“Professional nursing practice can only advance as much as individual nurses are aware that a knowledge gap exists in their practice, feel empowered to access further learning, and integrate evidence based competencies into their professional practice to provide safe, effective, efficient, patient centered, equitable care.”

www.tigersummit.com
UNDERSTANDING WHY WE DO WHAT WE DO

Differentiating mortality benefit from symptom relief.

TODAY’S PURPOSE: FINDING THE “SO WHAT”
Impacting Cardiac Output to Improve Myocardial Performance

Paradigm Shift

- Hemodynamics does not equal invasive monitoring

One must be comfortable with shades of grey!!
The Heart as a Pump

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

**Flow** is determined by:
- √ Pressure
- √ Resistance
- √ Volume

![Diagram of the Cardiovascular System](image)
KEY PHYSIOLOGICAL PRINCIPALS

Neurologic Control of the Heart

• Autonomic Nervous System
  – SNS
  – PNS
• Chemoreceptors
• Baroreceptors
Autonomic Nervous System

- Both divisions of the autonomic nervous system extend into the heart
- The atria are innervated by both parasympathetic and sympathetic fibers
- The ventricles are almost entirely innervated by sympathetic fibers only
Sympathetic Nervous System

- **Fight or Flight**

  **Alpha₁ Receptors**
  - Vasoconstriction of vessels

  **Beta₁ Receptors** (Heart)
  - Increased heart rate
    - Chronotropic response
  - Increased conductivity
    - Dromotropic response
  - Increased contractility
    - Inotropic response
  - Increased automaticity

  **Beta₂ Receptors** (Vessels, Lungs)
  - Bronchodilation
  - Peripheral vasodilatation
  - *Causes renin release and activation of the RAAS*

  **Dopaminergic Receptors**
  - Renal and mesenteric vasodilation

Parasympathetic (Vagal) Nervous System

- Maintains a steady state
- Causes – chronotropic, dromotropic effects
- Causes minimal decrease in inotropic effects
- Primarily slow heart rate and conduction
- Cardiovascular effects of PNS generally undesirable
Chemoreceptors

- Located in carotid and aortic bodies
- Sensitive to changes in $\text{PaO}_2$, $\text{PaCO}_2$, and pH.
- $\downarrow$ in pH or $\downarrow$ in $\text{O}_2$ or $\uparrow$ in $\text{CO}_2$  
  $\Rightarrow$ SNS response
- $\uparrow$ in pH or $\downarrow$ in $\text{CO}_2$  
  $\Rightarrow$ PNS response

Baroreceptors

- Located in the carotid sinus and aortic arch
- Sensitive to arterial wall tension
- Cause reflex response in either SNS or PNS

- Decrease BP $\Rightarrow$ SNS (adrenergic) response
- Increase BP $\Rightarrow$ PNS (cholinergic) response
Key Principles in Understanding Hemodynamic Assessment

- **Pulse pressure** tells us about arterial compliance
- **Variation of up to 15mm Hg between arms** is normal
- **MAP = Calculated**
  - Systolic BP
    - Very dynamic
    - Arterial pulse waveform proportional to SV - SBP can be used to reflect stroke volume
  - Diastolic BP
    - Continuous / less dynamic pressure
    - Reflects state of arterioles
    - Drives capillary opening pressure
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 and narrowing pulse pressure

Key Principles in Understanding Hemodynamic Assessment

• **Pressure** does not always = **Flow**

  – “We measure BP because we can” – Barbara Mclean
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%
Basic Hemodynamic Formula

Cardiac Output

Heart Rate X Stroke Volume

Preload  Afterload  Contractility

Same four components also determine myocardial oxygen demand

Determinants of Myocardial Performance

Stroke Volume
  Preload  Afterload  Contractility

Heart Rate

Synergy
Synchonry
Preload

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

- 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: Indirect

**Right ventricular preload**

- Noninvasive assessment
  - JVD
  - Hepatogigular reflux
  - Peripheral edema
  - Weight

**Left ventricular preload**

- Noninvasive Assessment
  - Orthopnea
  - CXR
  - BNP
  - Lungs sounds
  - $S_3$
  - Blood Pressure
  - Urine Output
  - Weight

Also assess skin turgor, mucous membranes, and orthostatic blood pressures.

Right Side and Left Side are Related
Afterload

- **After the ventricle is loaded: It must work!**
- **Pressure ventricle needs to overcome to eject blood volume**
  - SVR for left ventricle
  - PVR for right ventricle
- **Smaller vessel resistance is major component of LV afterload**
- **Other components of LV afterload**
  - Valve compliance
  - Viscosity of blood
  - Arterial wall (aortic) compliance

More on Vascular Tone

- Increased vascular tone is usually associated with compensation for low SV
  - Acute Cardiogenic shock
  - Hypovolemic shock

- Decreased vascular tone is usually due to abnormally pathology
  - Sepsis
  - Anaphylaxis
  - Altered neurological control
Afterload Assessment

- Left ventricle:
  - Noninvasive assessment: Diastolic blood pressure and pulse pressure

- Right ventricle:
  - Pulmonary HTN increases RV afterload
  - Hypoxemia / Positive Pressure Ventilation / PEEP increase RV afterload

Blood Pressure and Afterload

\[
\text{Cardiac Output} \times \text{SVR} = \text{Blood Pressure}
\]

- Afterload is related to blood pressure but not synonymous
BP = CO x SVR

• Low BP could be due to:
  — Low CO
    • HR too slow or too fast
    • Preload too low or too high
    • Contractility low
  — Low SVR
    • Vasodilation due to sepsis, anaphylaxis, altered neurological function, drugs

So – When systolic BP is low, we look to the pulse pressure for the answer.

When you have Tachycardia Ask Yourself:

Why is my patient compensating?

Look to the pulse pressure for your answer.
Use of Pulse Pressure

- PP < 35 with tachycardia (in absence of beta blocker)
  
  Early sign of hypovolemia
  * Can also sign of cardiac failure / cardiogenic shock

- PP > 35 with tachycardia
  
  Early sign of vasodilatory state such as sepsis

Blood Pressure:
CO x SVR

- BP: 88/64
  - Is problem low cardiac output or low SVR?
  - How to treat?

- BP: 82/30
  - Is problem low cardiac output or low SVR?
  - How to treat?
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
  \[ \Rightarrow \] ↑ myocardial workload
  \[ \Rightarrow \] ↑ 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.
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)
## 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

## 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
<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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cold and Dry</th>
<th>Cold and Wet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Perfusion</td>
<td>Low Perfusion</td>
</tr>
<tr>
<td>No Congestion</td>
<td>Congestion</td>
</tr>
</tbody>
</table>

Drugs Used to Manipulate 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>Diuretics</td>
<td>• A loop diuretic such as furosemide eliminates circulating volume</td>
</tr>
<tr>
<td>Venous Vasodilators</td>
<td>• Intravenous nitroglycerin, neseritide, or morphine sulfate (<em>Venous vasodilatation pools blood away from the heart and decreases preload</em>)</td>
</tr>
</tbody>
</table>
|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. |
Drugs Used to Manipulate Afterload

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

<table>
<thead>
<tr>
<th>Smooth muscle relaxants</th>
<th>Calcium channel blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Nitroprusside</td>
<td>• Dihydropyridines (ending in “ine”) calcium channel blockers such as amlodipine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alpha, receptor blockers</th>
<th>Central anti-adrenergics</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Labetolol (combination alpha and beta blocker)</td>
<td>Clonidine, Methyldopa</td>
</tr>
<tr>
<td>• Prazoxin, Terazosin</td>
<td>Risperine, Guanethidine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACE Inhibitors</th>
<th>Angiotensin II Receptor Blockers (ARBs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Interrupt the RAAS and limit production of angiotensin II a potent arterial vasoconstrictor</td>
<td>• Directly block the effects angiotensin II</td>
</tr>
<tr>
<td>• Medications ending in “pril”</td>
<td>• Medications ending in “sartan”</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phosodiesterase Inhibitors (PDE Inhibitors)</th>
<th>Drugs Used to Decrease Right Sided Afterload</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Milrinone</td>
<td>Pulmonary Vasodilators</td>
</tr>
<tr>
<td>• Is used as an intravenous inotrope but also has arterial vasodilator properties</td>
<td>• Oxygen</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pulmonary Arterial HTN Specific</th>
<th>Inhaled</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Prostacyclins (PG12)</td>
<td>• Nitric Oxide</td>
</tr>
<tr>
<td>• Endothelin antagonists (oral)</td>
<td>• Oxygen</td>
</tr>
<tr>
<td>• Phosphodiesterase inhibitors</td>
<td>• IV</td>
</tr>
<tr>
<td>• Soluble Guanylate Cyclase (SGC)</td>
<td>• - NTG</td>
</tr>
<tr>
<td>• Riociguat (Adempas)</td>
<td>• Sodium Nitroprusside</td>
</tr>
<tr>
<td></td>
<td>• Inhaled</td>
</tr>
<tr>
<td></td>
<td>• - Nitric Oxide</td>
</tr>
</tbody>
</table>
Drugs Used to Manipulate Contractility

Pharmacological Options for Increasing Contractility

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

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
</table>
| 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 |
| Phosphodiesterase 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 |

### Drugs Used to Manipulate Heart Rate
### Pharmacological Options for Increasing Heart Rate

| Parasympatholytic (lyses the parasympathetic nervous system) | • Atropine |
| Sympathomimetics stimulating the β₁ receptors of the sympathetic nervous system | • Epinephrine  
• Dopamine |

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

1. Beta Blockers blocking the β₁ receptors of the sympathetic nervous system  
   • “olol” medications  
   • Class II antiarrhythmics
2. Calcium Channel Blockers  
   • Diltiazem / Verapamil  
   • Class IV antiarrhythmic
3. Cardiac Glycoside  
   • Digoxin
4. Unclassified antiarrhythmic  
   • Adenosine: Slows conduction through the AV node
5. Other antiarrhythmics  
   • Class I and Class III antiarrhythmics  
   • Used to establish and / or maintain a normal rhythm and therefore control heart rate
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.

Epinephrine

Endogenous catecholamine

| 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 10 minutes; Peak 10 to 20 minutes
- Half-life 2 minutes
- Maximal dose 20 mcg/kg/min

---

More on Dobutamine

- Low dose 2-5 mcg/kg/min will result in decrease in SVR
- Higher doses associated with more arrhythmias

- Monitor for side effects associated with increased myocardial oxygen demand
- **Note:** Blood pressure response is variable; $\beta_2$ causes vasodilatation; $\beta_1$ increases cardiac output and may increase BP
**Dopamine**

- **What receptors are stimulated:**
  - Dopaminergic at low doses (0.5-3.0 mcg/kg/min)
  - $\beta_1$ also at moderate doses (5.0-15.0 mcg/kg/min)
  - Pure alpha stimulation at high doses > 15mcg/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 within 5 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 and peak 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

- Low dose exogenous
  - 0.04 units / min

- Use in refractory shock
  - Also consider methylene blue
  - Also consider adrenal insufficiency as cause
Non Sympathomimetic Inotrope: Selective Phosphodiesterase Inhibitor – Milrinone

- 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)

Milrinone

- **Indications:**
  - Refractory heart failure (in combination with dobutamine)
  - Left ventricular failure in MI
  - Patients waiting transplant
- **Side Effects:**
  - Ventricular arrhythmias and other arrhythmias
  - Hypotension
  - Angina
- **Dosing adjustments for renal dysfunction**
- **No loading dose recommended**
  - Similar effects on filling pressures and cardiac index at 2 to 3 hours as compared to use of loading dose.
  - At 0.5 mcg/kg/min hemodynamic changes seen at 30 minutes
  - Maintenance 0.125mcg/kg/min to 0.75mcg/kg/min

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
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

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 neseritide and 377 to control therapy. Death within 30 days tended to occur more often among patients randomized to neseritide 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

  – Start 5 to 10 mcg/min and titrate by 5mcg/min q 3 to 5 minutes, if no response at 20mcg/min may increase in increments of 10mcg/min.
  – Max dose: 200mcg/min.

Nitroglycerin

• Uses: Acute MI, unstable angina, CHF
• Side Effects: H/A, Hypotension, flushing
• Decreases activity of Heparin

• Nursing Considerations:
  – Contraindicated with Sildenafil like drugs
  – Caution (all venous vasodilators) with:
    • Hypertrophic cardiomyopathy, aortic stenosis, right ventricular MI
    • Any condition with volume depletion

  – Treat H/A with pain meds and decrease dose
    • Pain activates the SNS

  – Onset IV: 2-5 minutes
  – Duration: 3-5 minutes

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

- Mixed venous and arterial dilator (primarily arterial)
- Decreases afterload and preload, also dilates pulmonary vasculature
- Uses:
  - Hypertensive crisis
  - CHF
  - Acute mitral regurgitation
  - Other indications for acute afterload reduction

- Side Effects:
  - Hypotension (arterial line recommended)
  - Thiocyanate toxicity:
    - Tinnitus, blurred vision, delirium, seizures, muscle twitching, absent reflexes, dilated pupils
    - Several days – high doses – Doses > 400mcg/min not recommended
More on Nitroprusside: Dosing

- Start 5 to 10 mcg/min for HF and 0.3 to 0.5 mcg/kg/minute for HTN
- Titrate q 5 minutes
- Titrate by 0.5/mcg/kg in HTN
- Usual dose 5 to 300 mcg/min
- Max dose 10mcg/kg/min, however, to reduce toxicity maximum recommended dose is 2mcg/kg/min.

- Onset: 1-2 minutes
- Duration: 1-10 minutes
- Half life 2 minutes

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 (beta blockers first!)

- Not to be used in severe aortic stenosis
Acute Coronary Syndrome

Imbalance between myocardial oxygen supply and demand.

Hospitalizations in the U.S. Due to ACS

<table>
<thead>
<tr>
<th>Acute Coronary Syndromes*</th>
<th>1, 190,000 Hospital Discharges with primary or secondary diagnosis of ACS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UA/NSTEMI</strong></td>
<td><strong>STEMI</strong></td>
</tr>
<tr>
<td>NRMI-4*: 71%</td>
<td>NRMI-4*: 29%</td>
</tr>
<tr>
<td>AHA Get with the Guidelines: 69%</td>
<td>AHA Get with the Guidelines: 31%</td>
</tr>
<tr>
<td>GRACE**: Study: 62%</td>
<td>GRACE**: Study: 38%</td>
</tr>
</tbody>
</table>

*NRMI-4: National Registry of Myocardial Infarction; **GRACE Study: Global Registry of Acute Coronary Events.
Acute Coronary Syndrome refers to any rupture of plaque or thrombotic event that leads to symptomatic ischemia or infarction.

Acute Coronary Syndrome (ACS)

- **No ST Elevation**
  - NonSTEMI
  - Unstable Angina

- **ST Elevation**
  - STEMI
STEMI

- Roughly 30% of ACS patients
- Complete occlusion of a vessel by a thrombus
- Classified more specifically by the portion of the left ventricle suffering the injury.
- Mortality is greatest within the first 24 to 48 hours of symptom onset
- Pathophysiology involves a fibrin stable clot (red clot)
- TREATMENT FOCUS = REPERFUSION

NSTEMI

- Higher mortality and morbidity than STEMI
- Nationally under treated according to evidence based practice guidelines approximately 25% of the time (Crusade Registry)
- Differentiated from unstable angina by troponin levels
- Pathophysiology often involves a platelet plug or white clot
  - Less stable clot
  - Opportunity for spontaneous reperfusion
- TREATMENT FOCUS = ANTIPLATELET THERAPY
Drugs Used to Alter Clotting in ACS

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

• **Anticoagulants**
  o STEMI / NonSTEMI / UA
  o Unfractionated Heparin
  o Low Molecular Weight Heparin
  o Direct Thrombin Inhibitors
  o Factor Xa Inhibitors

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

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 of thromboplastin tissue factor (secondary to tissue injury)
• 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 Common Pathway
  - Prothrombin is converted to thrombin
  - Thrombin permits fibrinogen to be converted to fibrin
  - Result is fibrin stable clot (red clot)
Anticoagulants in ACS

- Unfractionated Heparin
  - STEMI
  - Non-STEMI / UA
- Low Molecular Weight Heparin
  - STEMI
  - Non-STEMI / UA
- Direct Thrombin Inhibitors
  - History of heparin induced thrombocytopenia
  - PCI
  - Non-STEMI / UA
- Factor Xa Inhibitors
  - Non-STEMI / UA
  - Not sole anticoaulant in PCI

[Image of coagulation cascade and platelets diagram]
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 Xa and 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

- Must monitor safety and efficacy
  - aPTT (activated partial thromboplastin time): Goal is aPTT 1.5 Xs the control
  - Unfractionated heparin levels by anti-Xa activity: 0.3 to 0.7 IU/mL
- 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) or Heparin Induced Thrombocytopenia with Thrombosis (HITT)
  – 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
  – Severe thrombocytopenia is due to an immune response

More on HIT / HITT

• Immune system forms antibodies against heparin when heparin is bound to the protein platelet factor 4 [PF4]
  – PF4 antibodies formed in many people receiving heparin
    • Not necessarily associated with thrombocytopenia or thrombotic risk
    • Can disappear 3 months after exposure - antibody does not persist for longer than 3 months
  – First test ELISA
    • All PF4 antibodies detected in ELISA testing – not just those associated with HIT/HITT
  – Confirmatory test is washed platelet assay test

• HIT antibodies are usually IgG class
  – Take 5 days to form
  – Antibodies form a complex with heparin and PF4, tail of antibody binds to a protein on the platelet – this results platelet activation and increased thrombin generation

• Called HITT (heparin induced thrombocytopenia and thrombosis)
• Called HIT (heparin induced thrombocytopenia) when there is not associated thrombosis
Treatment of HIT / HITT

1. Discontinue and avoid all heparin.
2. Give a non-heparin alternative anticoagulant: Direct thrombin inhibitors (argatroban).
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 – warfarin necrosis.
4. **Avoid platelet transfusions – leads to platelet activation.**
5. Test for HIT antibodies (ELISA and washed assay)

---

**Low Molecular Weight Heparin**

- **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
- 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 posterorlateral 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)
The Role of Platelets

• Platelet aggregation can be large enough to form a platelet plug or a white clot that seals a damaged vessel
  – This white clot is primary culprit in NonSTEMI or Unstable Angina

• Platelets cross link with fibrinogen via the GP IIb/IIIa receptors to form a fibrin mesh which gives a clot more substance resulting in a fibrin stable clot
  – This red clot is the primary culprit in STEMI
Oral Antiplatelet Therapy

- ASA
- 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

Role of Antiplatelet Therapy in ACS

- Dual antiplatelet therapy (DAPT) recommended post discharge in STEMI / Non-STEMI and Unstable Angina
- DAPT includes P2Y₁₂ inhibitor and Aspirin
- GPIIb/IIIa Inhibitors recommended in acute care setting only in select patients
- All antiplatelet therapy aimed at reduction of mortality.
Role of Dual Antiplatelet Therapy in Prevention of Instant Thrombosis

P2Y$_{12}$ Receptor Inhibitors

- Thienopyridines
  - Clopidogrel
  - Prasugrel

- Non thienopyridine
  - Ticagrelor
Thienopyridines

- Thienopyridines are a class of adenosine diphosphate (ADP) / P2Y12 receptor blockers
  - Clopidogrel (Plavix)
  - Prasugrel (Effient)

- Thienopyridines
  - ADP Receptor blockers
    - Adenosine Diphosphate (ADP) - Stored in platelets and released upon platelet activation.
    - ADP interacts with P2Y12 chemoreceptors to enhance adhesiveness and aggregation of platelets through the activation of the GP IIb/IIIa pathway
      - Irreversibly inhibits P2Y12 receptor
      - Referred to as platelet inhibitors

![Diagram of the coagulation cascade and platelet activation](image)
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.

P2Y\textsubscript{12} Receptor Inhibitors:
Clopidogrel versus Prasugrel

• TRITON TIMI 38 Trial
  – 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**

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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 P2Y$_{12}$ Receptor Inhibitors

- Ticagrelor (Brillinta)
  - Antiplatelet agent
  - **Reversibly** binds to 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 I2 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

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| Preoperative Discontinuation Time Frames for Drugs Impacting Coagulation: STS Guidelines |
| Aspirin (2012 Guidelines) | Should be administered preoperatively (100mg – 325mg) |
| Clopidogrel / Ticagrelor | 5 days |
| Prasugrel | 7 days |
| Tirofiban and Eptifibatide | 2 to 4 hours |
| Abciximab | 12 to 24 hours |
| Warfarin | 4 days (generally INR < 1.5) |
| Unfractionated Heparin | Continued up to time of surgery |
| Low Molecular Weight Heparin | 12 to 24 hours |
| Direct Thrombin Inhibitors | Continued up to time of surgery |
| Fondaparinux | 24 hours pre CABG |
| Dabigatran (Pradaxa®) | 1-2 days (3-4 for major surgeries) |
| Rivaroxaban (Xaralto®) | 24 hours |
Nitroglycerin

• Minimal mortality benefit
  – Nitrates may be more helpful in patients > 70 years in reduction of death and heart failure @ 6 month follow up

• Symptom benefit

• Mixed venous and arterial vasodilator
  – Dosage < 1mcg/kg/min = venous vasodilator
    • Decrease preload
  – Dosage > 1mcg/kg/min = arterial and venous vasodilator
    • Decrease preload and afterload
  – Sublingual tablets provide high enough dosage to dilate arteries and veins
    • Decrease preload and afterload

Nitrate Contraindications

• Systolic BP < 90 mm Hg or ≤ 30 mm Hg below baseline
• Bradycardia < 50 BPM
• Tachycardia > 100 BPM (in absence of clinical HF)
• Right ventricular infarct
• Within 24 hours of sildenafil
• Within 48 hours of tadalafil

Question female patients: Pulmonary HTN

Mortality reducing agents should always take precedence over non mortality reducing agents: I.E. Beta blockers precede nitrate use
SL NTG Instruction Post Discharge

• No more than 1 dose of SL NTG
  – If chest discomfort is unimproved or is worsening 5 min after 1 NTG call 9-1-1 immediately before taking additional NTG.
  – May take additional NTG while waiting for EMS.
  – Chew ASA while waiting for EMS.

• In chronic stable angina if symptoms are significantly improved by 1 dose of NTG may repeat NTG every 5 min for a maximum of 3 doses and call 9-1-1 if symptoms have not resolved completely.

A Closer Look at Beta Blockers
Decreases Myocardial Oxygen Demand

Decrease HR
Decrease Contractility

\[ \text{Blood pressure} = \text{CO} \times \text{SVR} \]
Beta Blockers

• Nonselective: Block both Beta_1 and Beta_2
  – Propranolol (Inderal)
  – Timolol (Blocadren)
  – Nandolol (Corgard)
  – Sotolol (Betapace)
  – Labetolol (Normodyne, Trandate) (also alpha blockade)
  – Carvedilol (Coreg) (also alpha blockade)

• Cardio selective: Block Beta 1
  – Acebutolol (Sectral)
  – Metoprolol tartrate (Lopressor)
  – Metoprolol succinate (Toprol XL)
  – Atenolol (Tenormin)
  – Esmolol (Breviblock)
  – Bisoprolol (Z Beta)
  – Nebivolol (Bystol) (also nitric oxide vasodilatory properties)

Beta Blockers in ACS

• Immediate beta-blocker therapy benefit
  – 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 \( \geq 0.24 \text{ sec} \)
    • 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

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
  - Timololol

- Heart Failure
  - Bisoprolol
  - Carvedilol
  - Metoprolol Succinate (XL)

ACE Inhibitors in ACS

- Mortality and morbidity benefit – even better when used in combination with beta blockers
- Initiate within 1st 24 hours of STEMI/NonSTEMI
- At Minimum
  - All anterior MIs
  - Anyone with signs of pulmonary congestion (CHF)
  - Any MI with EF < 40% even if no signs of CHF
- Hold for BP < 100 mmHg or < 30 mmHg below baseline
- No mortality benefit with IV ACE Inhibitors
  - Do not give IV ACE I within 1st 24 hours post AMI
Eplerenone (Inspira)

- 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 Dysfunction
  - Prevent progression of heart failure
  - Prevent sudden cardiac death
  - Prevent recurrent MI

Discharge Profile for ACS

- ASA
- Clopidogrel/Prasugrel/Ticagrelor
- Beta blocker
- ACE Inhibitor
  - Based on additional criteria
- Eplerenone
  - Based on additional criteria
- Statin
  - Regardless of baseline LDL-C

- Medications to control ischemia for medical management / angina
  - Beta-blockers
  - Calcium channel blockers
  - Long Acting Nitrate
  - Ranolazine (Ranexa)

SL Nitroglycerin
ACS Clinical Case Examples

**Inferior Wall STEMI**
- LVEF – preserved
- Uncomplicated hospital course
- Past medical history: Tobaccoism
- Hem A1C – 5.6%
- LDL – 98 mg/dL
- BP 130/84, HR 76

**Anterior Wall STEMI**
- LVEF 30%
- Hospital course complicated by pulmonary edema
- History of HTN, BP on current meds 122/76, HR 94
- Past medical history: Diabetes mellitus type 2, HTN, CKD

**Medication recommendations?**

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) ≥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

**Pooled Cohort Equations for ASCVD Risk Prediction.**

• 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.

• Source: Based on the Pooled Cohort Equations\(^2\) and the work of Lloyd-Jones, et al., *Circulation*, 2006.
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.

HMG CoA Reductase Inhibitors (Statins)

• **Agents**
  – Atorvastatin (Lipitor)
  – Provastatin (Pravachol)
  – Fluvostatin (Lescol)
  – Simvastatin (Zocor)
  – Lovastatin (Mevacor)
  – Rosuvastatin (Crestor)

• **Mechanism of Action**
  – Inhibition of HMG-CoA reductase
  – HMG-CoA reductase catalyzes an early step in cholesterol biosynthesis

✓ Decrease mortality
✓ Reduce risk of major coronary events by 30%
✓ Stimulate plaque regression
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

Statin Dosing

<table>
<thead>
<tr>
<th>High Intensity</th>
<th>Moderate Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients ≤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 \( \geq 50\% \)

• Moderate intensity: daily dose that lowers LDL-C by 30% to 50%

Statin Therapy

• Short or unknown half life: administration in evening for maximum efficacy
  – Simvastatin, lovastatin, and immediate release fluvastatin

• Hydrophilic (fluvastatin, pravastatin, and rosuvastatin)
  – Minimally metabolized by the cytochrome P450 (CYP450) enzyme system
  – Lowest rates of myopathy *

• The lipid soluble statins are associated with insulin resistance and an increased Hemoglobin A1C.
  – Use cautiously with medications with strong CYP3A4 inhibition
  – Benefit of cardiovascular risk reduction is felt to outweigh the downside of elevated glucose levels.
Statin Therapy: Myopathy

CPK Levels
• Total CPK levels prior to initiation and repeated for suspected myopathy.
• **Asymptomatic CPK elevations are common.**
• Discontinue if CPK levels are > 10x the upper limit of normal.

Risk Factors
• Advanced age (> 80 years)
• Frailty
• Small body size
• Renal insufficiency
• Under treated hypothyroidism
• Co-administration of other drugs such as colchicine

Interactions
• No > 1 quart per day of grapefruit juice – particularly with simvastatin and atorvastatin.
• Combined with gemfibrozil (a fibrate), increase the risk of rhabdomyolysis.

Statin Therapy and Liver Enzymes
• Liver enzymes should be assessed at baseline and as clinically indicated.
• **Routine monitoring of liver enzymes is not necessary.**
• Statin therapy can result in an elevation of liver enzymes not associated with liver toxicity.
  – Association with higher dose statins.
• Contraindicated in active liver disease or in persistently and unexplained elevated liver enzymes.
  – AST and ALT > 3x the upper limit of normal.
• **Considered safe in patients with mild to moderately elevated liver enzymes attributable to chronic conditions such as nonalcoholic fatty liver and hepatitis C.**
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.
  – Information included on negative trials for niacin and fenofibrates.
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 Dysfunction

• Impaired wall motion and ejection
• Dilated chamber
• **Hallmark:** Decreased LV Ejection Fraction < 40%
• Coronary artery disease is cause in 2/3 of patients

Cardiomyopathy not synonymous with HF

Diastolic Dysfunction

• Filling impairment
• Normal chamber size
• Normal EF or elevated
• Caused by
  – Hypertension
  – Restrictive myopathy
  – Ischemic heart disease
  – Ventricular hypertrophy
  – Valve disease
  – Idiopathic

Seen often in elderly women with HTN
Pathophysiology

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

The Real Culprit: Neurohormonal Response

SNS Response + RAAS Response → Ventricular Remodeling
Activation of SNS

• First Responder
  – Decreased CO → ↓ BP → activates baroreceptors and vasomotor regulatory centers in medulla

• Increase circulating catecholamines
  – Stimulates alpha and beta receptors
    • Increase HR
    • Peripheral vasoconstriction
    • Contractility

  Positive effect: ↑ CO and BP
  Negative effect: ↑ O2 demand → ischemia, arrhythmias, sudden death

Chronic Stimulation of SNS

• Norepinephrine (circulating catecholamine) is Cardiotoxic
  ☑ Decreases heart’s ability to respond to sympathetic stimulation
  ☑ Down regulation of B1 receptor sites (less sensitive)
  ☑ Contributes to decreased exercise tolerance
  ☑ Can also lead to ventricular remodeling

Be aware of your patient’s heart rate response to activity.
Activation of RAAS

- Kidney’s response to decreased perfusion due to decreasing CO
- Concentrations of angiotensin II, and aldosterone rise as end result
  - Potent vasoconstriction
  - Sodium/water absorption increases
- Result
  - Increased preload and increased afterload
  - Increased myocardial oxygen demand

Ventricular Remodeling

- Process of pathological growth
- Can occur from prolonged activation of SNS/RAAS
- Involves
  - Hypertrophy of myocytes
  - Pressure – thicken (concentric)
  - Volume – elongate (eccentric)
  - Genetically abnormal – inefficient contraction
  - Increased ventricular muscle mass, change in ventricular shape
  - Collagen matrix becomes fibrotic
**Changes in Systolic Dysfunction**

- Ventricular Dilatation
- Decreased Ventricular Contractility
- Decreased Ejection of Ventricular Contents
- Increased Ventricular Pressure / Volume
- Increased Atrial Pressure / Volume
- Atrial Dilatation
- Atrial Overload
- Increased Pulmonary Pressure / Volume
- Fluid Accumulates in Pulmonary Capillary Bed
- Symptoms

**Mitral Regurgitation**

- Dilated Mitral Valve Annulus
- Vasoconstriction / Fluid Retention
- Activation of Neuro-hormonal Responses

**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>Asymptomatic valvular disease</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family HX CM</td>
<td></td>
<td></td>
<td></td>
</tr>
</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</td>
<td>Cardiac disease with slight limitation</td>
<td>Cardiac disease with marked limitation on</td>
<td>Cardiac disease resulting in inability to</td>
</tr>
<tr>
<td>resulting limitation in</td>
<td>of physical activity.</td>
<td>physical activity.</td>
<td>carry out any physical activity without</td>
</tr>
<tr>
<td>physical activity.</td>
<td></td>
<td></td>
<td>discomfort.</td>
</tr>
<tr>
<td>Ordinal activity free of</td>
<td>Comfortable at rest but ordinary activity</td>
<td>Comfortable at rest but less than ordinary activity</td>
<td>May have symptoms of cardiac insufficiency at</td>
</tr>
<tr>
<td>fatigue, palpitation,</td>
<td>results in fatigue, palpitations, dyspnea,</td>
<td>results in fatigue, palpitations, dyspnea, or</td>
<td>rest.</td>
</tr>
<tr>
<td>or anginal pain.</td>
<td>or anginal pain.</td>
<td>anginal pain.</td>
<td></td>
</tr>
</tbody>
</table>

Guideline-Directed Medical Therapy

**GDMT**
### Stages, Phenotypes and Treatment of HF

#### STAGE A
At high risk for HF but without structural heart disease or symptoms of HF
- Patients with
  - HTN
  - Hypertrophic cardiomyopathy
  - Abnormal lipid profile
  - Metabolic syndrome
  - Patients with family history of cardiomyopathy

#### THERAPY
- **Goals**
  - Control symptoms
  - Improve HRQOL
  - Prevent hospitalization
  - Prevent mortality
- **Strategies**
  - Identification of comorbidities
  - ACEI or ARB
  - Beta blockers
  - Aldosterone antagonists
  - CRT
  - ICD
  - Revascularization or valvular surgery as appropriate

#### STAGE B
Structural heart disease but without signs or symptoms of HF
- Patients with
  - Structural heart disease
  - LV remodeling including LVH and/or EF
  - Asymptomatic vascular disease

#### THERAPY
- **Goals**
  - Control symptoms
  - HF signs and symptoms
- **Strategies**
  - Identification of comorbidities
  - ACEI or ARB
  - Beta blockers
  - Aldosterone antagonists
  - CRT
  - ICD
  - Revascularization or valvular surgery as appropriate

### At Risk for Heart Failure
- **Heart Failure**
  - Patients with
    - Marked HF symptoms at rest
    - Recurrent hospitalizations despite GDMT

- **STAGE A**
  - At high risk for HF but without structural heart disease or symptoms of HF
  - Patients with
    - HTN
    - Hypertrophic cardiomyopathy
    - Abnormal lipid profile
    - Metabolic syndrome
    - Patients with family history of cardiomyopathy

- **STAGE B**
  - Structural heart disease but without signs or symptoms of HF
  - Patients with
    - Structural heart disease
    - LV remodeling including LVH and/or EF
    - Asymptomatic vascular disease

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

- **STAGE D**
  - Refractory HF
  - Patients with
    - Marked HF symptoms at rest
    - Refractory symptoms despite GDMT

### Renin-Angiotensin System
- **Renal Flood Flow**
  - Renin release
  - Angiotensinogen
  - Angiotensin I (converting enzyme)
  - Angiotensin II
  - Angiotensin Receptor Blockers
  - Angiotensin II
  - Aldosterone release
  - Aldosterone Blockers
  - Vasoconstriction
  - Na+ & H2O retention
  - BP

**OR**
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

- Reduce mortality in patients with systolic heart failure
- Reduction of left ventricular mass in LV hypertrophy
- Slows progression of renal disease in diabetes and hypertensive nephrosclerosis

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
- Can cause bump in creatinine when initiated in patients with heart failure due to prevention of compensatory efferent vasoconstriction
  - Creatinine can be allowed to be 35% above baseline without stopping the drug.
ACE Inhibitors and GFR

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 Inhibitor

- Assess renal function and potassium within 1 to 2 weeks of initiation if outpatient
  - High risk features: diabetes, hyponatremia, hypotension, azotemia, potassium supplementation, combination with aldosterone antagonist.

- Cautions/Contraindications
  - Bilateral renal artery stenosis
  - Creatinine > 3 mg/dL
  - Potassium > 5.0 mEq/L
  - Systolic BP < 80 mmHg

Note * difference between AKI (hold regardless of creatinine) and CKD may give until creatinine of > 3.0

ESRD: ACE Inhibition ok. SBP most often limiting factor. Need reasonable SBP for dialysis.

A Closer Look at ACE Inhibitors

- pril medications
  - Captopril
    - HF, HPTN, HPTN Urgency, nephropathy, LV dysfunction post MI
  - Enalapril
    - HF, HPTN, asymptomatic LV dysfunction
  - Lisinopril
    - HF, HPTN, Post Acute MI
  - Quinapril
    - HF, HPTN
  - Ramipril
    - HF (off label), HF post MI, HPTN, reduction in risk of MI, stroke and death from CV causes
  - Benazepril
    - HPTN
  - Trandolapril
    - HF (off label), HPTN, post MI HF
  - Perindopril
    - HF (off label), HPTN, stable CAD
  - Fosinopril
    - HF, HPTN
Angiotensin Receptor Blockers
End in “SARTAN”

- ACE Inhibitors remain the first choice for inhibition of RAAS
- ARB’s may be reasonable alternative to ACE Inhibitor if intolerant to ACE Inhibitor due to cough or angioedema
- 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)
- Directly block angiotensin II

Combination of ACE I and ARB – not recommended in the treatment of HF.

A closer look at Angiotensin II Receptor Blockers

- “sartan” medications
  - Losartan
    - HPTN, Nephropathy, stroke prevention, HF (Off Label for HF)
  - Candesartan
    - HPTN, HF
  - Valsartan,
    - HPTN, HF, LV dysfunction post acute MI
  - Irbesartan
    - HPTN, nephropathy
    - Studied in HF trials
  - Telmisartan
    - HPTN
  - Eprosartan
    - HPTN

Source Lexi – Drugs 2014
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) All pts. reduced EF and no symptoms of HF. (IA) Beneficial in pts with HPTN &amp; LVH with no HF symptoms. (IIB)</td>
<td>Class I recommendations Stage A/B (IA,B,C) All pts. with current or prior symptoms of HF &amp; ↓ EF.</td>
<td>Same as Stage C</td>
</tr>
</tbody>
</table>

Beta Blockers Therapy

- Decrease mortality/hospitalization
- Even better in combination with ACE Inhibitor
- Slows disease progression
- Inhibits ventricular remodeling and apoptosis
- Inhibits adverse effects of SNS
- Decrease myocardial oxygen consumption
  - Decreases HR
  - Decreases contractility

**Titration to target dose essential**

**When to initiate?**

- Can be initiated in hospital for HF admission if inotropic therapy not required
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
- **Pearl:** Fatigue may be multifactorial – address over diuresis, sleep apnea and screen for depression

  **NURSING PRACTICE CONSIDERATION:** Educate patients regarding initial expectation of fatigue.

- **Pearl:** If hypotension – consider administration opposite of ACE-I or decrease in diuretic dose

Evidence Based Beta Blocker

- **Cannot assume class effect**
  - **Bisoprolol** – $\beta_1$
    - CIBIS III randomized trial – 2005 (enalapril)
  - **Metoprolol succinate** - $\beta_1$
    - MERIT-HF randomized trial – 1999 (placebo)
  - **Carvedilol** - $\beta_1$, $\beta_2$, $\alpha_1$
    - CAPRICORN randomized trial – 2001 (placebo)
    - COMET randomized trial – 2003 (metoprolol tartrate)
## Beta-Blockers

<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>Class I recommendations Stage A/B (IA,B,C)</td>
<td>Stable pts. with Current or prior symptoms of HF &amp; reduced EF</td>
<td>Same as Stage C</td>
</tr>
<tr>
<td>All pts. reduced EF and no symptoms of HF. (IA)</td>
<td></td>
<td></td>
<td></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

- Hyperkalemia – especially when used with ACE Inhibitor or ARB

- Hold: Creatinine of 2.5 in men / 2.0 in women

- Mortality reduction
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.
- Rationale: Less renin responsive
- Morality benefit
- Compliance is difficult

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
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

- 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 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
<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</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>ARB</td>
<td>Cozaar losartan</td>
<td>25 mg BID or 50 mg once daily 12.5 mg BID or 25 mg once daily if weak liver function</td>
<td>50 mg BID</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 80 mg once daily if weak liver function</td>
</tr>
<tr>
<td>ARB</td>
<td>Apro 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 50 mg BID over 187 pounds</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>Toprol XL metoprolol extended release (succinate)</td>
<td>12.5 mg for class 3 to 4 patients 25 mg for class 1 to 2 patients</td>
<td>200 mg once daily</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>Zebeta bisoprol</td>
<td>2.5 mg once daily</td>
<td>10 mg once daily</td>
</tr>
<tr>
<td>Aldosterone Antagonist</td>
<td>Aldactone spironolactone</td>
<td>25 mg once daily</td>
<td>25 mg once daily</td>
</tr>
<tr>
<td>Aldosterone Antagonist</td>
<td>Inspira eplerenone</td>
<td>25 mg once daily</td>
<td>50 mg once daily</td>
</tr>
</tbody>
</table>
Medical Therapy for Stage C HFrEF: 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)

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 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
- Inpatient more aggressive with daily monitoring
- Adjustable diuretic dosing
  - Weight gain
  - Change in oral intake or during periods of illness
- Use with moderate sodium restriction

**Diuretic Resistance**

- Reasons
  - High sodium levels
  - NSAIDs
  - Severe renal impairment
  - Renal hypoperfusion
- Strategies
  - IV
  - Continuous infusion (BP concerns)
  - Different loop
  - Addition of thiazide diuretic (metolazone)
Cardiorenal Syndrome

- Moderate to severe renal dysfunction with fluid overload
  - Continue to treat with diuretics
- In severe fluid overload renal dysfunction may 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

<table>
<thead>
<tr>
<th>Equivalent</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bumetanide (Bumex)</td>
<td>Furosemide 40 mg</td>
</tr>
<tr>
<td></td>
<td>Torsemide 20 mg</td>
</tr>
<tr>
<td></td>
<td>Bumetanide 1 mg</td>
</tr>
<tr>
<td>Furosemide (Lasix)</td>
<td>Adequate to relieve symptoms</td>
</tr>
<tr>
<td></td>
<td>Start equal or greater than home maintenance dose</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. Better pharmacokinetic profile (oral bioavailability) than furosemide but torsemide has evidence of more efficacy and more safety. (<a href="#">Wargo &amp; Banta, 2009</a>)</td>
<td>BID Dosing when GFR is low</td>
<td>2 randomized trials comparing Torsemide and Furosemide N=471 Torsemide associated with reduction in HF and CV readmission in systolic HF with a trend towards reduction of all cause mortality. (<a href="#">DiNicolantonio, 2012</a>)</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>Bentiazide (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>Cyclohexiazide (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

<table>
<thead>
<tr>
<th>Hypokalemia</th>
<th>AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>• DC’d with K+ = 3.5</td>
<td>• Discharged with creatinine 3.12 (2.63)</td>
</tr>
<tr>
<td>• Furosemide 60 mg BID and metolazone 5 every other day</td>
<td>• Discharged on Furosemide 40 BID &amp; metolazone 10 mg daily (dose increased day prior to discharge)</td>
</tr>
<tr>
<td>• No potassium supplementation, BMP stated in DC summary but not ordered and not on patient DC instructions</td>
<td>• Readmitted from home with BUN&gt; 100 with GI bleed</td>
</tr>
<tr>
<td>• Readmitted with potassium of 2.6 mEq/L.</td>
<td>• Dialysis required – coded during dialysis</td>
</tr>
</tbody>
</table>

Angiotensin-Neprilysin Inhibitor

FUTURE AGENTS
Joint National Committee

- Joint National committee on the prevention, detection, evaluation and treatment of high blood pressure

- JNC 8 Guidelines released December 2013

- Rigorous examination of evidence to make recommendations

- Three questions were asked in the review of evidence
  - Smaller scope than JNC 7 Guidelines
Questions Addressed

- In adults with hypertension – does initiating antihypertensive pharmacological therapy at specific BP thresholds improve health outcomes?
- In adults with hypertension, does treatment with antihypertensive pharmacology to a specified BP goal lead to improvements in health outcomes?
- In adults with hypertension, do various antihypertensive drugs or drug classes differ in comparative benefits and harms on specific health outcomes.

Key Features of JNC 8

- Age < 60 years general population (strongest recommendation ages 30 to 59 years)
  - Initiate at DBP > 90 mmHg and treat to < 90 mmHg
  - Initiate at SBP > 140 mmHg and treat to < 140 mmHg

- Age > 18 years, diabetes, chronic kidney disease (CKD)
  - BP goal < 140/90 mmHg

- Age > 60 years without diabetes or CKD
  - Treat > 150/90
  - BP goal < 150/90 mmHg
  - * if treatment achieves goal of < 140/90 with no adverse effects
    - this is acceptable
Key Features of JNC 8

• For CKD: ACE-I or ARB as first line agent

• Without CKD
  – Nonblack: Thiazide diuretic or ACE-I/ARB or calcium channel blocker
  – Black: Thiazide diuretic or calcium channel blocker

However!

• AHA / ACC November 2013 statement recommend < 140/90 mmHg as goal for all patients.

• AHA / ACC Guidelines for HTN to be published?
American Society of Hypertension: Position Papers

- Evaluation and Treatment of Orthostatic Hypotension
- Obesity-Related Hypertension: Pathogenesis, Cardiovascular Risk, and Treatment
- Blood Pressure and Treatment of Persons with Hypertension as it Relates to Cognitive Outcomes Including Executive Function
- ASH Compendium of Antihypertensive Pharmacology
- Management of Hypertension in the Transplant Patient
- Adherence and Persistence With Taking Medication to Control High Blood Pressure
- Combination Therapy in Hypertension
- Dietary Approaches to Lower Blood Pressure
- Hypertension in Pregnancy
- When and How to Use Self (Home) and Ambulatory Blood Pressure Monitoring
- Treatment of Hypertension in Patients with Diabetes

JNC 7: CLASSIFICATION OF BLOOD PRESSURE

*Classification of blood pressure for adults age 18 years and older

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic (mm Hg)</th>
<th>Diastolic (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>less than 120</td>
<td>and less than 80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-139</td>
<td>or 80-90</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>140-159</td>
<td>or 90-99</td>
</tr>
<tr>
<td>Stage 2</td>
<td>160 or higher</td>
<td>or 100 or higher</td>
</tr>
</tbody>
</table>

Unusually low readings should be evaluated for clinical significance.
*(From the Seventh Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure)
Hypertension

- Primary (essential) hypertension
  - Without known cause
  - 90 to 95% of hypertension in adults

- Secondary hypertension
  - Identifiable cause that can be corrected
  - More than 80% of hypertension in children

Systolic Hypertension

- Isolated systolic hypertension accounts for 70% in the elderly
- Systolic hypertension correlates with cardiovascular disorders more than diastolic hypertension
- *Pulse pressure as predictor or coronary events*
- *Clinical Application: The coronary arteries are perfused during diastole so it is important to maintain an adequate diastolic blood pressure.*
Hypertension Management

**Lifestyle Interventions**

- **Weight reduction**
  - 5 – 20 mmHg / 10 kg

- **Physical Activity**
  - 4-9 mmHg

- **Sodium restriction**
  - 2-8 mmHg

- **Alcohol intake reduction**
  - 2-4 mmHg

- **DASH Diet**
  - 8-14 mmHg

**Pharmacological Management**

- **Diuretics (Thiazide)**
  - Thiazide diuretics cost effective with relatively low risk of side effects
    - Concern: impact of thiazide induced hyperglycemia and diabetes mellitus on long term CHD risk (Rosendorff, et al., 2007).

- **ACE Inhibitors**
- **Angiotensin II receptor blockers**
- **Calcium Channel Blockers**
- **Beta Blockers**
- **Alpha Blockers**
- **Centrally Acting Drugs**
- **Direct Vasodilators**
- **Many combination medications available for dual therapy**
Stage II Hypertension = 2 Drug Therapy

Thiazide diuretic plus another agent based on specific disease process or other risks.

✓ Obtaining BP goal is most important objective.
✓ Use what works.
✓ Let co-morbid conditions (if present) impact choices.
Resistant Hypertension

• **Definition:** A patient is considered to have resistant hypertension if he or she is on 3 or more medications at full-dose therapy, including a diuretic and still unable to achieve target blood pressure.

• A patient is also considered to have resistant hypertension if it takes 4 medications to achieve goal (Calhoun et al., 2008).

Consultation with hypertension specialist

Resistant Hypertension

• Before the diagnosis of resistant hypertension is made, pseudo resistance must be ruled out.

• Common causes of pseudo resistance include:
  – White coat effect
  – Poor technique
  – Poor adherence
Blood Pressure Measurement

Proper technique for blood assessment includes using a proper sized cuff that encircles 80% of the patient’s arm. Use of a cuff that is too small is one of the most causes of inaccurate readings, resulting a recorded measurement that is falsely high.

Resistant Hypertension Causes

- **Lifestyle related**
  - High dietary sodium
  - Obesity
  - Heavy alcohol intake

- **Medication related**
  - Non narcotic analgesics especially NSAIDs
  - Sympathomimetics (decongestants / diet pills)
  - Stimulants
  - Oral contraceptives
  - Glucocorticoids and mineralcorticoids
  - Herbals (ephedra / ma huang)
  - Natural licorice (found in smokeless tobacco)
Resistant Hypertension Causes

<table>
<thead>
<tr>
<th>Secondary Diagnoses (Most Common)</th>
<th>Secondary Diagnoses (Less Common)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Obstructive sleep apnea</td>
<td>• Pheochromocytoma</td>
</tr>
<tr>
<td>• Chronic kidney disease</td>
<td>• Cushing’s disease</td>
</tr>
<tr>
<td>• Primary aldosteronism</td>
<td>• Hyperparathyroidism</td>
</tr>
<tr>
<td>• Renal artery stenosis</td>
<td>• Coarctation of the aorta</td>
</tr>
<tr>
<td></td>
<td>• Intracranial tumor</td>
</tr>
</tbody>
</table>

(Calhoun et al., 2008)

Pharmacological Strategies for Resistant Hypertension

• Maximize diuretic therapy with long acting thiazide diuretic.
  – Chlorthalidone is preferred agent in resistance.
• Consider addition of mineral corticoid antagonist such as spironolactone or eplerenone.
• Use loop diuretic if chronic kidney disease is present.
• Combine medications that have different modes of actions.
  – Recent research has shown favorable results when an ACE inhibitor or angiotensin receptor blocker is combined with a calcium channel blocker.
• Consider giving at least one antihypertensive at bedtime to achieve better overall control.
Antihypertensive Agents

Many agents can be used in the treatment of HTN. Several of these agents have already been discussed.

A Closer Look at Calcium 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

<table>
<thead>
<tr>
<th></th>
<th>Verapamil</th>
<th>Dihydropyridines</th>
<th>Diltiazem</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart Rate</strong></td>
<td>▼▼</td>
<td>▲</td>
<td>▼</td>
</tr>
<tr>
<td><strong>AV Nodal Conduction</strong></td>
<td>▼▼</td>
<td>------</td>
<td>▼</td>
</tr>
<tr>
<td><strong>Contractility</strong></td>
<td>▼▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td><strong>Arterial Vasodilatation</strong></td>
<td>▲▲</td>
<td>▲▲▲</td>
<td>▲</td>
</tr>
</tbody>
</table>

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**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)
Non ACE Inhibitor Arterial Vasodilators

- All non ACE Inhibitor 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

- Alpha, Adrenergic Blockers
  - Examples: Prazosin, Terazosin, Doxazosin

- Central anti-adrenergics
  - Examples: Clonidine, moxonidine

- Peripheral anti-adrenergics
  - Examples: Resperine, Guanethidine

- “INE” Calcium Channel Blockers
  - Nifedipine, isradipine, amlodipine, felodipine, mimidopine

Alpha1 Adrenergic Blockers

- Terazosin (Hytrin) and Prazosin (Minipress) have the potential for a significant first dose hypotension and syncope, particularly in the elderly
  - Hyponatremia worsens hypotensive episodes
  - * First dose should be taken at bedtime and patient warned to use extreme caution if getting out of bed
  - These are not first choice medications and are reserved for refractory hypertension

- Alpha blockers (Prazosin, Terazosin, Doxazosin) are not recommended as first line antihypertensive therapy in the elderly
Central Anti-Adrenergics

- Clonidine, moxonidine
- Not a first line agent
- Sedation (particular concern in elderly)
- Bradycardia
- Abrupt discontinuation leads to hypertension and tachycardia

Direct Smooth Muscle Relaxers

- Hydralazine, minoxidil
- 4th line anti hypertensive agents
- Only used as part of combination therapy
- Concerns:
  - Tachycardia
  - Fluid accumulation (Minoxidil)
  - Atrial arrhythmias (Minoxidil)
Direct Renin Inhibitors

Aliskiren (Tekturna)
- FDA approved as antihypertensive
- Angioedema is potential serious adverse reaction
- Monitor potassium and renal function
- May increase uric acid levels
- Not studied in significant renal impairment
  - Creatinine > 1.7 in women or 2.0 in men and/or estimated GFR < 30 mL/min
Systolic vs Diastolic Dysfunction

Prevention of Stroke

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Estimated Percent Exposed</th>
<th>Estimated Relative Risk</th>
<th>Estimated Population-attributable Risk, %</th>
<th>Projected No. of Strokes Prevented</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>56.2</td>
<td>2.73</td>
<td>49.3</td>
<td>~246,500</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>27.0</td>
<td>1.52</td>
<td>12.3</td>
<td>~61,500</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3.98</td>
<td>3.60</td>
<td>9.4</td>
<td>~47,000</td>
</tr>
<tr>
<td>Heavy alcohol consumption</td>
<td>7.2</td>
<td>1.68</td>
<td>4.7</td>
<td>~23,500</td>
</tr>
</tbody>
</table>

Hypertensive Crisis

Life threatening elevation in blood pressure requiring emergency treatment (within 1 hour) to prevent end organ damage or death.

End organs:
- Heart
- Brain
- Kidneys

Signs and Symptoms

- BP > 250/150 mmHg
- Retinopathy
- Papilledema of optic disc
- Vomiting
- Severe headache
- Altered LOC
- Seizures
- S&S of heart failure
Hypertensive Encephalopathy

- BP > 250/150 mmHg
- Loss of cerebral autoregulation
  - Vasospasm
  - Ischemia
  - Increased capillary pressure
  - Cerebral edema – hemorrhage
    - Basal Ganglia

Etiology

- Uncontrolled hypertension
- Renal dysfunction
- Preeclampsia
- Adrenergic crisis
  - Drug reactions
  - Pheochromocytoma
- Post operative complication
- Pituitary tumor
- Adrenocortical hyperfunction
- Severe Burns
Treatment

- Nitroprusside is gold standard (contraindicated in pregnancy)

- Other agents
  - Fenoldopam (dopaminergic agonist)
  - Alpha blocking agent (or combination alpha and beta blocking agent) - labetolol
  - ACE inhibitors

MAP lowered no more than 25% in first 2 hours or to 160/100 mmHg
Atrial Fibrillation

- Rapid, irregular fib waves
- Atrial rate > 350
- Fib wave seen best in V1
- Irregularly irregular ventricular rate
- QRS usually normal
- If QRS is wide and rate > 200 then consider WPW with conduction over accessory pathway

AF can be coarse or fine
Fast or Slow

Conduct Aberrantly
Atrial Fibrillation

• Most common sustained cardiac rhythm disturbance
• Incidence increases with age
• Associated with structural damage
• Large portion of atrial fibrillation population have no detectable heart disease
Classifications

♥ Paroxysmal
   – Terminates spontaneously or with intervention
♥ Persistent
   – When sustained beyond 7 days
♥ Long Standing Persistent
   – When it lasts longer than one year
• Permanent
   – Joint decision by clinician and patient to accept atrial fibrillation / no further attempts at cardioversion
♥ Recurrent
   – Two or more episodes of paroxysmal or persistent AF
♥ “Lone AF”
   – Young adults without clinical or echocardiographic evidence of cardiopulmonary disease

Pathophysiology

• Atrial ischemia
• Atrial dilation (volume overload)
• Structural changes associated with aging
• Autonomic nervous system
   – Stimulation of parasympathetic system shortens atrial and PV refractory periods
• Atrial fibrosis and loss of atrial muscle mass.
   – Triggers of fibrosis include inflammation and autoimmune disorders
• AF itself causes alterations in atrial architecture and function contributing to atrial remodeling
• “Atrial fib begets atrial fib”
   – Atrial electrical remodeling
   – Progressive shortening of effective refractory periods
Causes

• Reversible
  – Acute, temporary causes
  – Alcohol intake
  – Surgery (common in cardiac surgery)
  – Electrocution
  – AMI
  – Pericarditis
  – Myocarditis
  – Pulmonary Embolism
  – Other pulmonary diseases
  – Hyperthyroidism
  – A flutter
  – WPW
  – AVNRT

• Medical Conditions
  – Obesity
    • LA size increases as BMI increases

• Without associated Heart Disease
  – “Lone AF”
  – Familial arrhythmia

Causes: Associated Heart Disease

• Valvular heart disease
  – Most often mitral valve
• HF
• CAD
• HPTN
  – Especially if LVH present
• HCM
• Dilated cardiomyopathy
• Restrictive cardiomyopathy
• Constrictive pericarditis
• Cardiac tumors
• Congenital diseases
  – Atrial septal defects
Hemodynamic Consequences

• Loss of synchronous atrial mechanical activity
  – Loss of atrial contraction
  – Compounded in cases of mitral stenosis, HPTN, HCM, restrictive cardiomyopathy
• Irregular ventricular response
  – Cardiac output falls
• Rapid heart rate
• Impaired coronary arterial blood flow
  – Diastolic duration inconsistent and unreliable
  – Increased coronary vascular resistance

Stroke: The Most Devastating Complication of AF

• Atrial fibrillation is an independent risk factor for stroke: increases risk about five-fold.
• AF is responsible for >15% of all strokes
• Strokes associated with AF are more severe and TIAS last longer than those due to carotid disease
• Strokes associated with AF have more disability and higher mortality than strokes that occur in absence of AF
# Atrial Fibrillation

<table>
<thead>
<tr>
<th>Rate Control</th>
<th>Rhythm Control</th>
<th>Prevention of Thromboembolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Calcium Channel Blockers (2)</td>
<td>• Electrical or chemical cardioversion</td>
<td>• All patients regardless of rate or rhythm control</td>
</tr>
<tr>
<td>• Beta Blockers</td>
<td>- Chemical effective if atrial fibr &lt; 7 days</td>
<td>• Amount of time in atrial fibrillation is not deciding factor</td>
</tr>
<tr>
<td>• Always first priority</td>
<td>- TEE guided or full anticoagulation</td>
<td>• Decision based on stroke risk</td>
</tr>
<tr>
<td>• Strict versus lenient rate control</td>
<td>• Class I and Class III antiarrhythmics</td>
<td>• CHADS2</td>
</tr>
<tr>
<td>- RACE II</td>
<td>• AFFIRM and RACE trials</td>
<td>• CHADS Vasc Score</td>
</tr>
<tr>
<td>- 2014 New Guideline Recommendation</td>
<td>• Registry data supports slowing progression of disease</td>
<td></td>
</tr>
<tr>
<td>• AV node ablation if pharmacological therapy cannot control rate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Rate Control

♥ Avoid development of tachycardia-induced cardiomyopathy

♥ Avoid toxic effects of antiarrhythmics

♥ Accomplished through medications that slow conduction through the AV node
  - Beta blockers, calcium channel blockers (verapamil, diltiazem) most common
  - Digoxin only effective at rest

♥ Pacemaker may be required if HR becomes too low

♥ AV Ablation is an option if pharmacological therapy is unsuccessful in controlling rate

♥ Continued anticoagulation required
Pharmacological Considerations in Rate Control

• Calcium channel blockers versus beta blockers

• Pros and Cons of Digoxin
  – Blood pressure effect
  – Heart rate control at rest versus exercise

• Pros and Cons of Amiodarone
  – Limiting use of other antiarrhythmics (terminal half-life elimination 40 to 55 days)
  – Use in heart failure

ACCF/AHA/HRS Atrial Fibrillation Guidelines

Class III Recommendation:

Treatment to achieve strict rate control of heart rate (<80 bpm at rest or <110 bpm during a 6-minute walk) is not beneficial compared to achieving a resting heart rate <110 bpm in patients with paroxysmal AF who have stable ventricular function (left ventricular ejection fraction >0.40) and no or acceptable symptoms related to the arrhythmia, though uncontrolled tachycardia may over time be associated with a reversible decline in ventricular performance. 

(Level of Evidence: B)
New 2014 Guideline Update

A randomized trial suggested that a lenient (<110 bpm) rate control strategy was as effective as a strict strategy (<80 bpm) in patients with persistent/permanent AF. However, the writing committee still advocates for the latter (Class IIa), as the results of this single trial were not thought to be definitive.

Rhythm Control

♥ Prevention of thrombus formation
♥ Prevention of atrial myopathy
♥ Relief of symptoms
♥ Initially mechanical cardioversion without antiarrhythmics
♥ Subsequent occurrences attempt cardioversion with antiarrhythmics
♥ Antiarrhythmics – toxic side effects
AFFIRM Trial (2002)

- Compared rate control and rhythm control in patients with AF to determine which approach was associated with better survival outcome
- Results
  - Mortality rate nearly equal in the two groups
  - More ischemic strokes in rhythm control group (anticoagulation often DC’d with NSR)
  - More adverse drug effects in rhythm control group
  - More hospitalizations in rhythm control group

AFFIRM

- Conclusions:
  - Rhythm control offers no survival advantage over rate control
    - Trend toward increased mortality with rhythm control
  - Potential advantages to rate control: fewer adverse drug effects
  - Anticoagulation should be continued in all AF patients at risk for stroke regardless of rate or rhythm control strategies
Rate Vs Rhythm Control
Recommendations

• Data from 7 trials do not support a routine strategy of rhythm control in patients with atrial fibrillation with or without HF
• Rate control recommended in most patients with AF
• Rhythm control can be considered based on specific patient considerations
  – Continuing symptoms on rate control
  – Exercise intolerance with rate control drugs
  – Patient preference

HOWEVER!

Registry data showing support for rhythm control in select patients to decrease disease progression. (Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation)
Cardioversion

- Pharmacological or electrical
- Pharmacological most effective in patients with AF < 7 days.
- Anticoagulation required in all patients with AF > 48 hours before cardioversion
- If > 48 hours
  - Anticoagulate with warfarin or other agent and wait 3-4 weeks OR
  - Anticoagulate with heparin and perform TEE to assess for thrombi
    - If no thrombi proceed with cardioversion
    - Heparin should continue until therapeutic on warfarin
    - Anticoagulation should continue for 4 weeks after cardioversion to NSR
    - If thrombi identified oral anticoagulants at least 3 weeks prior to cardioversion and 4 weeks after

Pharmacological Cardioversion

- Works best if AF present for < 7 days
- Most effective drugs are
  - Ibutilide (Corvert)
  - Flecainide (Tambocor)
  - Dofetilide (Tycosin)
  - Propafenone (Rhythmol)
  - Amiodarone
- Associated with side effects
  - Bradycardia (8%)
  - QT prolongation (1.5%)
  - Ventricular arrhythmias (1.3%)
### Antiarrhythmics in Atrial Fibrillation

<table>
<thead>
<tr>
<th>Class</th>
<th>Specific Medications</th>
<th>Purpose of Medication</th>
<th>Major Cardiac Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I A</td>
<td>Disopyramide, Procainamide, Quinidine</td>
<td>Rhythm Control, Rhythm Control</td>
<td>Torsade de pointes, HF</td>
</tr>
<tr>
<td>Class I B</td>
<td></td>
<td>Rhythm Control, Rhythm Control</td>
<td>Torsade de pointes, HF</td>
</tr>
<tr>
<td>Class I C</td>
<td>Flecaïnide, Propafenone</td>
<td>Rhythm Control, Rhythm Control</td>
<td>Ventricular tachycardia, HF, Atrial Flutter</td>
</tr>
<tr>
<td>Class II</td>
<td>Beta Blockers</td>
<td>Rate Control</td>
<td>Torsade de pointes (rare)</td>
</tr>
<tr>
<td>Class III</td>
<td>Amiodarone, Dronedarone, Dofetilide, Ibutilide, Sotalol (Also contains beta blocker)</td>
<td>Rhythm / Rate Control</td>
<td>Torsade de pointes (rare) <em>Organ toxicity</em></td>
</tr>
<tr>
<td>Class IV</td>
<td>Calcium Channel Blockers</td>
<td>Rate Control</td>
<td>Torsade de pointes, HF, Beta blocker side effects</td>
</tr>
</tbody>
</table>

*Organ toxicity*
Class I:
Na\(^+\) Channel Blockers

Class III: \(K^+\) Channel Blockers

Class IV: Calcium Channel Blockers

---

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

---

### 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 (Ethmozine)</td>
</tr>
<tr>
<td></td>
<td>Propafenone (Rhythmol)</td>
</tr>
</tbody>
</table>
### Class I C Antiarrhythmics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Properties/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flecainide (Tambocor)</td>
<td>Not a first line agent for ventricular arrhythmias</td>
</tr>
<tr>
<td></td>
<td>Will slow conduction over accessory pathways in WPW tachycardias</td>
</tr>
<tr>
<td></td>
<td>Used in atrial fibrillation (pill in the pocket)</td>
</tr>
<tr>
<td></td>
<td>CAST Trial: propensity for fatal proarrhythmic effects</td>
</tr>
<tr>
<td></td>
<td>Not used post MI or with depressed LV function</td>
</tr>
<tr>
<td>Moricizine (Ethmozine)</td>
<td>CAST studies: Reserved for life threatening ventricular arrhythmias</td>
</tr>
<tr>
<td></td>
<td>Has properties of class I B also</td>
</tr>
<tr>
<td>Propafenone (Rhythmol)</td>
<td>Used in supraventricular arrhythmias and life threatening ventricular arrhythmias</td>
</tr>
<tr>
<td></td>
<td>Also has small beta blocking actions and calcium channel blocking effects that can worsen HF</td>
</tr>
<tr>
<td></td>
<td>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>
<tr>
<td>Drugs</td>
<td>Amiodarone (Pacerone, Cordorone)</td>
</tr>
<tr>
<td></td>
<td>Dronedarone (Multaq)</td>
</tr>
<tr>
<td></td>
<td>Ibutilide (Corvert) – pure class III</td>
</tr>
<tr>
<td></td>
<td>Dofetilide (Tikosyn) – pure class III</td>
</tr>
<tr>
<td></td>
<td>Sotalol (Betapace)</td>
</tr>
</tbody>
</table>
### 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  
Use in atrial fibrillation is off label  
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 cardiomyoapthy)  
Proarrhythmias less frequent  
Is also a weak sodium channel blocker, also has effects similar to class II and IV, also has anticholinergic properties |

---

**More on Amiodarone**

- Peripheral IV concentration not to exceed 2mg/ml

- Oral administration = GI symptoms
Potential Extra Cardiac Effects

<table>
<thead>
<tr>
<th>Pulmonary toxicity without initial symptoms</th>
<th>Photosensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potentially lethal interstitial pneumonitis</td>
<td></td>
</tr>
</tbody>
</table>

- Pulmonary toxicity without initial symptoms
- Potentially lethal interstitial pneumonitis
- Photosensitivity
- Hepatotoxicity
- Corneal micro deposits
- Optic neuropathy / neuritis
- Thyroid dysfunction

Toxic side effects increase with length of use and increased dose

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**HOT OFF THE PRESS**

New 2014 Atrial Fibrillation Guidelines

**CHANGE IN RECOMMENDATION REGARDING AMIODARONE FOR PATIENTS WITH PRE-EXCITATION**
Postoperative CABG AF

• 20% to 50% of patients
• Almost always within 5 days
• Peak time: 2 days
• Increased risk morbidity
  – Up to 4 x risk for disabling embolic stroke
• Increased risk mortality
  – Up to 3 x risk for cardiac related mortality
• Most patients (without pre-existing AF) convert within 6 weeks

Postoperative CABG AF

• Class I Recommendations
  – Unless contraindicated, treatment with an oral beta blocker at least 24 hours before CABG to prevent post-operative AF is recommended for patients undergoing cardiac surgery.
    • Continued post operatively and at hospital discharge
  – Administration of AV nodal blocking agents is recommended to achieve rate control in patients who develop post-operative AF.

• Class Ila Recommendations
  – Preoperative administration of amiodarone is appropriate prophylactic therapy for patients at high risk for postoperative AF.
  – Digoxin and calcium channel blockers can be used for rate control
Inpatient Dosing Regimes in Atrial Fibrillation

**Cardioversion**
- PO - 1.2 to 1.8 g/day in divided doses until 10g total – then 200mg to 400mg daily for maintenance
- Or: PO 400mg TID x 5 to 7 days, then 400mg daily x 1 month, then 200mg daily

**Post Op Prevention**
- Post op: PO 400mg BID for up to 7 days
- Or: Start 7 days preoperatively 600mg PO per day and convert to 200mg per day until hospital discharge
- Or: IV – 1000mg/24 hours x 2 days

Class III Antiarrhythmics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</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 (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</td>
</tr>
<tr>
<td>Dofetilide (Tykosin)</td>
<td>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</td>
</tr>
</tbody>
</table>
Simultaneous 2-lead ECG (leads II and V1) showing initiation and termination of torsade de pointes in patient in AF after ibutilide infusion.

CLINICAL PEARL

ALWAYS check potassium level prior to use of ibutilide—potassium level should be in high normal range.
Class III Antiarrhythmics

| Sotalol (Betapace\textsuperscript{R}) (Betapace AF) | 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 |

Dronedarone

- Similar to amiodarone without iodine component and less fat soluble
- Class III antiarrhythmic (K\textsuperscript{+} 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
  • Avoid grapefruit juice
  • Multiple drug interactions

♥ 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
  • Interferes with digoxin metabolism

Concern: LIVER Dysfunction: 1/2011

ACCF/AHA/HRS Atrial Fibrillation Guidelines

Class II A Recommendation:
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%

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ACCF/AHA/HRS Atrial Fibrillation Guidelines

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)
More on Dronederone

♥PALLAS Trial

• Dronederone in **permanent atrial fibrillation**
• Stopped early due to adverse outcomes in dronederone arm
• Adverse outcomes were cardiovascular in nature and not hepatic in nature

CH\(\text{A}_2\)DS\(\text{S}_2\)VASc

• C – HF or LVEF ≤ 35%
• H – Hypertension
• A\(_2\) – < 65, 65 to 74, and ≥ 75
• D – Diabetes Mellitus
• S\(_2\) – Stroke, TIA, or Thromboembolism
• VA – Vascular Disease
• Sc – Gender
Preventing Thromboembolism

- Consideration in all patients with atrial fibrillation or atrial flutter
- Warfarin
- Surgical amputation of left atrial appendage

Newer oral anticoagulants

Important Nursing Consideration in Oral Anticoagulation:

HTN Control to Reduce the Risk of Cerebral Hemorrhage
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
- Bridging: Mechanical valve, recent stroke / TIA/ CHADS$_2$ 5 or 6
- 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 (rifampin)
- Dose:
  - 150 mg PO BID
  - 75 mg PO BID with creatinine clearance (CrC) 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
    - Avoid if CrC < 15 ml/min
    - CrC = 15-50 ml/min 15 mg
- 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 ≥ 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 \( \frac{1}{2} \) life
- 25% renal excretion
- Dose: 5 mg BID
- Dose: 2.5 mg BID (if 2 of the following)
  - Creatinine > 1.5 mg/dL
  - 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.

Edoxaban (Savaysa)

- 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
  - Not less GI bleeding
- Approved January 8th 2015
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
- Hold 24-48 hours prior to procedure that may cause bleeding

Atrial Fibrillation Clinical Considerations: Case Examples

38 year old female with palpitations and light headedness

- No past medical history
- Monitor – AVNRT and infrequent short (seconds) runs atrial fibrillation
- AVNRT associated with symptoms. Atrial fibrillation incidental finding.

Options?

86 year old male presenting with TIA symptoms.

- Found in atrial fibrillation of unknown origin.
- History of HTN and debilitating arthritic pain and spinal stenosis.

Options?
Additional Antiarrhythmic Pharmacology

Atropine

- Parasympatholytic drug
- Can only work where there are available parasympatholytic fibers
- Parasympathetic fibers exist in SA node, throughout atria, and in AV node
- Therefore atropine is effective for:
  - SB
  - Second degree type one block where the physiological problem is in the AV node.
Wenckebach (2\textsuperscript{nd} Degree Type I)

\begin{itemize}
  \item Progressive lengthening of the PR interval (problem in the AV node)
  \item Normal QRS width (no problem in the His Perkinje System)
\end{itemize}

Atropine

\begin{itemize}
  \item Atropine will not work when the block is below the level of the AV node (meaning the block is in the His Perkinje system)
    \begin{itemize}
      \item Second degree type 2 block
      \item High grade AV block with block below the AV node
      \item Complete heart block with ventricular escape rhythm
    \end{itemize}
\end{itemize}
Both of these examples:
1. One P wave at a time fails to conduct
2. There is a fixed PR interval – no problem in the AV node
3. There is a wider than normal QRS – problem in the His Perkinje System

Adenosine (Adenocard)

• Slows conduction through the AV Node
• Vasodilator
• Interrupts reentry pathways through the AV node and restores sinus rhythm
• Uses: Paroxysmal SVT, AVNRT, Drug stress testing
• Side Effects: Headache, arrhythmias (blocks), SOB, chest pressure
Adenosine

• **Nursing Considerations:**
  - Use cautiously in patients with asthma – could cause bronchospasm
  - Onset IV: Immediate
  - Peak: 10 sec
  - Duration 20-30 **seconds**
  - Dosing for conversion of arrhythmia:
    • 6mg IV rapid push
    • If no change within 1-2 minutes repeat with 12mg rapid push
    • Not indicated in WPW

Typical AV Nodal Re-entrant Tachycardia
AV Nodal Reentrant Tachycardia (Typical)

- Most common supraventricular tachycardia
- Least likely to be life threatening
- Narrow QRS has no visible P waves
  - Simultaneous depolarization
- Or, P waves are so close to QRS they look like part of it (pseudo R waves in V1 and pseudo R waves in inferior leads)
AVNRT

Adenosine to Diagnose
Antegrade Conduction over Accessory Pathway

Drugs that slow conduction over accessory pathway:
- Amiodarone
- Procainamide
- Flecainide
- Sotalol
- Propofenone

CHANGE IN RECOMMENDATION REGARDING AMIODARONE FOR PATIENTS WITH PRE-EXCITATION

HOT OFF THE PRESS

New 2014 Atrial Fibrillation Guidelines
Arrhythmias of WPW (AVRT or CMT)

Orthodromic SVT

Antidromic SVT

Atrial fibrillation

ECG showing atrial fibrillation
Example of WPW Atrial Fib
(antegrade conduction via accessory pathway)

Torsade's De Pointes

• Recognition of this life-threatening arrhythmia is important because it is not treated like other VTs
• Two groups: Acquired and congenital
• Acquired
  • Drugs prolonging repolarization
    – Most often as a result of blocking the potassium channel
  • Electrolyte abnormalities
    – Low potassium
    – Low magnesium
• Severe bradycardias / pauses
More on Drugs that Prolong Repolarization

- www.QTdrugs.org
- www.torsades.org

- Class Ia and Class III antiarrhythmics
- Antihistamines
- Antibiotics
- Antipsychotics
- Antidepressants
- Sedatives
- Gastric motility agents
- Anticancer agents
- Opiate agonists

Risk
Possible Risk
Conditional

Other Risk Factors for Torsade's de Pointes

- Rapid (IV) administration of QT prolonging agent
- Renal or hepatic dysfunction
- Female gender (particularly for drug induced)
- Advanced age
- Anorexia
- Heart disease
- Poly pharmacy
Acquired Torsade's De Pointes

• Warning Signs:
  – QTc prolongation
    • Usually greater than 0.5 sec
  – T Wave aberration or T wave alternans
  – Prominent U waves
  – Couple of PVCs and couplets
  – Initiated by short long RR interval (Pause dependent)

• 

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Torsade's de Pointes

- **Class I**
  - Discontinue offending drugs
    - Note: Class IA drug induced TdP usually appears soon after the initial administration of the drug
  - Correct electrolytes
    - Magnesium
    - Potassium
  - Increase HR
    - Isoproterenol
      - 2 mcg/min then titrate to HR of 100 beats per minute
    - Temporary pacing at rate of 100 to 110
    - Permanent pacing if bradycardia or CHB cannot be resolved.
- Defibrillation if sustained
  - However, continue to assess for and treat cause

**More on Magnesium in Torsade's de Pointes**

- 2 Gm IV bolus over 1-2 minutes
  - Followed in 15 minutes by another bolus if necessary
  - May start continuous infusion at rate of 3-20 mg/min
- Benefit occurs without shortening of QT interval and in presence of normal Magnesium level
QT Interval Monitoring Case Example

- Patient admitted for syncope after having motor vehicle crash while driving.
- Long standing history of paroxysmal atrial fibrillation – on dofetilide (Tykosin) for several years.
- Recent chemotherapy for breast CA resulting in a reduction of EF.
- Recent increase in carvedilol and lisinopril per general cardiology to improve EF.

- Next slide is admission ECG. Note the QTc interval.
1. Strip 1: QTc consistent with admission ECG.
2. Strip 2: Marked QTc prolongation when patient asleep.
3. Initial run of ventricular tachycardia initiated by PVC firing at end of T wave,

Same patient with sustained Torsades de Pointes. Treated effectively with 2 grams IV Magnesium (magnesium level was normal at baseline). Magnesium is the drug of choice to stabilize the cardiac membrane. Dofetilide (Tikosyn) was also discontinued.

Note: Although the patient had been on dofetilide (Tikosyn) for several years, the recent change in ejection fraction and increase in beta blocker therapy increased her risk for Torsades de Pointes.
General Considerations
American Geriatric Society – Beers Criteria for Elderly

www.americangeriatrics.org
• Failing to take medicine as prescribed is common, costly and deadly.
  – 75% of patients sometimes fail to take their medications as directed.
  – 33% of prescriptions are never filled.
  – 50% to 60% of the time, patients with chronic conditions do not take their medications.
  – 33% to 69% of medication-related hospitalizations are linked to drug nonadherence.
  – 125,000 patient deaths each year are linked to drug noncompliance.
  – $290 billion is spent annually on care needed because of medication noncompliance.

Sources: "Medication Adherence: Making the Case for Increased Awareness," National Consumers League, May; "Thinking Outside the Pillbox: A System-wide Approach to Improving Patient Medication Adherence for Chronic Disease," NEHI, Aug. 12, 2009

The Best Treatment Patient Education & Self-Care Maintenance and Self-Care Management

• Self-care maintenance
  – following the rules and instructions related to the disease process

• Self-care management
  – decision-making process and critical thinking to make decisions in response to changes in the client's current health status
Barriers to Self-Care Management

• Higher acuity
• Multiple needs
  – Co-morbidities
• Shorter LOS
• Noncompliance
• Transportation issues
• Financial concerns
• Depression / anxiety
• Lack of knowledge
• Literacy
• Multiple medications
• Fear of medication side effects
• Living alone (lack of social support)
• Memory problems

Medication Education

• Need to know trade/generic names
• Don’t wait until discharge!
• Are the discharge instructions clear/legible
• Use lay terms used?
• Create a schedule
• Be careful of “meds as at home”
• Understanding of the purpose of the medication
  – Mortality benefit vs symptom relief
• Alternatives for routine schedule
  – Lasix at 4pm
  – ACE Inhibitor at night
  – Sliding scale Lasix
Medication Education

- Include the person who will assist with medication
- What is the plan for filling prescriptions?
- What is the system for medication administration used at home?
- Discussion regarding medications to avoid
- Adherence history
  - Financial concerns
  - Wallet card
  - Need to understand they feel better because of taking their meds
  - Need to understand the progress made with disease management
  - Need to understand the importance of not running out of their medication
  - Regular follow-up with physician

- Use "teach back" method: I want to make sure I have done a good job explaining things. Will you please tell me why you think it is important to take __________ medication?

- Normalize and empathize with potentially non-adherent patients to encourage forthcoming responses. One way to phrase the question might be: "It's really hard to take medicine every day, and you're on a lot of medicines. I know that I sometimes miss a dose. Tell me: How are you doing taking your medications?"

- Stress the effects of failing to take medications. Patients respond strongly to messages about the health consequences of non-adherence, the eventual impact on their families and the value of taking control of their illnesses.
Questions?

BE THE BEST THAT YOU CAN BE EVERY DAY. YOUR PATIENTS ARE COUNTING ON IT!