Drug Therapy in Atrial Fibrillation: Options and Considerations

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Drug Therapy in Atrial Fibrillation: Options and Considerations

- **FINANCIAL DISCLOSURE:** No relevant financial relationship exists

- **UNLABELED/UNAPPROVED USES DISCLOSURE:** No unlabeled/unapproved uses exits
Objectives

• **Develop general understanding of AF**

• **Assess patient and develop strategy for rate and/or rhythm control**

• **Identify method of evaluating patient stroke risk**
You are an:

1. Inpatient provider
2. Outpatient provider

[Pie chart showing 79% Inpatient provider and 21% Outpatient provider]
Overview of AF

- Most common arrhythmia
- >3 million Americans have AF
- Increasing prevalence with age
- Affects 10% of population over 80 years old
- More common white, family history
- Symptomatic or asymptomatic
- Irregularly irregular, chaotic atrial activity > 300 bpm activity with no distinct P waves, frequently associated with rapid ventricular response
- Triggers and maintenance: enhanced automaticity, multiple wavelets reentry, electrical rotors and focal impulses
Overview of AF

- Substrate: shortening of ARP and non homogeneity, decrease velocity, patchy fibrosis, hypertrophy, apoptosis,
- Atrial mechanical dysfunction and enlargement
- Once atrial remodeling occurs, patients can become treatment refractory and are at increased risk for AF
- “AF begets AF”
- Ventricular myopathy in patients with inadequate rate control
- Early restoration of sinus rhythm may prevent further remodeling
Prevalence of atrial fibrillation by sex and age

Lifetime risk for developing atrial fibrillation (AF) from the Framingham Heart Study. Men and women without AF at 40 years of age were determined to have a 26 and 23 percent likelihood of developing incident AF by 80 years of age.

Overview of AF
Overview of AF

**Classification**

- **Paroxysmal** - self terminating or intermittent
- **Persistent** - fails to terminate within 7 days, often requires pharmacologic or electrical cardioversion
- **Permanent** - no longer pursuing rhythm control
- **Secondary** - setting of MI, surgery…
- **Nonvalvular or valvular** (rheumatic s/p valve replacement)
Stroke risk is a major concern managing AF

1. True
2. False
Overview of AF

*Initial Evaluation*

- History – symptoms, paroxysmal, persistent, chronic, duration, precipitating factors, contributing factors (HTN, CHD, RHD) modes of termination, comorbidities (heart disease, thyroid disease).
- Physical Exam – murmur, heart failure,
- EKG: Rhythm, Rate, LVH, pre-excitation, prior MI, intervals
- ECHO: valvular heart disease, atrial dimensions, LVEF, pulmonary HTN, LVH.
- Blood Tests: TSH, renal, hepatic function
Management: Rhythm or Rate Control

**AFFIRM Trial**

- Randomly assigned 4060 patients with recurrent AF to rate control or rhythm control
  - No significant difference in morbidity or mortality or quality of life (except ≥ 65 or HF, lower mortality with rate control)
  - Lower re-hospitalization in rate control
You are referred a 50 yo male with 7 days of symptomatic AF and VR 82 bpm on ASA and BB. No significant PMH.

Your plan:

1. Continue beta blocker and aspirin, schedule echo
2. Amiodarone and aspirin, schedule cardioversion
3. Xarelto and TEE/cardioversion
4. Flecainide, echo and schedule cardioversion
Management: Rhythm or Rate Control

NEWLY DISCOVERED AF

Paroxysmal
No therapy needed unless significant symptoms (e.g., hypotension, HF, angina pectoris)
Anticoagulation as needed

Persistent
Accept permanent AF
Anticoagulation and rate control* as needed

Rate control and anticoagulation as needed
Consider antiarrhythmic drug therapy
Cardioversion
Long-term antiarrhythmic drug therapy unnecessary
Management: Rhythm or Rate Control

RECURRENT PAROXYSMAL AF

- Minimal or no symptoms
  - Anticoagulation and rate control* as needed
    - No drug for prevention of AF

- Disabling symptoms in AF
  - Anticoagulation and rate control as needed
    - AAD therapy*
      - AF ablation if AAD treatment fails
Management: Rhythm or Rate Control

**RECURRENT PERSISTENT AF**
- Minimal or no symptoms: Anticoagulation and rate control* as needed
- Disabling symptoms in AF: Anticoagulation and rate control
  - AAD therapy*
  - Electrical cardioversion as needed

**PERMANENT AF**
- Anticoagulation and rate control* as needed

Consider ablation for severely symptomatic recurrent AF after failure of greater than or equal to 1 AAD plus rate control.
Management

**Vaughn Williams Classification**

- **I** – Sodium Channel Blockers
  - IA Procainamide, Disopyramide, Quinidine
  - IB Lidocaine, Mexiletine
  - IC Flecainide, Encainide, Propafenone
- **II** – Beta-blockers
- **III** – Potassium Channel Blockers
  - Sotalol, Dofetilide, Ibutilide, Amiodarone, Dronedarone
- **IV** – Calcium Channel Blockers
Action Potential
Rate Control in AF

**RACE II**

- 614 patients with permanent AF randomized to lenient (resting heart rate [HR] <110 beats/min) or strict (resting HR <80 beats/min, HR during moderate exercise <110 beats/min) rate control.

- QOL was assessed in 437 SF-36, AF severity scale, and Multidimensional Fatigue Inventory-20 (MFI-20) at baseline, 1 year, and end of study.

- No benefit in strict HR control as far as morbidity, mortality or quality of life
Rate Control in AF

Rate Control Benefits

• Avoid adverse effects, including proarrhythmia, with AAD
• Lower cost
• Less frequency of follow up
Rate Control in AF

Rate Control

- Beta Blockers
- Calcium Channel Blockers
- Digoxin
Rate Control in AF

**Metoprolol**

- Selective inhibitor of beta1-adrenergic receptors; competitively blocks beta1-receptors, with little or no effect on beta2-receptors at doses <100 mg PO
- **Metabolized**: Extensively hepatic via CYP2D6; significant first-pass effect (~50%)
- **Peak effect**: Oral: 1-2 hours
- **Duration**: Variable (dose-related); 50% reduction in maximum heart rate after single doses at 3.3- 6.4 hours, respectively), Extended release: ~24 hours; I.V.: 5-8 hours
Rate Control in AF

Metoprolol (tartrate, succinate)

- **Dosing**: I.V.: 2.5-5 mg every 2-5 minutes (maximum total dose: 15 mg over a 10-15 minute period). **Note**: Initiate cautiously in patients with concomitant heart failure; avoid in patients with decompensated heart failure.

- **Maintenance**: Oral (immediate release): 25-100 mg twice daily

- **Caution**: AV block, CHF, history anaphylaxis, bronchospasm, myasthenia gravis
Diltiazem

- Nondihydropyridine calcium channel blocker which inhibits calcium ion from entering the “slow channels” or select voltage-sensitive areas of vascular smooth muscle and myocardium during depolarization.

- Patients with impaired ventricular function and/or conduction abnormalities may have higher incidence of adverse reactions.

- **Onset of action**: Oral: Immediate release tablet: 30-60 minutes; I.V.: 3 minutes

- **Duration**: I.V.: Bolus: 1-3 hours; Continuous infusion (after discontinuation): 0.5-10 hours
Rate Control in AF

**Diltiazem**

- **Metabolism**: Hepatic (extensive first-pass effect); following single I.V. injection, plasma concentrations of N-monodesmethyldiltiazem and desacetyldiltiazem are typically undetectable; however, these metabolites accumulate following 24-hour constant rate infusion.

- **Half-life elimination**: Immediate release tablet: 3-4.5 hours, may be prolonged with renal impairment; Extended release tablet: 6-9 hours; Extended release capsules: 5-10 hours; I.V.: single dose: ~3.4 hours; continuous infusion: 4-5 hours
Rate Control in AF

*Diltiazem*

- **Dose:** Initial bolus dose: 0.25 mg/kg actual body weight over 2 minutes (average adult dose: 20 mg); ACLS guideline recommends 15-20 mg
- **Repeat bolus dose** (may be administered after 15 minutes if the response is inadequate): 0.35 mg/kg actual body weight over 2 minutes (average adult dose: 25 mg); ACLS guideline recommends 20-25 mg
- **Continuous infusion:** 5-15 mg/HR
- Conversion \([\text{rate (mg/hour)} \times 3 + 3] \times 10\).
- **PO total daily** 120-360 mg
Rate Control in AF

**Digoxin**

- Typically used in conjunction with other agents for rate control. Class IIb indication to use alone in rate control.
- Direct suppression of the AV node conduction to increase effective refractory period and decrease conduction velocity - positive inotropic effect, enhanced vagal tone, and decreased ventricular rate to fast atrial arrhythmias. Atrial fibrillation may decrease sensitivity and increase tolerance to higher serum digoxin concentrations.
Rate Control in AF

**Digoxin**

- **Atrial fibrillation (rate control) in patients with heart failure:** Loading: I.V.: 0.25 mg every 2 hours, up to 1.5 mg within 24 hours; for non acute situations, may administer 0.5 mg orally once daily for 2 days followed by oral maintenance dose. Maintenance dose: I.V., Oral: 0.125-0.375 mg once daily

- **If a loading dose is given:** Digoxin serum concentration may be drawn within 12-24 hours after the initial loading dose administration, otherwise, obtained after 3-5 days of therapy.
Rate Control in AF

**Digoxin**

- **Onset of action**: Heart rate control: Oral: 1-2 hours; I.V.: 5-60 minutes
- **Peak effect**: Heart rate control: Oral: 2-8 hours; I.V.: 1-6 hours, may be longer before rate control seen
- **Duration**: Adults: 3-4 days
- **Excretion**: Urine (50% to 70% as unchanged drug)
Rhythm Control in AF

**Benefit of rhythm control**

- Maintain atrial kick/ AV synchrony
- Exercise tolerance
- Prevention of atrial remodeling
- Prevent tachycardia mediated myopathy
- Does not reduced thromboembolic risk?
- Note:**AF > 48 Hr must be anticoagulated (therapeutic) for 3-4 weeks prior to chemical cardioversion/or TEE prior to initiation
Rhythm Control in AF

Maintenance of Sinus Rhythm

- No (or minimal) heart disease
  - Dronedarone
  - Flecaïnide
  - Propafenone
  - Sotalol
    - Amiodarone
    - Dofetilide
    - Catheter ablation

- Hypertension
  - Substantial LVH
    - No
      - Amiodarone
      - Catheter ablation
    - Yes
      - Dronedarone
      - Flecaïnide
      - Propafenone
      - Sotalol
        - Amiodarone

- Coronary artery disease
  - Dofetilide
  - Dronedarone
  - Sotalol
    - Amiodarone
    - Catheter ablation

- Heart failure
  - Amiodarone
  - Dofetilide
  - Catheter ablation
Rhythm Control in AF

**Class IA Procainamide**

- Used ACLS for irregular wide complex tachycardia (WPW), has also been for conversion AF to atrial flutter
- Sodium Channel Blocker/IKr effects
- **Metabolism:** Hepatically acetylated to N-acetyl procainamide which lacks the sodium channel activity of parent, but has IKr blocking effects – NAPA accumulates in renal failure. $t_{1/2} = 2.5-4.7\text{hr}$
- **Major side effects:** hypotension, torsades de pointes, positive ANA, Lupus like syndrome (10% of +ANA), nausea, bone marrow aplasia
Rhythm Control in AF

Class IA Procainamide

- **Therapeutic levels**: 4-8 mcg/ml of procainamide, but measure NAPA as well.

- **Dosing**: 1 gram at max rate of 50 mg/min do not exceed 17 mg/kg. Drip at 2-6 mg/min. PO dose up to 50 mg/kg/day in divided doses.
Rhythm Control in AF

Class IC Flecainide

• Sodium Channel Blocker/IKr blocker

• Metabolized: Renal/Hepatic: 25%/75%, t_{1/2} = 11hr.

• Major side effects: dizziness (up to 30%), can depress sinus node function (caution if starting in AF), nystagmus, blurred vision.

• Therapeutic levels: up to 1.0 mcg/ml. Toxic events usually associated with levels above 1. PR and QRS widening is expected to some degree but QRS>180msec is toxicity.
Rhythm Control in AF

**Class IC Flecainide**

- **Dosing**: 50-150mg BID. Can check levels or perform ETT to monitor QRS width at faster rates (QRS<150% baseline).
- *Give with AV nodal blocker*
- **Contraindicated** in structural heart disease, CAD
Rhythm Control in AF

**Class IC Flecainide 1:1 atrial flutter**
Rhythm Control in AF

**Class IC Propafenone**

- Sodium Channel Blocker/beta-blocker
- **Metabolized**: Hepatic (CYP2D6): 99%, $t_{1/2} = 2-32$ hr.
- **Major side effects**: dysgeusia (taste) (up to 25%), can depress sinus node function (caution if starting in AF).
- PR and QRS widening is expected to some degree (evidence of therapeutic effect). Can perform ETT to monitor QRS width at faster rates.
- **Dosing**: 150-300mg TID.
Rhythm Control in AF

Class IC Overdosage

![ECG Tracings](image-url)
Rhythm Control in AF

Class IC Overdosage

- QRS broadening
- Sine wave VT

Rx:
- NaHCO3 or hypertonic saline
- Beta-agonists
- Lidocaine (?)
- IABP
Rhythm Control in AF

**CAST Trial**

- Designed to test whether suppression of PVCs in a post-MI population would decrease the risk of SCD.
- Drugs: Flecainide, Encainide, Moricizine.
- 2309 patients – run-in period of suppression with each drug at increasing doses until PVCs were suppressed. Then randomized to continue or placebo.
- Increased mortality
Class III Sotalol

- IKr Blocker/beta-blocker
- Renal: >90%, $t_{1/2} = 10-20$ hr.
- Major side effects: fatigue, bradycardia, torsades de pointes (4% - risk factors: age, female, CHF, low EF, long QT at baseline, hypokalemia, ?LVH). QT prolongation by >25% or QT>500 should raise concern.
- “Reverse use dependence”, more pronounced QT lengthening at slower rates.
Rhythm Control in AF

Class III Sotalol

- AF: Poor for conversion – better for maintenance.
- Hospitalization required for initiation or dose increase.
- Dosing: 80-320mg BID (q 12 hrs).
## Class III Sotalol

<table>
<thead>
<tr>
<th>QTc Interval (msec)</th>
<th>Incidence of TdP</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;500</td>
<td>1.3% (1787)</td>
</tr>
<tr>
<td>500-525</td>
<td>3.4% (236)</td>
</tr>
<tr>
<td>525-550</td>
<td>5.6% (125)</td>
</tr>
<tr>
<td>&gt; 550</td>
<td>10.8% (157)</td>
</tr>
</tbody>
</table>

( ) Number of patients assessed

Sotalol package insert
Rhythm Control in AF

Class III Dofetilide

- IKr Blocker
- **Metabolism**: Hepatic/Renal: 30%/70%, $t_{1/2} = 8$-10hr.
- Possibly more AP prolongation in atria than ventricles
- Hepatic metabolism is via CYP3A4, verapamil increases drug levels by competition at renal transporter.
- **Major side effects**: torsades de pointes (1-3% - risk factors: age, female, CHF, low EF, long QT at baseline, bradycardia, hypokalemia). QTc prolongation of 15% or >500 requires dose adjustment.
Rhythm Control in AF

Class III Dofetilide

- “Reverse use dependence”
- Niche sought in low EF/CHF patients
- Hospitalization required for initiation or dose increase.
- Dosing: 125-500mcg BID (q 12hrs)
- Restricted prescribing
Rhythm Control in AF

**Class III Ibutilide**

- IKr Blocker

- **Metabolism**: Hepatic/Renal/Fecal: 74%/7%/19%, $t_{1/2} = 2-12$ hr.

- Hepatic metabolism is via CYP3A4, verapamil increases drug levels by competition at renal transporter.

- **Major side effects**: torsades de pointes up to 8% - with 1.7% requiring cardioversion. Events usually occur in first hour, but observation is recommended for 4hrs or until QT normalizes. Risk factors: hypoK, hypoMg, bradycardia, female.
Rhythm Control in AF

**Class III Ibutilide**

- **Dosing**: 1mg over 10min, 10min observation, 1mg over 10 minutes.
- Consider 2 grams Magnesium
- May be convenient for cardioversion without anesthesia available
Rhythm Control in AF

**Class III Amiodarone**

- IKr first IKs later, beta-blockade, Ca Channel Block, Na Channel Block
- **Metabolism**: Hepatic/Renal: 99%, $t_{1/2} = 3\text{-}15\text{wks.}$
- **Major side effects**: dermatologic, thyroid, ARDS, ocular, hepatic, pulmonary, neurologic,
- **Drug interactions**: with Coumadin, digoxin,
- “Drug of choice” for VT/VF arrest, also used in AF.
Rhythm Control in AF

Class III Amiodarone

- **Monitoring**: PFTs with DLCO, Ophthalmology, LFTs, TFTs required
- **Dosing**: atrial arrhythmias <200mg/d, ventricular 400mg/day.
Rhythm Control in AF

**Class III Dronedarone**

- Like amiodarone effects all AAD classes but without the iodine moiety. Shorter $t_{1/2}$ (13-19 Hrs) and can be loaded more easily than amiodarone.

- **Dose**: 400 mg BID

- **Metabolized**: predominantly by the liver (CYP3A4). It should not be administered with strong inhibitors of CYP3A4

- **Contraindicated**: Class IV HF, recent decompensation, AVB, SSS/bradycardia, permanent AF.
Class III Dronedarone

- **Monitor**: LFT particularly first 6 months, DOE evaluate for pulmonary toxicity

- *Cardiovert to SR if in AF as Dronedarone increased rates of heart failure, stroke, and death from cardiovascular causes in patients with permanent atrial fibrillation who were at risk for major vascular events. (Pallas Trial)*
Rhythm or Rate Control in AF

Pill in the Pocket

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage</th>
<th>Endpoint Time</th>
<th>ARR%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procainamide IV</td>
<td>1g/30min, 2mg/min Cl</td>
<td>1h</td>
<td>23</td>
</tr>
<tr>
<td>Amiodarone IV</td>
<td>5mg/kg bolus, 0.5mg/min Cl</td>
<td>8h</td>
<td>20</td>
</tr>
<tr>
<td>Ibutilide IV</td>
<td>1mg over 10’, rpt in 10’</td>
<td>60 min</td>
<td>24</td>
</tr>
<tr>
<td>Quinidine PO</td>
<td>300mg, 150mg q3hx4, 150mg q8</td>
<td>12h</td>
<td>19</td>
</tr>
<tr>
<td><strong>Flecainide</strong></td>
<td><strong>300mg x1</strong></td>
<td><strong>3h</strong></td>
<td><strong>39-41</strong></td>
</tr>
<tr>
<td><strong>Propafenone</strong></td>
<td><strong>600mg x1</strong></td>
<td><strong>8h</strong></td>
<td><strong>33-45</strong></td>
</tr>
<tr>
<td>Dofetilide PO</td>
<td>250mcg bid</td>
<td>30</td>
<td>11</td>
</tr>
</tbody>
</table>

Anticoagulation and Stroke Risk

*Tools to evaluate benefit and risk*

- CHADS2 score
- CHA2DS2VASc score
- HAS BLED
**CHADS2 Score**

- Points Annual Stroke Risk
  - 0  1.9%
  - 1  2.8%
  - 2  4.0%
  - 3  5.9%
  - 4  8.5%
  - 5  12.5%
  - 6  18.2%
Anticoagulation and Stroke Risk

**CHA2DS2VASc score**

- C-CHF/Left ventricular dysfunction 1
- H-Hypertension 1
- A2-Age≥75 2
- D-Diabetes mellitus 1
- S2-Stroke/TIA/TE (thromboembolism) 2
- V-Vascular disease-CAD, MI, PAD, or Ao plaque 1
- A-Age 65-74 1
- Sc-Sex category- Female gender 1
# Anticoagulation and Stroke Risk

**CHA2DS2VASc score**

<table>
<thead>
<tr>
<th>Score</th>
<th>Risk Percentage</th>
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<tbody>
<tr>
<td>1</td>
<td>1.3%</td>
</tr>
<tr>
<td>2</td>
<td>2.2%</td>
</tr>
<tr>
<td>3</td>
<td>3.2%</td>
</tr>
<tr>
<td>4</td>
<td>4.0%</td>
</tr>
<tr>
<td>5</td>
<td>6.7%</td>
</tr>
<tr>
<td>6</td>
<td>9.8%</td>
</tr>
<tr>
<td>7</td>
<td>9.6%</td>
</tr>
<tr>
<td>8</td>
<td>6.7%</td>
</tr>
<tr>
<td>9</td>
<td>15.2%</td>
</tr>
</tbody>
</table>
Anticoagulation and Stroke Risk

**HAS BLED**

- **Hypertension:** 1 point for uncontrolled SBP 160 or higher
- **Abnormal kidney and/or liver function:** 1 point each
- **Stroke:** 1 point for previous history of stroke
- **Bleeding:** 1 point bleeding, anemia or predisposition for
- **Labile INR:** 1 point for unstable or high INRs, poor TTR
- **Elderly:** 1 point for age 65 or older
- **Drugs +/- ETOH:** 1 point each for antiplatelet drugs and for consuming ETOH > 8 week
### HAS BLED

<table>
<thead>
<tr>
<th>Score</th>
<th>Risk</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>1.13</td>
</tr>
<tr>
<td>1</td>
<td>1.02</td>
</tr>
<tr>
<td>2</td>
<td>1.88</td>
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<tr>
<td>3</td>
<td>3.74</td>
</tr>
<tr>
<td>4</td>
<td>8.7</td>
</tr>
<tr>
<td>5</td>
<td>12.5...</td>
</tr>
</tbody>
</table>

>= score 3 is high risk
You are referred a 50 yo male with 7 days of symptomatic AF and VR 82 bpm on ASA and BB. No significant PMH. You plan:

1. Continue beta blocker and aspirin, schedule echo
2. Amiodarone and aspirin, schedule cardioversion
3. Xarelto and TEE/cardioversion
4. Flecainide, echo and schedule cardioversion
Summary

AF is the most common arrhythmia affecting more than 3 million Americans. Decisions surrounding management strategies are very complex and must take into account duration of AF, associated symptoms, comorbidities as well as stroke and bleeding risks.
Summary-Decreasing Readmissions

- Initial close follow-up, particularly for rate control
- Explicit patient instructions with prolonged episodes
- Accommodating outpatient electrical or chemical cardioversions +/- TEE
- Written protocols/algorithms
- “Pill-in-the-pocket” strategy
- Consider PVI ablation
References


References

- Groenveld, HF, Crijns, HJ, Van den Berg, MP, et. al. RACE II Investigators. The Effect of Rate Control on Quality of Life in Patients With Permanent Atrial Fibrillation: Data From the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation II) Study. *Journal of the American College of Cardiology*. 2011. 58 (17), 1795-1803.


- Lexicomp Drug information


- [www.uptodate.com](http://www.uptodate.com) Atrial fibrillation management
Additional Resources

- AHA: Guidelines for the Prevention of Stroke in Women: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association published online February 6, 2014; Print ISSN: 0039-2499. Online ISSN: 1524-4628 Stroke.


- [www.qtdrugs.org](http://www.qtdrugs.org)