Cardiovascular Pharmacology: Pearls for Practice

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Heart and Vascular Symposium

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Cardiovascular Nursing Education Associates / Key Choice

UNDERSTANDING WHY WE DO WHAT WE DO

Differentiating mortality benefit from symptom relief.

Finding the “So What”
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

**ACS**
- Unfractionated Heparin
- Low Molecular Weight Heparin
- Direct Thrombin Inhibitors
- Factor Xa Inhibitor: Fondaparinux

**Oral agents for Atrial Fibrillation**
- 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
- Different dose is used for venous thromboembolic event

![Platelet Activation Pathways](image-url)
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*

Oral anticoagulants with predictable dose-response relationship:
No lab monitoring of coagulation status needed
## Newer Oral Agents

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade Name</th>
<th>Class</th>
<th>Dosing for Atrial Fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Pradaxa</td>
<td>Direct thrombin inhibitor</td>
<td>▪ 150 mg PO BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>▪ 75 mg PO BID with Cr. Cl. 15 to 30 mL/minute</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Xarelto</td>
<td>Factor Xa inhibitor</td>
<td>Dose 20 mg PO daily</td>
</tr>
<tr>
<td>Abixaban</td>
<td>Eliquis</td>
<td>Factor Xa inhibitor</td>
<td>▪ Dose: 5 mg BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>▪ Dose: 2.5 mg BID (if 2 of the following)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Creatinine &gt; 1.5 mg/dL</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Age &gt; 80 years</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Weight ≤ 60 kg</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Savaysa</td>
<td>Factor Xa inhibitor</td>
<td>60 mg daily for Cr. Cl. &gt; 50 to ≤ 95</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30 mg daily for Cr. Cl. 15 to 50</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Generic</th>
<th>Peak Plasma Level</th>
<th>Elimination Half-life</th>
<th>Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>1.5 hrs</td>
<td>12 to 18 hr</td>
<td>Mostly by kidneys</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>3 hrs</td>
<td>5-9 hours (up to 11 to 13 hrs if &gt; 75 years old)</td>
<td>Hepatic and renal excretion</td>
</tr>
<tr>
<td>Abixaban</td>
<td>Rapid absorption</td>
<td>8 to 15 hours</td>
<td>25% cleared by the kidneys</td>
</tr>
<tr>
<td>Edoxaban</td>
<td></td>
<td></td>
<td><strong>Concern in patients with normal renal function</strong></td>
</tr>
</tbody>
</table>
## Drug Afib Study Highlights: Note – all studies tested for primary endpoint of stroke (ischemic and hemorrhagic) and systemic embolism

<table>
<thead>
<tr>
<th>Drug</th>
<th>Afib Study</th>
<th>Highlights: Note – all studies tested for primary endpoint of stroke (ischemic and hemorrhagic) and systemic embolism</th>
</tr>
</thead>
</table>
| Dabigatran    | RE-LY trial (Connolly et al., 2009) | ● 150 mg BID superior to warfarin (p< 0.001) (stroke / systemic embolism)  
● Ischemic stroke and hemorrhagic stroke both lower  
Rate of major bleeding same (potential concern for GI bleeding)  
● Did not test approved 75 mg dose  
● > 30% of patients with CHADS2 score > 2 |
| Rivaroxaban   | ROCKET AF (Patel et al., 2011) | ● Non-inferiority of rivaroxaban (P<0.001) (stroke / systemic embolism)  
● No significant difference in the risk of major bleeding, intracranial and fatal bleeding occurred less frequently in the rivaroxaban group  
● 87% to 86.9% had CHADS2 score ≥ 3 |
| Abixaban      | ARISTOTLE (Granger et al., 2011.) | ● Primary objective: Found to be non inferior to warfarin (p = <0.001)  
● Secondary objective: Found to be superior to warfarin (p= 0.01)  
● Major bleeding: Statistically less with apixaban (p<0.001)  
● Interesting: No statistical difference in ischemic stroke. |
| Edoxaban      | ENGAGE AF-TIMI 48            | ● Non-inferior to warfarin (P = < 0.001) for high dose and (P = 0.005) for low dose  
● Significantly lower rates of bleeding & CV death compared to warfarin at both doses (Not less GI bleeding) |

### Hold Times for Newer Oral Agents

<table>
<thead>
<tr>
<th>Surgery with high risk for bleeding (i.e. CABG)</th>
<th>Surgery Low Bleeding Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;table&gt;</td>
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</tr>
<tr>
<td>&lt;td&gt; Dabigatran &lt;/td&gt;</td>
<td>&lt;td&gt; Minimum hold time for low risk surgery and normal renal function is ≥ 24 hours &lt;/td&gt;</td>
</tr>
</tbody>
</table>
| - 3 to 5 days.  
- For urgent cases until clotting times are normal or until four half-lives has passed  
- Hold times for surgery are dependent on renal function  
- DO NOT USE INR. Can be falsely elevated | |
| <td> Rivaroxaban / Apixaban </td> | <td> Renal impairment  
Cr. Cl.: ≥ 50 = 3 days  
Cr. Cl. < 50 = 4 days  
Liver impairment  
Mild: 2 days  
Mod: At least 4 days  
Severe: At least 7 days  
Renal impairment  
Cr. Cl.: ≥ 50 = 1 days  
Cr. Cl. < 50 = 3 days  
Liver impairment  
Mild: 1 day  
Mod: At least 2 days  
Severe: At least 5 days | |
| <td> Edoxaban </td> | <td> Minimum hold time of at least 24 hours  
Not specifically addressed in product information. | |

| | 20 |
Assessment of Bleeding

<table>
<thead>
<tr>
<th>Assessment of Bleeding Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong></td>
</tr>
<tr>
<td>▪ Bleeding risk can be assessed by an ecarin clotting time if available</td>
</tr>
<tr>
<td>▪ If not available, a PTT can be assessed to determine clearance of the drug because dabigatran has been shown to prolong aPTT (aPTT not used for quantitative assessment)</td>
</tr>
<tr>
<td>▪ &gt; 2 x upper normal limit 12 to 24 hours after drug may be indicative of high risk for bleeding</td>
</tr>
<tr>
<td>▪ Thrombin time is most sensitive test. Diluted thrombin time (DTT) is a quantitative test (calibrated Hemoclot®)</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
</tr>
<tr>
<td><strong>Edoxaban</strong></td>
</tr>
<tr>
<td>▪ PT may provide qualitative assessment of presence of factor Xa; not sensitive for quantitative anticoagulation effect</td>
</tr>
<tr>
<td>▪ Point of care INR should not be used to gauge anticoagulation effects</td>
</tr>
<tr>
<td>▪ Chromogenic assay can provide quantitative assessment – not widely available, not fully studied, not recommended at this time</td>
</tr>
</tbody>
</table>

More on Factor Xa Inhibitors

- Not all drug to drug interactions are known
- Factor Xa inhibitor antidote, andexanet alfa – breakthrough therapy designation by FDA; orphan drug status
- Predictable pharmacokinetics, a relatively short half-life and a rapid onset of action after oral administration so bridging with another anticoagulant is not required when discontinued before or initiated after surgery
P2Y$_{12}$ Receptor Inhibitors / ADP Receptor Blockers

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

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

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

- 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
P2Y$_{12}$ 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 outweighs the possible adverse cardiovascular risk in patients with high risk of gastrointestinal bleeding, combination of clopidogrel with the less CYP2C19 inhibiting pantoprazole should be recommended.

• Several pharmacodynamic studies found a significant decrease of the clopidogrel platelet antiaggregation effect for omeprazole, but not for pantoprazole.
• More recent RCT and retrospective co-hort studies have not resulted in same concerns with PPIs as observational studies suggested.

Take Aways: Prasugrel

• 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
Take Aways: Ticagrelor

• **Recommended over 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**
• No more than 100 mg per day of ASA: North American effect
• Although shorter ½ life – recommendation to be held 5 days before surgery.


Beta Blockers

<table>
<thead>
<tr>
<th>Nonselective: Block both Beta₁ and Beta₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol (Inderal)</td>
</tr>
<tr>
<td>Timolol (Blocadren)</td>
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<tr>
<td>Nandolol (Corgard)</td>
</tr>
<tr>
<td>Sotolol (Betapace)</td>
</tr>
<tr>
<td>Labetolol (Normodyne, Trandate) (also alpha blockade)</td>
</tr>
<tr>
<td>Carvedilol (Coreg) (also alpha blockade)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardio selective: Block Beta 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol (Sectral)</td>
</tr>
<tr>
<td>Metoprolol tartrate (Lopressor)</td>
</tr>
<tr>
<td>Metoprolol succinate (Toprol XL)</td>
</tr>
<tr>
<td>Atenolol (Tenormin)</td>
</tr>
<tr>
<td>Esmolol (Breviblock)</td>
</tr>
<tr>
<td>Bisoprolol (Z Beta)</td>
</tr>
<tr>
<td>Nebivolol (Bystol) (also nitric oxide vasodilatory properties)</td>
</tr>
</tbody>
</table>
Decreases Myocardial Oxygen Demand and Lowers Blood Pressure

Decrease HR

Decrease Contractility

β₁ blockade

β₁ blockade

Blood pressure = CO x SVR

No direct vasodilator unless combined with an alpha blocker

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%.
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 \( \geq 0.24 \text{ sec} \)
    • 2\textsuperscript{nd} or 3\textsuperscript{rd} degree AV block
  – Heart rate < 60 BPM
  – SBP < 100 mm Hg
  – Moderate LV failure is present (signs of HF or shock)
  – Active asthma or reactive airway disease

Medication Pearls

• Start beta blocker prior ACE-inhibitor in ACS
  – 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 in Heart Failure

- 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 - after patient has been diuresed

Beta Blocker Considerations in HF

- 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
- **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

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

• **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)

A Closer Look at Calcium Channel Blockers

<table>
<thead>
<tr>
<th></th>
<th>Verapamil</th>
<th>Dihydropyridines</th>
<th>Diltiazem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate</td>
<td>♥ ♥</td>
<td>✷</td>
<td>♥</td>
</tr>
<tr>
<td>AV Nodal Conduction</td>
<td>♥ ♥</td>
<td>------</td>
<td>♥</td>
</tr>
<tr>
<td>Contractility</td>
<td>♥ ♥</td>
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<tr>
<td>Arterial Vasodilatation</td>
<td>♥♥♥♥</td>
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<td>♥</td>
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</tbody>
</table>
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
  - Dilation 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**

![Diagram showing effects of ACE inhibitors on renal function](https://www.medscape.com)
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

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.

**Absolute Contraindication:** Oral Angioedema

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

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

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

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 with reduced LVEF

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
## 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>

### Diuretics

- **Decrease congestive symptoms**
  - No mortality benefit
- **First line: Loop diuretics**
  - Thiazide diuretic may be added
- **Potassium and magnesium monitoring**
- **Use with moderate sodium restriction**
- **Fluid restriction criteria**

- **Monitor response to therapy**
  - Adequate diuresis
    - BNPt 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>Furosemide (Lasix)</th>
<th>Torsemide (Demadex)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equivalents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Furosemide 40 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Torsemide 20 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Bumetanide 1 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Adequate to relieve symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Start equal or greater than home maintenance dose</td>
<td></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

Diuretics and Renal Function

• Role of venous congestion in worsening renal function

  Versus

• Role of volume depletion / hypotension and worsening renal function
### Antiarrhythmics in Atrial Fibrillation

<table>
<thead>
<tr>
<th>Class</th>
<th>Specific Medications</th>
<th>Purpose of Medication</th>
<th>Major Cardiac Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Disopyramide</td>
<td>Rhythm Control</td>
<td>Torsade de pointes, HF</td>
</tr>
<tr>
<td>B</td>
<td>Procainamide</td>
<td>Rhythm Control</td>
<td>Torsade de pointes</td>
</tr>
<tr>
<td></td>
<td>Quinidine</td>
<td>Rhythm Control</td>
<td>Torsade de pointes</td>
</tr>
<tr>
<td></td>
<td>Not used in atrial fibrillation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Flecainide</td>
<td>Rhythm Control</td>
<td>Ventricular tachycardia, HF, Atrial Flutter</td>
</tr>
<tr>
<td></td>
<td>Propafenone</td>
<td>Rhythm Control</td>
<td></td>
</tr>
<tr>
<td><strong>Class II</strong></td>
<td>Beta Blockers</td>
<td>Rate Control</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Class III</strong></td>
<td>Amiodarone</td>
<td>Rhythm / Rate Control</td>
<td>Torsade de pointes (rare)</td>
</tr>
<tr>
<td></td>
<td>Dronedarone</td>
<td>Rhythm Control</td>
<td>* Organ toxicity</td>
</tr>
<tr>
<td></td>
<td>Dofetilide</td>
<td>Rhythm Control</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ibutilide</td>
<td>Rhythm Control</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sotalol (Also contains beta blocker)</td>
<td>Rhythm Control (also controls rate)</td>
<td></td>
</tr>
<tr>
<td><strong>Class IV</strong></td>
<td>Calcium Channel Blockers</td>
<td>Rate Control</td>
<td></td>
</tr>
</tbody>
</table>

---

In addition to cardiac criteria; sotalol and dofetilide are renally cleared.
Class I: Na⁺ Channel Blockers

Class III: K⁺ Channel Blockers

Class IV: Calcium Channel Blockers

Class I
Slow conduction (widen QRS).
Some prolongation of refractory period (prolong QT interval).

Class III
Marked prolongation of refractory period (prolong QT interval).
**Class III Antiarrhythmics**

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

**Amiodarone (ARREST Trial)**  
Survival to hospital admission improved 29%  

Approved for life threatening refractory ventricular arrhythmias; considered before lidocaine in pulseless VT or V fib; considered ahead of lidocaine for stable VT with impaired cardiac function; expanded to atrial and ventricular arrhythmias, conversion and maintenance of atrial fibrillation  

**Use in atrial fibrillation is off label**  
**Slows conduction in accessory pathways**  
Originally marketed as anti-anginal (potent vasodilator)  
Relaxes smooth and cardiac muscle, reduces afterload and preload (well tolerated in heart failure and cardiomyopathy)  

**Proarrhythmias less frequent**  
Is also a weak sodium channel blocker, also has effects similar to class II and IV, also has anticholinergic properties
Amiodarone Dosing

• **Life-threatening ventricular arrhythmias (with pulse)**
  – Rapid loading infusion 150 mg administered at a rate of 15 mg/minute (over 10 minutes); initial infusion rate should not exceed 30 mg/minute
  – The slow loading phase is 360 mg at a rate of 1 mg/minute (over 6 hours)
  – First maintenance phase of the infusion is 540 mg at a rate of 0.5 mg/minute (over 18 hours).
  – After the first 24 hours, maintenance infusion rate of 0.5 mg/minute should be continued; the rate of the maintenance infusion may be increased to achieve effective arrhythmia suppression.
  – In the event of breakthrough episodes supplemental infusions of 150 mg administered at a rate of 15 mg/minute (over 10 minutes) may be given.

• **For cardiac arrest secondary to pulseless ventricular tachycardia / ventricular fibrillation**
  – Initial adult loading dose is 300 mg (diluted in 20–30 mL of a compatible IV solution) given as a single dose, rapid IV

• **Peripheral IV concentration not to exceed 2mg/ml**

• **Oral administration = GI symptoms**

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More on Amiodarone

**Advantages**

• Efficacious
• Works on atrial and ventricular arrhythmias
• One of few antiarrhythmics tolerated in HF
• Although prolongs QT – least likely to cause torsades
• IV use short term does not lead to extra cardiac effects

**Potential Disadvantages**

• Although it slow conduction over accessory pathway – may slow it more over AV node and cannot be used in patients with WPW
• Long ½ life (40 to 55 days) limits the ability to change to another agent until amiodarone is cleared
Potential Extra Cardiac Effects

<table>
<thead>
<tr>
<th>Pulmonary toxicity without initial symptoms / Potentially lethal interstitial pneumonitis</th>
<th>Photosensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatotoxicity</td>
<td>Corneal micro deposits</td>
</tr>
<tr>
<td></td>
<td>Optic neuropathy / neuritis</td>
</tr>
</tbody>
</table>

Toxic side effects increase with length of use and increased dose

ACCF/AHA/HRS Atrial Fibrillation Guidelines: Dronedarone

Class III Recommendation:

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

(Level of Evidence: B)
Class III Antiarrhythmics

| Dofetilide (Tykosin) | More “pure” class III agent Conversion to and maintenance of SR in A fib and flutter
| Renal dose adjustment
| Prescribing limited by REMS program
| Widens the QT; cannot be given with many other drugs (prolong QT or inhibit metabolism or elimination); no negative inotropic effects, neutral effect on mortality from arrhythmias post MI and in in HF, can be used in this population to prevent worsening HF from atrial fib |

| Ibutilide (Corvert) | Indicated for rapid conversion of atrial fib or flutter to sinus rhythm; IV use only over 10 minutes; also facilitated cardioversion
| (Don’t convert atrial fib or flutter of duration without anticoagulation)
| Rather than blocking outward potassium currents – promotes influx of sodium through slow inward sodium channel |

CLINICAL PEARL

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

Hypomagnesaemia should also be corrected.
Simultaneous 2-lead ECG (leads II and V1) showing initiation and termination of torsade de pointes in patient in AF after ibutilide infusion.

Class III Antiarrhythmics

| Sotalol (Betapace\textsuperscript{R}) (Betapace \textsuperscript{AF}) | Used in atrial arrhythmias and life threatening ventricular arrhythmias  
| * Renal dose adjustment| Indicated for stable monomorphic VT or Polymorphic VT with normal QT in ACLS protocol  
| | Non selective beta blocking agent with class III properties  
| | **Significant class III effects are only seen at doses \(>\) 160 mg**  
| | Proarrhythmic potential (prolonged QT)  
| | More effective in preventing reoccurring arrhythmias than several other drugs |
BE THE BEST THAT YOU CAN BE EVERY DAY. YOUR PATIENTS ARE COUNTING ON IT!

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www.cardionursing.com