Anti-arrhythmic drugs: Practical Points for Primary Care

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Objectives

At the end of this presentation, the participant will be able to:
• Identify arrhythmias that can be treated pharmacologically and those that require urgent/emergent intervention.
• Differentiate between treatment and control of these arrhythmias.
• Identify common antiarrhythmic, rate controlling and risk reduction drugs and their initial doses and special considerations.
• Be familiar with related necessary diagnostic monitoring (labs, EKG).
• Identify the goals of drug therapy, rate vs. rhythm control, effects and evaluation of patients’ response, including management of adverse reactions and need for discontinuation.
• Give rationale for selecting a drug of choice, including evidence based guidelines and contraindications for specific antiarrhythmic drugs.
• Describe initial dosage, including age specific, renal and hepatic considerations.
• Discuss the results of relevant or current clinical trials: ATHENA, DIONYSOS, DAPHNE.
Rhythm ID

• **Supraventricular tachycardia:**
  - atrial fibrillation (AF)
  - atrial flutter (AFL)
  - multifocal atrial tachycardia (MAT)
  - atrial tachycardia (AT)
  - sinus tachycardia (ST)
  - AV nodal reentrant tachycardia (AVNRT)
  - AV reentrant tachycardia (AVRT)

• **Ventricular arrhythmias**
  - ventricular tachycardia (VT)
  - ventricular fibrillation (VF)
What am I looking at?

• Be sure your EKG is as clear as possible
• Be sure your EKG is as current as possible (do one in the office)
• Get as much info from the patient as possible:
  • Symptoms
  • Onset
  • Duration
  • Provoking/relieving factors
What am I looking at?

Remember your basic EKG:
• Regular?
• Rate?
• Is there a P wave for every QRS?
• QRS narrow or wide?
Clinical Manifestations of Arrhythmias

- Palpitations
- Dizziness or lightheadedness
- Loss of consciousness
- Dyspnea
- Weakness
- Asymptomatic
Atrial fibrillation
Atrial flutter
Multifocal atrial tachycardia
Sinus tachycardia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tr>
<td>Heart rate</td>
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<tr>
<td>PR interval</td>
<td>162 ms</td>
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<tr>
<td>QRS duration</td>
<td>86 ms</td>
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<tr>
<td>QT/QTc</td>
<td>320/452 ms</td>
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<td>P-R-T axes</td>
<td>50/85/79</td>
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<tr>
<td>P duration</td>
<td>86 ms</td>
</tr>
<tr>
<td>RR interval</td>
<td>498 ms</td>
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</table>

Otherwise normal ECG
AV nodal reentrant tachycardia
AV reentrant tachycardia
Ventricular tachycardia
Ventricular Tachycardia

- Will most likely be identified on event monitor, not EKG
- Refer to cardiology:
  - needs ischemia/cardiomyopathy work-up
  - management of symptoms (if any)
  - suppression drugs vs. ablation
Initial Treatment of most SVT

Determine whether or not it needs immediate attention
- Symptoms and/or poor rate control = yes
- Asymptomatic and rate controlled = no

...excepting atrial fibrillation of course.
Initial Treatment of Most SVT

Presently occurring in the office with symptoms:

- unstable goes to ER
- vagal maneuvers
- fails to terminate then rate control with beta blockers, verapamil, diltiazem and refer to cardiology
Vagal maneuvers

- Bear down
- Cough
- Ice water
- Or carotid massage
Long term Treatment

- Vagal maneuvers- enough
- Frequent recurrence, unable to terminate with vagal maneuvers- antiarrhythmic meds
- Meds fail or patient refuses meds- ablation
Treatment vs. Control

Both result in increased cardiac output.

• Treatment is aimed at eliminating the arrhythmia or reducing the frequency of its recurrence
  -may be vagal maneuvers, ablation or antiarrhythmic meds
• Control is aimed at managing HR, reducing symptoms and associated risks
  -may be antiarrhythmic meds, anticoagulation or ablate and pace therapy

(O’Brien, 2012)
Pregnancy

- SVT increases in frequency during pregnancy
- Most common is AVNRT
- Adenosine, digoxin, propranolol, procainamide and flecainide are considered safe, highest risk in first eight weeks
- Use of multiple drugs can lead to fetal bradycardia

(Perez-Silva, 2014)
And then there’s AF...

- Now projected to occur in 1:4 persons over the age of 65
- Wide range of associated symptoms from none to chest pain and hypotension
- Treatment/control can be difficult due to vague symptoms
- Associated stroke risk in some

(Rienstra, 2012)
Atrial Fibrillation: Clinical Syndromes

- Paroxysmal Atrial Fibrillation (< 48 hours); spontaneously converts

- Persistent Atrial Fibrillation; requires cardioversion (chemical or electrical)

- Permanent (Chronic) Atrial Fibrillation (> 6 months)
Reasons for Restoring Sinus Rhythm in Patients with Atrial Fibrillation

- mortality double in those with AF
- appropriate/physiologic rate control
- regularization of heart rhythm
- improved hemodynamics
- maintenance of normal electrophysiology
- prevention of left atrial dilatation
- prevention of left ventricular dysfunction
- reduce thromboembolic complications (?)
- relief of symptoms (dyspnea, fatigue, palpitations)

(O’Brien, 2012, p. 120)
## Drugs in Atrial Fibrillation

Eleven drugs available in US:

<table>
<thead>
<tr>
<th>IA</th>
<th>IC</th>
<th>III</th>
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<tbody>
<tr>
<td>Quinidine</td>
<td>Flecainide</td>
<td>Sotalol</td>
</tr>
<tr>
<td>Procainamide</td>
<td>Propafenone</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Disopyramide</td>
<td></td>
<td>Ibutilide</td>
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</table>

- **II** Propanolol
- **IV** Diltiazem
  - Verapamil

**OTHER**: Digoxin

**FDA Approved for Atrial Fibrillation**: Quinidine, Flecainide, Propafenone, Ibutilide, Sotalol, Dofetilide, Dronedarone

(Lehne, 2007)
SVT Meds

- Beta blockers may prevent or at least reduce symptoms
- Class IV meds: verapamil, diltiazem
- Class IC meds: flecainide, per cardiology
AF Treatment

- Quinidine
- Disopyramide
- Propafenone
- Flecainide
- Dofetilide
- Sotalol
- Amiodarone (not FDA approved)
- Ibutilide
- Dronedarone
Quinidine

- Class IA, depresses action potential
- 300-600 mg Q8-12 hours, individualize dose
- Adverse effects: arrhythmia, AV block, GI, headache, hypotension, blurred vision
- Monitor: Cr, LFT, EKG
Disopyramide

• Class IA, depresses action potential
• 400-750 mg daily, divided doses
• Adverse effects: CHF, hypotension, syncope, constipation, dizziness, headache
• Monitor: both renal and hepatic function, may need dose adjustment, ECG
Flecainide

• Class IC, depresses action potential
• 50-300 mg daily, divided doses
• Side effects: arrhythmias, CHF, heart block, hematologic, dyspnea, headache, nausea, fatigue
• Monitor: Cr, electrolytes, ECG
• Allow cardiology to manage
Propafenone

- Class IC, depresses action potential
- 150-300 mg Q8 hrs
- Adverse effects: ventricular arrhythmias, CHF, AV block, dizziness, nausea, fatigue, headache
- Monitor: ECG
Dofetilide

• Class III, prolongs action potential
• 500 mg Q 12 hrs, adjust for QTc
• Adverse effects: QT prolongation, ventricular arrhythmias, torsade's, headache, dizziness, nausea
• Monitor: QT, renal and hepatic function, MUST be started in house by cardiology
Sotalol

- Class III, beta-1/beta-2 antagonist, prolongs action potential
- 80-160 Q 12 hrs
- Adverse effects: CHF, bradycardia, bronchospasm, dyspnea, fatigue, headache
- Monitor: renal function, adjust dose, EKG
Amiodarone

- Class III, prolongs action potential
- 200-600 mg daily
- Adverse effects: bradycardia, AV block, pulmonary tox, thyroid tox, pancreatitis, etc...
- Monitor: LFT, TFT, PFT, ECG
Control

- Beta blockers
- Calcium channel blockers
- Amiodarone
- Digoxin
Beta blockers

- Class II, beta-1 antagonist
- Atenolol: 50-100mg daily
- Metoprolol: 20-200 mg daily
- Bisoprolol: 2.5-20 mg
- Nebivolol: 2.5-40 mg daily

Side effects general to drug class: bradycardia, hypotension, fatigue, dizziness, bronchospasm

No lab monitoring
Calcium channel blockers

- Class IV, prolongs AV refractory period
- Verapamil: 80-120 mg TID to QID
- Diltiazem: 30-420 mg, varies due to different formulations

Side effects general to drug class: bradycardia, AV block, hypotension, constipation
Monitor: BUN/Cr, LFTs
Digoxin

- Other, inhibits Na-K ATPase
- 0.125-0.5 mg daily
- Adverse effects: AV block, bradycardia, dizziness, headache, nausea/vomiting
- Monitor: Cr, electrolytes, drug level
AFFIRM Trial Results

Mortality: No difference

Strokes: No difference

Hospitalizations:*

4060 patients; enrolled 1995-99; age > 65 yrs or <65 yrs with HTN, CHF; AF duration > 6 hours

**PRIMARY ENDPOINT:** Mortality; **Secondary endpoints:** stroke, QOL

**RATE CONTROL:** Digoxin 51%, beta blockers 49%, Calcium channel blocker 41%, ablate and pace 5%

**RHYTHM CONTROL:** Amiodarone 39%, Sotalol 33%, Propafenone 10%, Procainamide 5%, Quinidine 5%

*AFFIRM Investigators* NEJM 2002; 347:1825-33
ATHENA

4628 patients with history of PAF/persistent AF; enrolled 2005-2006, follow-up for one year
> 70 yr old, HTN, DM, LAE and/or EF <40

**PRIMARY ENDPOINT:** first cardiovascular hospitalization or any cause death
Greatest benefit of Multaq demonstrated in stroke reduction and CV hospitalization

(Connolly 2009, Reynolds 2013, Hohnloser 2010, Torp-Pedersen 2011)
404 patients with persistent AF 2007-2008, aged >21, follow-up six mos

**PRIMARY ENDPOINT**: recurrent AF or premature study discontinuation

**MAIN SAFETY ENDPOINT**: occurrence of thyroid-, hepatic, pulmonary-, neurologic-, skin-, eye- or GI-specific events

(Le Huezey, 2010)
135 patients w/dual chamber pacemaker; follow-up 12 months

**PRIMARY ENDPOINT:** occurrence of atrial CV or cardiovascular hospitalization

**ADDTL OBSERVATION:** recurrence of ATA

(Capucci, 2008)
Treatment Drugs

- Quinidine
- Flecainide
- Propafenone
- Dronedarone
- Sotalol
- Dofetilide
Quinidine

- Class IA
- 200-600 mg, individualize dose
- Side effects: arrhythmias, AV block, hematologic, hypotension, GI, headache...
- Monitor: Cr, LFTs, ECG
Flecainide

- Class IC
- 50-300 mg daily, divided dose
- Side effects: arrhythmias, CHF, heart block, hematologic, dyspnea, headache, nausea, fatigue
- Monitor: Cr, electrolytes, ECG
Propafenone

• Class IC
• 150-300 mg daily, divided doses
• Side effects: arrhythmias, AV block, CHF, dizziness, constipation, headache...
• Monitor: electrolytes
Sotalol

- Class III, prolongs action potential
- 80-160 mg daily Q12 hrs
- Adverse effects: CHF, bradycardia, QT prolongation, dizziness, fatigue, diaphoresis
- Monitor: Cr, EKG for QT at initiation and with dose titration
Dofetilide

- Class III
- 500 mcg Q12
- Must be managed by cardiology and initiated in-hospital
- DC if QT longer than 500 ms or > 15% baseline
Dronedarone

- Properties of all four classes
- 400 mg BID
- Side effects: GI, CHF, bradycardia
- Monitor: BUN/Cr, ECG, LFT
Control

• Beta blockers (Class II)
• Calcium channel blockers (Class IV)
• Amiodarone (Class III)
How do I choose?

- Goal
- Comorbidities
- Side effect profile
- Cost
Anticoagulation

• Indication
  - arrhythmia
  - CHA2DS2VASC score
• Contraindications
  - adherence
  - fall risk
  - HASBLED score
Indication

- AVNRT, AVRT, AT do not need anticoagulation
- AFL with clear onset and no evidence of AF does not necessarily
- AF of brief duration or no CHA2DS2VASc does not
- AF with unknown onset, long duration and/or CHA2DS2VASc >2 does

(Sparks, 2001)
### CHA2DS2-VASc

<table>
<thead>
<tr>
<th>CHA2DS2-VASc Risk</th>
<th>Score</th>
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<tbody>
<tr>
<td>CHF or LVEF &lt;40%</td>
<td>1</td>
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<tr>
<td>Hypertension</td>
<td>1</td>
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<tr>
<td>Age &gt;75</td>
<td>2</td>
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<tr>
<td>Diabetes</td>
<td>1</td>
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<tr>
<td>Stroke/TIA/Thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>1</td>
</tr>
<tr>
<td>Age 65-74</td>
<td>1</td>
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<tr>
<td>Female</td>
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## CHA2DS2VASc

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<tr>
<th>CHA2DS2VASc Score</th>
<th>Adjusted stroke rate (%/year)</th>
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<tr>
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<td>8</td>
<td>6.7</td>
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<tr>
<td>9</td>
<td>15.2</td>
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Contraindications

- Medical nonadherence puts patient at greater risk than benefit
- Renal disease/valvular heart disease limits drug choice to warfarin
- Bleeding diathesis or liver failure
- Fall risk
- HASBLED score
# HAS-BLED

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
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<tbody>
<tr>
<td>Hypertension (systolic BP &gt; 160 mmHg)</td>
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<tr>
<td>Abnormal renal/liver function</td>
<td>1 point each</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding history or predisposition</td>
<td>1</td>
</tr>
<tr>
<td>Labile INR (unstable/high or &lt;60% time therapeutic)</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt;65</td>
<td>1</td>
</tr>
<tr>
<td>Drugs (anti-platelet) and/or ETOH</td>
<td>1 point each</td>
</tr>
</tbody>
</table>

(Pisters 2010)
Chronic anticoagulants

- Warfarin
- Apixaban (Eliquis)
- Dabigatran (Pradaxa)
- Rivaroxaban (Xarelto)
warfarin

- Vitamin k antagonist
- Indications: DVT, PE, thromboembolic risk w/AF/valve, MI/CVA
- Long onset, long half life (72-96 hrs, 20-60 hrs)
- Requires lab monitoring
- Cost effective
warfarin

- Many drug interactions
- Food interactions
- Variable once daily dosing
- Must hold 5 days prior to surgery
apixaban

- Factor Xa inhibitor
- Indication: reduce the risk of stroke and systemic embolism in non-valvular AF
- Rapid onset, short half-life (3-4 hrs, 6-12 hrs)
- No lab monitoring
- Costly
- Fewer drug interactions, few food interactions
- Twice daily dosing
dabigatran

- Direct thrombin inhibitor
- Indication: thromboembolic w/AF
- Rapid onset, short half life (1-2 hrs, 12-17 hrs)
- No lab monitoring
- Reasonable cost
- Fewer drug interactions, no food interactions
- Twice daily dosing
rivaroxaban

- Factor Xa inhibitor
- Indications: thromboembolic w/AF, DVT/PE
- Rapid onset, short half life (2-4 hrs, 5-9 hrs)
- No lab monitoring
- Costly
- Fewer drug interactions, no food interactions
- Once daily dosing
Efficacy vs bleeding

- rivaroxaban
- dabigatran
- apixaban
- warfarin

Legend:
- bleeding
- efficacy
In summary...

- Treat symptomatic SVT, consider referral to cardiology
- Control or treat AF and prevent risk of stroke
- Anticoagulate only those with true risk for thromboembolic event
References