Cardiovascular Pharmacology: Drugs by Disease

Karen Marzlin DNP, RN, CCNS, CCRN-CMC, CHFN

Seton Medical Center
Raising the Bar for Excellence in Cardiac Care

www.cardionursing.com
“I’m not telling you it is going to be easy, I’m telling you it is going to be worth it.”
~ Art Williams
UNDERSTANDING WHY WE DO WHAT WE DO

Differentiating mortality benefit from symptom relief.
Drugs Used to Alter Clotting in ACS

• **Fibrinolytics**
  – **STEMI**
  – tPA
    • Alteplase
    • Retaplace
    • 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**
    • Eptifibitide (Integrelin)
    • 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 (secondary to tissue injury) of thromboplastin tissue factor
- From initiation to clot is 15 to 20 seconds
- Measured by Protime

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

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

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

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

- Antithrombin activator that inhibits factors Xa and IIa
- Prevents conversion of prothrombin to thrombin by binding to antithrombin III
- Antithrombin III naturally inhibits thrombin; when heparin binds with it the inhibition is increased 1000 times
- Neutralizes the clotting capabilities of thrombin
- Works in the intrinsic and common pathway
- Also inhibits platelets (*thrombin is most potent platelet stimulator*)
- Anticoagulation is almost instant
- ½ life relatively short
- Antidote: Protamine 1 mg per 100 units
• aPTT (activated partial thromboplastin time) is used to monitor effectiveness and safety
• Goal is aPTT 1.5 Xs the control
• Weight based heparin dosing reaches goal 90% of time compared to 77% with standard therapy
• Baseline aPTT, PT/INR, platelets and CBC
• Increased bleeding can occur with renal failure
  – Heparin has dual clearance mechanism but greater effect on platelet function than LMWH
Complications of Heparin

• Bleeding
• Mild thrombocytopenia
  – Mild thrombocytopenia occurs in 10-20% of patients
• Severe thrombocytopenia occurs in 1-2% of patients
  – Heparin Induced Thrombocytopenia (HIT)
  – Platelet aggregation resulting in venous or arterial thrombosis
  – Determining patients at risk is unpredictable
  – Generally occurs 5 to 10 days after initiation of heparin
    • Could be sooner if recent exposure to heparin
  – DC heparin if platelets fall below 100,000 (< 50% reduction)
  – Severe thrombocytopenia is due to an immune response
More on Heparin Induced Thrombocytopenia

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

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

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

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

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

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

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

- Prevention of DVT
  - 40 mg daily in most situations
  - 30 mg daily for renal adjustment (CR Clearance < 30 ml/min)

- Venous thrombosis / DVT
  - 1mg/kg BID or 1.5 mg/kg daily depending of specific circumstances

- Unstable Angina / NSTEMI (or as adjunct in STEMI)
  - 1 mg/kg BID
  - IV dosing can be used in STEMI

- Embolism with Atrial Fib
  - 1 mg/kg BID

- Dosing adjustments are required in several renal impairment
Direct Thrombin Inhibitor

- Indicated for patients with HIT
- **Approved in Non STEMI guidelines and for PCI**
- Ability to inactivate fibrin bound thrombin
- Less binding to plasma proteins, therefore more reliable anticoagulation effect
- Examples
  - Lipirudin and desirudin (hirudin)
  - Argatroban
  - Bivalirudin* (Angiomax)
Synthetic Factor Xa Inhibitor

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

- **Adhesion**: Platelets adhere to the subendothelium exposed.
- **Recruitment and Activation**: ADP and TXA₂ stimulate platelet activation.
- **Aggregation**: Fibrin strand forms, indicating aggregation.

Diagram illustrating the processes of platelet adhesion, recruitment, activation, and aggregation.
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
Role of Antiplatelet Therapy in ACS

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

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

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

• Thienopyridines
  – Clopidogrel
  – Prasugrel

• Ticagrelor (Non thienopyridine)
Thienopyridines

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

- ACCF/AHA Clopidogrel Clinical Alert
- FDA Boxed Warning March 2010
- Role of genotype testing or routine platelet function testing
  - Class II b recommendation pending results of randomized controlled clinical trials.

- Prodrug
  - 2 step process
  - Involves several CYP450 isoenzymes
    - CYP2C19 isoenzyme responsible for almost half of the first step formation
    - 3 major genetic polymorphisms are associated with loss of function
    - Observational studies have shown an association between an increased risk of adverse cardiovascular events and the presence of one nonfunctioning allele
Clopidogrel and PPIs


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

• Because PPI induced risk reduction clearly 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.
P2Y$_{12}$ Receptor Inhibitors: Clopidogrel versus Prasugrel

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

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

• Prasugrel approved 2009

Clopidogrel versus Prasugrel

• TRILOGY
  – Prasugrel versus clopidogrel in patients with NSTEMI or unstable angina who were not treated with PCI
  – 7,243 patients
  – No statistically significant difference in primary outcome (composite of: death from cardiovascular causes, myocardial infarction, or stroke) among patients under the age of 75 years
  – A weak trend toward a reduced risk in the prasugrel group after 12 months (P = 0.07)
  – Rates of severe and intracranial bleeding were similar in the two groups in all age groups. This is different than TRITON TIMI 38. Dose was adjusted in Trilogy for weight < 60 kg and age ≥ 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
Non-Thienopyridine $\textit{P2Y}_{12}$ Receptor Inhibitors (ADP Receptor Blocker)

• Ticagrelor (Brillinta)
  – Antiplatelet agent
  – **Reversibly** binds to $\textit{P2Y}_{12}$ 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
Long Term ASA in ACS

- Mortality reduction
- STEMI / NonSTEMI / UA with Intervention
  - BMS
    - 162-325 mg for 1 month
    - 75-162 mg indefinitely
  - DES
    - Sirolimus eluting stent
      - 162-325 mg for 3 months
      - 75-162 mg indefinitely
    - Paclitaxel eluting stent
      - 162-325 mg for 6 months
      - 75-162 mg indefinitely
- NonSTEMI / UA without intervention
  - 75-162 mg indefinitely
- < 100 mg if on ticagrelor
Oxygen

• ? Impact on outcomes mortality
  – May limit ischemic myocardial injury
  – May reduce ST-segment elevation
• Increase myocardial oxygen supply
• Oxygen should be administered when SaO2 less than 90%
• Reasonable to administer supplemental oxygen to all patients with uncomplicated STEMI or NonSTEMI / UA during the first 6 hours.
  – Excess administration of oxygen can lead to systemic vasoconstriction
  – High flow rates can be harmful to patients with chronic obstructive airway disease.
  – In the absence of compelling evidence for established benefit in uncomplicated cases there appears to be little justification for continuing its routine use beyond 6 hours.
Nitroglycerin

• Decreases myocardial oxygen demand
• Increases myocardial oxygen supply
• 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.
Morphine Sulfate

• Decreases myocardial oxygen demand
  – Primarily Venous dilator – decreases preload
  – Decreases SNS effect
• Primarily for symptom relief
• Analgesic of choice for management of pain associated with ACS (IIa Recommendation in NSTEMI/UA)
• 2 to 4 mg IV with increments of 2 to 8 mg IV repeated at 5- to 15-minute intervals
• Pain increase sympathetic activity -> increased sympathetic activity increases myocardial oxygen demand

DON’T HESITATE TO MEDICATE!
A Closer Look at Beta Blockers
Decreases Myocardial Oxygen Demand

- Decrease HR
  - $\beta_1$ blockade

- Decrease Contractility
  - $\beta_1$ blockade

Blood pressure = CO x SVR
Beta Blockers in ACS

• Immediate as well as long term mortality benefit

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

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

• **DO NOT** administer in acute presentation **IF:**
  – STEMI precipitated by cocaine
    • Risk of exacerbating coronary spasm
  – Heart blocks
    • 1\textsuperscript{st} degree AV block with PR > 0.24 sec
    • 2\textsuperscript{nd} or 3\textsuperscript{rd} degree AV block
  – Heart rate < 60 BPM
  – SBP < 100 mm Hg
  – Moderate LV failure is present (signs of HF or shock)
  – Active asthma or reactive airway disease
Beta Blockers in ACS Recovery

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

Linking Knowledge to Practice

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

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

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

• Heart Failure
  – Bisoprolol
  – Carvedilol★ ★
  – Metoprolol Succinate (XL) ★
ACE Inhibitors in ACS

• Mortality and morbidity benefit – even better when used in combination with beta blockers
• Decrease myocardial oxygen demand
  – Reduce preload and afterload
• Initiate within 1\textsuperscript{st} 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 \textit{IV} ACE I within 1\textsuperscript{st} 24 hours post AMI
Discharge Profile for ACS

- ASA
- Clopidogrel/Prasugrel/Ticagrelor
- Beta blocker
- ACE Inhibitor
  - STEMI
  - Non STEMI
    - HF
    - EF<40%
    - HPTN
    - DM
- 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)

- Patient Education
  - Medication Instructions
    - Purpose of medications
      - Live longer versus feel better
  - Stress possibility of in-stent thrombosis and importance of compliance the dual platelet regimen

Look for the Magic Five
ACS Clinical Case Examples

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

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?
New Cholesterol Guidelines
November 2013
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.
### Statin Dosing

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

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

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

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

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

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

• Lifestyle: Important prior to and during statin therapy

• Non-statin therapies, whether alone or in addition to statins, do not provide acceptable ASCVD risk reduction benefits compared to their potential for adverse effects in the routine prevention of ASCVD.
  – Addition of these other agents can be considered in patients with LDL-C > 190 mg/dL.
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
HMG CoA Reductase Inhibitors (Statins)

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

- Decrease LDL-C (18-55%); increase HDL (5 to 15%) and decrease triglycerides (7 to 30%)
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.**
Niacin and AIM High Study

• The purpose of the AIM-HIGH trial was to test whether adding Niaspan to patients at LDL-C goal but with continued low HDL-C levels, would improve cardiovascular outcomes.

• Despite an improvement in lipid levels the study was stopped early due to lack of effectiveness in achieving the primary endpoint which was a composite of cardiovascular death, non-fatal myocardial infarction, acute coronary syndrome, ischemic stroke, or symptom driven cardiac or cerebral revascularization (Boden et al., 2011).
Niacin ER and THRIVE STUDY

• TREDAPTIVE: Niacin ER plus laropiprant
  – No US approval
  – No longer marketed outside US

• Failure to improve cardiovascular outcomes

• Increased adverse events
  – Diabetic complications
  – New onset diabetes
  – GI problems
  – Musculoskeletal complaints
  – Heart failure
  – Bleeding
  – Skin complaints
Fibric Acids

• ACCORD Study
  – No reduction in cardiovascular mortality or non-fatal myocardial infarction or stroke when a fenofibrate was added to simvastatin in patients with type 2 diabetes mellitus (Ginsberg et al., 2010).

• The FIELD study
  – effects of long-term fenofibrate therapy on cardiovascular events in people with type 2 diabetes did not show a statistically significant reduction in major coronary events in persons treated with fenofibrate therapy compared to placebo (Keech et al., 2005).
Statin plus Fibrate Combination Therapy

• May be associated with a greater risk of myopathy and rhabdomyolysis

• The myopathy risk is enhanced under these situations:
  - High doses of statins
  - Renal insufficiency (Cr > 2.0)
  - Concomitant medications:
    - Itraconazole, Ketoconazole
    - Cyclosporin A
    - Erythromycin
  - Age > 70 years
Heart Failure
Definition of Heart Failure

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

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

**Cardiomyopathy not synonymous with HF**
Diastolic Dysfunction

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

Primarily disease of elderly women with HTN
Diastolic Dysfunction

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

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

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

The Real Culprit = Neurohormonal Response

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

• First Responder
  – Decreased CO $\rightarrow$ ↓ BP $\rightarrow$ 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 $\rightarrow$ 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
Harmful Result of RAAS Activation

- Enhanced preload increases end-diastolic volume dilating the LV
- LV becomes overstretched
- LV changes size and shape (ventricular remodeling)
- Contractility decreases
- Congestive symptoms develop
HF as Progressive Disorder

- Initial injury or stress on myocardium
- Change in geometry of left ventricle
  - Dilates
  - Hypertrophies
  - Becomes more spherical
- Decreases mechanical performance of LV and increases regurgitation thru mitral valve
- These effects sustain and enhance the remodeling process
## 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 CAD DM Obesity Metabolic syndrome Family HX CM</td>
<td>Previous MI LV Remodeling including LVH and low EF Asymptomatic valvular disease</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>
</tbody>
</table>
# Classification of Heart Failure

**New York Heart Association**

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

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
  - Obesity
  - 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 LHV and low EF
  - Asymptomatic valvular 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

HFpEF

- Refractory symptoms of HF at rest, despite GDMT

HF/EF

Goals
- Control symptoms
- Patient education
- Prevent hospitalization
- Prevent mortality

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

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

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

STAGE D
Refractory HF

- e.g., Patients with:
  - Marked HF symptoms at rest
  - Recurrent hospitalizations despite GDMT

HF

Goals
- Prevent HF symptoms
- Prevent further cardiac remodeling

Drugs
- ACEI or ARB as appropriate
- Beta blockers as appropriate

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

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

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

Heart Failure

THERAPY
Goals
- Control symptoms
- Prevent hospitalization
- Prevent mortality

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

THERAPY
Goals
- Prevent vascular, coronary disease
- Prevent LV structural abnormalities

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

THERAPY
Goals
- Control symptoms
- Prevent hospitalization
- Prevent mortality

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

↓ Renal Flood Flow
  ↓
  Renin release

Angiotensinogen → Angiotensin I (converting enzyme)

ACE inhibitors

Angiotensin II

Angiotensin Receptor Blockers

↑ BP

Vasoconstriction

Aldosterone release

\[ \text{Aldosterone Blockers} \]

\[ \text{Na}^+ \& \text{H}_2\text{O} \text{ retention} \]
A Closer Look at ACE Inhibitors and Angiotensin II Receptor Blockers

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

• Angiotensin II Receptor Blockers ("sartan" medications)
  – Losartan, Irbesartan, Candesartan, Telmisartan, Valsartan, Eprosartan
A Closer Look at ACE Inhibitors

• ACE Inhibitors impact afterload and preload because they block the vasoconstrictive effects of angiotensin II
  – Very important in reducing workload of left ventricle in systolic dysfunction
  – Decrease systemic vascular resistance without reflex stimulation of heart rate and contractility

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

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

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

Absolute Contraindication: Oral Angioedema!
ACE Inhibitors and Renal Function

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

Diagram showing the effects of hypoperfusion and ACE inhibitor treatment on the renal arterioles.

- **Hypoperfusion**:
  - Afferent Arteriole (Decreased flow)
  - Efferent Arteriole (Constricted)

- **ACE Inhibitor Treated**:
  - Afferent Arteriole (Decreased or normal flow)
  - Efferent Arteriole (Dilated)

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

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

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

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

• ACE Inhibitors remain the first choice for inhibition of RAAS
• ARB’s are a reasonable alternative to ACE Inhibitor if intolerant to ACE Inhibitor due to cough or angioedema
• 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
# ACE Inhibitors

<table>
<thead>
<tr>
<th>Stage A</th>
<th>Stage B</th>
<th>Stage C</th>
<th>Stage D</th>
</tr>
</thead>
</table>
| In patients at high risk for developing or history of atherosclerotic vascular disease, DM or HPTN. (IIA) | 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 & LVH with no HF symptoms. (IIB) | Class I recommendations Stage A/B (IA,B,C)  
All pts. with current or prior symptoms of HF & ↓ EF. | Same as Stage C |

99
Beta Blockers

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

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

• Cannot assume class effect
  
  • Bisoprolol – β1
    – CIBIS III randomized trial – 2005 (enalapril)
  
  • Metoprolol succinate - β1
    – MERIT-HF randomized trial – 1999 (placebo)
  
  • Carvedilol - β1, β2, α1
    – CAPRICORN randomized trial – 2001 (placebo)
    – COMET randomized trial – 2003 (metoprolol tartrate)
Beta Blocker Considerations

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

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

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

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

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

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

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

- Mortality reduction
Eplerenone (Inspra)

• Selective aldosterone receptor antagonist

Eliminates most gynecomastia and sexual side effects associated with aldactone

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

• Indicated in MI with LV Dsyfunction
  – Prevent progression of heart failure
  – Prevent sudden cardiac death
  – Prevent recurrent MI
<table>
<thead>
<tr>
<th>Drug class</th>
<th>Brand name generic name</th>
<th>Starting dose</th>
<th>Target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE Inhibitor</td>
<td>Prinivil or Zestril lisinopril</td>
<td>5 mg once daily</td>
<td>20 mg once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>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</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>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 captoril</td>
<td>25 mg 2 to 3 times a day</td>
<td>100 mg TID (450 mg per day maximum)</td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>Lotensin benazepril</td>
<td>5 mg once daily if on diuretic 10 mg once daily if not on diuretic</td>
<td>40 mg per day in one 40 mg dose or two 20 mg doses</td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>Accupril quinapril</td>
<td>5 mg BID 2.5 mg BID if weak kidneys</td>
<td>20 mg BID</td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>Altace ramipril</td>
<td>1.25 mg to 2.5 mg BID</td>
<td>10 mg BID</td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>Aceon perindopril erbumine</td>
<td>1 mg BID if on diuretic 2 mg BID if not on diuretic</td>
<td>4 mg BID (8 mg BID maximum)</td>
</tr>
<tr>
<td>Drug class</td>
<td>Brand name generic name</td>
<td>Starting dose</td>
<td>Target dose</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------------------------------------</td>
<td>---------------------------------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>ARB</td>
<td>Cozaar losartan</td>
<td>25 mg BID or 50 mg once daily</td>
<td>50 mg BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12.5 mg BID or 25 mg once daily if weak liver function</td>
<td></td>
</tr>
<tr>
<td>ARB</td>
<td>Atacand candesartan cilexetil</td>
<td>4 to 8 mg once daily</td>
<td>32 mg once daily</td>
</tr>
<tr>
<td>ARB</td>
<td>Diovan valsartan</td>
<td>80 mg once daily</td>
<td>160 mg once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>80 mg once daily if weak liver function</td>
</tr>
<tr>
<td>ARB</td>
<td>Avapro irbesartan</td>
<td>150 mg</td>
<td>300 mg once daily</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>Coreg carvedilol</td>
<td>3.125 mg BID</td>
<td>25 mg BID under 188 pounds</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>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</td>
<td>200 mg once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25 mg for class 1 to 2 patients</td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>Zebeta bisoprolol</td>
<td>2.5 mg once daily</td>
<td>10 mg once daily</td>
</tr>
<tr>
<td>Aldosterone 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>Inispra eplerenolone</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)

- ACEI/ARB
  - +20% to -68%
  - P=0.1566

- ACEI/ARB + BB
  - -77%

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

Diuretics

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

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

Considerations

• Outpatient: Weight loss goal of 0.5 to 1.0 kg per day

• Adjustable diuretic dosing
  • Weight gain
  • Weight loss
  • Change in oral intake or during periods of illness

• Use with moderate sodium restriction

Diuretic Resistance

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

• Role of venous congestion in worsening renal function

Versus

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

• Moderate to severe renal dysfunction with fluid overload
  – Continue to treat with diuretics
• In severe fluid overload renal dysfunction 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

Diagram showing the process of Glomerular Filtration, Tubular Reabsorption, and Tubular Secretion. The nephron consists of an afferent arteriole, glomerulus, and efferent arteriole, followed by the proximal convoluted tubule, distal convoluted tubule, and collecting duct. Water (H₂O) reabsorption and secretion processes are indicated throughout the nephron. The diagram also highlights the loop of the nephron and renal pelvis.
Loop Diuretics

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

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

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

### Table

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bumetanide (Bumex)</td>
<td></td>
</tr>
<tr>
<td>Furosemide (Lasix)</td>
<td></td>
</tr>
<tr>
<td>Torsemide (Demadex)</td>
<td></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 turosemide has evidence of more efficacy and more safety. (Wargo &amp; Banta, 2009)</td>
<td></td>
<td>Torsemide associated with reduction in HF and CV readmission in systolic HF with a trend towards reduction of all cause mortality. (DiNicolantonio, 2012)</td>
</tr>
</tbody>
</table>
More on Loop Diuretics

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

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

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

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Side effects:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendrofluazide (Naturetin)</td>
<td>Blood Chemistry changes:</td>
</tr>
<tr>
<td>Benthiazide (Aquatag, Exna)</td>
<td>Hyponatremia (↓ Na⁺)</td>
</tr>
<tr>
<td>Chlorothiazide (Diuril)</td>
<td>Hypokalemia (↓ K⁺)</td>
</tr>
<tr>
<td>Chlorthalidone (Hygroton)</td>
<td>Hypomagnesemia (↓ Mg⁺)</td>
</tr>
<tr>
<td>Cyclothiazide (Anhydron)</td>
<td>Hyperglycemia (↑ blood sugar)</td>
</tr>
<tr>
<td>Hydrochlorothiazide (HCTZ) (HydroDiuril, Esidrix)</td>
<td>Hyperuricemia (↑ uric acid)</td>
</tr>
<tr>
<td>Hydroflumethazide (Saluron, Diucardin)</td>
<td>Hypercalcemia (↑ Ca²⁺)</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>
</tbody>
</table>

Other side effects:  
Impaired glucose tolerance  
Gout  
Impotence  
Ventricular arrhythmias (↓ K⁺)  
Nausea, dizziness, headache
Ultrafiltration

UNLOAD Trial

• Veno-venus ultrafiltration (UF) vs standard IV diuretic therapy for hypervolemic HF
• 200 patients randomized
• UF with statistical significance for: greater weight loss (48 hours), greater fluid loss (48 hours), less 90-day resource utilization for HF.
• No statistically significant difference in dyspnea scores or creatinine levels (safety endpoint)

CARESS-HF Trial

• Treatment of ADHF, worsening renal function, persistent congestion with stepped pharmacologic approach vs ultrafiltration
• 188 patients randomized
• UF: inferior to pharmacologic therapy and associated with adverse events.
CASE EXAMPLES IN DIURETIC THERAPY COMPLICATIONS

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

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

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

• Positive inotropic effect – weak effect

• Enzyme inhibition in noncardiac tissues – reduces sympathetic flow

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

• No reduction in mortality

• Beta-blocker better for rate control

• Low dose: 0.125mg daily

• No need for loading dose
Hydralazine & Isosorbide Dinitrate

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

• Compliance is difficult
The nurse is the patient advocate

- Assess the patient’s response to medications and report that response – know what you should expect
- Listen to your patient
- Continuously assess impact on preload, afterload, contractility and HR
- Monitor for changes that will impact myocardial oxygen supply and demand

Understand if the medication you are administering is for mortality benefit or symptom relief

- Help the patient understand the same – may improve compliance
- Understand your patients barriers to medication compliance
- Consider alterations in the “routine” for medication administration – may improve compliance
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, diabetes, chronic kidney disease (CKD)
  – BP goal < 140/90 mmHg

• Age > 60 years without diabetes or CKD
  – BP goal < 150/90 mmHg
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 2014
Joint National Committee: 7 Key Points

• People over age 50: SBP>140 a more important cardiovascular risk factor than high DBP
• People with normal blood pressure at age 55 have a 90% life time risk of developing hypertension
• Stricter guidelines of blood pressure classification
• Thiazide diuretics are often first line treatment
  – Note: Updated information
• Two agents usually required
• Patient motivation
General Considerations
American Geriatric Society
– Beers Criteria for Elderly

www.americangeriatrics.org
Patient Education / Compliance

Self Care Counseling
• 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
- Compliance 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
Medication Education

- Assess the likelihood of noncompliance.

- When prescribing a new drug, explain the purpose of the medication, the name, anticipated adverse effects, frequency of administration and dosing.

- Use "teach back" method.

- Follow up with patients, asking about medicine-taking occasionally and clinical effect.

- Normalize and empathize with potentially noncompliant 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 noncompliance, 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!

Karen@cardionursing.com