ashp® MIDYEAR 2016
Clinical Meeting & Exhibition

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

Karen J. McConnell, Pharm.D., FCCP, BCPS- AQ Cardiology, ASH-CHC
Clinical Director and Cardiology Subject Matter Expert, Cardinal Health
Clinical Associate Professor, University of Colorado Skaggs School of Pharmacy
and
Shannon W. Finks, Pharm.D., FCCP, BCPS- AQ Cardiology, ASH-CHC
Professor of Clinical Pharmacy, University of Tennessee College of Pharmacy
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

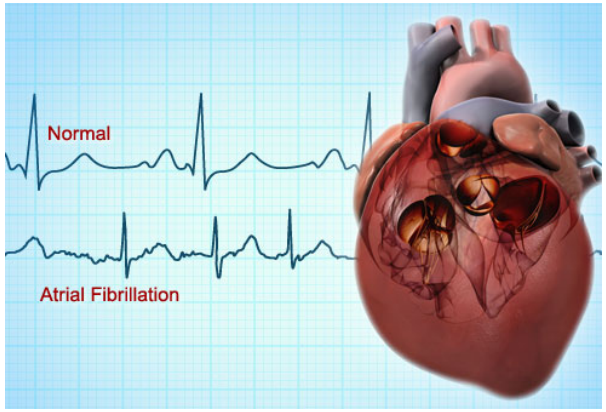
- *Pharmacists play a vital role in the appropriate use of AAD dosing, adverse effects, interactions, and monitoring.*

Treatment and Monitoring of Atrial Fibrillation

ashp MIDYEAR 2016 Clinical Meeting & Exhibition

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

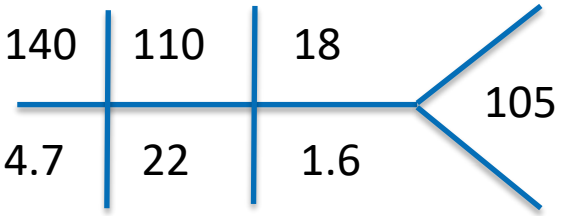
60 y/o AA woman with a PMH including HF*r*EF (EF 35%), atrial fibrillation(AF), CKD, HTN

- **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?

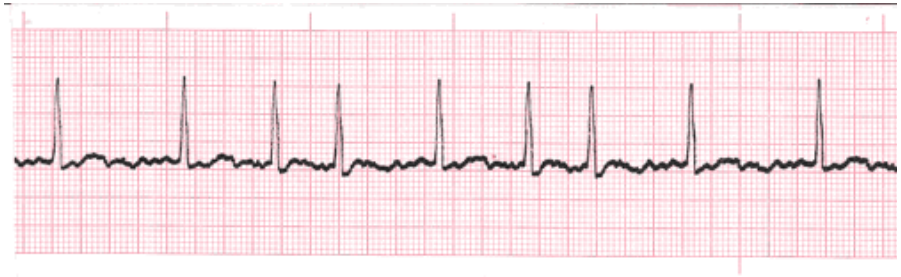
Atrial Fibrillation

Classification of AF

Paroxysmal	Persistent	Longstanding Persistent	Permanent	Non-Valvular vs. Valvular
≤7 days	>7 days	>12 months	*No longer pursue rhythm control strategy*	*Refers to if AF is secondary to valve disease*
Terminates spontaneously, recurrence spontaneous	*Often requires cardioversion to restore NSR*			

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

- $CHA_2DS\text{-}VAS_2c$ 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.

J Am Coll Cardiol. 2004;43:1201–8.
N Engl J Med. 2002;347:1834–40.

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.

N Engl J Med. 2005;352:1861–72. 315.
J Am Coll Cardiol. 2004;43:241–7

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

Class	Agent	Clinical Utility
Class I Na^+ channel blockers	IA: Quinidine, procainamide, disopyramide 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

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

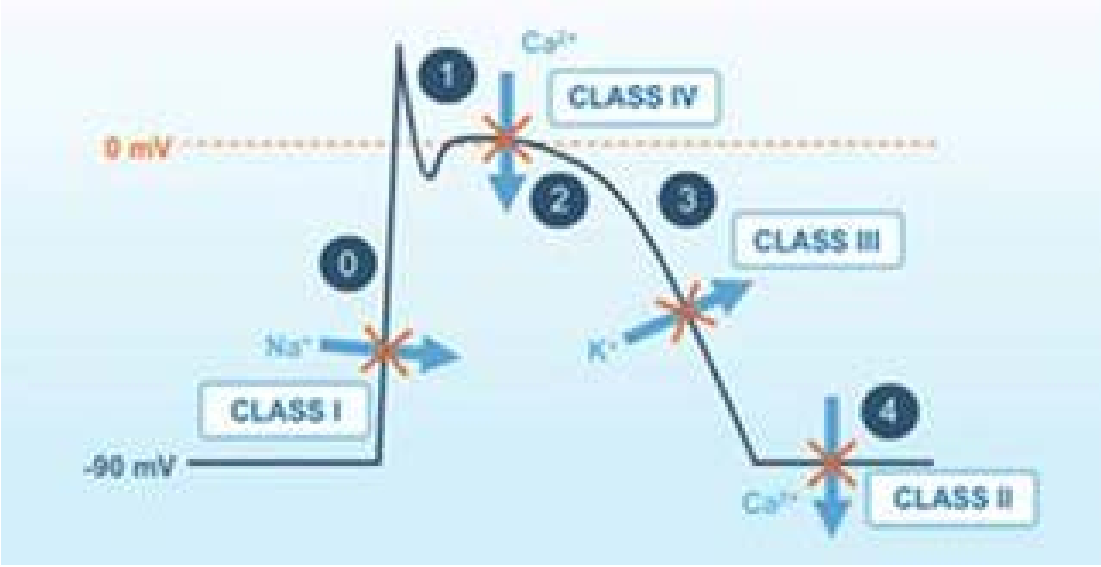
- Prolong *repolarization* (phase 3) and ↑ refractoriness

Class IV: Ca^{++} channel blockers

- Major effects on AV > sinus node

Other drugs:

- Adenosine, digoxin, atropine, Mg^{++}



Antiarrhythmic Agent Overview

Class	Agent	Clinical Utility
Class I Na^+ channel blockers	IA: Quinidine, procainamide, disopyramide 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 **Class I**
    - Recommended to restore NSR; may be repeated
  - Pharmacologic
    - Flecainide, dofetilide, propafenone and IV ibutalide 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

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

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	Agent	Clinical Utility
Class I Na^+ channel blockers	IA: Quinidine, procainamide, disopyramide 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

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.

N Engl J Med 1991; 324:781-788

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

Drug	ECG	SCr	ALT	CAD Evaluation
Flecainide	Annual*	Annual*		Periodically#
Propafenone	Annual*		Annual*	Periodically#

*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.*

Antiarrhythmic Agent Overview

Class	Agent	Clinical Utility
Class I Na^+ channel blockers	IA: Quinidine, procainamide, disopyramide 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* (DAIDS)	A & V
Class IV CCBs	Diltiazem, verapamil	A & V

* 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)
    - o > 60 mL/min Q12 hours
    - o 40-60 mL/min Q24 hours
    - o < 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

Drug	ECG	Mg^{++}	K^{+}	SCr
Sotalol	Q6mo*	Q6mo*	Q6mo*	Q3mo*

*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

Drug	ECG	Mg^{++}	K^{+}	SCr
Dofetilide	**Q3mo**	**Q6mo***	**Q6mo***	**Q3mo**

*No interval specified, parameter in PI

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	
Chest X-ray	Baseline and Q12 months
Electrocardiogram	Baseline and Q12 months
LFTs (ALT and AST)	Baseline and Q6 months
Thyroid function (TSH and T4)	Baseline and Q6 months
PFTs with DLCO	Baseline and if toxicity suspected

Recommended Action	
If cough, dyspnea or fever develop	CXR and PFTs with DLCO; consider pulmonary toxicity from amiodarone and discontinue immediately upon diagnosis
Hyper- or Hypo-thyroidism	Levothyroxine or methimazole/PTU Dosage reduction or withdrawal
LFTs (ALT and AST)	If > 3 times ULN, reduce dose or discontinue

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

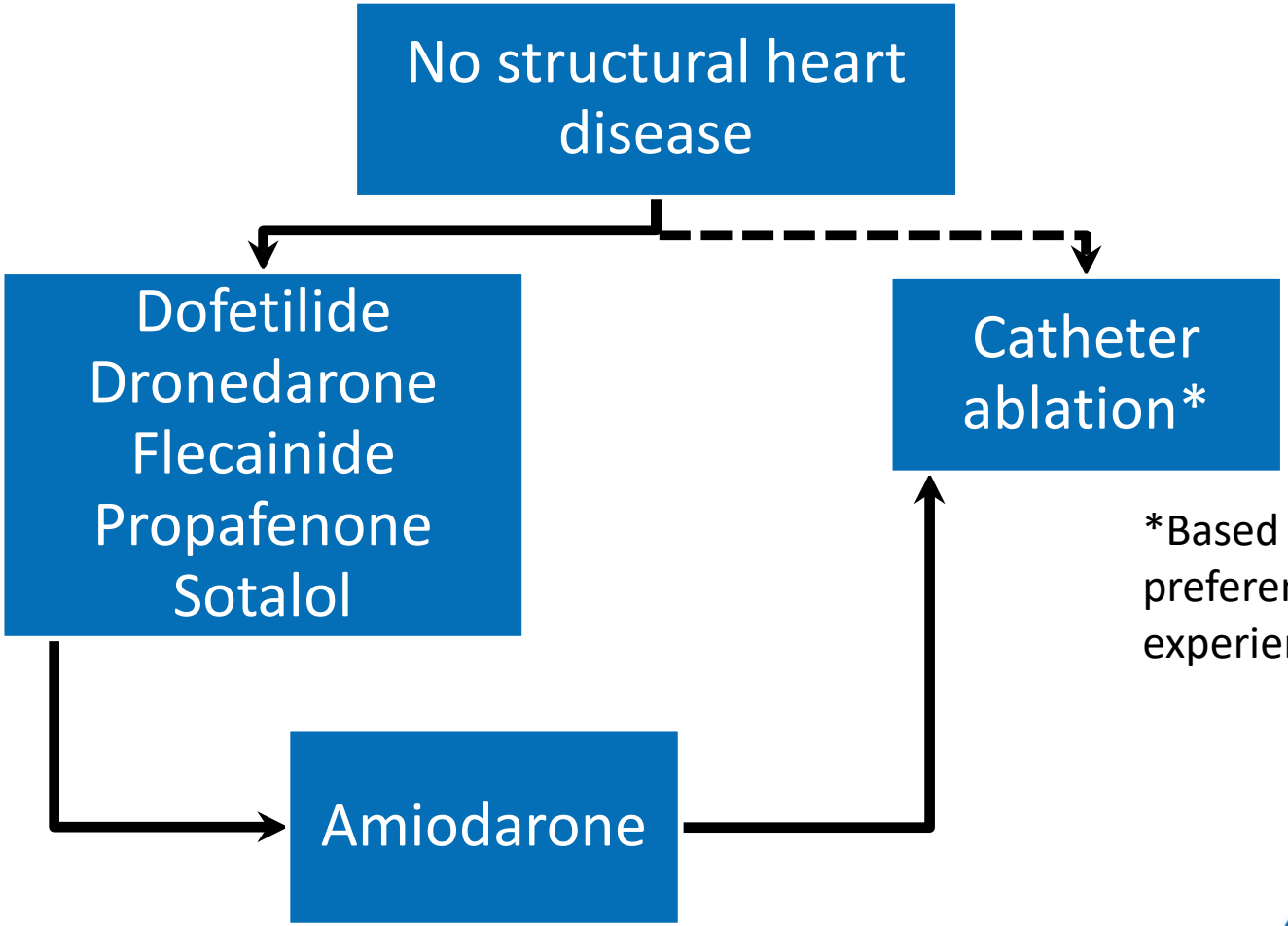
Drug	ECG	SCr	ALT
Dronedarone	**Q3mo**	**Annual***	**Within first 6 months then annual***

*No interval specified, parameter in PI

Rhythm Rule #6

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

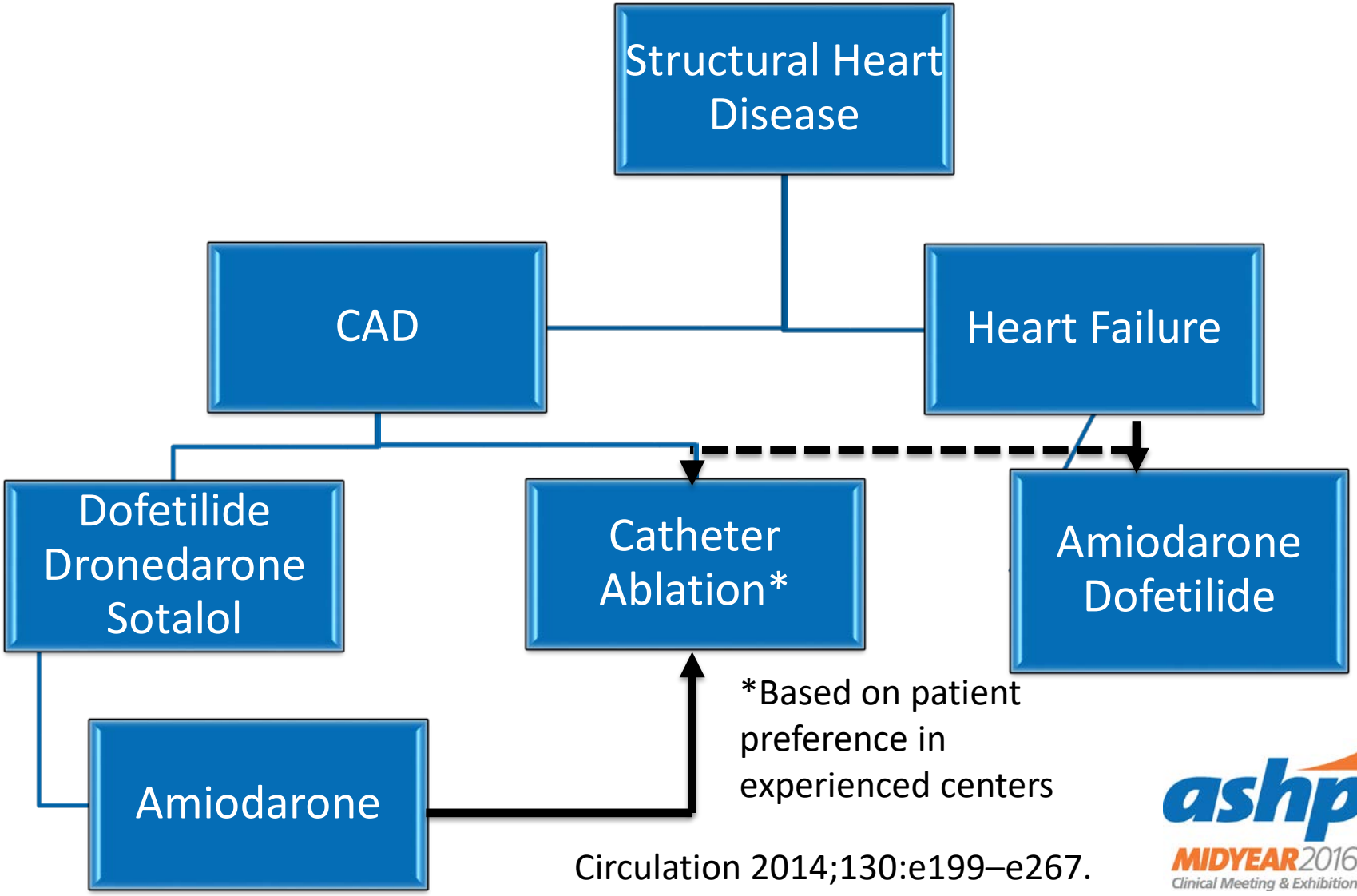
When to Use What



*Based on patient preference in experienced centers

Circulation 2014;130:e199–e267.

When to Use What



Circulation 2014;130:e199–e267.

Case #1: Mary Rhythm

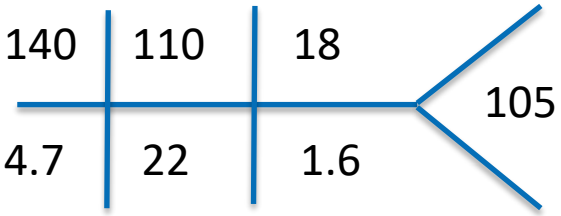
60 y/o AA woman with a PMH including HF*r*EF (EF 35%), atrial fibrillation(AF), CKD, HTN

- **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?

Mary Rhythm

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

ashp MIDYEAR 2016 Clinical Meeting & Exhibition

Case #2: Mr. Rhythmchange

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

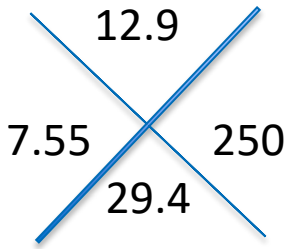
- SHx: No alcohol, denies illicit drug use, 40 pack year hx quit 6 mo. ago

- **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**:

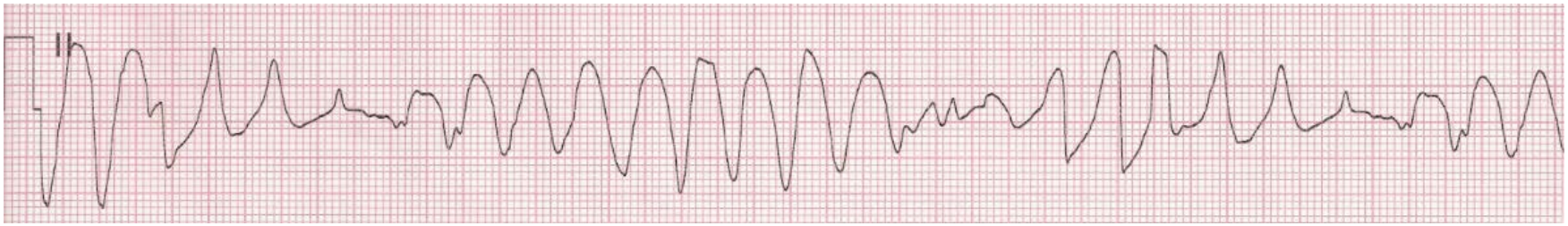
Est. CrCl~ 39 ml/min/1.73m^2 Mg=1.8 mg/dL

INR	2.85
A1C	6.4



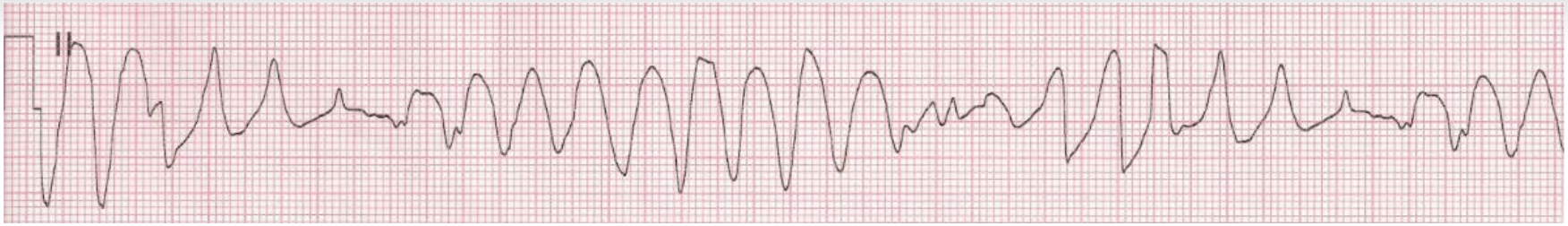
BP	89/65 mm Hg	**HT**	72 cm
HR	86 bpm	**WT**	99.7 kg

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 arrythmias; 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

- β-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

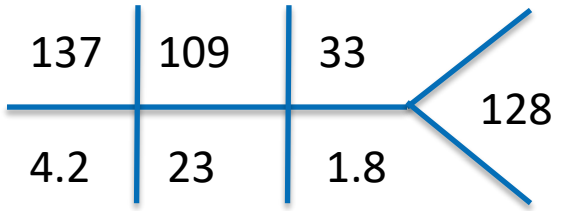
With Pulse

- 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

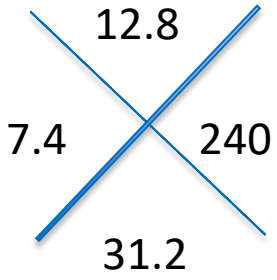
- **2 days have passed**
  - **Dofetilide is *discontinued***
  - **Milrinone is *weaned successfully***
  - ***IV furosemide converted to oral***
- **Current Inpatient Medications:**
  - aspirin 81 mg daily
  - lisinopril 10 mg daily
  - carvedilol 12.5 mg twice daily
  - spironolactone 25 mg daily
  - 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**:



Mg=2.2 mg/dL

INR	2.85
digoxin	1.2 mg/dL



BP	94/60 mm Hg	**HT**	72 cm
HR	76 bpm	**WT**	96 kg

Stable Ventricular Arrhythmias

	Nonsustained VT	Sustained VT
Quality	>3 consecutive VT beats lasting < 30 seconds	>3 consecutive VT beats lasting > 30 seconds
Termination	Spontaneous	Does not self-terminate, or <30 seconds that requires termination due to hemodynamic compromise
Treatment if asymptomatic	Reassurance	Further evaluation required
Treatment if symptomatic*	Beta blockers ± antiarrhythmic therapy	Device therapy ± antiarrhythmic therapy

**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*

Structural Heart Disease
Heart failure (i.e. dilated cardiomyopathy)
ACS past or present
Valvular heart disease
Left ventricular hypertrophy

Rhythm Rule #8

- *In ventricular arrhythmias, device therapy will provide superior mortality reduction than drug therapy*

Implantable Devices approved for:

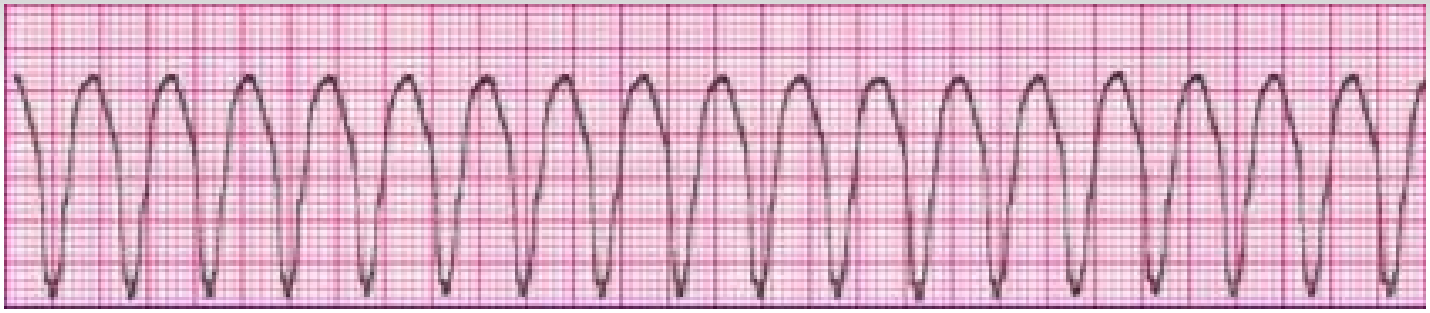
Primary Prevention	Secondary Prevention
Previous MI, at least 40 d prior and EF ≤ 35%	Previous resuscitated VF/VT, sustained VT with CHD
Nonischemic dilated cardiomyopathy and EF≤ 35%	Must be on optimal chronic meds (BB, ACEI)
Syncope with heart disease and inducible VT/VF	Must have >1 yr survival expectation
High risk for VT/VF; congenital long QT, torsades	
Must have > 1 yr survival expectation	

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)

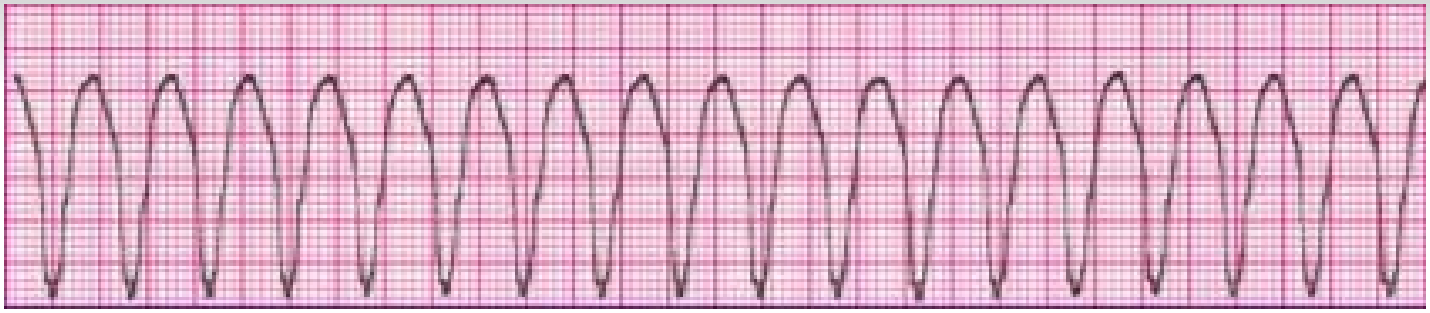
Rhythm Rule # 9

- *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?

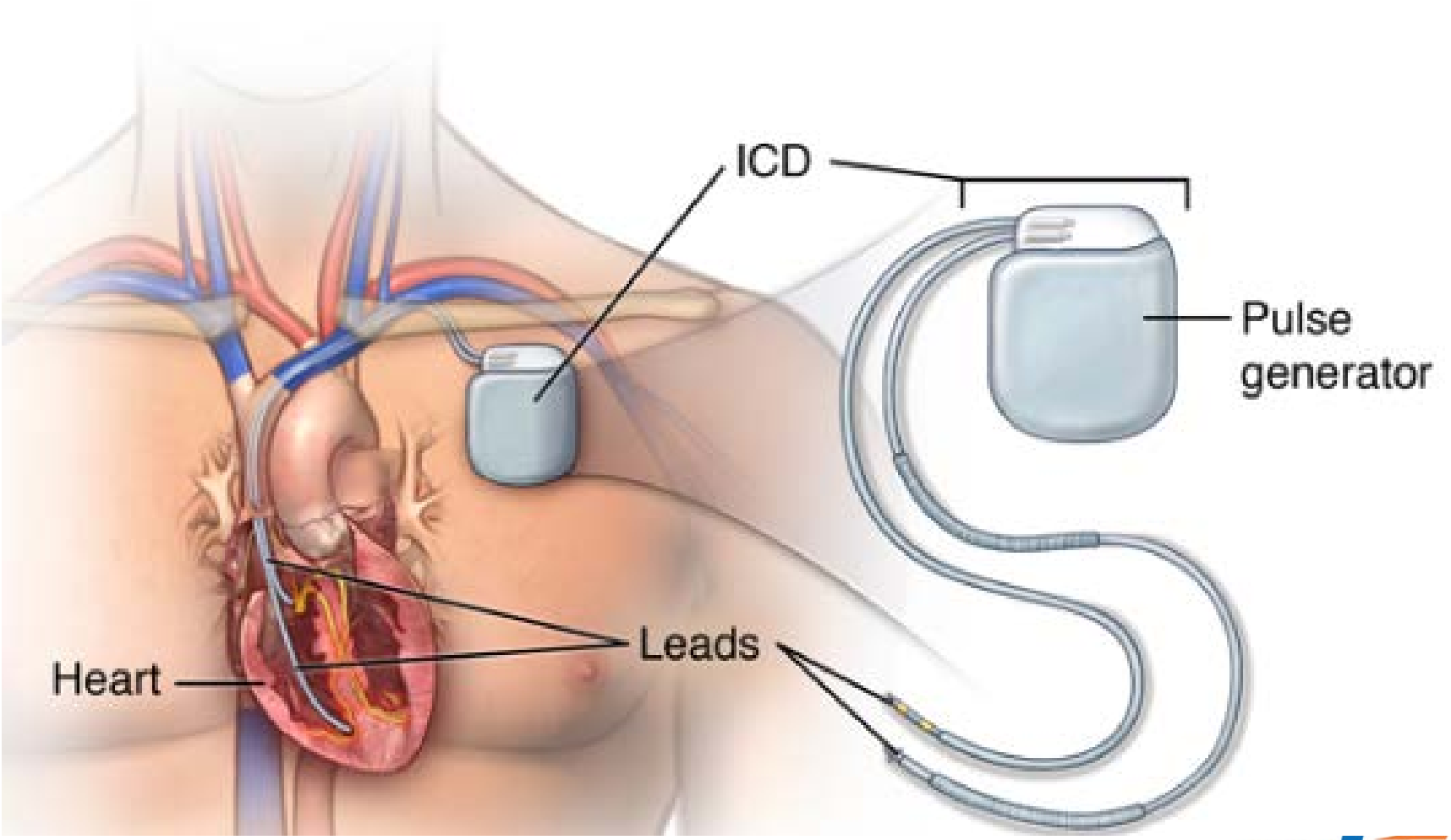
a. Mexiletine 300 mg po q8 hours
   - Ib agent- not preferred in HFrEF

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

Herendael HV et al. Europace 2010;12:618-25.

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

1A2	2D6	3A4	P-gp	2C9	2C19
	Quinidine*	Quinidine			
Mexilitine					
Propafenone^			Propafenone#		
	Flecainide				
		Dronedarone			
Amiodarone					
Theophylline Tylenol clozapine duloxetine Propranolol	25-30% all drug metabolism Warfarin, digoxin, paroxetine, Morphine Metoprolol	50% all drug metabolism Warfarin Protease Inhibitors Grapefruit juice Verapamil Ketoconazole	Digoxin Amiodarone Dronedarone PIs Azole antifungals Verapamil	Phenytoin S-Warfarin Fluconazole Fluoxetine Losartan NSAIDs	PPIs TCAs Diazepam Propranolol

*Potent inhibitor; #Moderate inhibitor

AAD Interactions- CYP450

AAD	Substrate/Activity	Potential interacting medications
Quinidine	Potent Inhibitor of 2D6 Substrate and inhibitor 3A4	Warfarin, digoxin
Mexiletine	Inhibitor of 1A2 Substrate 2D6, 1A2	Sotalol, clozapine, duloxetine Reduce dose with amiodarone
Propafenone	Inhibitor of 1A2 and 2D6 Substrate 2D6, 1A2, and 3A4 Moderate Pgp inhibitor	Digoxin ⇧70%; Warfarin ⇧50% Contraindicated with dronedarone, Avoid amiodarone (⇧propafenone)
Flecainide	Inhibitor 2D6 Substrate 2D6, 1A2	Contraindicated with dronedarone, protease inhibitors; amiodarone ⇧flecainide 50%; Digoxin ⇧50%
Amiodarone	Inhibitor of 3A4, 2D6, 2C9, 1A2, 2C19 and P-gp Substrate 3A4, 1A2, 2C19, 2D6	Warfarin, digoxin, statins (lova/simva capped dosing), phenytoin ⇧50%, multiple interactions
Dronedarone	Inhibits P-gp Substrate 3A4	3A4 inhibitors, QT prolonging agents, warfarin, digoxin, P-gp substrates like dabigatran, edoxaban

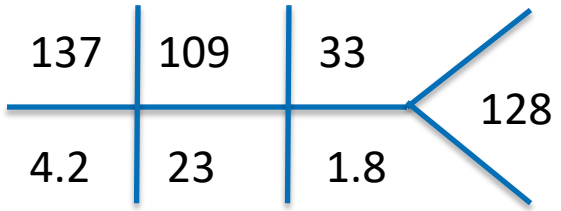
AAD Interactions- Other

AAD	Mechanism	Interacting Medications
Sotalol	Synergistic AV nodal blockade or negative inotropic effects	Other BB or K channel blockers
Dofetilide	3A4 substrate OCT2 substrate Interactions via Competitive renal excretion by active tubular transport	Contraindicated with Amiloride, cimetidine, hydrochlorothiazide, azole antifungals, megestrol, metformin, prochlorperazine, ranolazine, triamterene, trimethoprim

Case #2: Mr. Rhythmchange

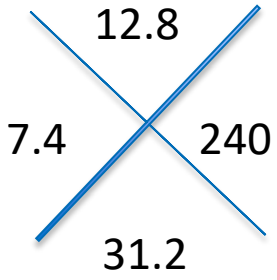
- *Starting amiodarone*
- **Current Inpatient Medications:**
  - aspirin 81 mg daily
  - lisinopril 10 mg daily
  - carvedilol 12.5 mg twice daily
  - spironolactone 25 mg daily
  - digoxin 0.125 mg daily
  - warfarin 3 mg daily
  - furosemide 80 mg po twice daily
- EKG:
  - Several episodes of **NSVT**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

- **Laboratory data**:



Mg=2.2 mg/dL

INR	2.85
digoxin	1.2 mg/dL



BP	94/60 mm Hg	**HT**	72 cm
HR	76 bpm	**WT**	96 kg

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

Finks SW et al. *IJPP* 2011;19(4): 281-6.

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

Snider M et al. *Clin Ther* 2009;31(6):1209-18.

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