Get in Rhythm with the Safe and Effective Use of Antiarrythmic Drugs

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Clinical Specialist Cardiology, Veterans Affairs Medical Center Memphis
Disclosure

The program chair and presenters for this continuing education activity have reported no relevant financial relationships.
Objectives

- Design patient-specific treatment and monitoring plans for antiarrhythmic drugs (AADs) to treat atrial fibrillation (AF)
- Differentiate among appropriate monitoring strategies for various agents used in ventricular arrhythmia suppression
- Avoid potential adverse drug events with AADs by identifying important drug interactions
- Ensure safe and effective dosing of AADs based upon specific patient factors
Rhythm Rule #1

- Pharmacists play a vital role in the appropriate use of AAD dosing, adverse effects, interactions, and monitoring.
Treatment and Monitoring of Atrial Fibrillation
Atrial Fibrillation

- Most common type of serious arrhythmia
- In U.S., affects 2-5 million patients
- Frequently seen with comorbidities
  - AF complicates management of comorbidity
  - Comorbidity complicates management of AF
- Associated with stroke, heart failure, death
- Most common arrhythmia requiring hospitalization
Case #1: Mary Rhythm

60 y/o AA woman with a PMH including HFrEF (EF 35%), atrial fibrillation(AF), CKD, HTN

- **Inpatient Medications:**
  - apixaban 5 mg twice daily
  - lisinopril 20 mg daily
  - metoprolol succinate 50 mg/day
  - furosemide 40 mg twice daily
  - spironolactone 25 mg/day
  - atorvastatin 20 mg/day

**HPI:**

Presents to cardiology clinic with a recent history of fatigue and palpitations, no symptoms today. She has failed other beta blockers and feels more fatigued on higher doses of metoprolol.

**Laboratory data:**

- BP: 115/78 mm Hg
- HT: 67 in
- HR: 70 bpm
- WT: 75 kg

- ECG: NSR

What is the next best step?
### Atrial Fibrillation

#### Classification of AF

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal ≤7 days</td>
<td>Terminates spontaneously, recurrence spontaneous*</td>
<td><em>Terminates spontaneously, recurrence spontaneous</em></td>
</tr>
<tr>
<td>Persistent &gt;7 days</td>
<td>Often requires cardioversion to restore NSR*</td>
<td>Often requires cardioversion to restore NSR*</td>
</tr>
<tr>
<td>Longstanding Persistent &gt;12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permanent</td>
<td><em>No longer pursue rhythm control strategy</em></td>
<td><em>No longer pursue rhythm control strategy</em></td>
</tr>
<tr>
<td>Non-Valvular vs. Valvular</td>
<td><em>Refers to if AF is secondary to valve disease</em></td>
<td><em>Refers to if AF is secondary to valve disease</em></td>
</tr>
</tbody>
</table>
Atrial Fibrillation

• Electrocardiogram
  • Atrial rates may exceed 300-600 bpm
  • Rhythm is irregularly irregular
  • Ventricular rates vary

• Symptoms
  • Often asymptomatic
  • Dyspnea
  • Palpitations
  • Fatigue
  • Dizziness
  • Reduced excise capacity
Management Issues

Prevention of thrombus

- CHA₂DS-VAS₂c score ≥2 (and some 1), anticoagulate **Class I**

Rate vs. Rhythm Control

- Nearly all patients will require rate control **Class I**
  - Beta blockers, non-dihydropyridine calcium channel blockers (verapamil or diltiazem) or amiodarone (refractory)
  - Question is whether or not to add rhythm control too
Rhythm Rule #2

- If you see atrial fibrillation ask yourself
  1. Is anticoagulation indicated?
  2. Rate vs. rhythm control?
Rhythm Control

- Restore and maintain normal sinus rhythm (NSR), with appropriate anticoagulation and rate control
  - Cardioversion
  - AAD
  - Radiofrequency catheter ablation
- Rhythm-control with AADs failed to show superiority over rate control on mortality
- In patients who are candidates for rhythm or rate control, a rhythm-control strategy results in more hospitalizations.
- Routine use of a rhythm-control strategy is not warranted for some patients.

Favoring Rhythm Control

- **Persistent AF symptoms** are the most compelling indication for a rhythm-control strategy.
- Other factors that favor rhythm control
  - Difficulty achieving adequate rate control
  - Younger patient age
  - Tachycardia-mediated cardiomyopathy
  - First episode of AF
  - AF precipitated by an acute illness
  - Patient preference.

- AF progresses from paroxysmal to persistent in many patients and results in electrical and structural remodeling that becomes irreversible.
- Early intervention with rhythm-control to prevent progression of AF may be beneficial.

Rhythm Rule #3

- Rhythm control with long-term antiarrhythmic drugs is not for everyone.
  - Consider for those:
    - Who remain symptomatic after an adequate trial of the rate control strategy
    - With tachycardia-induced myopathy
    - Who are younger patients
# Antiarrhythmic Agent Overview

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Clinical Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I Na⁺ channel blockers</td>
<td>IA: Quinidine, procainamide, disopyramide</td>
<td>la: A &amp; V</td>
</tr>
<tr>
<td></td>
<td>IB: Lidocaine, mexiletine</td>
<td>lb: V</td>
</tr>
<tr>
<td></td>
<td>IC: Propafenone, flecainide</td>
<td>lc: SVT &amp; VT</td>
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<td>Amiodarone, sotalol, dofetilide*, ibutilide*, dronedarone*</td>
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<tr>
<td>Class IV CCBs</td>
<td>Diltiazem, verapamil</td>
<td>A &amp; V</td>
</tr>
</tbody>
</table>

* FDA approved for atrial arrhythmias
Classification of AADs: Vaughan-Williams

**Class I**: Na⁺ channel blockers
- Inhibit *depolarization (phase 0)*
- Slow conduction velocity

**Class II**: β-blockers
- Major effects on sinus and AV nodes
- Additional effect on autonomic NS

**Class III**: K⁺ channel blockers
- Prolong *repolarization (phase 3)* and ↑ refractoriness

**Class IV**: Ca++ channel blockers
- Major effects on AV > sinus node

**Other drugs**:
- Adenosine, digoxin, atropine, Mg++
# Antiarrhythmic Agent Overview

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                         | IB: Lidocaine, mexiletine                  
                         | IC: Propafenone, flecainide               | Ia: A & V  
                         |                                              | Ib: V  
                         |                                              | Ic: SVT & VT |
| Class II β-blockers  | Metoprolol, esmolol, atenolol              | A & V            |
| Class III K⁺ channel blockers | Amiodarone, sotalol, dofetilide*, ibutilide*, dronedarone* | A & V |
| Class IV CCBs        | Diltiazem, verapamil                       | A & V            |

* FDA approved for atrial arrhythmias
Cardioversion

- Anticoagulate according length of AF duration  
  - Class I

- Two types of cardioversion
  - Direct current  
    - Recommended to restore NSR; may be repeated  
    - Class I
  
  - Pharmacologic
    - Flecainide, dofetilide, propafenone and IV ibutilide may be used if no contraindications  
      - Class I
    - Amiodarone is reasonable  
      - Class IIa

Circulation 2014;130:e199–e267.
Pharmacologic Cardioversion

- Used to convert to NSR or facilitate electrical cardioversion
- Most effective when used within 7 days of onset of AF
- Remember to anticoagulate appropriately for both pharmacologic and electrical cardioversion
## Pharmacologic Cardioversion

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route and Dose</th>
<th>Potential ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>• PO – 600 to 800 mg/day in divided doses (up to total load of 10 g) then 200 mg/day&lt;br&gt;• IV – 150 mg over 10 min then 1 mg/min for 6 hours then 0.5 mg/min for 18 hours</td>
<td>Phlebitis (IV), hypotension, bradycardia, QT prolongation, GI upset</td>
</tr>
<tr>
<td>Dofetilide</td>
<td><strong>CrCl (ml/min)</strong>&lt;br&gt;60&lt;br&gt;40-60&lt;br&gt;20-40&lt;br&gt;&lt;20</td>
<td>Dose (mcg PO BID)&lt;br&gt;500&lt;br&gt;250&lt;br&gt;125&lt;br&gt;Not recommended</td>
</tr>
<tr>
<td>Flecaainide</td>
<td>PO – 200 to 300 mg one time</td>
<td>Hypotension, ventricular proarrhythmia</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>IV – 1 mg over 10 min, may repeat 1mg once prn (if &lt;60 kg, use 0.01 mg/kg)</td>
<td>QT prolongation, TdP, hypotension</td>
</tr>
<tr>
<td>Propafenone</td>
<td>PO – 450 to 600 mg one time</td>
<td>Hypotension, ventricular proarrhythmia</td>
</tr>
</tbody>
</table>

Circulation. 2014;130:e199-e267.
Rhythm Rule #4

- Electricity and AADs can cardiovert patients from AF to NSR. Appropriate anticoagulation is key.
Maintenance of Sinus Rhythm

- AADs that can be used, depending on underlying heart disease and comorbidities **Class I**
  - Class I: Flecainide and Propafenone
  - Class III: Dofetilide, sotalol, amiodarone, dronedarone
- Risks, including pro-arrhythmia, should be considered prior to initiation **Class I**

Circulation 2014;130:e199–e267.
# Antiarrhythmic Agent Overview

## Class I

**Na⁺ channel blockers**
- **IA:** Quinidine, procainamide, disopyramide
- **IB:** Lidocaine, mexiletine
- **IC:** Propafenone, flecainide

<table>
<thead>
<tr>
<th>Clinical Utility</th>
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<tbody>
<tr>
<td>Ia: A &amp; V</td>
</tr>
<tr>
<td>Ib: V</td>
</tr>
<tr>
<td>Ic: SVT &amp; VT</td>
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</tbody>
</table>

## Class II

**β-blockers**
- Metoprolol, esmolol, atenolol

<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>A &amp; V</td>
</tr>
</tbody>
</table>

## Class III

**K⁺ channel blockers**
- Amiodarone, sotalol, dofetilide*, ibutilide*, dronedarone*

<table>
<thead>
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<th>Clinical Utility</th>
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## Class IV

**CCBs**
- Diltiazem, verapamil

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* FDA approved for atrial arrhythmias
CAST Trial

- NHLBI’s Cardiac Arrhythmia Suppression Trial (CAST)
  - Multicenter, randomized, double-blind study
  - Patients with asymptomatic non-life-threatening ventricular arrhythmias who had a MI >6 days but <2 years previously
  - Average duration of encainide or flecainide was 10 months
  - Outcomes: Excessive mortality or non-fatal cardiac arrest rate (7.7 %) in patients on encainide or flecainide vs. matched placebo-treated group (3.0 %).

- Applicability to other populations (e.g. no recent MI) is uncertain.

IC: Flecainide

- **Do not use** with structural heart disease
- Use with a rate control drug to lower the risk of paradoxical increases in the ventricular rate (1:1 conduction)
- Dosing: 50 mg to 150 mg every 12 hours
  - Pill in the pocket: 200 to 300 mg once for cardioversion
- ADRs:
  - Ophthalmic
    - **Blurred vision** (10% to 38%)
    - Corneal deposit (14.5%)
    - Photopsia (25% to 30%)
  - Neurologic
    - Asthenia (4.9% to 6%)
    - **Dizziness** (18.9% to 30%)
    - Headache (10%)
IC: Propafenone

- **Do not use** with structural heart disease
  - Not used in CAST trial, but results still apply
- Similar to flecainide, but has some β-blocking activity
- Use with a rate control drug to lower the risk of paradoxical increases in the ventricular rate (1:1 conduction)
- **Dosing:**
  - Immediate release: 150 to 300 mg every 8 hours
  - Extended release: 225 to 425 mg every 12 hours
  - Pill in pockets: 450 to 600 mg once for cardioversion
- **ADRs**
  - Gastrointestinal
    - Constipation (8% to 14%)
    - Nausea (9% to 17%)
    - Taste sense altered (6% to 22%)
  - Neurologic
    - **Dizziness** (21% to 23%)
  - Respiratory:
    - **Dyspnea** (13% to 17%)
Recommended Monitoring – Class IC

- Ensure that patients do not have structural heart disease
- Ensure patient remains in NSR
- Outpatient monitoring

<table>
<thead>
<tr>
<th>Drug</th>
<th>ECG</th>
<th>SCr</th>
<th>ALT</th>
<th>CAD Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flecainide</td>
<td>Annual*</td>
<td>Annual*</td>
<td></td>
<td>Periodically#</td>
</tr>
<tr>
<td>Propafenone</td>
<td>Annual*</td>
<td></td>
<td>Annual*</td>
<td>Periodically#</td>
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*No interval specified, parameter in PI
# Not in PI, EP opinion
Rhythm Rule #5

- The 1C AADs, flecainide and propafenone, are NOT an option if a patient has heart disease.
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* FDA approved for atrial arrhythmias
III: Sotalol

- Class II (β blocking, non-cardioselective) and Class III (K⁺ blocking) properties
- Efficacy: 50-60%
- For the maintenance of NSR in patients with symptomatic AFIB/AFL
- QT interval prolongation is directly related to the dose.
  - Factors such as reduced creatinine clearance, gender (female) and larger doses increase the risk of TdP.
- Dose: 80 to 160 mg
  - Renally dose adjusted (calculated using Cockcroft-Gault)
    - > 60 mL/min Q12 hours
    - 40-60 mL/min Q24 hours
    - < 40 mL/min, contraindicated
- ADRs
  - Dizziness (13.1% to 20%)
  - Dyspnea (9.2% to 21%)
  - Fatigue (18.9% to 20%)
  - Heart failure (5%)
  - Torsades de pointes (0.5% to 5.8%)
Sotalol Monitoring

- Close monitoring of QTc for 72 hours after initiation
  - Inpatient initiation recommended
    - Betapace AF (atrial arrhythmias)
      - Baseline QTc > 450 msec – contraindicated
      - QTc > 500 msec during initiation – adjust dose
      - QTc > 520 msec during maintenance – adjust dose
    - Monitor QTc, renal function, electrolytes

- Outpatient recommendations

<table>
<thead>
<tr>
<th>Drug</th>
<th>ECG</th>
<th>Mg++</th>
<th>K+</th>
<th>SCr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sotalol</td>
<td>Q6mo*</td>
<td>Q6mo*</td>
<td>Q6mo*</td>
<td>Q3mo*</td>
</tr>
</tbody>
</table>

*No interval specified, parameter in PI
III: Dofetilide

- For the maintenance of NSR in patients with symptomatic atrial fibrillation/atrial flutter
- Efficacy: 50-60%
- QT interval prolongation is directly related to plasma concentrations
- Dosage adjustment based on CrCl (calculated using Cockcroft-Gault)
  - CrCl >60 ml/min: 500 mcg twice daily
  - CrCl 40-60 ml/min: 250 mcg twice daily
  - CrCl 20-40 ml/min: 125 mcg twice daily
  - Contraindicated with Clcr <20 ml/min
- ADRs
  - Neurologic
    - Dizziness (8%)
    - Headache (11%)
  - Cardiovascular
    - Ventricular arrhythmia (up to 14.5%)
Dofetilide Monitoring

- Requires at least 3 day hospitalization for drug initiation with continuous ECG monitoring
  - Inpatient initiation recommended
    - Baseline QTc > 440 msec – contraindicated
    - QTc ↑ by 15% or more or >500 msec, decrease dose by 50%
    - If QTc > 500 msec again during maintenance, discontinue
    - Monitor QTc, renal function, electrolytes (K should be maintained within normal range)

- Outpatient recommendations

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<tr>
<td>Dofetilide</td>
<td>Q3mo</td>
<td>Q6mo*</td>
<td>Q6mo*</td>
<td>Q3mo</td>
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III: Amiodarone

- Features of all 4 Vaughan-Williams classes
- **Most effective drug** for preventing recurrent AF (85-95% efficacy)
- May use for patients with HF
- Dosing – atrial fibrillation
  - Load: 3-10 grams target
    - 600 to 800 mg/day (in divided doses) for up to 2-4 weeks
  - MD: 200 mg daily
- Only FDA approved for VT
  - Used *off label* for AF
- LONG half-life (over 50 days)

- Adverse reactions
  - Hyperthyroidism (1%)
  - Hypothyroidism (10%)
  - Pulmonary fibrosis (1-2%); less common with lower doses/duration
  - Hepatitis (5%) - typically reversible
  - Corneal deposits – typically not clinically significant
  - Photosensitivity / skin pigmentation (1-2%) – “Smurf syndrome”
  - Neuropathy – tremor (50%), ataxia (1-2%)
  - TdP very rare clinically (<1%)
## Amiodarone Monitoring

### Recommended Amiodarone Monitoring

<table>
<thead>
<tr>
<th>Test</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest X-ray</td>
<td>Baseline and Q12 months</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>Baseline and Q12 months</td>
</tr>
<tr>
<td>LFTs (ALT and AST)</td>
<td>Baseline and Q6 months</td>
</tr>
<tr>
<td>Thyroid function (TSH and T4)</td>
<td>Baseline and Q6 months</td>
</tr>
<tr>
<td>PFTs with DLCO</td>
<td>Baseline and if toxicity suspected</td>
</tr>
</tbody>
</table>

### Recommended Action

<table>
<thead>
<tr>
<th>Condition</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>If cough, dyspnea or fever develop</td>
<td>CXR and PFTs with DLCO; consider pulmonary toxicity from amiodarone and discontinue immediately upon diagnosis</td>
</tr>
<tr>
<td>Hyper- or Hypo-thyroidism</td>
<td>Levothyroxine or methimazole/PTU Dosage reduction or withdrawal</td>
</tr>
<tr>
<td>LFTs (ALT and AST)</td>
<td>If &gt; 3 times ULN, reduce dose or discontinue</td>
</tr>
</tbody>
</table>
III: Dronedarone

- Has electrophysiologic properties of classes I–IV
- To reduce the risk of hospitalization due to paroxysmal or persistent AFib
- **21-25% efficacy**
- Structurally related to amiodarone, but without the iodine moiety
- Should **not** be used to control the ventricular rate in patients with permanent AF (increased risk of stroke, MI, systemic embolism, or CV death)
- Contraindicated in
  - NYHA class II or III HF with recent decompensation requiring hospitalization, NYHA class IV HF
  - Severe liver impairment
  - HR less than 50 beats/minute
  - Concurrent use of strong CYP3A4 inhibitors or QTc-interval–prolonging agents
  - History of amiodarone-induced hepatotoxicity or pulmonary toxicity,
  - Pregnancy,
  - QTc interval greater than 500 milliseconds
Dronedarone Monitoring

- Some cardiologists will start on outpatient basis
- MUST monitor for efficacy
- Outpatient monitoring

<table>
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<th>Drug</th>
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<th>ALT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dronedarone</td>
<td>Q3mo</td>
<td>Annual*</td>
<td>Within first 6 months then annual*</td>
</tr>
</tbody>
</table>

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Rhythm Rule #6

- AADs can be harmful if not used and monitored appropriately. For Class III AADs (the DAIDS), careful monitoring is particularly important.
When to Use What

No structural heart disease

Dofetilide
Dronedarone
Flecainide
Propafenone
Sotalol

Amiodarone

Catheter ablation*

*Based on patient preference in experienced centers

Circulation 2014;130:e199–e267.
When to Use What

Structural Heart Disease

CAD
- Dofetilide
- Dronedarone
- Sotalol

Heart Failure
- Amiodarone
- Dofetilide

Catheter Ablation*

Amiodarone
- Dofetilide

*Based on patient preference in experienced centers

Circulation 2014;130:e199–e267.
Case #1: Mary Rhythm

60 y/o AA woman with a PMH including HFrEF (EF 35%), atrial fibrillation(AF), CKD, HTN

- **Inpatient Medications:**
  - apixaban 5 mg twice daily
  - lisinopril 20 mg daily
  - metoprolol succinate 50 mg/day
  - furosemide 40 mg twice daily
  - spironolactone 25 mg/day
  - atorvastatin 20 mg/day

**HPI:**

Presents to cardiology clinic with a recent history of fatigue and palpitations, no symptoms today. She has failed other beta blockers and feels more fatigued on higher doses of metoprolol.

**Laboratory data:**

<table>
<thead>
<tr>
<th>BP</th>
<th>115/78 mm Hg</th>
<th>HT</th>
<th>67 in</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>70 bpm</td>
<td>WT</td>
<td>75 kg</td>
</tr>
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</table>

**ECG:** NSR

What is the next best step?
Mary has remained symptomatic despite adequate trials of beta blocker therapy

1. What are her AAD options?
   a) Dofetilide
   b) Amiodarone

2. How should these drugs be initiated?
   Inpatient vs. outpatient?

3. How should these drugs be monitored?
   Labs vs. diagnostic testing?
Mary Rhythm – Answers

- Her CrCl (actual body weight): 44 ml/min
- Due to HF, her only AAD options are
  - Dofetilide
    - Initiation: Must be admitted for 3 days to initiate
    - Dose 250 mcg BID
    - Monitor Mg, K, Cr, QTc (ECG)
  - Amiodarone
    - Initiation: Location is dependent on cardiologist
    - Dose: Load (up to 10g) then 200 mg/day
    - Monitor TSH, ALT, pulmonary function (PFTs with DLCO at baseline, then chest x-rays), ECG
    - Counsel about other possible ADRs
Treatment and Monitoring of VENTRICULAR Arrhythmias
Case #2: Mr. Rhythmchange

49 y/o WM with a PMH including HFrEF (EF 15%), AF, HTN, DM, and depression

- SHx: No alcohol, denies illicit drug use, 40 pack year hx quit 6 mo. ago

- Inpatient Medications:
  - aspirin 81 mg daily
  - lisinopril 10 mg daily
  - carvedilol 12.5 mg twice daily
  - spironolactone 25 mg daily
  - digoxin 0.125 mg daily
  - dofetilide 250 mcg twice daily
  - warfarin 3 mg daily
  - milrinone drip 0.3 mcg/kg/min
  - furosemide 0.3 mg/kg/min

- HPI: Heart failure exacerbation admitted to ICU; possible transplant candidate

- Laboratory data:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>INR</td>
<td>2.85</td>
</tr>
<tr>
<td>A1C</td>
<td>6.4</td>
</tr>
<tr>
<td>BP</td>
<td>89/65 mm Hg</td>
</tr>
<tr>
<td>HR</td>
<td>86 bpm</td>
</tr>
<tr>
<td>HT</td>
<td>72 cm</td>
</tr>
<tr>
<td>WT</td>
<td>99.7 kg</td>
</tr>
<tr>
<td>BP</td>
<td>137/110</td>
</tr>
<tr>
<td>Mg</td>
<td>1.8 mg/dL</td>
</tr>
<tr>
<td>CrCl</td>
<td>39 ml/min/1.73m²</td>
</tr>
<tr>
<td>A1C</td>
<td>7.55</td>
</tr>
<tr>
<td>BP</td>
<td>12.9</td>
</tr>
<tr>
<td>Mg</td>
<td>29.4</td>
</tr>
<tr>
<td>A1C</td>
<td>250</td>
</tr>
<tr>
<td>BP</td>
<td>135</td>
</tr>
</tbody>
</table>

Est. CrCl~ 39 ml/min/1.73m²  Mg=1.8 mg/dL
Question

Which one is the most likely etiology for this ventricular arrhythmia?

a. EF 15%
b. Inappropriate milrinone dose
c. Inappropriate dofetilide dose
d. Electrolyte abnormalities
Which one is the most likely etiology for this ventricular arrhythmia?

a. EF 15%
   • Most common arrhythmia in HF is atrial fibrillation
   • Might qualify for ICD therapy

b. Inappropriate milrinone dose
   • Common inotropic infusion in HF; can cause ventricular arrhythmias; adjusted for renal dysfunction

c. Inappropriate dofetilide dose
   • CrCl 39 ml/min/1.73m2- 125 mcg twice daily
   • Risk for torsades is dose dependent

d. Electrolyte abnormalities
   • Goal K>4.0 mmol/L; Mag > 2.0 mg/dL
Rhythm Rule #7

- Pharmacists play a key role in prevention of drug-induced ventricular arrhythmias.
**Prevent Drug-Induced Events**

**QT prolongation**

- Ensure proper renal/hepatic dosing adjustments
- Review electrolyte abnormalities and thyroid function
- Replace lytes appropriately
  - $K^+ > 4$ mmol/L and $Mg^{++} > 2$ mg/dL
- Ensure that all ECG parameters are within normal limits (e.g., QT interval less than 500 milliseconds).

**Bradyarrhythmias**

- $\beta$-Blocker, calcium channel blocker, digoxin
- Administer antidote if appropriate (e.g., calcium for calcium channel blocker toxicity)
Life-threatening VT

Pulseless ➔ ACLS

- Defibrillation and HQCPR are most beneficial in life threatening arrhythmias
- NO drug therapy has been shown to improve survival to discharge
- Amiodarone is only antiarrhythmic drug with IIb Class recommendation, to be given AFTER 3rd shock

With Pulse

- Amiodarone
  - Safe for HFrEF
  - Careful in this patient due to BP and possible transplant status
- Electrolyte replacement
  - IV Magnesium in *torsades de pointes* (with pulse)
  - Replace K+
- Supportive measures
Case #2: Mr. Rhythmchange

- **2 days have passed**
  - Dofetilide is *discontinued*
  - Milrinone is *weaned successfully*
  - IV furosemide converted to oral

- **Current Inpatient Medications:**
  - aspirin 81 mg daily
  - lisinopril 10 mg daily
  - carvedilol 12.5 mg twice daily
  - spironolactone 25 mg daily
  - digoxin 0.125 mg daily
  - warfarin 3 mg daily
  - furosemide 80 mg po twice daily

- **EKG:**
  - Several episodes of **NSVT** over 24 hours

- **Laboratory data:**
  - INR 2.85
  - **digoxin** 1.2 mg/dL
  - Mg=2.2 mg/dL
  - BP 94/60 mm Hg
  - HR 76 bpm
  - **HT** 72 cm
  - **WT** 96 kg

# Stable Ventricular Arrhythmias

<table>
<thead>
<tr>
<th></th>
<th>Nonsustained VT</th>
<th>Sustained VT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality</td>
<td>&gt;3 consecutive VT beats lasting &lt; 30 seconds</td>
<td>&gt;3 consecutive VT beats lasting &gt; 30 seconds</td>
</tr>
<tr>
<td>Termination</td>
<td>Spontaneous</td>
<td>Does not self-terminate, or &lt;30 seconds that requires termination due to hemodynamic compromise</td>
</tr>
<tr>
<td>Treatment if asymptomatic</td>
<td>Reassurance</td>
<td>Further evaluation required</td>
</tr>
<tr>
<td>Treatment if symptomatic*</td>
<td>Beta blockers ± antiarrhythmic therapy</td>
<td>Device therapy ± antiarrhythmic therapy</td>
</tr>
</tbody>
</table>

*The risk of cardiac events is often dictated by the underlying heart disease*
More Aggressive Therapy in SHD

- **Patients with structural heart disease are at highest risk for a life-threatening event**

<table>
<thead>
<tr>
<th>Structural Heart Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure (i.e. dilated cardiomyopathy)</td>
</tr>
<tr>
<td>ACS past or present</td>
</tr>
<tr>
<td>Valvular heart disease</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
</tr>
</tbody>
</table>
Rhythm Rule #8

- In ventricular arrhythmias, *device therapy will provide superior mortality reduction than drug therapy*
<table>
<thead>
<tr>
<th>Primary Prevention</th>
<th>Secondary Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous MI, at least 40 d prior and EF ≤ 35%</td>
<td>Previous resuscitated VF/VT, sustained VT with CHD</td>
</tr>
<tr>
<td>Nonischemic dilated cardiomyopathy and EF ≤ 35%</td>
<td>Must be on optimal chronic meds (BB, ACEI)</td>
</tr>
<tr>
<td>Syncope with heart disease and inducible VT/VF</td>
<td>Must have &gt;1 yr survival expectation</td>
</tr>
<tr>
<td>High risk for VT/VF; congenital long QT, torsades</td>
<td></td>
</tr>
<tr>
<td>Must have &gt; 1 yr survival expectation</td>
<td></td>
</tr>
</tbody>
</table>
Drug Therapy in VT

- Used to prevent life-threatening arrhythmias in those patients in whom device therapy is inappropriate or unavailable (prevention)
- Used to reduce inappropriate firing from ICD (suppression)
Rhythm Rule # 9

- Antiarrhythmic drugs should be chosen on their clinical utility for suppressing conduction in atrial or ventricular tissue and safety for use in certain patient populations
Which agent is the best choice treating ventricular tachycardia in Mr. Rhythmchange?

a. Mexiletine 300 mg po q8 hours
b. Lidocaine 1-4 mg/minute
c. Amiodarone 400 mg daily (after loading)
d. Sotalol 80 mg po twice daily
Which agent is the best choice treating ventricular tachycardia in Mr. Rhythmchange?

a. Mexiletine 300 mg po q8 hours
   - Ib agent- not preferred in HFrEF
b. Lidocaine 1-4 mg/minute
   - Ib agent- not preferred in HFrEF
c. Amiodarone 400 mg daily (after loading)
   - Only agent preferred for VT in HF (device tx better)
d. Sotalol 80 mg po twice daily
   - Avoid in HFrEF; needs renal adjustment
Implantable Cardioverter Defibrillator
Suppression of AICD firing

- Inappropriate firing of ICD → mortality and ↓ QOL
- Same rules apply for drug therapy
  - ADEs are not avoided in ICD placement
- OPTIC trial (Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients)
  - N=412 patients with ICD for VT (EF < 40% or syncope)
  - Compared amiodarone (200 mg QD) + BB vs. sotalol alone (adjusted for renal function) vs. BB alone
  - Amiodarone + BB significantly reduced shock over BB (HR 0.27, p< 0.001) and sotalol alone (HR 0.43, p=0.02)
  - No difference between BB and sotalol (p=NS)
  - BB were best tolerated
- Small evidence for adding Class Ib agent to amiodarone for refractory shocks

Notable Drug Interactions with AADs
Rhythm Rule #10

- Important drug interactions place patients receiving antiarrhythmic drugs at risk for adverse drug events.
# AAD Inhibitors of CYP and P-gp

<table>
<thead>
<tr>
<th>1A2</th>
<th>2D6</th>
<th>3A4</th>
<th>P-gp</th>
<th>2C9</th>
<th>2C19</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quinidine*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quinidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mexilithine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propafenone^</td>
<td></td>
<td></td>
<td>Propafenone#</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flecaainide</td>
<td></td>
<td></td>
<td>Dronedarone</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25-30% all drug metabolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theophylline, Tylenol, clozapine, duloxetine, Propranolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Warfarin, digoxin, paroxetine, Morphine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metoprolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50% all drug metabolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Warfarin, Protease Inhibitors, Grapefruit juice</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Verapamil, Ketoconazole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Digoxin, Amiodarone, Dronedarone, PIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Azole, Antifungals</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phenytoin, S-Warfarin, Fluconazole, Fluoxetine, Losartan, NSAIDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PPIs, TCAs, Diazepam, Propranolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Potent inhibitor; #Moderate inhibitor
<table>
<thead>
<tr>
<th>AAD</th>
<th>Substrate/Activity</th>
<th>Potential interacting medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine</td>
<td>Potent Inhibitor of 2D6 Substrate and inhibitor 3A4</td>
<td>Warfarin, digoxin</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>Inhibitor of 1A2 Substrate 2D6, 1A2</td>
<td>Sotalol, clozapine, duloxetine Reduce dose with amiodarone</td>
</tr>
<tr>
<td>Propafenone</td>
<td>Inhibitor of 1A2 and 2D6 Substrate 2D6, 1A2, and 3A4 Moderate Pgp inhibitor</td>
<td>Digoxin  ( \uparrow ) 70%; Warfarin  ( \uparrow ) 50% Contraindicated with dronedarone, Avoid amiodarone (( \uparrow ) propafenone)</td>
</tr>
<tr>
<td>Flecaainide</td>
<td>Inhibitor 2D6 Substrate 2D6, 1A2</td>
<td>Contraindicated with dronedarone, protease inhibitors; amiodarone ( \uparrow ) flecaainide 50%; Digoxin ( \uparrow ) 50%</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Inhibitor of 3A4, 2D6, 2C9, 1A2, 2C19 and P-gp Substrate 3A4, 1A2, 2C19, 2D6</td>
<td>Warfarin, digoxin, statins (lova/simva capped dosing), phenytoin ( \uparrow ) 50%, multiple interactions</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>Inhibits P-gp Substrate 3A4</td>
<td>3A4 inhibitors, QT prolonging agents, warfarin, digoxin, P-gp substrates like dabigatran, edoxaban</td>
</tr>
<tr>
<td>AAD</td>
<td>Mechanism</td>
<td>Interacting Medications</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Sotalol</td>
<td>Synergistic AV nodal blockade or negative inotropic effects</td>
<td>Other BB or K channel blockers</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>3A4 substrate; OCT2 substrate; Interactions via Competitive renal excretion by active tubular transport</td>
<td>Contraindicated with Amiloride, cimetidine, hydrochlorothiazide, azole antifungals, megestrol, metformin, prochlorperazine, ranolazine, triamterene, trimethoprim</td>
</tr>
</tbody>
</table>
Case #2: Mr. Rhythmchange

- **Starting amiodarone**
  - **Current Inpatient Medications:**
    - aspirin 81 mg daily
    - lisinopril 10 mg daily
    - carvedilol 12.5 mg twice daily
    - spironolactone 25 mg daily
    - digoxin 0.125 mg daily
    - warfarin 3 mg daily
    - furosemide 80 mg po twice daily
  - **EKG:**
    - Several episodes of **NSVT** over 24 hours

- **Laboratory data:**
  - BP: 94/60 mm Hg
  - HR: 76 bpm
  - WT: 96 kg
  - HT: 72 cm
  - INR: 2.85
  - digoxin: 1.2 mg/dL
  - Mg: 2.2 mg/dL
  - 137 109 33 128
  - 4.2 23 1.8

What drugs may need to be adjusted based on amiodarone initiation?
Pharmacists Improve AAD Safety

Pharmacist Inpatient

- N=36, all prescribed sotalol
- 89% inappropriately dosed per renal function
- 42% ADEs were identified
  - Hypotension requiring vasopressor support (2); bradycardia evaluated for PPM
- 36% DIs were identified
- Pharmacist recommendations resulted in dose adjustments/discontinuation in patients
- Added to high risk drug monitoring protocol

Pharmacist Run Clinics

- N=134 patients on various AADs
  - Amio (58), Sotalol (40), dofetilide (28), propaf (8)
- Adherence to monitoring improved in patients receiving all AADs (except sotalol)
- 38% visits had drug interactions or ADEs identified
- Amiodarone associated with highest rate of ADE (23% of patient visits)

Patient Specific Factors to consider with AADs
Appropriate Selection and Monitoring are Key

- **ECG**
  - Monitor for prolonged QTc or arrhythmias

- **Renally eliminated AADs**
  - Dofetilide
  - Sotalol

- **Liver monitoring**
  - Amiodarone
  - Dronedarone

- **Electrolytes**
  - Magnesium
  - Potassium

- **Other (amiodarone)**
  - TSH
  - Eye exam as needed
  - Pulmonary function testing
  - Chest x-ray
Think/Pair/Share: Atrial Fibrillation Options

- If a patient’s PMH is one of the below:
  - CAD
  - Healthy, no PMH
  - HF
  - QTc >500 msec
  - Hypokalemia
  - CrCl 30 ml/min
  - Chronic pulmonary disease

- Which of the AADs can they use?
  - Flecainide
  - Propafenone
  - Sotalol
  - Dofetilide
  - Amiodarone
  - Dronedarone
Think/Pair/Share: Atrial Fibrillation Answers

- CAD – may use
  - Sotalol
  - Dofetilide
  - Dronedarone
  - Amiodarone
- Healthy, no PMH
  - Any
- HF
  - Dofetilide
  - Amiodarone
- QTc >500 msec
  - Consult with EP

- Hypokalemia
  - Correct prior to initiating; correct ASAP
  - Do not use sotalol or dofetilide if chronic hypokalemia

- CrCl <30 ml/min
  - Any except sotalol
  - Do not use dofetilide if CrCl <20 ml/min

- Chronic, severe pulmonary disease
  - Any except amiodarone and dronedarone
Key Takeways (i.e. Rhythm Rules)

- **Pharmacists** play a vital role in the appropriate use of AAD dosing, ADRs, interactions, and monitoring.
- If you see atrial fibrillation ask yourself
  1. Is anticoagulation indicated?
  2. Rate vs. rhythm control?
- Rhythm control with long-term antiarrhythmic drugs is not for everyone. Consider for those
  - Who remain **symptomatic** after an adequate trial of the rate control strategy
  - With tachycardia-induced myopathy
  - Who are younger patients
- Electricity and AADs can cardiovert patients from AF to NSR. Appropriate anticoagulation is key.
- The **1C** AADs, flecainide and propafenone, are not an option if a patient has heart disease.
- AADs can be **harmful** if not used and monitored appropriately. For Class III AADs (the DAIDS), careful monitoring is particularly important.
Key Takeways (i.e. Rhythm Rules)

- Pharmacists play a key role in prevention of drug-induced ventricular arrhythmias.
- In ventricular arrhythmias, device therapy will provide superior mortality reduction than drug therapy.
- Antiarrhythmic drugs should be chosen on their clinical utility for suppressing conduction in atrial or ventricular tissue and safety for use in certain patient populations.
- Important drug interactions place patients receiving antiarrhythmic drugs at risk for adverse drug events.
Interactive Q&A Session

Questions and Answers