistance = increased DBP
Causes of Increased LV Afterload

- Arterial vasoconstrictors
- Hypertension
- Aortic valve stenosis
- Increased blood viscosity
- Hypothermia
- Compensatory vasoconstriction from hypotension in shock

Causes of Decreased LV Afterload

- Arterial vasodilators
- Hyperthermia
- Vasogenic shock states (sepsis and anaphylactic) where the body cannot compensate with vasoconstriction
- Aortic Regurgitation — hyperdynamic cardiac output therefore lowering systemic vascular resistance
Contractility

• **Ability of myocardium to contract independent of preload or afterload**
  – Velocity and extent of myocardial fiber shortening
  – Inotropic state

• Related to degree of myocardial fiber stretch (preload) and wall tension (afterload).

• Influences myocardial oxygen consumption

• **↑** contractility
  ⇒ **↑** myocardial workload
  ⇒ **↑** myocardial oxygen consumption
Important Points about Contractility

• No accurate way to measure contractility

Noninvasive Assessment: Ejection Fraction

• Low cardiac output does not necessarily mean diminished contractility (i.e. hypovolemia)

• Correct preload and afterload problems first in a patient with a low ejection fraction.

• Increasing contractility with medications will also increase myocardial oxygen demand.
Factors Altering Contractility

• Decreased contractility
  – Excessive preload or afterload
  – Drugs – negative inotropes
  – Myocardial damage
  – Ischemia
  – Cardiomyopathy
  – Hypothyroidism
  – Changes in ionic environment: hypoxia, acidosis or electrolyte imbalance

• Increased contractility
  – Drugs
    • Positive inotropes
  – Hyperthyroidism
  – Adrenal Medulla Tumor
Heart Rate

- Mathematically heart rate increases cardiac output

- Physiological limit where increased heart rate will decrease cardiac output due to decreased filling time (decreased preload)
Blood Pressure Monitoring

- Systolic: Maximum pressure when blood is expelled from the left ventricle
  - Represents stroke volume

- Diastolic: Measures rate of flow of ejected blood and vessel elasticity
  - Represents state of arterioles

- Pulse Pressure: Difference between systolic and diastolic pressure
<table>
<thead>
<tr>
<th>Warm and Dry</th>
<th>Warm and Wet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Perfusion</td>
<td>Normal Perfusion</td>
</tr>
<tr>
<td>No Congestion</td>
<td>Congestion</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold and Dry</td>
<td>Cold and Wet</td>
</tr>
<tr>
<td>Low Perfusion</td>
<td>Low Perfusion</td>
</tr>
<tr>
<td>No Congestion</td>
<td>Congestion</td>
</tr>
</tbody>
</table>
Hemodynamic and Clinical Subsets

**Normal Hemodynamics (I)**
- No pulmonary congestion:
  - PWP < 18; Dry lungs
- No hypoperfusion:
  - CI > 2.2; Warm skin

**Backwards Failure (II)**
- Pulmonary congestion
  - PWP > 18; Wet lungs
- No hypoperfusion
  - CI > 2.2; Warm skin

**Forwards Failure (III)**
- No pulmonary congestion
  - PWP < 18; Dry lungs
- Hypoperfusion
  - CI < 2.2; Cold skin

**The Shock Box (IV)**
- Pulmonary congestion
  - PWP > 18; Wet lungs
- Hypoperfusion
  - CI < 2.2; Cold skin

Preload: PAOP (other volume indicators)
Relationship of CI to Clinical Signs of Hypoperfusion

<table>
<thead>
<tr>
<th>CI</th>
<th>Clinical State</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.7 – 4.7</td>
<td>Normal</td>
</tr>
<tr>
<td>2.2 – 2.7</td>
<td>Subclinical depression</td>
</tr>
<tr>
<td>1.8 – 2.2</td>
<td>Clinical hypoperfusion</td>
</tr>
<tr>
<td>&lt; 1.8</td>
<td>Cardiogenic shock</td>
</tr>
</tbody>
</table>

The value for CI that best separates patients with and without hypoperfusion is 2.2 L/min/M²
## Relationship of PAOP Clinical Signs of Pulmonary Congestion

<table>
<thead>
<tr>
<th>PAOP</th>
<th>Clinical State</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 – 20 mmHg</td>
<td>Pulmonary Congestion</td>
</tr>
<tr>
<td>20 – 25 mmHg</td>
<td>Moderate Congestion</td>
</tr>
<tr>
<td>25 – 30 mmHg</td>
<td>Severe Congestion</td>
</tr>
<tr>
<td>&gt; 30 mmHg</td>
<td>Pulmonary Edema</td>
</tr>
</tbody>
</table>

The value for PAOP that best separates patients with and without pulmonary congestion is 18 mmHg.
Backwards Failure: Pulmonary Congestion

Forwards Failure: Hypoperfusion
Left Ventricular Function Curves

Preload: PAOP (other indicators of volume status)
Changing Preload: Moves patient along the curve they are on.
Changing Contractility: Moves patient to a higher curve
Changing Afterload: Moves patient up and to the left (improves forwards flow and reduces preload)
## Pharmacological Options for Increasing Preload

| Volume expanders | Isotonic crystalloids such as 0.9% saline or lactated ringers  
|                  | Colloids such as albumin, dextran, or hetastarch  
|                  | Blood and/or blood products |
| Decrease dose or stop diuretics or drugs that cause venous vasodilatation. | Decrease or stop medications such as: loop diuretics, intravenous nitroglycerin, neseritide, and morphine sulfate (venous vasodilatation pools blood away from the heart and decreases preload – direct impact on right sided preload) |

Exercise also increases venous return to the heart.
# Pharmacological Options for Decreasing Preload

<table>
<thead>
<tr>
<th>Stop or decrease fluid</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diuretics</strong></td>
<td>▪ A loop diuretic such as furosemide eliminates circulating volume</td>
</tr>
</tbody>
</table>
| **Venous Vasodilators**| ▪ Intravenous nitroglycerin, neseritide, or morphine sulfate  
  *(Venous vasodilatation pools blood away from the heart and decreases preload)* |
| **ACE Inhibitors or Angiotensin II Receptor Blockers (ARBs)** | ▪ Interrupt renin- Angiotensin- aldosterone system. (RAAS). Aldosterone secretion is decreased and there is less sodium and water retention.  
  ▪ ACE inhibitors end in “pril” / ARBs end in “sartan” |
| **Aldosterone antagonists** | ▪ Spironolactone or epleranone  
  ▪ Directly block aldosterone and there is decreased sodium and water retention. |
Pharmacological Options for Increasing Afterload

**Vasopressor** is the term given to medications used to increase afterload.

| Sympathomimetics stimulating the alpha receptors of the sympathetic nervous system | ▪ Dopamine  
▪ Norepinephrine  
▪ Phenylephrine  
▪ Epinephrine |
|---|---|
| Arginine Vasopressin | ▪ Vasoconstrictive and antidiuretic effect  
▪ Restores catecholamine sensitivity |
### Pharmacological Options for Decreasing Afterload

All therapies involve **arterial vasodilatation**

| Smooth muscle relaxants                      | ▪ Nipride   |
|                                           | ▪ Hydralazine |
| Calcium channel blockers                  | ▪ Dihydropyridines (ending in “ine”) calcium channel blockers such as amlodipine |
| Alpha₁ receptor blockers                  | ▪ Labetolol (combination alpha and beta blocker) |
|                                           | ▪ Prazoxin, Terazosin |
| Central anti-adrenergics                  | Clonidine, Methyldopa |
| Peripheral anti-adrenergics               | Resperine, Guanthidine |
| **ACE Inhibitors**                         | ▪ Interrupt the RAAS and limit production of angiotensin II a potent arterial vasoconstrictor |
|                                           | ▪ Medications ending in “pril” |
| **Angiotensin II Receptor Blockers (ARBs)** | ▪ Directly block the effects angiotensin II |
|                                           | ▪ Medications ending in “sartan” |
| **Phosodiesterase Inhibitors** (PDE Inhibitors) | ▪ Milrinone |
|                                           | ▪ Is used as an intravenous inotrope but also has arterial vasodilator properties |
Pharmacological Options for Increasing Contractility

**Inotrope** is the term used for medications used to increase contractility

| Sympathomimetics stimulating the $\beta_1$ receptors of the sympathetic nervous system | ▪ Dobutamine: most commonly used because it is predominant beta one stimulator  
▪ Other sympathomimetics may have inotropic properties even if not used primarily for an inotropic purpose |
| --- | --- |
| Phosodiesterase Inhibitors (PDE Inhibitors) | ▪ Milrinone  
▪ Is used as an intravenous inotrope but also has arterial vasodilator properties |
| Cardiac Glycoside | ▪ Digoxin  
▪ weak inotrope and is never used intravenously to support left ventricular dysfunction. Exerts weak inotropic properties when given orally. |
Pharmacological Options for Decreasing Contractility

| Beta Blockers blocking the $\beta_1$ receptors of the sympathetic nervous system | ▪ Metoprolol  
▪ Carvedilol  
▪ “olol” medications |
| --- | --- |
| Calcium Channel Blockers | ▪ Diltiazem  
▪ Verapamil |
Pharmacological Options for Increasing Heart Rate

<table>
<thead>
<tr>
<th>Parasympatholytic (lyses the parasympathetic nervous system)</th>
<th>Atropine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathomimetics stimulating the $\beta_1$ receptors of the sympathetic nervous system</td>
<td>Epinephrine, Dopamine</td>
</tr>
</tbody>
</table>

Note: The non-pharmacological intervention of pacing the heart with either an external, temporary or permanent pacemaker is often the preferred method of increasing the heart rate to a set and controlled rate.
### Pharmacological Options for Decreasing Heart Rate

<table>
<thead>
<tr>
<th>1. Beta Blockers blocking the $\beta_1$ receptors of the sympathetic nervous system</th>
<th>“olol” medications ▪ Class II antiarrhythmics</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Calcium Channel Blockers</td>
<td>▪ Diltiazem / Verapamil ▪ Class IV antiarrhythmic</td>
</tr>
<tr>
<td>3. Cardiac Glycoside</td>
<td>▪ Digoxin</td>
</tr>
<tr>
<td>4. Unclassified antiarrhythmic</td>
<td>▪ Adenosine: Slows conduction through the AV node</td>
</tr>
<tr>
<td>5. Other antiarrhythmics</td>
<td>▪ Class I and Class III antiarrhythmics ▪ Used to establish and / or maintain a normal rhythm and therefore control heart rate</td>
</tr>
</tbody>
</table>
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.
Autonomic Nervous System

Sympathetic

Parasympathetic

Beta 1

Beta 2

Alpha 1

Vagal Response
Sympathetic Nervous System

• Fight or flight

**Alpha\textsubscript{1} Receptors**
- Vasoconstriction of vessels

**Beta\textsubscript{1} Receptors** (Heart)
- Increased heart rate
  - Chronotropic Response
- Increased conductivity
  - Dromotropic Response
- Increased contractility
  - Inotropic Response
- Increased automaticity

**Beta\textsubscript{2} Receptors** (Vesseles, Lungs)
- Bronchodilation
- Peripheral Vasodilatation
A Closer Look at Sympathomimetics

- Sympathomimetics that increase heart rate ($\beta_1$ receptors)
  - Dopamine
  - Epinephrine
  - Isuprel (no longer used except with cardiac transplants)

- Sympathomimetics that increase afterload (vasopressors) ($\alpha_1$ receptors)
  - Dopamine
  - Norepinephrine (Levophed)
  - Phenylephrine (Neo-Synephrine)
  - Epinephrine
A Closer Look at Sympathomimetics

- Sympathomimetics that increase contractility (inotropes) \((\beta_1\text{ receptors})\)
  - Epinephrine
  - Dobutamine
  - Dopamine
  - Norepinephrine

- Used primarily as inotrope
- Used primarily as vasopressor but has inotropic properties when used
**Epinephrine**

| What receptors are stimulated: | $\beta_1$ and $\beta_2$  
Alpha receptors |
|-------------------------------|-----------------|
| What are the resultant actions: | Increase contractility (+inotrope) $\beta_1$  
(+chronotrope) $\beta_1$  
Bronchodilation $\beta_2$  
Selective vasoconstriction (alpha) |
| 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 |
## Dobutamine

| What receptors are stimulated: | Primarily $\beta_1$
Some alpha$_1$ receptor stimulation
Some $\beta_2$ stimulation
Modest $\beta_2$ (more $\beta_2$ than alpha$_1$) |
|--------------------------------|--------------------------------------------------|
| What are the resultant actions: | Increase contractility (+ inotrope) ($\beta_1$)
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; $\beta_2$ causes vasodilatation; $\beta_1$ increases cardiac output and may increase BP |

*Synthetic Compound*
## Dopamine

| What receptors are stimulated: | **Dopaminergic** at low doses (0.5-2.0 mcg/kg/min)  
β₁ 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 |

Mimics endogenous dopamine; metabolic precursor of norepinephrine and epinephrine
### Norepinephrine

| What receptors are stimulated: | Primarily alpha stimulation  
Some $\beta_1$  
(In lower doses $\beta_1$ 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**

| What receptors are stimulated:                      | Direct effect: Dominant alpha stimulation  
No substantial $\beta_1$ effect at therapeutic doses  
Indirect effect: Releases norepinephrine |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>What are the resultant actions:</td>
<td>Vasoconstriction (increased afterload)</td>
</tr>
<tr>
<td>When and why do we use:</td>
<td>As a vasopressor for Unresponsive hypotension</td>
</tr>
</tbody>
</table>
| 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
Comparison of Dopamine to Norepinephrine in Shock

- Backer et al.
- Multi Center Randomized Controlled Trial
- New England Journal of Medicine
- March 4th 2010

- There were no significant differences between the groups in the rate of death at 28 days or in the rates of death in the ICU, in the hospital, at 6 months, or at 12 months
- More patients with arrhythmia in the dopamine group

*Rate of death was higher in predefined subgroup analysis for patients with cardiogenic shock treated with dopamine.*
Non Sympathomimetic Vasopressor: Arginine Vasopressin

• Vasoconstrictive effects
  – Allowing for regional vasodilation

• Antidiuretic 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
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
Phosphodiesterase Inhibitors: Non Sympathomimetic Inotropes

Used as an Inotrope

BUT......

Preload Reduction

Also has......

Afterload Reduction
OPTIME Trial

- Milrinone approved by FDA based on hemodynamic data
- Future trials need to include symptom relief and post discharge outcome data
- OPTIME
  - Prospective trial, randomized, placebo controlled
  - 951 patients
  - Patients had indication for but not all required inotrope for end organ perfusion.
  - Results: No difference in LOS, No difference in subjective improvement
  - Treatment failures more common in milrinone group due to hypotension, more atrial fibrillation in milrinone
  - Not powered for mortality differences

- Conclusion: Hemodynamic improvement does not translate into clinical improvement
A Closer Look at Venous Versus Arterial Vasodilators

Venous Vasodilators

Decrease Preload

Arterial Vasodilators

Decrease Afterload
A Closer Look at Venous Versus Arterial Vasodilators

• Some medications do both

• Some depend on dose
  • Nesiritide
  • NTG
  • Nitroprusside
  • CA Channel blockers
  • PDE Inhibitors
  • ACE Inhibitors
  • Other Vasodilators
Nesiritide (Natrecor)

- 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 (Natrecor)

- 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 (Natrecor)

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

Monitor BP closely during administration.
Neseritide: Where do we stand?


  - In the 3 trials, 485 patients were randomized to nesiritide and 377 to control therapy. Death within 30 days tended to occur more often among patients randomized to nesiritide therapy (35 [7.2%] of 485 vs 15 [4.0%] of 377 patients; risk ratio from meta-analysis.

  - P value did not achieve .05 or less.
Randomized Trial

- Effect of Nesiritide in Patients with Acute Decompensated Heart Failure
- O'Connor et al.
- July 7 2011

- 7141 patients

- Nesiritide was not associated with an increase or a decrease in the rate of death and rehospitalization.
- It was not associated with a worsening of renal function, but it was associated with an increase in rates of hypotension.
- Neseritide cannot be recommended for routine use.
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

  – Nitrate tolerance can be avoided by providing nitrate free interval preferably during night time hours

  – Decreases activity of Heparin
Nitroglycerin

- **Uses**: Acute MI, unstable angina, CHF

- **Side Effects**: H/A, Hypotension, flushing

- **Nursing Considerations**:
  - Contraindicated with Sildenefil like drugs
  - Caution (all venous vasodilators) with:
    - Hypertrophic cardiomyopathy, aortic stenosis, right ventricular MI
  - Treat H/A with pain meds and decrease dose
  - Onset IV: 1-2 minutes
  - Duration: 3-5 minutes
Nitroprusside

- Mixed venous and arterial dilator (primarily arterial)
- Decreases BP, SVR, 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
Acute Coronary Syndrome

Imbalance between myocardial oxygen supply and demand.
Drugs Used to Alter Clotting in ACS

• **Fibrinolytics**
  – **STEMI**
  – tPA
    • Alteplase
    • Retaplace
    • Tenecteplase
  – Streptokinase (*no longer used*)

• **Antiplatelets**
  – **STEMI / NonSTEMI / UA**
    – **GP IIb/IIIa Inhibitors**
      • Eptifibatide (Integrelin)
      • Tirofiban (Aggrastat)
      • Abciximab (Repro)
    – **ADP Receptor Blockers**
      • Clopidogrel
      • Prasugrel
      • Ticagrelor
  – **Thromboxane A₂ Inhibitor**
    • ASA

• **Anticoagulants**
  o **STEMI / NonSTEMI / UA**
  o Unfractionated Heparin
  o Low Molecular Weight Heparin
  o Direct Thrombin Inhibitors
  o Factor Xa Inhibitors
Clot Formation: Clotting Cascade

Intrinsic Pathway
• Initiated by vascular injury and direct exposure to collagen
• From initiation to a clot is 2-6 minutes
• Measured by APTT

Extrinsic Pathway
• Initiated by endothelial release (secondary to tissue injury) of thromboplastin tissue factor
• From initiation to clot is 15 to 20 seconds
• Measured by Protime

A clot can be produced by activation of either the intrinsic or extrinsic pathway.
The Clotting Cascade
The Clotting Cascade

• The Common Pathway
  – Prothrombin is converted to thrombin
  – Thrombin permits fibrinogen to be converted to fibrin
  – Result is fibrin stable clot (red clot)
  – This fibrin stable clot is cause of STEMI MI
Anticoagulants

- **Unfractionated Heparin**
  - Heparin by Weight
  - STEMI, NonSTEMI, UA
  - Mortality benefit
- **Low Molecular Weight Heparin**
  - STEMI, NonSTEMI, UA
- **Direct Thrombin Inhibitors**
  - If history of HIT, PCI NonSTEMI
- **Factor Xa Inhibitors**
  - Not in PCI

- **Warfarin** (Vitamin K antagonist)
- **Dabigatran** (Direct thrombin inhibitor)
- **Rivaroxaban** (Factor Xa inhibitor)
- **Apixaban** (Factor Xa inhibitor)
A Closer Look at Heparin

- Antithrombin activator that inhibits factors Xa and IIa
- 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
- ½ 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**
  - Heparin Induced Thrombocytopenia (HIT)
  - Platelet aggregation resulting in venous or arterial thrombosis
  - Determining patients at risk is unpredictable
  - Generally occurs 5 to 10 days after initiation of heparin
    - Could be sooner if recent exposure to heparin
  - DC heparin if platelets fall below 100,000 (< 50% reduction)
  - Severe thrombocytopenia is due to an immune response
More on Heparin Induced Thrombocytopenia

• Immune system forms antibodies against heparin when bound to the protein platelet factor 4 [PF4]
  – PF4 antibodies detected in ELISA testing
  – Not necessarily associated with thrombotic risk
  – Can disappear 3 months after exposure

• HIT antibodies are usually IgG class
  – Take 5 days to form
  – IgG antibodies associated with platelet activation and increased thrombin generation
  – Detected by washed platelet assays

• Antibodies bind to platelets and trigger the development of thrombosis.
Treatment of HIT

1. Discontinue and avoid all heparin.
2. Give a non-heparin alternative anticoagulant: Direct thrombin inhibitors (bivalrudin).
3. **Postpone warfarin pending substantial platelet count recovery** (give vitamin K if warfarin has already been started). Warfarin is associated with protein C deficiency and increased risk for microthrombosis.
4. **Avoid platelet transfusions** – leads to platelet activation.
5. Test for HIT antibodies (ELISA and washed assay)
7. Avoid prophylactic platelet transfusions.
Low Molecular Weight Heparin

- Enoxaprin, 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
• 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 ½ 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
  - 40 mg daily in most situations
  - 30 mg daily for renal adjustment (CR Clearance < 30 ml/min)
- Venous thrombosis / DVT
  - 1mg/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 HIT
- **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)
Synthetic Factor Xa Inhibitor

- Fondaparinux (Arixtra)
  - Used for venous thromboembolism and PE
  - Approved for DVT prophylaxis in certain surgical patients
  - 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 (initial dose IV)
- 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)
Role of Antiplatelet Therapy in ACS

• Dual antiplatelet therapy (DAPT) recommended long term in STEMI / NonSTEMI and Unstable Angina
• DAPT includes Adenosine Diphosphate Receptor Blocker and Aspirin
• GPIIb/IIIa Inhibitors recommended in acute care setting in select patients
• All antiplatelet therapy aimed at reduction of mortality.
# AntiPlatelet Therapy

## STEMI
- Clopidogrel (Plavix)
  - 600 mg initial dose
  - 75 mg daily for minimum of 12 months
- Prasugrel (Effient)
  - 60 mg initial dose
  - 10 mg daily for minimum of 12 months
- Ticagrelor (Brilinta)
  - 180 mg initial dose
  - 90 mg twice daily for minimum of 12 months

## For UA/NSTEMI
- Planning initial invasive strategy
  - Antiplatelet therapy in addition to aspirin should be initiated before diagnostic angiography (upstream)
    - Clopidogrel
    - Ticagrelor
    - Prasugrel (*)
  - IV GP IIb/IIIa Inhibitor
- Initial conservative therapy (no cath)
  - Clopidogrel for at least one month and ideally for 12 months
P2Y$_{12}$ Receptor Inhibitors

- Thienopyridines
  - Clopidogrel
  - Prasugrel

- Ticagrelor (Non thienopyridine)
Thienopyridines

- Thienopyridines are a class of ADP / P2Y$_{12}$ receptor blockers
  - Clopidogrel (Plavix)
  - Prasugrel (Effient)

- Thienopyridines
  - ADP Receptor blockers
    - Adenosine Diphosphate (ADP) - Stored in platelets and released upon platelet activation.
    - ADP interacts with P2Y$_{12}$ chemoreceptors to enhance adhesiveness and aggregation of platelets through the activation of the GP IIb/IIIa pathway
      - **Irreversibly** inhibits P2Y$_{12}$ receptor
      - Referred to as platelet inhibitors
Clopidogrel and Non Responders

- ACCF/AHA Clopidogrel Clinical Alert
- FDA Boxed Warning March 2010
- Role of genotype testing or routine platelet function testing
  - Class II b recommendation pending results of randomized controlled clinical trials.
- Prodrug
  - 2 step process
  - Involves several CYP450 isoenzymes
    - CYP2C19 isoenzyme responsible for almost half of the first step formation
    - 3 major genetic polymorphisms are associated with loss of function
    - Observational studies have shown an association between an increased risk of adverse cardiovascular events and the presence of one nonfunctioning allele
Clopidogrel and PPIs


- Using proton pump inhibitors (PPIs) and antiplatelet drugs (thienopyridines) together is an appropriate way of treating patients with cardiovascular (CV) disease who are at high risk of upper gastrointestinal (GI) bleeds, despite recent concerns about an adverse interaction between these two types of drugs, according to an Expert Consensus Document released jointly today by the American College of Cardiology (ACC), the American College of Gastroenterology (ACG), and the American Heart Association (AHA).
Clopidogrel and PPIs
2012: World Journal of Gastroenterology

• Because PPI induced risk reduction clearly outweighs the possible adverse cardiovascular risk in patients with high risk of gastrointestinal bleeding, combination of clopidogrel with the less CYP2C19 inhibiting pantoprazole should be recommended.

• Several pharmacodynamic studies found a significant decrease of the clopidogrel platelet antiaggregation effect for omeprazole, but not for pantoprazole.

• More recent RCT and retrospective co-hort studies have not resulted in same concerns with PPIs as observational studies suggested.
P2Y₁₂ Receptor Inhibitors: Clopidogrel versus Prasugrel

- **TRITON TIMI 38 Trail**
  - 13,608 patients with moderate to high risk ACS – all referred for PCI; 3,534 STEMI
  - Randomized to clopidogrel 300mg load and 75mg daily or prasugrel 60mg load and 10mg daily
  - Median follow up 14 ½ months

- Prasugrel (compared to Clopidogrel) associated with
  - Significant 2.2% reduction in absolute risk and a 19% reduction in relative risk in the composite endpoint of death due to CV disease, nonfatal MI, or nonfatal stroke during the follow up period
  - Significant increase in TIMI major hemorrhage (1.8% vs 2.4%)

- Prasugrel approved 2009

**Clopidogrel versus Prasugrel**

**TRILOGY**

- Prasugrel versus clopidogrel in patients with NSTEMI or unstable angina who were not treated with PCI
- 7,243 patients
- No statistically significant difference in primary outcome (composite of: death from cardiovascular causes, myocardial infarction, or stroke) among patients under the age of 75 years
- A weak trend toward a reduced risk in the prasugrel group after 12 months ($P = 0.07$)
- Rates of severe and intracranial bleeding were similar in the two groups in all age groups. *This is different than TRITON TIMI 38. Dose was adjusted in Trilogy for weight $< 60$ kg and age $\geq 75$ years.*

- Conclusion: More research needed

- **Current practice guidelines – only support use in PCI population**
Take Away Prasugrel Points

- Greater anti-ischemic protection
- Less concern with PPI administration
- Less concern regarding non responders
  - Prodrug but not as dependent on CYP2C19 isoenzyme
- Only used in patients with planned PCI
- Increased bleeding risk
  - $\geq 75$ years old
  - $\leq 60$ KG
  - Previous CVA / TIA
Non-Thienopyridine $\text{P2Y}_{12}$ Receptor Inhibitors (ADP Receptor Blocker)

- Ticagrelor (Brillinta)
  - Antiplatelet agent
  - **Reversibly** binds to $\text{P2Y}_{12}$ receptor
  - Not a PRO drug: does not requiring metabolic activation
  - FDA approved July 2011
  - Prevention of thrombotic events in patients with acute coronary syndromes.
  - Loading dose 180 mg then **90 mg twice daily**
  - Contraindicated in history of intracranial bleeding, active pathological bleeding, severe hepatic impairment
  - **Must not be given with maintenance ASA doses > 100mg**
Clopidogrel versus Ticagrelor (Brillinta)

- PLATO trial
  - Better anti-ischemic effect compared to clopidogrel
  - No significant increase in major bleeding
  - Faster onset and shorter duration than clopidogrel (known as reversible mode of action)
  - BID dosing is a potential concern for compliance
  - North American effect – thought to be due to higher dose ASA
  - Although shorter ½ life – recommendation to be held 5 days before surgery.

A Closer Look at Aspirin Use in ACS

• Produces rapid clinical antithrombotic effect caused by immediate and near-total inhibition of thromboxane A2 production (released with vascular injury).
• Diminishes platelet reactivity
• Also inhibits the endothelium’s production of prostaglandin I\textsubscript{2} which decreases platelet aggregation and induces vasodilation.
  – Reduces mortality
  – Increase myocardial oxygen supply

**STEMI / UA/NSTEMI**

  – Administered as soon as possible after presentation
  – Initial dose: 162 mg to 325 mg chewed
  – Long Term: 81 mg daily
A Closer Look at Beta Blockers

Decreases Myocardial Oxygen Demand

- Decrease HR
- Decrease Contractility

\[ \beta_1 \text{ blockade} \]

Blood pressure = \( CO \times SVR \)
Beta Blockers in ACS

• Immediate as well as long term mortality benefit

• Immediate beta-blocker therapy
  – Reduces the magnitude of infarction and incidence of associated complications
    • Decreases myocardial oxygen demand
  – Reduces rate of reinfarction
  – Reduces frequency of life-threatening ventricular tachyarrhythmias.

• Long term benefit post ACS
  – Decreases myocardial oxygen demand
    • HR Benefit
  – Enhances overall well being
  – Slows disease progression
  – Inhibits ventricular remodeling and apoptosis
  – Inhibits adverse effects of SNS
  – Reduces mortality and repeat hospitalizations
Beta Blockers at Presentation

**DO NOT** administer in acute presentation IF:

- STEMI precipitated by cocaine
  - Risk of exacerbating coronary spasm
- Heart blocks
  - 1\textsuperscript{st} degree AV block with PR > 0.24 sec
  - 2\textsuperscript{nd} or 3\textsuperscript{rd} degree AV block
- Heart rate < 60 BPM
- SBP < 100 mm Hg
- Moderate LV failure is present (signs of HF or shock)
- Active asthma or reactive airway disease
Beta Blockers in ACS Recovery

• Beta blockers should be used in all patients with acute MI regardless of LVEF to reduce long term mortality
• In the immediate recovery beta blockers used to reduced myocardial work load and reduce ischemic burden
  – Watch for ventricular ectopy

• If not received on arrival due to contraindication consider initiation with 24-48 hours after contraindication resolved
Polymorphic VT with normal QT:

- Seen frequently in ischemic conditions (role of beta blockers)
Beta Blockers
Recommended by Disease State

• Post MI
  – Atenolol
  – Carvedilol★★
  – Metoprolol★★
  – Propanolol
  – Timolololol

• Heart Failure
  – Bisoprolol
  – Carvedilol★★★★
  – Metoprolol Succinate (XL) ★★
New Guidelines

DYSLIPIDEMIA
Relationship to ATP III-IV

• The 2013 ACC/AHA Expert Panel included all 16 members of the National Heart, Lung, and Blood Institute Adult Treatment Panel (ATP) IV.

• Commissioned by NHLBI in June 2013

• Guidelines replace ATP III
Transition from Treating Numbers to Treating Patients and Their Risk

• Focus is no longer on targeting the LDL-C
  – Treat to level of risk not to target LDL-C

• New guidelines focus on 4 groups of patients who can benefit from statin therapy with a good safety margin

• Benefit includes reduction in atherosclerotic cardiovascular disease events (ASCVD)
Patient Group 1

• Individuals with clinical ASCVD (acute coronary syndromes, or a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin) without New York Heart Association (NYHA) class II-IV heart failure or receiving hemodialysis.
Patient Group 2

- Individuals with primary elevations of low-density lipoprotein cholesterol (LDL-C) $\geq 190$ mg/dl.
Patient Group 3

• Individuals 40-75 years of age with diabetes, and LDL-C 70-189 mg/dl without clinical ASCVD.
Patient Group 4

• Individuals without clinical ASCVD or diabetes, who are 40-75 years of age with LDL-C 70-189 mg/dl, and have an estimated 10-year ASCVD risk of 7.5% or higher.

• **Pooled Cohort Equations for ASCVD risk prediction.**
  
  – Men and women; black and non-Hispanic white
    • May use non Hispanic White calculator for other populations (may under estimate risk in certain populations)

  – Ages 40 to 79

  – Identifies cohorts most likely to benefit from statin therapy
Required information to estimate ASCVD risk includes age, sex, race, total cholesterol, HDL cholesterol, systolic blood pressure, blood pressure lowering medication use, diabetes status, and smoking status.

Non Recommendations

• No recommendations for treatment outside the 4 groups.

• No recommendation to start or stop statins in NYHA Class II-IV systolic HF that is ischemic in etiology

• In patients with a 10-year risk < 7.5%, other factors can be considered:
  – Family history
  – LDL-C > 160mg/dL
  – HS C-reactive protein > 2mg/dL
  – Coronary calcium score > 300
  – ABI < 0.9
  – Etc.
# Statin Dosing

<table>
<thead>
<tr>
<th>High Intensity</th>
<th>Moderate Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients &lt;75 years with ASCVD</td>
<td>Patients with diabetes with a 10 year ASCVD &lt;7.5%</td>
</tr>
<tr>
<td>All patients &gt; 75 years?</td>
<td>Patients with indication for high intensity but who are not able to take high intensity</td>
</tr>
<tr>
<td>Patients with LDL-C ≥ 190 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Patients with diabetes with a 10 year ASCVD ≥7.5%</td>
<td></td>
</tr>
<tr>
<td>Persons 40-75 years with a ≥7.5% 10-year ASCVD risk should receive moderate- to high-intensity statin therapy.</td>
<td></td>
</tr>
</tbody>
</table>
Statin Dosing

• High intensity: daily dose that lowers LDL-C by > 50%

• Moderate intensity: daily dose that lowers LDL-C by 30% to 50%
Statin Therapy: Greatest LDL-C Lowering Effect:

- **atorvastatin**
  - 80 mg: 55-60% reduction
  - 40 mg: 50% reduction
  - 20 mg: 43% reduction
  - 10 mg: 35-39% reduction

- **rosuvastatin**
  - 40 mg: 55-63% reduction
  - 20 mg: 47-55% reduction
  - 10 mg: 46-52% reduction
  - 5 mg: 45% reduction
More on Lipids

• Atorvastatin (80 mg daily) in the PROVE-IT TIMI 22 demonstrated reduced mortality and ischemic events in patients with acute coronary syndrome.
  – 7 day median initiation
  – Mean follow up 24 months – difference 30 days to end
  – LDL result versus difference in statin versus stabilization of plaque
Lifestyle and Other Lipid Lowering Agents

• Lifestyle: Important prior to and during statin therapy
• Non-statin therapies, whether alone or in addition to statins, do not provide acceptable ASCVD risk reduction benefits compared to their potential for adverse effects in the routine prevention of ASCVD.
  – Addition of these other agents can be considered in patients with LDL-C > 190 mg/dL.
Definition of Heart Failure

• Heart Failure is a complex clinical syndrome resulting from any structural or functional cardiac disorder impairing the ability of the ventricle to either fill (diastolic dysfunction) or eject (systolic dysfunction).
Systolic vs Diastolic Dysfunction
Systolic Dysfunction

- Impaired wall motion and ejection
- Dilated chamber
- 2/3 of HF Population
- **Hallmark:** Decreased LV Ejection Fraction < 40%
- Coronary artery disease is cause in 2/3 of patients
- Remainder – other causes of LV dysfunction

Cardiomyopathy not synonymous with HF
Diastolic Dysfunction

- Filling impairment
- Normal chamber size
- 20 to 40% of patients with HF have preserved LV function
- Normal EF or elevated
- Caused by
  - Hypertension
  - Restrictive myopathy
  - Ischemic heart disease
  - Ventricular hypertrophy
  - Valve disease
  - Idiopathic

Primarily disease of elderly women with HTN
Diastolic Dysfunction

• Diagnosis is made when rate of ventricular filling is slow
• Elevated left ventricular filling pressures when volume and contractility are normal

In practice: the diagnosis is made when a patient has typical signs and symptoms of heart failure and has a normal or elevated ejection fraction with no valve disease.
Pathophysiology

• Complex process involving continually emerging symptoms and deterioration
• Myocardial dysfunction initially results from any number of triggers
• Normal compensatory mechanisms used to help ultimately harm
Pathophysiology

The Real Culprit = Neurohormonal Response

• Three significant events occur
  1. Sympathetic Nervous System (SNS) stimulation
  2. Activation of the Renin-Angiotensin-Aldosterone System (RAAS)
  3. Ventricular Remodeling
HF as Progressive Disorder

• Initial injury or stress on myocardium
• Change in geometry of left ventricle
  – Dilates
  – Hypertrophies
  – Becomes more spherical
• Decreases mechanical performance of LV and increases regurgitation thru mitral valve
• These effects sustain and enhance the remodeling process
Symptoms

Fluid Accumulates in Pulmonary Capillary Bed
Increased Pulmonary Pressure / Volume

Atrial Overload
Increased Pulmonary Pressure / Volume
Fluid Accumulates in Pulmonary Capillary Bed
Symptoms

Ventricular Dilatation
Decreased Ventricular Contractility
Decreased Ejection of Ventricular Contents
Increased Ventricular Pressure / Volume
Increased Atrial Pressure / Volume
Atrial Dilatation
Atrial Overload

Mitral Regurgitation
Dilated Mitral Valve Annulus

Activation of Neuro-hormonal Responses
Vasoconstriction / Fluid Retention
## Stages of Heart Failure: ACC/AHA

<table>
<thead>
<tr>
<th>Stage A</th>
<th>Stage B</th>
<th>Stage C</th>
<th>Stage D</th>
</tr>
</thead>
<tbody>
<tr>
<td>At high risk for HF but without structural heart disease or symptoms of HF.</td>
<td>Structural heart disease but without signs or symptoms of Heart Failure</td>
<td>Structural heart disease with prior or current symptoms of HF.</td>
<td>Refractory HF requiring specialized interventions.</td>
</tr>
<tr>
<td>HPTN</td>
<td>Previous MI</td>
<td>Know structural disease and SOB, fatigue, reduced exercise tolerance.</td>
<td>Marked symptoms of HF at rest despite maximal medical therapy.</td>
</tr>
<tr>
<td>CAD</td>
<td>LV Remodeling including LVH and low EF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>Asymptomatic valvular disease</td>
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<tr>
<td>Obesity</td>
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<tr>
<td>Metabolic syndrome</td>
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<tr>
<td>Family HX CM</td>
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</tbody>
</table>
## Classification of Heart Failure

**New York Heart Association**

<table>
<thead>
<tr>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Class IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac disease no resulting limitation in</td>
<td>Cardiac disease with slight limitation of physical</td>
<td>Cardiac disease with marked limitation on physical</td>
<td>Cardiac disease resulting in inability to carry out</td>
</tr>
<tr>
<td>physical activity.</td>
<td>activity.</td>
<td>activity.</td>
<td>any physical activity without discomfort.</td>
</tr>
<tr>
<td>Ordinary activity free of fatigue, palpitation, dyspnea or anginal pain.</td>
<td>Comfortable at rest but ordinary activity results in fatigue, palpitations, dyspnea, or anginal pain.</td>
<td>Comfortable at rest but less than ordinary activity results in fatigue, palpitations, dyspnea, or anginal pain.</td>
<td>May have symptoms of cardiac insufficiency at rest.</td>
</tr>
</tbody>
</table>
Stages, Phenotypes and Treatment of HF

**Stage A**
- At high risk for HF but without structural heart disease or symptoms of HF
- Goals: Control symptoms, Improve HRQOL, Prevent hospitalization, Prevent mortality
- Drugs: ACEI or ARB as appropriate, Beta blockers as appropriate
- Treatment: Diuresis to relieve symptoms of congestion, Follow guideline driven indications for comorbidities, e.g., HTN, AF, CAD, DM
- In selected patients: ICD, Revascularization or valvular surgery as appropriate

**Stage B**
- Structural heart disease but without signs or symptoms of HF
- Development of symptoms of HF
- Goals: Control symptoms, Patient education, Prevent hospitalization, Prevent mortality
- Drugs for routine use: Diuretics for fluid retention, ACEI or ARB, Beta blockers, Aldosterone antagonists
- Drugs for use in selected patients: Hydralazine/isosorbide dinitrate, ACEI and ARB, Digoxin
- In selected patients: CRT, ICD, Revascularization or valvular surgery as appropriate

**Stage C**
- Structural heart disease with prior or current symptoms of HF
- Refractory symptoms of HF at rest, despite GDMT
- Patients with: Marked HF symptoms at rest, Recurrent hospitalizations despite GDMT

**Stage D**
- Refractory HF
- Goals: Control symptoms, Improve HRQOL, Reduce hospital readmissions, Establish patient’s end-of-life goals
- Drugs for routine use: Diuretics for fluid retention, ACEI or ARB, Beta blockers, Aldosterone antagonists
- Drugs for use in selected patients: Hydralazine/isosorbide dinitrate, ACEI and ARB, Digoxin
- In selected patients: CRT, ICD, Revascularization or valvular surgery as appropriate

**Therapy**
- Goals: Heart healthy lifestyle, Prevent vascular, coronary disease, Prevent LV structural abnormalities
- Drugs: ACEI or ARB in appropriate patients for vascular disease or DM, Statins as appropriate
- Options: Advanced care measures, Heart transplant, Chronic inotropes, Temporary or permanent MCS, Experimental surgery or drugs, Palliative care and hospice, ICD deactivation

**At Risk for Heart Failure**
- e.g., Patients with:
  - HTN
  - Atherosclerotic disease
  - DM
  - Obesity
  - Metabolic syndrome or Patients Using cardiotoxins
  - With family history of cardiomyopathy

**Heart Failure**
- e.g., Patients with:
  - Previous MI
  - LV remodeling including LVH and low EF
  - Asymptomatic valvular disease
  - Known structural heart disease and HF signs and symptoms

**HFpEF**
- Development of symptoms of HF
- e.g., Patients with:
  - Previous MI
  - LV remodeling including LVH and low EF
  - Asymptomatic valvular disease

**HF/EF**
- Refractory symptoms of HF at rest, despite GDMT
- e.g., Patients with:
  - Marked HF symptoms at rest
  - Recurrent hospitalizations despite GDMT

**Options**
- Advanced care measures
- Heart transplant
- Chronic inotropes
- Temporary or permanent MCS
- Experimental surgery or drugs
- Palliative care and hospice
- ICD deactivation
Renin-Angiotensin System

↓ Renal Flood Flow

<table>
<thead>
<tr>
<th>Renin release</th>
</tr>
</thead>
</table>

β blockers

Angiotensinogen → Angiotensin I

(ACE inhibitors)

(converting enzyme)

Angiotensin II

Angiotensin Receptor Blockers

Vasoconstriction

Aldosterone release

Na⁺ & H₂O retention

↑ BP

CNEA / Key Choice

Aldosterone Blockers
A Closer Look at ACE Inhibitors and
Angiotensin II Receptor Blockers

• Angiotensin-converting enzyme inhibitors ("pril" medications)
  – Captopril, Enalapril, Lisinopril, Quinapril, Ramipril, Benazepril, Fosinopril

• Angiotensin II Receptor Blockers ("sartan" medications)
  – Losartan, Irbesartan, Candesartan, Telmisartan, Valsartan, Eprosartan
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
  – Decrease systemic vascular resistance without reflex stimulation of heart rate and contractility

• ACE Inhibitors additionally assist with preload reduction by blocking the effects of aldosterone release
A Closer Look at ACE Inhibitors

• Overall cardioprotective and vasculoprotective effect
  – Reduce mortality in patients with systolic heart failure
  – Reduction of left ventricular mass in LV hypertrophy
  – Slows progression of both renal disease in diabetes and hypertensive nephrosclerosis
Cough in ACE-I

• 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!
ACE Inhibitors and Renal Function

• Can cause acute renal failure in patients with bilateral renal artery stenosis
  – Dilation of efferent glomerular arterioles with no ability to dilate afferent arterioles which results in decreased glomerular filtration
• Creatinine can be allowed to be 35% above baseline without stopping the drug.
• If acute kidney injury develops from ACE – I, then hydralazine in combination with isosorbide dinitrate should be used
  – Combination achieves venous and arterial vasodilatation
  – Hyperkalemia can occur in renal insufficiency, when taking potassium supplementation, or when combined with an aldosterone antagonist
ACE Inhibitors and GFR

Conditions Causing Hypoperfusion:
- Hypotension
- Renal arterial disease
- Dehydration
- Congestive heart failure

HYPOPERFUSION

Afferent Arteriole (Decreased flow)

Efferent Arteriole (Constricted)

ACE INHIBITOR TREATED

Afferent Arteriole (Decreased or normal flow)

Efferent Arteriole (Dilated)

Source: J Clin Hypertens © 2004 Le Jacq Communications, Inc.
ACE Inhibitor

- Start low – attempt to reach target dose
  - If not tolerating use lower doses
- Assess renal function and potassium within 1 to 2 weeks of initiation
  - High risk features: diabetes, hyponatremia, hypotension, azotemia, potassium supplementation

- Cautions / Contraindications
  - Creatinine > 3 mg /dL (* difference between AKI and CKD)
  - Potassium > 5.0 mEq/L
  - Systolic BP < 80 mmHg
  - Bilateral renal artery stenosis
    - Efferent vasoconstriction
Angiotensin Receptor Blockers End in “SARTAN”

- ACE Inhibitors remain the first choice for inhibition of RAAS
- ARB’s are a reasonable alternative to ACE Inhibitor if intolerant to ACE Inhibitor due to cough or angioedema
- Directly block angiotensin II
- Combination of ACE I and ARB – not recommended
- Reasonable alternative to ACE I as 1st line therapy for patients with mild / moderate HF & reduced LVEF, especially if already take ARB for other reason (HTN)
# ACE Inhibitors

<table>
<thead>
<tr>
<th>Stage A</th>
<th>Stage B</th>
<th>Stage C</th>
<th>Stage D</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients at high risk for developing or history of atherosclerotic vascular disease, DM or HPTN. (IIA)</td>
<td>All pts. with recent or remote history of MI regardless of EF or presence of HF. (IA)</td>
<td>Class I recommendations Stage A/B (IA,B,C)</td>
<td>Same as Stage C</td>
</tr>
<tr>
<td>All pts. reduced EF and no symptoms of HF. (IA)</td>
<td>Beneficial in pts with HPTN &amp; LVH with no HF symptoms. (IIB)</td>
<td>All pts. with current or prior symptoms of HF &amp; ↓ EF.</td>
<td></td>
</tr>
</tbody>
</table>

**Nursing Practice Consideration:** Up titration is important / monitor response to medications.
Beta Blockers

- Decrease mortality/hospitalization
- Even better in combination with ACE Inhibitor
- Enhances overall well being
- Slows disease progression
- Inhibits ventricular remodeling and apoptosis
- Inhibits adverse effects of SNS
- Decrease myocardial oxygen consumption
  - Decreases HR
  - Decreases contractility
- **When to initiate?**
- Titration to max doses essential

*NURSING PRACTICE CONSIDERATION: Educate patients regarding initial expectation of fatigue.*
Evidence Based Beta Blocker

• **Cannot assume class effect**

• **Bisoprolol – β1**
  – CIBIS III randomized trial – 2005 (enalapril)

• **Metoprolol succinate - β1**
  – MERIT-HF randomized trial – 1999 (placebo)

• **Carvedilol - β1, β2, α1**
  – CAPRICORN randomized trial – 2001 (placebo)
  – COMET randomized trial – 2003 (metoprolol tartrate)
Beta Blocker Considerations

• Initiate before getting to target dose of ACE-I
• Start very low doses with gradual up-titration
• Must be used with diuretic if any recent or current fluid retention
• Can be initiated in hospital for HF admission if inotropic therapy not required
• **Pearl**: If hypotension – consider administration opposite of ACE-I or decrease in diuretic dose
• **Pearl**: Fatigue may be multifactorial – address over diuresis, sleep apnea and screen for depression
<table>
<thead>
<tr>
<th>Stage A</th>
<th>Stage B</th>
<th>Stage C</th>
<th>Stage D</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts. with recent or remote history of MI regardless of EF or presence of HF. (IA)</td>
<td>All pts. reduced EF and no symptoms of HF. (IA)</td>
<td>Class I recommendations Stage A/B (IA,B,C) Stable pts. with Current or prior symptoms of HF &amp; reduced EF</td>
<td>Same as Stage C</td>
</tr>
</tbody>
</table>
Aldosterone Antagonists

• ACC/AHA 2013 HF Guidelines
• Class IA Recommendation
• LVEF ≤ 35% with NYHA Class II-IV Heart Failure to reduce mortality and morbidity

Diuretic effect is not primary reason for administration.
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
<table>
<thead>
<tr>
<th>Drug class</th>
<th>Brand name generic name</th>
<th>Starting dose</th>
<th>Target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE Inhibitor</td>
<td>Prinivil or Zestril lisinopril</td>
<td>5 mg once daily</td>
<td>20 mg once daily (maximum dose might be 40 mg once daily)</td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>Monopril fosinopril sodium</td>
<td>10 mg once daily 5 mg if weak kidneys</td>
<td>40 mg once daily</td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>Vasotec enalapril maleate</td>
<td>2.5 mg BID</td>
<td>20 mg BID (maximum dose might be 40 mg BID)</td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>Mavik trandolapril</td>
<td>one mg once daily</td>
<td>4 mg once daily</td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>Capoten captopril</td>
<td>25 mg 2 to 3 times a day</td>
<td>100 mg TID (450 mg per day maximum)</td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>Lotensin benazepril</td>
<td>5 mg once daily if on diuretic 10 mg once daily if not on diuretic</td>
<td>40 mg per day in one 40 mg dose or two 20 mg doses</td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>Accupril quinapril</td>
<td>5 mg BID 2.5 mg BID if weak kidneys</td>
<td>20 mg BID</td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>Altace ramipril</td>
<td>1.25 mg to 2.5 mg BID</td>
<td>10 mg BID</td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>Aceon perindopril erbumine</td>
<td>1 mg BID if on diuretic 2 mg BID if not on diuretic</td>
<td>4 mg BID (8 mg BID maximum)</td>
</tr>
<tr>
<td>Drug class</td>
<td>Brand name generic name</td>
<td>Starting dose</td>
<td>Target dose</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>ARB</td>
<td>Cozaar losartan</td>
<td>25 mg BID or 50 mg once daily</td>
<td>50 mg BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12.5 mg BID or 25 mg once daily if weak liver function</td>
<td></td>
</tr>
<tr>
<td>ARB</td>
<td>Atacand candesartan cilexetil</td>
<td>4 to 8 mg once daily</td>
<td>32 mg once daily</td>
</tr>
<tr>
<td>ARB</td>
<td>Diovan valsartan</td>
<td>80 mg once daily</td>
<td>160 mg once daily</td>
</tr>
<tr>
<td>ARB</td>
<td>Avapro irbesartan</td>
<td>150 mg</td>
<td>300 mg once daily</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>Coreg carvedilol</td>
<td>3.125 mg BID</td>
<td>25 mg BID under 188 pounds</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>Toprol XL</td>
<td>12.5 mg for class 3 to 4 patients</td>
<td>200 mg once daily</td>
</tr>
<tr>
<td></td>
<td>metoprolol extended</td>
<td>25 mg for class 1 to 2 patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td>release (succinate)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>Zebeta bisoprolol</td>
<td>2.5 mg once daily</td>
<td>10 mg once daily</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>Aldactone spironolactone</td>
<td>25 mg once daily</td>
<td>25 mg once daily</td>
</tr>
<tr>
<td>Antagonist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldosterone</td>
<td>Inspra eplerenone</td>
<td>25 mg once daily</td>
<td>50 mg once daily</td>
</tr>
<tr>
<td>Antagonist</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Medical Therapy for Stage C HF rEF: Magnitude of Benefit Demonstrated in RCTs

<table>
<thead>
<tr>
<th>GDMT</th>
<th>RR Reduction in Mortality</th>
<th>NNT for Mortality Reduction (Standardized to 36 mo)</th>
<th>RR Reduction in HF Hospitalizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor or ARB</td>
<td>17%</td>
<td>26</td>
<td>31%</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>34%</td>
<td>9</td>
<td>41%</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>30%</td>
<td>6</td>
<td>35%</td>
</tr>
<tr>
<td>Hydralazine/nitrate</td>
<td>43%</td>
<td>7</td>
<td>33%</td>
</tr>
</tbody>
</table>
Incremental Benefit with HF Therapies
(Cumulative % Reduction in Odds of Death at 24 Months Associated with Sequential Treatments)

- ACEI/ARB: -38%
  +20% to -68%
  \( P=0.1566 \)

- ACEI/ARB + BB: -77%
  -43% to -91%
  \( P<0.0001 \)

- ACEI/ARB + BB + CRT + ICD: -90%
  -70% to -96%
  \( P<0.0001 \)

Diuretics

- Decrease congestive symptoms
  - No mortality benefit
- First line: Loop diuretics
  - Thiazide diuretic may be added
- Potassium and magnesium goals
- NA restriction
- Fluid restriction criteria

- Monitor response to therapy
  - Adequate diuresis
    - BNP pt goal
    - JVP assessment
    - Orthopnea
  - Over diuresis
    - Hypotension
    - Dizziness
    - Orthostatic BP
Diuretic Therapy

Considerations

- Outpatient: Weight loss goal of 0.5 to 1.0 kg per day
- Adjustable diuretic dosing
  - Weight gain
  - Weight loss
  - Change in oral intake or during periods of illness
- Use with moderate sodium restriction

Diuretic Resistance

- Diuretic resistance
  - Reasons
    - High sodium levels
    - NSAIDs
    - Severe renal impairment
    - Renal hypoperfusion
  - Strategies
    - IV
    - Continuous infusion (BP concerns)
    - Different loop
    - Addition of metolazone
Diuretics and Renal Function

• Role of venous congestion in worsening renal function

Versus

• Role of volume depletion / hypotension and worsening renal function
Cardiorenal Syndrome

• Moderate to severe renal dysfunction with fluid overload
  – Continue to treat with diuretics
• In severe fluid overload renal dysfunction my improve with continued treatment
• May need to hold ACE I secondary to AKI
• Venous congestion plays a role in worsening renal function (not just hypoperfusion)
Renal Anatomy: Nephron
Loop Diuretics

- Work in ascending loop of Henle
- Loss of H2O, K+, Na+, Cl-, H+
- More loss of H2O and less K+ and Na+ than thiazides
- Promotes venous vasodilatation
- Rapid onset and short duration
- Can be effective in presence of renal failure
- High ceiling diuretic
Loop Diuretics

**Equivalents**
- Furosemide 40 mg
- Torsemide 20 mg
- Bumetanide 1 mg

**Dosing**
- Adequate to relieve symptoms
- Start equal or greater than home maintenance dose

<table>
<thead>
<tr>
<th>Bumetanide (Bumex)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide (Lasix)</td>
</tr>
<tr>
<td>Torsemide (Demadex)</td>
</tr>
</tbody>
</table>
Differences in Loop Diuretics

<table>
<thead>
<tr>
<th>Bumetanide</th>
<th>Furosemide</th>
<th>Torsemide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of randomized control data with comparison to furosemide.</td>
<td>BID Dosing when GFR is low</td>
<td>2 randomized trials comparing Torsemide and Furosemide N=471</td>
</tr>
<tr>
<td>Better pharmacokinetic profile (oral bioavailability) than furosemide but turomamide has evidence of more efficacy and more safety. (Wargo &amp;Banta, 2009)</td>
<td></td>
<td>Torsemide associated with reduction in HF and CV readmission in systolic HF with a trend towards reduction of all cause mortality. (DiNicolantonio, 2012)</td>
</tr>
</tbody>
</table>
More on Loop Diuretics

• DOSE Trial
  – NEJM: Felker et al., 2011

  – No significant difference in symptoms or renal function between continuous drip versus intermittent dosing

  – Non significant trend toward improvement in symptoms with high dose (IV at 2.5 x PO dose) versus low dose; (IV at same as PO dose) no change in renal function
Thiazide Diuretics

– Inhibit reabsorption of Na+ and Cl-
  • In the distal tubule.
– Delayed onset but longer duration of action than loop diuretics
– Low ceiling diuretics
– Less potent diuretic than loop diuretics
– Diminished effectiveness in presence of renal failure
### Thiazide Diuretics

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Side effects:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendrofluazide (Naturetin)</td>
<td>Blood Chemistry changes:</td>
</tr>
<tr>
<td>Benthiazide (Aquatag, Exna)</td>
<td>Hyponatremia (↓ Na⁺)</td>
</tr>
<tr>
<td>Chlorothiazide (Diuril)</td>
<td>Hypokalemia (↓ K⁺)</td>
</tr>
<tr>
<td>Chlorthalidone (Hygroton)</td>
<td>Hypomagnesemia (↓ Mg⁺)</td>
</tr>
<tr>
<td>Cyclothiazide (Anhydron)</td>
<td>Hyperglycemia (↑ blood sugar)</td>
</tr>
<tr>
<td>Hydrochlorothiazide (HCTZ) (HydroDiuril, Esidrix)</td>
<td>Hyperuricemia (↑ uric acid)</td>
</tr>
<tr>
<td>Hydroflumethazide (Saluron, Diucardin)</td>
<td>Hypercalcemia (↑ Ca⁺⁺)</td>
</tr>
<tr>
<td>Indapamide (Lozol)</td>
<td>Decreased glomerular filtration in kidneys (↑ BUN, creatinine)</td>
</tr>
<tr>
<td>Metolazone (Zaroxolyn)</td>
<td>↑ cholesterol</td>
</tr>
<tr>
<td>Polythiazide (Renese)</td>
<td>↑ triglycerides</td>
</tr>
<tr>
<td>Trichlormethiazide (Metahydrin, Naqua)</td>
<td>↓ HDL cholesterol</td>
</tr>
<tr>
<td></td>
<td>Other side effects:</td>
</tr>
<tr>
<td></td>
<td>Impaired glucose tolerance</td>
</tr>
<tr>
<td></td>
<td>Gout</td>
</tr>
<tr>
<td></td>
<td>Impotence</td>
</tr>
<tr>
<td></td>
<td>Ventricular arrhythmias (↓ K⁺)</td>
</tr>
<tr>
<td></td>
<td>Nausea, dizziness, headache</td>
</tr>
</tbody>
</table>
CASE EXAMPLES IN DIURETIC THERAPY COMPLICATIONS

Hypokalemia:
• DC’d K+ = 3.5
• Furosemide 60 mg BID and metolazone 5 every other day
• No potassium supplementation, BMP stated in DC summary but not ordered and not on patient DC instructions
• Readmitted with potassium of 2.6 mEq/L.

AKI:
• Readmitted with BUN> 100 with GI bleed – from home,
• Dialysis required – coded during dialysis
• Discharged with creatinine 3.12 (2.63)
• Discharged on Furosemide 40 BID & metolazone 10 mg daily (dose increased day prior to discharge)
Digoxin

- **Stage C Recommendations**
  - Added in patients with persistent symptoms already on ACE Inhibitor, Beta-blocker and diuretic

- **Positive inotropic effect** – weak effect

- **Enzyme inhibition in noncardiac tissues** – reduces sympathetic flow

- **Improved symptoms**, exercise tolerance and quality of life

- **No reduction in mortality**

- **Beta-blocker better for rate control**

- **Low dose**: 0.125mg daily

- **No need for loading dose**
Hydralazine & Isosorbide Dinitrate

• Combination of fixed dose of Hydralazine & Isosorbide Dinitrate to a standard medical regimen for HF, including ACEIs and beta blockers, is recommended in order to improve outcomes for patients self-described as African Americans, with NYHA functional class II of IV HF.

• Compliance is difficult
The Electronics

Action Potential of Cardiac Cells

- Phase 0: Rapid depolarization – Sodium Influx (beginning of QRS complex)
- Phase 1: Brief, rapid initiation of repolarization
The Electronics

- Phase 2: Slowing of the repolarization – **Calcium Influx** – correlates with ST segment
- Phase 3: Sudden acceleration in the rate of repolarization - **Potassium Efflux** – Correlates with T wave
- Phase 4: Resting membrane potential
Class I
Slow conduction (widen QRS). Some prolongation of refractory period (prolong QT interval).

Class III
Marked prolongation of refractory period (prolong QT interval).
Antiarrhythmic Medications Effecting the Action Potential

• **Class I** – Fast sodium channel blockers
  – IA: Quinidine, Procainamide, Disopyramide
  – IB: Lidocaine, Mexiletine, Tocainide
  – IC: Flecainide, Propafenone

• **Class III** – Potassium channel blockers
  – Amiodarone, Ibutilide, Dofetilide, Sotalol

• **Class IV** – Calcium channel blockers
  – Verapamil, Diltiazem
Effects of Class 1 Antiarrhythmics

• All Class 1 antiarrhythmics by definition block the fast sodium channel
  – Different drugs do this to a different degree
    – IC > IA > IB

• Blocking of the fast sodium channel interferes with rapid depolarization and decreases conduction velocity
  – This will increases the duration of the cardiac action potential
  – Note: This effect is seen in the action potential of the purkinje fibers but not in the action potential of the nodal tissue
Benefits of Reducing Rate and Degree of Depolarization

• Decrease in conduction velocity in non-nodal tissue is called negative dromotropy.

• This is suppress reentrant tachycardias because reentrant tachycardias are caused by abnormal conduction.
Effects of Class 1 Antiarrhythmics

• In addition to blocking the fast sodium channel (Phase 0) – some class I agents also block the potassium channel (Phase 3)
• Potassium channel blockade directly affects the duration of the cardiac action potential and the effective refractory period.
• Benefits and disadvantages of effecting refractory period
  – Beneficial in reentrant tachycardias
  – Can increase risk for Torsades
• Different drugs do this to a different degree
  – IA (increase refractory period) > IC (no effect) > IB (decrease refractory period)
Effects of Class 1 Antiarrhythmics

Depression of Automaticity

- Can suppress abnormal automaticity
- Not related to sodium channel effect
- Mechanism not fully understood

Anticholinergic Effect

- Strong inhibitors of vagal activity
- Offsets some of benefit (i.e. an increase ventricular rate during the treatment of atrial arrhythmias)
- Can increase SA rate and conduction through the AV node
# Class I C Antiarrhythmics

<table>
<thead>
<tr>
<th>Action Potential</th>
<th>Potent inhibition of fast sodium channel; decrease in maximal rate of phase 0 depolarization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actions</td>
<td>Slow His-Purkinge conduction and cause QRS widening; QT intervals are also usually prolonged</td>
</tr>
<tr>
<td></td>
<td>No effect on refractory period</td>
</tr>
<tr>
<td>Cautions</td>
<td>Proarrhythmic effects</td>
</tr>
<tr>
<td>Uses</td>
<td>Life threatening ventricular arrhythmias</td>
</tr>
<tr>
<td></td>
<td>Conversion to SR (Flecainide)</td>
</tr>
<tr>
<td>Drugs</td>
<td>Flecainide (Tambocor)</td>
</tr>
<tr>
<td></td>
<td>Moricizine (Ethomozine)</td>
</tr>
<tr>
<td></td>
<td>Propafenone (Rhythmol)</td>
</tr>
</tbody>
</table>
# Class I C Antiarrhythmics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Flecainide</strong> (Tambocor)**</td>
<td>Not a first line agent for ventricular arrhythmias  &lt;br&gt;Will slow conduction over accessory pathways in WPW tachycardias  &lt;br&gt;Used in atrial fibrillation (pill in the pocket)  &lt;br&gt;CAST Trial: propensity for fatal proarrhythmic effects  &lt;br&gt;Not used post MI or with depressed LV function</td>
</tr>
<tr>
<td><strong>Moricizine</strong> (Ethmozine)**</td>
<td>CAST studies: Reserved for life threatening ventricular arrhythmias  &lt;br&gt;Has properties of class I B also</td>
</tr>
<tr>
<td><strong>Propafenone</strong> (Rhythmol)**</td>
<td>Used in supraventricular arrhythmias and life threatening ventricular arrhythmias  &lt;br&gt;Also has small beta blocking actions and calcium channel blocking effects that can worsen HF  &lt;br&gt;Must be initiated in hospital setting to monitor ECG</td>
</tr>
</tbody>
</table>
# Class III Antiarrhythmics

<table>
<thead>
<tr>
<th>Action Potential</th>
<th>Inhibits potassium ion fluxes during phase II and III of the action potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actions</td>
<td>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</td>
</tr>
<tr>
<td>Cautions</td>
<td>Proarrhythmic Effects (amiodarone less)</td>
</tr>
<tr>
<td>Uses</td>
<td>Drug dependent</td>
</tr>
</tbody>
</table>
| Drugs            | Amiodarone (Pacerone, Cordorone)  
Ibutilide (Corvert) – pure class III  
Dofetilide (Tikosyn) – pure class III  
Sotalol (Betapace) |
## Class III Antiarrhythmics

| Amiodarone (ARREST Trial) | 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
Slows conduction in accessory pathways
Originally marketed as anti-anginal (potent vasodilator)
Relaxes smooth and cardiac muscle, reduces afterload and preload (well tolerated in heart failure and cardiomyopathy)
**Proarrhythmias less frequent**
Is also a weak sodium channel blocker, also has effects similar to class II and IV, also has anticholinergic properties |

---

180
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
## Class III Antiarrhythmics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibutilide (Corvert)</td>
<td>Indicated for rapid conversion of atrial fib or flutter to sinus rhythm; IV use only; also facilitated cardioversion&lt;br&gt;(Don’t convert atrial fib or flutter of duration without anticoagulation)&lt;br&gt;Rather than blocking outward potassium currents – promotes influx of sodium through slow inward sodium channel</td>
<td>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 HF, can be used in this population to prevent worsening HF from atrial fib</td>
</tr>
<tr>
<td>Dofetilide (Tykosin)</td>
<td>More “pure” class III agent&lt;br&gt;Conversion to and maintenance of SR in A fib and flutter&lt;br&gt;Reserved for very symptomatic patients, monitored 3 days in hospital</td>
<td></td>
</tr>
</tbody>
</table>
Class III Antiarrhythmics

| Sotalol (Betapace<sup>R</sup>) (Betapace<sup>AF</sup>) | Used in atrial arrhythmias and life threatening ventricular arrhythmias
Indicated for stable monomorphc 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 > 160 mg
Proarrhythmic potential (prolonged QT)
More effective in preventing reoccurring arrhythmias than several other drugs |
Dronedarone

• Similar to amiodarone without iodine component and less fat soluble
• Class III antiarrhythmic (K\(^+\) channel blocker) with effects from all four classes
• **Less effective than amiodarone at maintaining sinus rhythm but also less toxic**
• Elimination half-life 13-19 hours
• Has both rate and rhythm control effects but is primarily indicated for rhythm control
• May reduce incidence of stroke (mechanism uncertain)
Dronedarone (ATHENA)

• Approved for maintenance of sinus rhythm in patients with history of paroxysmal or persistent AF or flutter with EF > 35% who are in sinus rhythm or will be cardioverted
• Dose: 400 mg PO bid with meals (no grapefruit juice)
• Contraindicated in patients with NYHA Class IV HF or NYHA Class II-III HF with recent decompensation requiring hospitalization or referral to a specialized HF clinic
  – > twofold increase in mortality in HF patients
• Side Effects
  – GI, skin disorders
  – Can prolong QTc but low risk of Torsades
  – Increases serum creatinine
  – Interferes with digoxin metabolism

Concern: LIVER Dysfunction: 1/2011
Dronedarone is reasonable to decrease the need for hospitalization for cardiovascular events in patients with paroxysmal AF or after conversion of persistent AF. Dronedarone can be initiated during outpatient therapy (Level of Evidence: B).

Reduces risk of recurrent atrial fibrillation after cardioversion by 25%.
Class III Recommendation:

Dronedarone should not be administered to patients with class IV heart failure or patients who have had an episode of decompensated heart failure in the past 4 weeks, especially if they have depressed left ventricular function (left ventricular ejection fraction 35%)

(Level of Evidence: B)
Beta Blockers and Calcium Channel Blockers

RATE CONTROL IN ATRIAL FIBRILLATION
A Closer Look at Calcium Channel Channel Blockers

- Decrease HR
- Decrease Contractility
- Decrease Afterload

**Note:** 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

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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)
Anticoagulants in Atrial Fibrillation: Warfarin

• Target INR of 2.0-3.0 in most patients
• Target INR adjusted in those with mechanical heart valve – at least 2.5
• It takes 4-5 days to reach a therapeutic level.
  – Can have initial transient hypercoagulable state
  – Must be overlapped with heparin

• Chronic conditions require lifelong therapy
• Acute conditions (PE, DVT) usually require at least six months of therapy
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
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
Nursing Considerations with Warfarin

- Many many drugs interact with coumadin to alter PT
- Consistency in diet is important especially with known high vitamin K foods (green vegetables)
- Patient compliance is critical
- Antidote: Vitamin K
- Fresh frozen plasma if severe hemorrhage
- Recombinant factor VIIa is also an option for life threatening bleeding
Dabigatran (Pradaxa)

• Oral direct thrombin inhibitor
  – Is a prodrug (dabigatran etexilate) that is converted in liver to active form
  – Peak plasma levels in 1.5 hours; half-life 12 to 18 hours
  – Eliminated mostly by kidneys (reduced dose for moderate renal failure, not recommended in severe renal failure)

• Predictable dose-response relationship so no lab monitoring of coagulation status needed

• Drug to drug interactions exist

• Dose:
  – 150 mg PO BID
  – 75 mg PO BID with creatinine clearance 15 to 30 mL/minute
    • These patients and this dose not tested in clinical trials
Dabigatran

♥ No known antidote
♥ For surgeries with a high risk for bleeding (i.e. CABG), recommended hold time is 3 to 5 days. For urgent cases of major surgery delay until clotting times are normal or until four half-lives has passed
  ♥ Hold times for surgery are dependent on renal function
  ♥ Minimum hold time for low risk surgery and normal renal function is > 24 hours
♥ Bleeding risk can be assessed by an ecarin clotting time if available
  ♥ If not available, a PTT can be assessed to determine clearance of the drug because dabigatran has been shown to prolong aPTT (aPTT not used for quantitative assessment)
  ♥ > 2 x upper normal limit 12 to 24 hours after drug may be indicative of high risk for bleeding
♥ Thrombin time is most sensitive test. Diluted thrombin time (DTT) is a quantitative test (calibrated Hemoclot®)

DO NOT USE INR. Can be falsely elevated.
Dabigatran

- RE-LY trial (Connolly et al, 2009)
- Study results (stroke / systemic embolism) compared to warfarin:
  - 110 mg BID non-inferior to warfarin (p < 0.001)
  - 150 mg BID superior to warfarin (p< 0.001)
- Rate of major bleeding
  - 110 mg BID lower than warfarin (p=0.003)
  - 150 mg BID no different from warfarin dose of dabigatran (p=0.31)
    • One area of concern GI Bleed
- Ischemic stroke
  - Statistically lower with dabigatran at 150 mg PO BID
- Hemorrhagic stroke
  - Statistically lower with dabigatran at both doses (p < 0.001).
- Approved for reduction of stroke in patients with AF at intermediate or high risk of stroke.
- Specific patient characteristics
  - 30.9% to 32.6% CHADS2 score = 0-1
  - 34.7% to 37.0% CHADS2 score = 2
Rivaroxaban (Xarelto)

• Oral direct factor Xa inhibitor
  – Maximum plasma level in 3 hours
  – Half-life 5-9 hours (up 11 to 13 hrs if > 75 years old)
  – Dose 20 mg PO daily
  – Should be taken with food
  – Hepatic and renal excretion
    • Contraindicated in severe renal failure

• Predictable dose-response relationship so no lab monitoring needed
Rivaroxaban

♥ Recommended hold time prior to high bleeding risk surgeries is 2 to 4 days depending on the patient’s age and renal function

♥ Minimum hold time for low risk surgery in patients with normal renal function is $\geq 24$ hours

♥ With severe hepatic impairment the elimination half-life is not known - recommended the drug be held for 7 days prior to major surgery

♥ No known reversal agent
Rivaroxaban

• ROCKET AF (Patel et al., 2011)
  – Double-blind randomized trial
  – 14,264 patients with nonvalvular atrial fibrillation (at increased risk for stroke)
  – Mean CHADS2 score 3.5
    • 87% to 86.9% had CHADS2 score > 3
  – Rivaroxaban (at a daily dose of 20 mg) or dose-adjusted warfarin
  – Composite of stroke (ischemic or hemorrhagic) and systemic embolism
  – P<0.001 for non-inferiority of rivaroxaban
  – No significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group
Apixaban (Eliquis)

- Oral factor Xa inhibitor
- Rapid absorption; 8 to 15 hour elimination ½ life
- 25% renal excretion
- Dose: 5 mg BID
- Dose: 2.5 mg BID
  - Creatinine > 1.5 mg/dL and either
  - Age > 80 years
  - Weight ≤ 60 kg
Apixaban

♥ Recommended to be held for at least 48 hours prior to surgery with a moderate to high risk for bleeding.

♥ Minimum hold time for low risk surgery in patients with normal renal function is ≥ 24 hours

♥ No known reversal agent
Apixaban

- ARISTOTLE (Granger et al., 2011.)
- Randomized, double blind, double dummy
- 18,201 patients; median age 70 years; 35% female
- Apixaban 5 mg BID versus warfarin (INR 2.0 to 3.0)
  - 2.5 mg BID used in subset of patients
- Primary objective evaluated for non-inferiority for primary endpoint of Ischemic stroke/ hemorrhagic stroke / systemic embolism
  - Found to be non inferior to warfarin (p = <0.001)
- Secondary objective evaluated for superiority for primary endpoint of Ischemic stroke/ hemorrhagic stroke / systemic embolism
  - Found to be superior to warfarin (p= 0.01)
- Primary safety outcome: Major bleeding
  - Statistically less with apixaban (p<0.001)
- Delayed by FDA for review of data management and verification
- No statistical difference in ischemic stroke.
Apixaban

**AVERROES** : Apixaban versus ASA.

**APPRAISE – 2**: Apixaban added to DAPT in ACS in high risk patient.
Enoxaban

- ENGAGE AF-TIMI 48
- Randomized, double-blind, double-dummy trial
- 21,105 patients, follow up 2.8 years
- Tested for non-inferiority for stroke or systemic embolism
- P = < 0.001 for high dose and P = 0.005 for low dose
- Significantly lower rates of bleeding and cardiovascular death compared to warfarin at both doses
More on Factor Xa Inhibitors

- PT may provide qualitative assessment of presence of factor Xa
- Not sensitive for quantitative anticoagulation effect
- Point of care INR should not be used to gauge anticoagulation effects
- Chromogenic assay can provide quantitative assessment – not widely available, not fully studied, not recommended at this time
- Not all drug to drug interactions are known
- Factor Xa inhibitor antidote, andexanet alfa – breakthrough therapy designation by FDA
BE THE BEST THAT YOU CAN BE EVERY DAY. YOUR PATIENTS ARE COUNTING ON IT!

Karen@cardionursing.com