UNDERSTANDING WHY WE DO WHAT WE DO

Differentiating mortality benefit from symptom relief.

Finding the “So What”
Impacting Cardiac Output to Improve Myocardial Performance

The Heart as a Pump

Goal: Forward propulsion of blood to perfuse the body.

Flow is determined by:
- Pressure
- Resistance
- Volume
Right Sided versus Left Sided System
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
Synchrony

Preload

- The ventricle is preloaded with blood at the end of diastole:

  Creates stretch on myocardial muscles fibers

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

TO A POINT
Preload Assessment

**Right ventricular preload**
- Central venous pressure or right atrial pressure
- **Noninvasive assessment**
  - JVD
  - Hepatojugular reflux
  - Peripheral edema
  - Weight

**Left ventricular preload**
- Pulmonary artery occlusive pressure (to reflect left atrial pressure)
- **Noninvasive Assessment**
  - Lungs sounds
  - CXR
  - Orthopnea / Bendopnea / PND
  - Hypoxemia
  - S₃
  - Blood Pressure
  - Urine Output

Factors Influencing Preload

- Body Position
- Venous Tone
- Intrathoracic pressure
- Intrapericardial pressure
- Dysrhythmias
- Atrial Kick
- LV Function
- Circulating blood volume
  - Hypervolemia
  - Hypovolemia
  - Third spacing
- Size of Container
  - Sepsis
  - Anaphylaxis
  - Venous vasodilators
Afterload

- **After the ventricle is loaded:**
  - Pressure ventricle needs to overcome to eject blood volume
- Blood pressure is major component of afterload but it does not equal afterload
- Other components
  - Valve compliance
  - Viscosity of blood
  - Arterial wall compliance
    - Aortic compliance

Afterload Assessment

- **Left ventricle:**
  - Systemic vascular resistance
  - (Pulse pressure and DBP)
  - Other components
    - Valve compliance
    - Viscosity of blood
    - Arterial wall compliance
      - Aortic compliance

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

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

• Vessel resistance changes more quickly than large vessel compliance

• Increased resistance = increased DBP

Causes of Increased LV Afterload
  – Arterial vasoconstrictors
  – Hypertension
  – Aortic valve stenosis
  – Increased blood viscosity
  – Hypothermia
  – Compensatory vasoconstriction from hypotension in shock

Causes of Decreased LV Afterload
  – Arterial vasodilators
  – Hyperthermia
  – Vasogenic shock states (sepsis and anaphylactic) where the body cannot compensate with vasoconstriction
  – Aortic Regurgitation – hyperdynamic cardiac output therefore lowering systemic vascular resistance
Contractility

- **Ability of myocardium to contract independent of preload or afterload**
  - Velocity and extent of myocardial fiber shortening
  - Inotropic state
- Related to degree of myocardial fiber stretch (preload) and wall tension (afterload).
- Influences myocardial oxygen consumption
- **↑ contractility**
  - ⇒ **↑ myocardial workload**
  - ⇒ **↑ myocardial oxygen consumption**

Important Points about Contractility

- No accurate way to measure contractility

**Noninvasive Assessment: Ejection Fraction**

- Low cardiac output does not necessarily mean diminished contractility (i.e. hypovolemia)
- Correct preload and afterload problems first in a patient with a low ejection fraction.
- Increasing contractility with medications will also increase myocardial oxygen demand.
Factors Altering Contractility

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

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

Heart Rate

• Mathematically heart rate increases cardiac output

• Physiological limit where increased heart rate will decrease cardiac output due to decreased filling time (decreased preload)
<table>
<thead>
<tr>
<th>Condition</th>
<th>Perfusion</th>
<th>Congestion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warm and Dry</td>
<td>Normal Perfusion</td>
<td>No Congestion</td>
</tr>
<tr>
<td>Warm and Wet</td>
<td>Normal Perfusion</td>
<td>Congestion</td>
</tr>
<tr>
<td>Cold and Dry</td>
<td>Low Perfusion</td>
<td>No Congestion</td>
</tr>
<tr>
<td>Cold and Wet</td>
<td>Low Perfusion</td>
<td>Congestion</td>
</tr>
</tbody>
</table>
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>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
</tr>
<tr>
<td></td>
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<tr>
<td>Venous Vasodilators</td>
</tr>
<tr>
<td></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. |
**Pharmacological Options for INCREASING Afterload**

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

| Sympathomimetics stimulating the alpha receptors of the sympathetic nervous system | Dopamine  
|                               | Norepinephrine  
|                               | Phenylephrine  
|                               | Epinephrine  
| Arginine Vasopressin | Vasoconstrictive and antidiuretic effect  
|                               | Restores catecholamine sensitivity |

**Pharmacological Options for DECREASING Afterload**

All therapies involve arterial vasodilatation

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

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

| Sympathomimetics stimulating the β1 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 β1 receptors of the sympathetic nervous system | Metoprolol  
Carvedilol  
“lol” medications |
|---|---|
| Calcium Channel Blockers | Diltiazem  
Verapamil |
Pharmacological Options for INCREASING Heart Rate

<table>
<thead>
<tr>
<th>Parasympatholytic (lyses the parasympathetic nervous system)</th>
<th>• Atropine</th>
</tr>
</thead>
</table>
| 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 |
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*

### Autonomic Nervous System

- **Sympathomimetics**
  - Sympathetic
    - Beta 1
    - Beta 2
  - Parasympathetic
    - Alpha 1
    - Vagal Response
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

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**Epinephrine**

**Endogenous catecholamine**

| What receptors are stimulated: | β₁ and β₂  
| Alpha receptors |
| What are the resultant actions: | Increase contractility (+inotrope) β₁  
| Increased heart rate (+chronotrope) β₁  
| Bronchodilation β₂  
| Selective vasoconstriction (alpha) |
| When and why do we use: | ACLS first line drug for cardiac standstill; V-fib; pulseless electrical activity  
| Hypotension or profound bradycardia  
| Anaphylactic Shock |
| What are special nursing considerations: | Onset instant  
| Peak 20 minutes  
| 1mg every 3-5 minutes during cardiac standstill |
### Dobutamine

| What receptors are stimulated: | Primarily $\beta_1$
|                               | Some $\alpha_1$ receptor stimulation
|                               | Some $\beta_2$ stimulation
|                               | Modest $\beta_2$ (more $\beta_2$ than $\alpha_1$) |
| What are the resultant actions: | Increase contractility (+ inotrope) ($\beta_1$)
|                               | Increase AV node conduction
|                               | Modest vasodilation |
| When and why do we use:       | **Used as an inotrope** (resultant preload reduction) with modest afterload reduction (ACC / AHA Guidelines for Heart Failure*)
| What are special nursing considerations: | Onset 1 to 2 minutes; Peak 10 minutes
|                               | Half-life 2 minutes
|                               | Note: Blood pressure response is variable; $\beta_2$ causes vasodilatation; $\beta_1$ increases cardiac output and may increase BP

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**HOCM**

**No inotropes**

**SAM**
## Dopamine

| What receptors are stimulated: | **Dopaminergic** at low doses (0.5-2.0 mcg/kg/min)  
β₁ also at moderate doses (2.0-10.0 mcg/kg/min)  
Pure alpha stimulation at high doses > 10mcg/kg/min |
|-------------------------------|-----------------------------------------------|
| What are the resultant actions: | Increase GFR at low doses  
Increase contractility at moderate doses (greater effects on contractility than heart rate)  
Vasoconstriction (alpha) at high doses |
| When and why do we use: | Refractory hypotension / shock  
* Not indicated for routine treatment or prevention of acute renal failure |
| What are special nursing considerations: | Onset 1-2 minutes; Peak 10 minutes  
Maximal effects @20/mcg/kg/min  
Large IV line or central line; Regitine (alpha blocker) for infiltrate |

**Mimics endogenous dopamine; metabolic precursor of norepinephrine and epinephrine**

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## Norepinephrine

| What receptors are stimulated: | Primarily alpha stimulation  
Some β₁  
(In lower doses β₁ 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 |

**Endogenous precursor of epinephrine**
## Phenylephrine

**What receptors are stimulated:**
- Direct effect: Dominant alpha stimulation
- No substantial β₁ effect at therapeutic doses
- Indirect effect: Releases norepinephrine

**What are the resultant actions:**
- Vasoconstriction (increased afterload)

**When and why do we use:**
- As a vasopressor for Unresponsive hypotension

**What are special nursing considerations:**
- Pressor effect occurs almost immediately
- Persists for 10 to 15 minutes

### Remember!!

- Titrate up based on onset of action & peak action
- Wean based on duration of action / half life
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

Phosphodiesterase Inhibitors

- **New generation:** Milrinone (Primacor)

- **Creates + inotropic effect by increasing availability of calcium**
  - Inhibits the degradation of cyclic AMP which is indirectly responsible for increasing the influx of calcium through the calcium channel

- **Smooth muscle relaxant** (venous and arterial vasodilator)
  - Indications:
    - Refractory heart failure (in combination with dobutamine)
    - Left ventricular failure in MI
    - Patients waiting transplant

- **Side Effects:**
  - Ventricular arrhythmias

- **Nursing Considerations:**
  - Onset IV: Immediate
  - Peak: 10 minutes
Phosphodiesterase Inhibitors: Non Sympathomimetic Inotropes

Used as an Inotrope

BUT.....

Preload Reduction

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

- Some medications do both
- Some depend on dose
  - Nesiritide
  - NTG
  - Nitroprusside
  - CA Channel blockers
  - PDE Inhibitors
  - ACE Inhibitors
  - Other Vasodilators
Nesiritide (Natrecor)

- Recombinant form of human B type natriuretic peptide (BNP)

- BNP is a naturally occurring cardiac neurohormone secreted by the heart in the body’s response to heart failure

- BNP allows the heart to participate in the regulation of vascular tone and extracellular volume status

- The BNP system and the renin-angiotensin system counteract each other in heart failure

- BNP levels are elevated in heart failure

Nesiritide (Natrecor)

- Balanced arterial and venous vasodilatation
  - Causes rapid reduction in right and left sided ventricular filling pressures (preload reduction)
  - Reduces afterload

- Indicated for acutely decompensated heart failure patients who have dyspnea at rest
Nesiritide (Natrecor)

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

Monitor BP closely during administration.

Nesiritide: Where do we stand?


  - In the 3 trials, 485 patients were randomized to nesiritide and 377 to control therapy. Death within 30 days tended to occur more often among patients randomized to nesiritide therapy (35 [7.2%] of 485 vs 15 [4.0%] of 377 patients; risk ratio from meta-analysis.
  - P value did not achieve .05 or less.
Randomized Trial

- Effect of Nesiritide in Patients with Acute Decompensated Heart Failure
- O'Connor et al.
- July 7 2011
- 7141 patients

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

Nitroglycerin

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

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

  - Decreases activity of Heparin
Nitroglycerin

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

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

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

- Mixed venous and arterial dilator (primarily arterial)
- Decreases BP, SVR, PVR, PAOP, RAP
- Uses:
  - Hypertensive crisis
  - CHF
  - Acute Mitral Regurgitation
  - Other Indications for Afterload Reduction

- Side Effects:
  - Hypotension
  - Thiocyanate toxicity: tinnitus, blurred vision, delirium, seizures, muscle twitching, absent reflexes, dilated pupils [several days – high doses]

- Nursing Considerations:
  - Onset: 1-2 minutes
  - Duration: 1-10 minutes
  - Monitor BP carefully - arterial line encouraged

Acute Coronary Syndrome

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

- **Fibrinolytics**
  - STEMI
  - tPA
    - Alteplase
    - Retaplase
    - Tenecteplase
  - Streptokinase (*no longer used*)

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

- **Antiplatelets**
  - STEMI / NonSTEMI / UA
  - *GP IIb/IIIa Inhibitors*
    - Eptifibatide (*Integrelin*)
    - Tirofiban (*Aggrastat*)
    - Abciximab (*Reopro*)
  - *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 (secondary to tissue injury) of thromboplastin tissue factor
- From initiation to clot is 15 to 20 seconds
- Measured by Protime

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

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

- **Unfractionated Heparin**
  - Heparin by Weight
  - STEMI, NonSTEMI, UA
  - Mortality benefit
- **Low Molecular Weight Heparin**
  - STEMI, NonSTEMI, UA
- **Direct Thrombin Inhibitors**
  - If history of HIT, PCI NonSTEMI
- **Factor Xa Inhibitors**
  - Not in PCI
- **Warfarin** (Vitamin K antagonist)
- **Dabigatran** (Direct thrombin inhibitor)
- **Rivaroxaban** (Factor Xa inhibitor)
- **Apixaban** (Factor Xa inhibitor)
- **Edoxaban** (Factor Xa inhibitor)
A Closer Look at Heparin

- Works in the intrinsic and common pathway
- Antithrombin activator that inhibits factors Xa and IIa (thrombin)
  - Inactivates thrombin by binding to antithrombin III (Neutralizes the clotting capabilities of thrombin)
  - Antithrombin III naturally inhibits thrombin; when heparin binds with it the inhibition is increased 1000 times
- Concern that unfractionated heparin results in platelet activation - although thrombin is a strong platelet activator and heparin is an antithrombin drug
- Anticoagulation is almost instant
- ½ life relatively short
- Antidote: Protamine 1 mg per 100 units
- In NSTEMI: continue for 48 hours or until PCI
More About Heparin

• aPTT (activated partial thromboplastin time) is used to monitor effectiveness and safety
• Goal is aPTT 1.5 Xs the control
• Weight based heparin dosing reaches goal 90% of time compared to 77% with standard therapy
• OR – Anti factor Xa levels
• 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) – Type 2
  – Platelet aggregation resulting in venous or arterial thrombosis (HITT – Thrombocytopenia with thrombosis)
  – Determining patients at risk is unpredictable
  – Generally occurs 5 to 10 days after initiation of heparin
    • Could be sooner if recent exposure to heparin
  – DC heparin if platelets fall below 100,000 (or > 50% reduction from baseline)
  – Severe thrombocytopenia is due to an immune response
More on Heparin Induced Thrombocytopenia

- Immune system forms antibodies against heparin when bound to protein platelet factor 4 (PF4) – antibodies bind to PF4-heparin complexes and induce platelet activation
  - Immunoassay identify antibodies against PF4
    - Detected in ELISA testing
  - Function Assay
    - Heparin-induced platelet aggregation assay (HIPA)
    - Platelet activation test
- HIT antibodies are usually IgG class
  - Take 5 days to form
  - IgG antibodies associated with platelet activation and increased thrombin generation
  - Antibodies not necessarily associated with thrombotic risk
  - Can disappear 3 months after exposure
- Antibodies bind to platelets and trigger the development of thrombosis.

Treatment of HIT

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

- Enoxaparin, dalteparin, tinzaparin, and nadroparin
- In NSTEMI: for the duration of the hospitalization or until PCI
- Smaller in size
  - Antithrombin by inhibiting factor Xa
  - Causes less inactivation of thrombin 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 concern than with UFH
- Can be self administered with Sub – Q administration
- ½ life 4-6 hours
- Protamine reverses 60% of drug effect
Administration of Enoxaparin

- Full length of 27 gauge ½ needle (prepackaged) should be injected
- Skin fold held until needle withdrawn
- Use anterolateral or posterolateral walls of abdomen
- Rotate sites frequently
- Do not massage site

- Prevention of DVT
  - 40 mg daily in most situations
  - 30 mg daily for renal adjustment (CR Clearance < 30 ml/min)
- Venous thrombosis / DVT
  - 1mg/kg BID or 1.5 mg/kg daily depending of specific circumstances
- Unstable Angina / NSTEMI (or as adjunct in STEMI)
  - 1 mg/kg BID
  - IV dosing can be used in STEMI
- Embolism with Atrial Fib
  - 1 mg/kg BID

- Dosing adjustments are required in several renal impairment

Direct Thrombin Inhibitor

- Indicated for patients with HIT /HITT
- 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): Until diagnostic angiography or PCI is performed in patients with early invasive strategy only
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
    - for the duration of hospitalization or until PCI is performed
    - Cannot be used as sole anticoagulant during PCI
- Neutralizes Factor Xa and interrupts the clotting cascade
- Does not inhibit thrombin
- No reported HIT / HITT
- 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)

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Dual Antiplatelet Therapy with ACS

**ASA**
Indefinitely for all
* What to do with triple therapy?

**Elective DES:**
P2Y₁₂ inhibitor ≥ 12 months

**Elective BMS:**
P2Y₁₂ inhibitor a minimum of 1 month ideally up to 12 months

**ACS DES:**
P2Y₁₂ inhibitor ≥ 12 months

**ACS BMS:**
P2Y₁₂ inhibitor ≥ 12 months

**ACS Medical Management**
P2Y₁₂ inhibitor ≥ 12 months
Aspirin

- 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

P₂Y₁₂ Receptor Inhibitors / ADP Receptor Blockers

- **Clopidogrel (Plavix)**
  - 600 mg initial dose
  - 75 mg daily

- **Prasugrel (Effient)**
  - 60 mg initial dose
  - 10mg daily
  - Contraindicated: > 75, < 60 kg, previous TIA, CVA

- **Ticagrelor (Brilinta)**
  - 180mg initial dose
  - 90mg twice daily
  - Not to be given with ASA doses > 100mg

- 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
P2Y\textsubscript{12} Receptor Inhibitors / ADP Receptor Blockers

- Thienopyridines
  - Clopidogrel
  - Prasugrel
- Non thienopyridine
  - Ticagrelor
Thienopyridines

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

  – **Irreversibly** inhibits P2Y$_{12}$ receptor

Clopidogrel

Issue of 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 overweighs 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.
Prasugrel

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

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

**Prasugrel approved 2009**


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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 ≥ 75 years.
- Conclusion: More research needed

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

- Greater anti-ischemic protection
- Less concern with PPI administration
- Less concern regarding non responders
  - Prodrug but not as dependent on CYP2C19 isoenzyme
- Only used in patients with planned PCI
- Increased bleeding risk
  - ≥ 75 years old
  - ≤ 60 KG
  - Previous CVA / TIA

Ticagrelor (Non-Thienopyridine)

- **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**
- Higher recommendation for ticagrelor in NSTE over clopidogrel in either ischemia guided or early invasive option
Clopidogrel versus Ticagrelor

• 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.


Guideline Directed Medical Therapy for ACS / CAD

✓ Dual Antiplatelet Therapy
  • ASA
  • Clopidogrel/Prasugrel/Ticagrelor
✓ Beta Blocker
✓ ACE Inhibitor
  – Based on additional criteria
✓ Eplerenone
  – Based on additional criteria
✓ Statin
  – Regardless of baseline LDL-C
✓ SL Nitroglycerin

Medications to control ischemia for medical management / angina

• Beta-blockers
• Calcium channel blockers
• Long acting nitrate
• Ranolazine (Ranexa)
Beta Blockers in ACS

- Immediate as well as long term mortality benefit
- Immediate beta-blocker therapy
  - Reduces the magnitude of infarction and incidence of associated complications
    - Decreases myocardial oxygen demand
  - Reduces rate of reinfarction
  - Reduces frequency of life-threatening ventricular tachyarrhythmias.
- Long term benefit post ACS
  - Decreases myocardial oxygen demand
    - HR Benefit
  - Enhances overall well being
  - Slows disease progression
  - Inhibits ventricular remodeling and apoptosis
  - Inhibits adverse effects of SNS
  - Reduces mortality and repeat hospitalizations

Polymorphic VT with normal QT:

- Seen frequently in ischemic conditions (role of beta blockers)
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 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

A Closer Look at Beta Blockers

Decreases Myocardial Oxygen Demand

Blood pressure = CO $\times$ SVR

Decrease HR

Decrease Contractility

$\beta_1$ blockade $\beta_1$ blockade
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)

### Medication Pearls

- **Start beta blocker prior ACE-inhibitor**
  - Beta blockers most important medication to reduce mortality early
  - However, cannot be given in patients at high risk for shock

- **Do not start beta blocker and ACE-I at the same time**

- **Hold ACE inhibitors for BP < 100 mm Hg systolic or < 30 mm Hg below baseline.**
  - Ideally ACE-I should be initiated within 24 hours
Beta Blockers
Recommended by Disease State

Post MI
• Atenolol
• Carvedilol
• Metoprolol
• Propanolol
• Timololol

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

Use GDMT for Heart Failure in all patients with ACS and LVEF ≤ 40%.

Medical Therapy Issues in the Elderly
• Altered responses and vulnerability to drugs with:
  – Hypotensive action (nitrates, calcium blockers)
  – Cerebral effects (beta blockers)
• Caution with renally cleared drugs

START LOW and GO SLOW!!
Ranolazine (Ranexa)

- Indicated for treatment of chronic angina
- Mechanism of action in treating angina is unknown
  - Possible relaxation of myocardium
- Does not impact heart rate or blood pressure
- Dose: 500-1000mg BID
- May prolong QTc interval
- May worsen renal failure – DC if marked increase in serum creatinine
- Contraindicated in hepatic cirrhosis
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

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)
- Nonfatal MI, CHD Death, nonfatal stroke
Patient Group 1

- Individuals with clinical ASCVD
  - acute coronary syndromes
  - History of MI
  - Stable or unstable angina
  - Coronary or other arterial revascularization
  - Stroke/TIA
  - Peripheral arterial disease presumed to be of atherosclerotic origin
- **Without** New York Heart Association (NYHA) class II-IV heart failure or receiving hemodialysis.
- High intensity statin – adults < 75

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 Analysis for ASCVD Risk

• Required information to estimate ASCVD risk:
  – Age
  – Sex
  – Race
  – Total cholesterol
  – HDL cholesterol
  – Systolic blood pressure
  – Blood pressure lowering medication use
  – Diabetes status
  – Smoking status.

Source: Based on the Pooled Cohort Equations² and the work of Lloyd-Jones, et al., Circulation, 2006

No 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)**

<table>
<thead>
<tr>
<th>AGENTS</th>
<th>MECHANISM OF ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Atorvastatin (Lipitor)</td>
<td>• Inhibition of HMG-CoA reductase</td>
</tr>
<tr>
<td>• Provastatin (Pravachol)</td>
<td>• HMG –CoA reductase catalyzes an early step in cholesterol biosynthesis</td>
</tr>
<tr>
<td>• Fluvostatin (Lescol)</td>
<td></td>
</tr>
<tr>
<td>• Simvastatin (Zocor)</td>
<td></td>
</tr>
<tr>
<td>• Lovastatin (Mevacor)</td>
<td></td>
</tr>
<tr>
<td>• Rosuvastin (Crestor)</td>
<td></td>
</tr>
</tbody>
</table>

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

**Statin Dosing**

<table>
<thead>
<tr>
<th>High Intensity</th>
<th>Moderate Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients ≤75 years with ASCVD (Group 1)</td>
<td>All patients &gt; 75 years with ASCVD - consider</td>
</tr>
<tr>
<td>Patients (age &gt; 21) with LDL-C≥ 190 mg/dL (Group 2)</td>
<td></td>
</tr>
<tr>
<td>Diabetic patients (age 40-75) with a 10 year ASCVD ≥7.5% (Group 3)</td>
<td>Diabetic patients with with a 10 year ASCVD &lt;7.5% (Group 3)</td>
</tr>
<tr>
<td>Persons 40-75 years with a ≥7.5% 10-year ASCVD risk should receive moderate- to high-intensity statin therapy. (Group 4)</td>
<td></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>
</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%

> Atorvastatin (80 mg daily) in the PROVE-IT TIMI 22 demonstrated reduced mortality and ischemic events in patients with acute coronary syndrome.

**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
<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL–C on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL–C on average, by approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL–C on average, by &lt;30%</td>
</tr>
<tr>
<td>Atorvastatin 40-80 mg Rosuvastatin 20-40 mg</td>
<td>Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20–40 mg† Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg bid Pitavastatin 2–4 mg</td>
<td>Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg</td>
</tr>
</tbody>
</table>

**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.
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 if at increased risk for adverse events and repeated for suspected myopathy.

### 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.**

Heart Failure

Preserved (HFpEF) LVEF (Diastolic Dysfunction)
Reduced (HFrEF) LVEF (Systolic Dysfunction)
Heart Failure Stage
New York Association Classification
Definition of Heart Failure

<table>
<thead>
<tr>
<th>Classification</th>
<th>LVEF</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Failure with Reduced Ejection Fraction (HFrEF)</td>
<td>≤40%</td>
<td>Systolic HF. Randomized clinical trials have mainly enrolled patients with HFrEF and it is only in these patients that efficacious therapies have been demonstrated to date.</td>
</tr>
<tr>
<td>Heart Failure with Preserved Ejection Fraction (HFrpEF)</td>
<td>≥50%</td>
<td>Diastolic HF. The diagnosis of HFrpEF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.</td>
</tr>
<tr>
<td>HFrpEF, Borderline</td>
<td>41% - 49%</td>
<td>These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patient with HFrpEF.</td>
</tr>
<tr>
<td>HFrpEF Improved</td>
<td>&gt;40%</td>
<td>It has been recognized that a subset of patients with HFrpEF previously had HFrEF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF.</td>
</tr>
</tbody>
</table>

Stages, Phenotypes and Treatment of HF

At Risk for Heart Failure

- **STAGE A**
  - At high risk for HF but without structural heart disease or symptoms of HF
  - e.g.: Patients with:
    - HTN
    - Atherosclerotic disease
    - DM
    - Obesly
    - Metabolic syndrome or patients
    - Using cardiotoxins
    - With family history of cardiomyopathy

- **STAGE B**
  - Structural heart disease but without signs or symptoms of HF
  - e.g.: Patients with:
    - Previous MI
    - LV remodeling including LVH and low EF
    - Asymptomatic vascular disease
  - Development of symptoms of HF

- **STAGE C**
  - Structural heart disease with prior or current symptoms of HF
  - e.g.: Patients with:
    - Known structural heart disease and HF signs and symptoms
  - Refractory symptoms of HF at rest despite GDMT

Heart Failure

- **STAGE D**
  - Refractory HF
  - e.g.: Patients with:
    - Marked HF symptoms at rest
    - Recurrent hospitalizations despite GDMT

**THERAPY**

- **Goals**
  - Prevent further cardiac remodeling
  - Prevent mortality
  - Improve HRQoL
  - Patient education
  - Prevent hospitalization
  - Prevent readmissions

- **Stages**
  - Identification of comorbidities
  - Treatment
  - Refractory HF

- **Options**
  - Experimental surgery or palliative care measures
  - Heart transplant
  - Chronic inotropes
  - Temporary or permanent MCS
  - Palliative care and hospice
  - ICD deactivation
  - ICD or CRT
  - Advanced care measures
  - Heart transplant
  - Chronic inotropes
  - Temporary or permanent MCS
  - Palliative care and hospice
  - ICD deactivation

- **Drugs**
  - ACEI or ARB as appropriate
  - Beta blockers as appropriate
  - In selected patients
  - ICD
  - Revascularization or vascular surgery as appropriate

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- **Drugs**
  - ACEI or ARB as appropriate
  - Beta blockers as appropriate
  - In selected patients
  - ICD
  - Revascularization or vascular surgery as appropriate
## Classification of Heart Failure

**New York Heart Association**

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
</table>
| 1     | - No limitation of physical activity  
       | - Physical activity does not cause fatigue, palpitation or shortness of breath |
| 2     | - Slight limitation of physical activity  
       | - Comfortable at rest, but physical activity results in fatigue, palpitations or shortness of breath |
| 3-A   | - Limitation of physical activity  
       | - Comfortable at rest, but ordinary activity causes fatigue, palpitations or shortness of breath |
| 3-B   | - Significant limitation of physical activity  
       | - Comfortable at rest, but minimal activity causes fatigue, palpitation or shortness of breath |
| 4     | - Unable to carry on any physical activity without discomfort  
       | - Symptoms of heart failure at rest |

### Stages / Classification of Heart Failure

<table>
<thead>
<tr>
<th>ACC-AHA Stage</th>
<th>NYHA Functional Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>A At high risk for heart failure but without structural heart disease or symptoms of heart failure (e.g., patients with hypertension or coronary artery disease)</td>
<td>None</td>
</tr>
<tr>
<td>B Structural heart disease but without symptoms of heart failure.</td>
<td>I Asymptomatic</td>
</tr>
<tr>
<td>C Structural heart disease with prior or current symptoms of heart failure.</td>
<td>II Symptomatic with moderate exertion</td>
</tr>
<tr>
<td>D Refractory heart failure requiring specialized interventions</td>
<td>III Symptomatic with minimal exertion</td>
</tr>
<tr>
<td></td>
<td>IV Symptomatic at rest</td>
</tr>
</tbody>
</table>
**STAGE A**
At high risk for HF but without structural heart disease or symptoms of HF

- Patients with:
  - HTN
  - Atherosclerotic disease
  - DM
  - Obesidy
  - Metabolic syndrome or
  - Obesity
  - Using cardiotoxins
  - With family history of cardiomyopathy

**STAGE B**
Structural heart disease but without signs or symptoms of HF

- Patients with:
  - Possible MI
  - LV remodeling including LVH and low EF
  - Asymptomatic valvular disease

**STAGE C**
Structural heart disease with prior or current symptoms of HF

- Patients with:
  - Known structural heart disease and
  - HF signs and symptoms

**STAGE D**
Refractory HF

- Patients with:
  - Marked HF symptoms at rest
  - Recurrent hospitalizations despite GDMT

---

**THERAPY**

**Goals**
- Heart healthy lifestyle
- Prevent vascular, coronary disease
- Prevent LV structural abnormalities

**Strategies**
- ACEI or ARB as appropriate
- Beta blockers as appropriate
- In selected patients
- ICD
- Revascularization or valvular surgery as appropriate

**THERAPY**

**Goals**
- Control symptoms
- Improve HRQOL
- Prevent hospitalization
- Prevent mortality

**Strategies**
- Identification of comorbidities
- Treatment
- Disease to release symptoms of congestion
- Follow guidelines driven indications for comorbidities, e.g., HTN, AF, CAD, DM
- Revascularization or valvular surgery as appropriate

**THERAPY**

**Goals**
- Control symptoms
- Patient education
- Prevent hospitalization
- Prevent mortality
- Drugs for routine use
- Drugs for use in selected patients
- Drugs for use in selected patients
- Drug management (disease)
- ACEI and ARB
- Digoxin
- In selected patients
- ICD
- Revascularization or valvular surgery as appropriate

---

**Renin-Angiotensin System**

- Renal flood flow
- Renin release
- Angiotensinogen
- Angiotensin I
- Angiotensin II
- Aldosterone release
- Aldosterone blockers
- Vasoconstriction
- Aldosterone release
- Na+ & H2O retention
- BP

---

**At Risk for Heart Failure**

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

**Heart Failure**

- Patients with:
  - Marked HF symptoms at rest
  - Recurrent hospitalizations despite GDMT
• 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 by preventing its formation**
  – 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 have additional benefit in preload reduction by blocking the effects of aldosterone release
A Closer Look at ACE Inhibitors

• Overall cardioprotective, vasculoprotective effect, and renal protective
  – Prevents ventricular remodeling
  – Reduce mortality in patients with systolic heart failure
  – Reduction of left ventricular mass in LV hypertrophy
  – Slows progression of both renal disease in diabetes and hypertensive nephrosclerosis

ACE Inhibitors and Renal Function: Sorting Out the Confusion

• Renal protective in chronic kidney disease
• However, can cause acute kidney injury (AKI) in patient’s at risk (i.e. low stroke volume) due to preventing the compensatory mechanism of efferent vasoconstriction
  – When there is decreased blood flow into the glomerulus via the afferent arterioles, the efferent arterioles constrict to raise glomerular filtration pressure on the back end
  – ACE-I prevent efferent vasoconstriction
• Creatinine can be allowed to be 35% above baseline without stopping the drug.
  – As forward flow to the glomerulus improves – there is less need for efferent vasoconstriction to compensate and glomerular filtration will stabilize
• Will cause acute renal failure in patients with bilateral renal artery stenosis
  – Dilatation of efferent glomerular arterioles with no ability to dilate afferent arterioles which results in decreased glomerular filtration
  – In bilateral renal artery stenosis there is fixed flow into the glomerulus – an improvement in stroke volume will not improve flow into the glomerulus
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

Source: J Clin Hypertens © 2006 La Jolla Communications, Inc.
ACE Inhibitor Monitoring and Contraindications

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

• 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.

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

Angiotensin Receptor Blockers End in “SARTAN”

• ACE Inhibitors remain the first choice for inhibition of RAAS
• ARB’s are a reasonable alternative to ACE Inhibitor if intolerant to ACE Inhibitor due to cough or angioedema
• 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 blocks angiotensin II
• Combination of ACE I and ARB – not recommended
Stages, Phenotypes and Treatment of HFc

**At Risk for Heart Failure**

**STAGE A**
At high risk for HF but without structural heart disease or symptoms of HF

- Patients with: HTN, Atherosclerotic disease, DM, Obese, Metabolic syndrome or Patients with using cardiotoxins and with family history of cardiomyopathy

**STAGE B**
Structural heart disease but without signs or symptoms of HF

- Patients with: Previous MI, LV remodeling including LVM and low EF, Asymptomatic atherosclerotic disease

**THERAPY**
- Goals: 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 (however, benefit outweighs)
- Titration to target dose essential
- When to initiate?
- Can be initiated in hospital for HF admission if inotropic therapy not required
Beta Blocker Considerations

• Started after initiation of ACE-I but before getting to target dose of ACE-I
• Must be used with diuretic if any recent or current fluid retention
• Start very low doses with gradual up-titration
  • NURSING PRACTICE CONSIDERATION: Educate patients regarding initial expectation of fatigue.
• Pearl: If hypotension – consider administration opposite of ACE-I or decrease in diuretic dose
• Pearl: Fatigue may be multifactorial – address over diuresis, sleep apnea and screen for depression

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)
Stages, Phenotypes and Treatment of HFc

**STAGE A**
At high risk for HF but without structural heart disease or symptoms of HF

- Patients with:
  - HTN
  - Atherosclerotic disease
  - DM
  - Obese
  - Metabolic syndrome
  - Using cardiotoxins
  - With family history of cardiomyopathy

**THERAPY**
Goals
- Heart healthy lifestyle
- Prevent vascular, coronary disease
- Prevent LV structural abnormalities

Strategies
- ACEI or ARB in appropriate patients for vascular disease or DM
- Statins as appropriate

**STAGE B**
Structural heart disease but without signs or symptoms of HF

- Patients with:
  - Prior MI
  - LV remodeling including LVH and low EF
  - Asymptomatic valvular disease

**THERAPY**
Goals
- Prevent HF symptoms
- Prevent further cardiac remodeling

Strategies
- ACEI or ARB as appropriate
- Beta blockers as appropriate
- In selected patients
  - ICD
  - Revascularization or valvular surgery as appropriate

**STAGE C**
Structural heart disease with prior or current symptoms of HF

- Patients with:
  - Known structural heart disease and HF signs and symptoms

**THERAPY**
Goals
- Control symptoms
- Improve HRQOL
- Prevent hospitalization
- Prevent mortality

Strategies
- Identification of comorbidities
- Treatment
  - Diuresis to relieve symptoms of congestion
  - Follow guideline driven indications for comorbidities, e.g., HTN, AF, CAD, DM
  - Revascularization or valvular surgery as appropriate

**STAGE D**
Refractory HF

- Patients with:
  - Known HF symptoms at rest
  - Refractory symptoms of HF at rest despite GDMT

**THERAPY**
Goals
- Prevent HF symptoms
- Prevent further cardiac remodeling

Strategies
- Drugs for routine use
  - Diuretics for fluid retention
  - ACEI or ARB
  - Beta blockers
  - Aldosterone antagonists

- Drugs for use in selected patients
  - Hydralazine / isosorbide dinitrate
  - ACEI and ARB
  - Digoxin

- In selected patients
  - CRT
  - ICD
  - Revascularization or valvular surgery as appropriate

**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.

---

**At Risk for Heart Failure**

- Patients with:
  - HTN
  - Atherosclerotic disease
  - DM
  - Obese
  - Metabolic syndrome
  - Using cardiotoxins
  - With family history of cardiomyopathy

**Heart Failure**

- Patients with:
  - Marked HF symptoms at rest despite GDMT
  - Recurrent hospitalizations despite GDMT

**Diuretic effect is not primary reason for administration.**
Clinical Effects of Aldosterone

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

Spironolactone (Aldactone)

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

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

- Side effect of hyperkalemia, especially when used with ACE Inhibitor or ARB

- Mortality reduction
Eplerenone (Inspra)

- Selective aldosterone receptor antagonist
  - Eliminates most gynecomastia and sexual side effects associated with aldactone

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

- Studies in post MI with LV dysfunction
  - Prevent progression of heart failure
  - Prevent sudden cardiac death
  - Prevent recurrent MI

Hydralazine & Isosorbide Dinitrate

- Combination of fixed dose of Hydralazine & Isosorbide Dinitrate (ISDN) 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 III to IV HF.

- Rationale: Less renin responsive

- **Morality benefit**
  - Compliance is difficult

- **Target dose**: 3 times a day, for a total **DAILY** dose of 120 mg ISDN (40mg TID) and 225 mg hydralazine (75mg TID)

- **Bidil**: ISDN 20mg / hydralazine 37.5mg
  - 1 up to 2 tablets TID
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
<table>
<thead>
<tr>
<th>Drug class</th>
<th>Brand name</th>
<th>generic name</th>
<th>Starting dose</th>
<th>Target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE Inhibitor</td>
<td>Prinivil or Zestril</td>
<td>lisinopril</td>
<td>5 mg once daily</td>
<td>20 mg once daily</td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>Monopril</td>
<td>fosinopril sodium</td>
<td>10 mg once daily</td>
<td>40 mg once daily</td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>Vasotec</td>
<td>enalapril maleate</td>
<td>2.5 mg <strong>BID</strong></td>
<td>20 mg <strong>BID</strong></td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>Mavik</td>
<td>trandolapril</td>
<td>one mg once daily</td>
<td>4 mg once daily</td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>Capoten</td>
<td>captopril</td>
<td>25 mg 2 to 3 times a day</td>
<td>100 mg <strong>TID</strong> (450 mg per day maximum)</td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>Lotensin</td>
<td>benazepril</td>
<td>5 mg once daily if 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</td>
<td>quinapril</td>
<td>5 mg <strong>BID</strong></td>
<td>20 mg <strong>BID</strong></td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>Altace</td>
<td>ramipril</td>
<td>1.25 mg to 2.5 mg <strong>BID</strong></td>
<td>10 mg <strong>BID</strong></td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>Aceon</td>
<td>perindopril erbumine</td>
<td>1 mg <strong>BID</strong> if on diuretic</td>
<td>4 mg <strong>BID</strong> (8 mg <strong>BID</strong> maximum)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Brand name</th>
<th>generic name</th>
<th>Starting dose</th>
<th>Target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARB</td>
<td>Cozaar</td>
<td>losartan</td>
<td>25 mg <strong>BID</strong> or 50 mg once daily</td>
<td>50 mg <strong>BID</strong></td>
</tr>
<tr>
<td>ARB</td>
<td>Atacand</td>
<td>candesartan cilexetil</td>
<td>4 to 8 mg once daily</td>
<td>32 mg once daily</td>
</tr>
<tr>
<td>ARB</td>
<td>Diovan</td>
<td>valsartan</td>
<td>80 mg once daily</td>
<td>160 mg once daily</td>
</tr>
<tr>
<td>ARB</td>
<td>Avapro</td>
<td>irbesartan</td>
<td>150 mg</td>
<td>300 mg once daily</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>Coreg</td>
<td>carvedilol</td>
<td>3.125 mg <strong>BID</strong></td>
<td>25 mg <strong>BID</strong> under 188 pounds</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>Toprol XL</td>
<td>metoprolol extended release (succinate)</td>
<td>12.5 mg for <strong>class 3 to 4 patients</strong></td>
<td>200 mg once daily</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>Zebeta</td>
<td>bisoprolol</td>
<td>2.5 mg once daily</td>
<td>10 mg once daily</td>
</tr>
<tr>
<td>Aldosterone Antagonist</td>
<td>Aldactone</td>
<td>spironolactone</td>
<td>25 mg once daily</td>
<td>25 mg once daily</td>
</tr>
<tr>
<td>Aldosterone Antagonist</td>
<td>Inspra</td>
<td>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 my be added
- Potassium and magnesium monitoring
- Use with moderate NA restriction
- Fluid restriction criteria

## Monitor response to therapy
- Adequate diuresis
  - BNP t goal
  - JVP assessment
  - Orthopnea
- Over diuresis
  - Hypotension
  - Dizziness
  - Orthostatic BP

## Diuretic Therapy

### Outpatient
- Weight loss goal of 0.5 to 1.0 kg per day
- Patients can be educated for adjustable diuretic dosing
  - Weight gain
  - Weight loss
  - Change in oral intake or during periods of illness

### Diuretic Resistance
- Diuretic resistance
  - Reasons
    - High sodium levels
    - NSAIDs
    - Severe renal impairment
    - Renal hypoperfusion
  - Strategies
    - IV instead of PO
    - Continuous infusion versus intermittent dosing if BP is a concern
    - Change the loop diuretic
    - Addition of thiazide
Renal Anatomy:
Nephron and Loop Diuretics

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

Loop Diuretics

<table>
<thead>
<tr>
<th>Bumetanide (Bumex)</th>
<th>Equivalents</th>
</tr>
</thead>
<tbody>
<tr>
<td></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>
</tbody>
</table>

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

More on Loop Diuretics

- **DOSE Trial**
  - NEJM: Felker et al., 2011
    - No significant difference in symptoms or renal function between continuous drip versus intermittent dosing
    - Non significant trend toward improvement in symptoms with high dose (IV at 2.5 x PO dose) versus low dose; (IV at same as PO dose) no change in renal function
Thiazide Diuretics

– Inhibit reabsorption of Na+ and Cl-
  • In the distal tubule
  • More sodium loss than loop diuretics
– Delayed onset but longer duration of action than loop diuretics
  • Give 30 minutes before a loop diuretic
– Low ceiling diuretics
– Less potent diuretic than loop diuretics
– Diminished effectiveness in presence of renal failure

Thiazide Diuretics

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Side effects:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendrofluazide (Naturetin)</td>
<td>Blood Chemistry changes:</td>
</tr>
<tr>
<td>Benthiazide (Aquatag, Exna)</td>
<td>Hyponatremia (↓ Na+)</td>
</tr>
<tr>
<td>Chlorothiazide (Diaril)</td>
<td>Hypokalemia (↓ K+)</td>
</tr>
<tr>
<td>Chlorthalidone (Hygroton)</td>
<td>Hypomagnesemia (↓ Mg+)</td>
</tr>
<tr>
<td>Cyclothiazide (Anhydron)</td>
<td>Hyperglycemia (↑ blood sugar)</td>
</tr>
<tr>
<td>Hydrochlorothiazide (HCTZ) (HydroDiuril, Esidrix)</td>
<td>Hyperuricemia (↑ uric acid)</td>
</tr>
<tr>
<td>Hydroflumethazide (Saluron, Diucardin)</td>
<td>Hypercalcemia (↑ Ca++)</td>
</tr>
<tr>
<td>Indapamide (Lozol)</td>
<td>Decreased glomerular filtration in kidneys (↑ BUN, creatinine)</td>
</tr>
<tr>
<td>Metolazone (Zaroxolyn)</td>
<td>↑ cholesterol</td>
</tr>
<tr>
<td>Polythiazide (Renese)</td>
<td>↑ triglycerides</td>
</tr>
<tr>
<td>Trichlormethazide (Metahydrin, Naqua)</td>
<td>↓ HDL cholesterol</td>
</tr>
</tbody>
</table>

Other side effects:
- Impaired glucose tolerance
- Gout
- Impotence
- Ventricular arrhythmias (↓ K+)
- Nausea, dizziness, headache
Diuretics and Renal Function

- Role of venous congestion in worsening renal function

**Versus**

- Role of volume depletion / hypotension and worsening renal function

Cardiorenal Syndrome

- Moderate to severe renal dysfunction with fluid overload
  - Continue to treat with diuretics
- In severe fluid overload renal dysfunction 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)**
Pharmacology for Atrial Fibrillation will be discussed during atrial fibrillation class in the AM.

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