Managing Atrial Fibrillation:
Rate vs. Rhythm Control and New Ways to Prevent Stroke

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Division of Cardiology, Section of Cardiac Electrophysiology
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Disclosures

- **Honoraria**
  - Medtronic, Abbott, Boston Scientific, Biotronik, Biosense-Webster, Janssen Pharmaceuticals, Bristol-Myers Squibb

- **Research Grants**
  - Biosense Webster, Biotronik

- **Equity**
  - Acutus Medical
Objectives

• Evaluate the importance and options for considering rate versus rhythm control in patients with atrial fibrillation

• Review novel therapy options for stroke risk reduction (left atrial appendage occlusion) in patients with AF
Atrial fibrillation (AF) is the most common cardiac arrhythmia.

In those older than 40 years of age, an estimated 1 in 4 lifetime risk.

Large projected increase in prevalence by the year 2050.
Two Pillars of AF Management

Rate vs. Rhythm Control (Symptoms)  OAC vs. LAAO (Stroke Risk Stratification)
Medical Management of Atrial Fibrillation

Controlling the ventricular rate and/or attempted maintenance of sinus rhythm
AF: Rate vs. Rhythm Control

• Two main therapeutic strategies
  • Rate control
    • Slow conduction of the ventricular response of AF through the AV node
  • Rhythm Control
    • Often cardioversion, with maintenance of sinus rhythm with anti-arrhythmic drugs
Key Points

• Almost everyone with a diagnosis of persistent AF deserves at least 1 attempt at maintaining sinus rhythm
  • Cardioversion + antiarrhythmic drug
  • Catheter ablation

• Atrial fibrillation has been associated with:
  • Heart failure
  • Mortality
  • Dementia
Rate Control Strategy

• In AF, ventricular rate is controlled by conduction properties of AV node
  • In untreated AF, ventricular rate can be high

• Main reasons for rate control
  • Avoidance of hemodynamic instability and/or symptoms
  • Avoidance of tachycardia-mediated cardiomyopathy
    • Some evidence for mortality benefit from rate control
### Summary of Recommendations for Rate Control

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control ventricular rate using a beta blocker or nondihydropyridine calcium channel antagonist for paroxysmal, persistent, or permanent AF</td>
<td>I</td>
<td>B</td>
<td>(93-95)</td>
</tr>
<tr>
<td>IV beta blocker or nondihydropyridine calcium channel blocker is recommended to slow ventricular heart rate in the acute setting in patients without pre-excitation. In hemodynamically unstable patients, electrical cardioversion is indicated</td>
<td>I</td>
<td>B</td>
<td>(96-99)</td>
</tr>
<tr>
<td>For AF, assess heart rate control during exertion, adjusting pharmacological treatment as necessary</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>A heart rate control (resting heart rate &lt;80 bpm) strategy is reasonable for symptomatic management of AF</td>
<td>IIa</td>
<td>B</td>
<td>(95,100)</td>
</tr>
<tr>
<td>IV amiodarone can be useful for rate control in critically ill patients without pre-excitation</td>
<td>IIa</td>
<td>B</td>
<td>(101-103)</td>
</tr>
<tr>
<td>AV nodal ablation with permanent ventricular pacing is reasonable when pharmacological therapy is inadequate and rhythm control is not achievable</td>
<td>IIa</td>
<td>B</td>
<td>(104-106)</td>
</tr>
<tr>
<td>A lenient rate-control strategy (resting heart rate &lt;110 bpm) may be reasonable when patients remain asymptomatic and LV systolic function is preserved</td>
<td>IIb</td>
<td>B</td>
<td>(100)</td>
</tr>
<tr>
<td>Oral amiodarone may be useful for ventricular rate control when other measures are unsuccessful or contraindicated</td>
<td>IIb</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>AV nodal ablation should not be performed without prior attempts to achieve rate control with medications</td>
<td>III: Harm</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>Nondihydropyridine calcium channel antagonists should not be used in decompensated HF</td>
<td>III: Harm</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>With pre-excitation and AF, digoxin, nondihydropyridine calcium channel antagonists, or amiodarone should not be administered</td>
<td>III: Harm</td>
<td>B</td>
<td>(107)</td>
</tr>
<tr>
<td>Dronedarone should not be used to control ventricular rate with permanent AF</td>
<td>III: Harm</td>
<td>B</td>
<td>(108,109)</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; AV, atrioventricular; bpm, beats per minute; COR, Class of Recommendation; HF, heart failure; IV, intravenous; LOE, Level of Evidence; LV, left ventricular; and N/A, not applicable.
# Rate Control Agents

**TABLE 9**  
Common Medication Dosage for Rate Control of AF

<table>
<thead>
<tr>
<th>Intravenous Administration</th>
<th>Usual Oral Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta blockers</strong></td>
<td></td>
</tr>
<tr>
<td>Metoprolol tartrate</td>
<td>2.5–5.0 mg IV bolus over 2 min; up to 3 doses</td>
</tr>
<tr>
<td>Metoprolol XL (succinate)</td>
<td>N/A</td>
</tr>
<tr>
<td>Atenolol</td>
<td>N/A</td>
</tr>
<tr>
<td>Esmolol</td>
<td>500 mcg/kg IV bolus over 1 min, then 50–300 mcg/kg/min IV</td>
</tr>
<tr>
<td>Propranolol</td>
<td>1 mg IV over 1 min, up to 3 doses at 2-min intervals</td>
</tr>
<tr>
<td>Nadolol</td>
<td>N/A</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>N/A</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Nondihydropyridine calcium channel antagonists</strong></td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>0.075–0.15 mg/kg IV bolus over 2 min; may give an additional 10.0 mg after 30 min if no response, then 0.005 mg/kg/min infusion</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>0.25 mg/kg IV bolus over 2 min, then 5–15 mg/h</td>
</tr>
<tr>
<td><strong>Digitalis glycosides</strong></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>0.25 mg IV with repeat dosing to a maximum of 1.5 mg over 24 h</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
</tr>
<tr>
<td>Amiodarone*</td>
<td>300 mg IV over 1 h, then 10–50 mg/h over 24 h</td>
</tr>
</tbody>
</table>

*Multiple dosing schemes exist for the use of amiodarone.

AF indicates atrial fibrillation; BID, twice daily; ER, extended release; IV, intravenous; N/A, not applicable; QD, once daily; QID, 4 times a day; and TID, 3 times a day.
Rate Control Agents

• Beta Blockers
  • Widely used as primary therapy for rate control
    • Decrease resting heart rate
    • Blunt heart rate response to exercise
  • Additional properties- more preferable
    • AF with reduced LVEF, may improve LVEF and decrease hospitalization for CHF and death

• Calcium Channel Blockers
  • Verapamil and diltiazem- negative inotropy
    • Caution in Heart Failure
Rate Control Agents

- **Digoxin**
  - Generally not as effective as BB or CCB
  - Concern for association with higher mortality in observational studies
  - Often reserved for patients with AF and CHF

- **Amiodarone**
  - Rhythm control agent, but can slow the ventricular rate
  - Often used in critically ill patients, hypotension
  - Long-term risk of side effects - 2nd line for rate control
Rhythm Control Strategy

• Persistent symptoms
  • Palpitations, dyspnea, light-headedness, heart failure
  • Despite adequate rate control

• Inability to attain adequate rate control

• Patient preference
  • Symptoms
  • Association with heart failure, other outcomes such as mortality
## Class IA Agents - Rarely Used

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Doses</th>
<th>Exclude/Use With Caution</th>
<th>Major Pharmacokinetic Drug Interactions</th>
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<tr>
<td><strong>Vaughan Williams class IA</strong></td>
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</table>
| Disopyramide                  | • Immediate release: 100–200 mg once every 6 h  
• Extended release: 200–400 mg once every 12 h | • HF                                           | • Metabolized by CYP3A4: caution with inhibitors (e.g., verapamil, diltiazem, ketoconazole, macrolide antibiotics, protease inhibitors, grapefruit juice) and inducers (e.g., rifampin, phenobarbital, phenytoin) |
|                              |                                | • Prolonged QT interval                       |                                                                                                         |
|                              |                                | • Prostatism, glaucoma                        |                                                                                                         |
|                              |                                | • Avoid other QT interval–prolonging drugs     |                                                                                                         |
| Quinidine                     | • 324–648 mg every 8 h         | • Prolonged QT interval                       | • Inhibits CYP2D6: ↑ concentrations of tricyclic antidepressants, metoprolol, antipsychotics; ↓ efficacy of codeine |
|                              |                                | • Diarrhea                                     | • Inhibits P-glycoprotein: ↑ digoxin concentration                                                      |
## Class IC Agents

<table>
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<tr>
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<tbody>
<tr>
<td><strong>Vaughan Williams class IC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flecainide</td>
<td>50-200 mg once every 12 h</td>
<td>Sinus or AV node dysfunction, HF, CAD, Atrial flutter, Infranodal conduction disease, Brugada syndrome, Renal or liver disease</td>
<td>Metabolized by CYP2D6 (inhibitors include quinidine, fluoxetine, tricyclics; also genetically absent in 7%-10% of population) and renal excretion (dual impairment can ↑↑ plasma concentration)</td>
</tr>
<tr>
<td>Propafenone</td>
<td>Immediate release: 150-300 mg once every 8 h, Extended release: 225-425 mg once every 12 h</td>
<td>Sinus or AV node dysfunction, HF, CAD, Atrial flutter, Infranodal conduction disease, Brugada syndrome, Liver disease, Asthma</td>
<td>Metabolized by CYP2D6 (inhibitors include quinidine, fluoxetine, tricyclics; also genetically absent in 7%-10% of population)—poor metabolizers have ↑β blockade, Inhibits P-glycoprotein: ↑digoxin concentration, Inhibits CYP2C9: ↑warfarin concentration (↑INR 25%)</td>
</tr>
</tbody>
</table>
Class IC Agents

- Caution in heart failure population
  - Particularly depressed LV function
- Caution in CAD population
- Best to use AV nodal blocking agent in addition
  - Can organize to atrial flutter (slower), and have 1:1 conduction to the ventricle
# Class III Agents

<table>
<thead>
<tr>
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<td><strong>Vaughan Williams class III</strong></td>
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| Amiodarone    | - Oral: 400–600 mg daily in divided doses for 2–4 wk; maintenance typically 100–200 mg QD  
- IV: 150 mg over 10 min; then 1 mg/min for 6 h; then 0.5 mg/min for 18 h or change to oral dosing; after 24 h, consider decreasing dose to 0.25 mg/min | - Sinus or AV node dysfunction  
- Infranodal conduction disease  
- Lung disease  
- Prolonged QT interval | - Inhibits most CYPs to cause drug interaction:  
  ↑ concentrations of warfarin (↑INR 0%–200%), statins, many other drugs  
  Inhibits P-glycoprotein: ↑digoxin concentration |
| Dofetilide    | - 125–500 mcg once every 12 h                     | - Prolonged QT interval  
- Renal disease  
- Hypokalemia  
- Hypomagnesemia  
- Diuretic therapy  
- Avoid other QT interval–prolonging drugs | - Primary renal elimination involving glomerular filtration and active tubular secretion: verapamil, HCTZ, cimetidine, ketoconazole, trimethoprim, prochlorperazine, and megestrol are contraindicated; discontinue amiodarone at least 3 mo before initiation |
| Dronedarone   | - 400 mg once every 12 h                         | - Bradycardia  
- HF  
- Long-standing persistent AF/flutter  
- Liver disease  
- Prolonged QT interval | - Metabolized by CYP3A: caution with inhibitors (e.g., verapamil, diltiazem, ketoconazole, macrolide antibiotics, protease inhibitors, grapefruit juice) and inducers (e.g., rifampin, phenobarbital, phenytoin)  
  Inhibits CYP3A, CYP2D6, P-glycoprotein:  
  ↑ concentrations of some statins, sirolimus, tacrolimus, beta blockers, digoxin |
| Sotalol       | - 40–160 mg once every 12 h                      | - Prolonged QT interval  
- Renal disease  
- Hypokalemia  
- Hypomagnesemia  
- Diuretic therapy  
- Avoid other QT interval–prolonging drugs  
- Sinus or AV nodal dysfunction  
- HF  
- Asthma | - None (renal excretion) |
Amiodarone

- Very frequently used, especially in critically ill and CHF population

- Drug Interactions
  - Coumadin
  - Many other drugs

- Monitor for organ toxicity, particularly long term
  - Thyroid
  - Liver
  - Lung
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<td>IV: 150 mg over 10 min; then 1 mg/min for 6 h; then 0.5 mg/min for 18 h or change to oral dosing; after 24 h, consider decreasing dose to 0.25 mg/min</td>
<td>Infra-nodal conduction disease</td>
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<td></td>
<td>Lung disease</td>
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<td></td>
<td>Hypomagnesemia</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Diuretic therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Avoid other QT interval—prolonging drugs</td>
<td></td>
</tr>
<tr>
<td>Dronedarone</td>
<td>400 mg once every 12 h</td>
<td>Bradycardia</td>
<td>Metabolized by CYP3A: caution with inhibitors (e.g., verapamil, diltiazem, ketoconazole, macrolide antibiotics, protease inhibitors, grapefruit juice) and inducers (e.g., rifampin, phenobarbital, phenytoin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HF</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Long-standing persistent AF/flutter</td>
<td>Inhibits CYP3A, CYP2D6, P-glycoprotein: †concentrations of some statins, sirolimus, tacrolimus, beta blockers, digoxin</td>
</tr>
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<td></td>
<td></td>
<td>Liver disease</td>
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</tr>
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<td>Prolonged QT interval</td>
<td></td>
</tr>
<tr>
<td>Sotalol</td>
<td>40–160 mg once every 12 h</td>
<td>Prolonged QT interval</td>
<td>None (renal excretion)</td>
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<td></td>
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<td>Sinus or AV nodal dysfunction</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>HF</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Asthma</td>
<td></td>
</tr>
</tbody>
</table>
DIAMOND: sinus rhythm and mortality

- 506 pts with LV dysfunction
- Randomized to Dofetilide or Placebo
- No effect on mortality
- Effect of SR on mortality RR 0.44 (0.30-0.64)

Survival according to rhythm

Survival according to Rx

Pedersen et al. Circulation 2001;104:292
Dofetilide

- Requires hospital stay
  - Usually 3 days, 5 doses
- Drug Contraindications
  - Verapamil
  - HCTZ
  - Azoles
  - Bactrim (Trimethoprim)
- Dose adjustment and be careful
  - Renal dysfunction
  - QT prolongation
# Class III Agents

<table>
<thead>
<tr>
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• Infra nodal conduction disease  
• Lung disease  
• Prolonged QT interval | • Inhibits most CYPs to cause drug interaction:  
↑ concentrations of warfarin (↑ INR 0%–200%), statins, many other drugs  
• Inhibits P-glycoprotein: ↑ digoxin concentration |
| Dofetilide    | • 125–500 mcg once every 12 h                                                | • Prolonged QT interval  
• Renal disease  
• Hypokalemia  
• Hypomagnesemia  
• Diuretic therapy  
• Avoid other QT interval–prolonging drugs | • Primary renal elimination involving glomerular filtration and active tubular secretion: verapamil, HCTZ, cimetidine, ketoconazole, trimethoprim, prochlorperazine, and megestrol are contraindicated; discontinue amiodarone at least 3 mo before initiation |
| Dronedarone   | • 400 mg once every 12 h                                                     | • Bradycardia  
• HF  
• Long-standing persistent AF/flutter  
• Liver disease  
• Prolonged QT interval | • Metabolized by CYP3A: caution with inhibitors (e.g., verapamil, diltiazem, ketoconazole, macrolide antibiotics, protease inhibitors, grapefruit juice) and inducers (e.g., rifampin, phenobarbital, phenytoin)  
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• HF  
• Asthma | • None (renal excretion) |

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*Note: The table provides a general overview of Class III agents, their usual doses, considerations for use, and potential drug interactions. Always consult a healthcare professional for specific guidance.*
ATHENA: Reduction in Time to 1st CV Hospitalization or Death

**Cumulative Incidence of Primary Outcome (%)**

- **Placebo (n = 2327)**
- **Dronedarone (n = 2301)**

**Months**

24% Relative risk reduction
Primarily related to ↓CV hospitalization

HR = 0.76
P < 0.001

ANDROMEDA: Study Primary Endpoint and Results

- **Primary endpoint**
  - The primary composite endpoint was all-cause mortality or hospitalization for HF vs placebo

- **Results**

<table>
<thead>
<tr>
<th>Analysis Up to Study Discontinuation</th>
<th>Placebo (n = 317)</th>
<th>Dronedarone 800 mg/day (n = 310)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients who died</strong></td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td><strong>Relative risk (relative to placebo)</strong></td>
<td></td>
<td>2.13</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>1.07, 4.25</td>
</tr>
<tr>
<td><em>P value</em></td>
<td></td>
<td>.03</td>
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<td>None (renal excretion)</td>
</tr>
</tbody>
</table>
Sotalol

- Consider hospital stay
  - Loading like Dofetilide, many start as outpatient
- Dose adjustment and be careful
  - Renal dysfunction
  - QT prolongation
- Caution in LVH (Interventricular septum 1.5 cm or greater)
- Safe to use in coronary artery disease
**Figure 2** Strategies for rhythm control in patients with paroxysmal* and persistent AF.†

*Catheter ablation is only recommended as first-line therapy for patients with paroxysmal AF (Class IIa recommendation).
†Drugs are listed alphabetically.
‡Depending on patient preference when performed in experienced centers.
§Not recommended with severe LVH (wall thickness >1.5 cm).
||Should be used with caution in patients at risk for torsades de pointes ventricular tachycardia.
¶Should be combined with AV nodal blocking agents.
AF indicates atrial fibrillation; AV, atrioventricular; CAD, coronary artery disease; HF, heart failure; and LVH, left ventricular hypertrophy.
Catheter Ablation

• Best proven way to maintain sinus rhythm in patients with AF
  • Symptomatic relief
  • Reduction in heart failure
  • Can be done safely
Atrial Fibrillation Ablation

• Targets
  • Elimination of triggers
    • Most commonly triggers from pulmonary veins
  • Modifying atrial substrate responsible for AF maintenance

• Goal
  • Improve patient symptoms
    • AF burden reduction
Estimates of All-Cause Mortality Risk (ITT)

Ablation vs. Drug
Hazard ratio: 0.85 (95% CI, 0.60–1.21)
P = 0.377

Number at risk
Ablation: 1108, 1058, 1035, 1013, 933, 814, 724, 632, 555, 455, 332

Figure 2. Atrial Fibrillation Effect on Quality of Life (AFEQT) Summary Scores

(A) Mean AFEQT summary score

(B) Between-group AFEQT summary score difference

<table>
<thead>
<tr>
<th>Interval, mo</th>
<th>No. of Patients Ablation (n=1108)</th>
<th>No. of Patients Drug Rx (n=1096)</th>
<th>Adjusted Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1084</td>
<td>1078</td>
<td>-0.2 (-1.9 to 1.5)</td>
</tr>
<tr>
<td>3</td>
<td>971</td>
<td>983</td>
<td>3.0 (1.3 to 4.7)</td>
</tr>
<tr>
<td>12</td>
<td>915</td>
<td>903</td>
<td>5.3 (3.7 to 6.9)</td>
</tr>
<tr>
<td>24</td>
<td>856</td>
<td>798</td>
<td>4.3 (2.7 to 6.0)</td>
</tr>
<tr>
<td>36</td>
<td>645</td>
<td>605</td>
<td>2.5 (0.8 to 4.1)</td>
</tr>
<tr>
<td>48</td>
<td>476</td>
<td>473</td>
<td>3.0 (1.1 to 4.9)</td>
</tr>
<tr>
<td>60</td>
<td>329</td>
<td>320</td>
<td>2.6 (0.3 to 4.8)</td>
</tr>
<tr>
<td>All</td>
<td>4192</td>
<td>4082</td>
<td>3.4 (2.1 to 4.8)</td>
</tr>
</tbody>
</table>

A COMPARISON OF RATE CONTROL AND RHYTHM CONTROL IN PATIENTS WITH ATRIAL FIBRILLATION

The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators*
AFFIRM – Study Overview

• Comparison of two treatment strategies for patients with atrial fibrillation needing treatment
  Rate control and anticoagulation
  Rhythm control and anticoagulation

• Multicenter, randomized trial

• Patients with atrial fibrillation and risk factors predicting a high risk for stroke and death

• Null hypothesis: survival is equal with the two treatment strategies
**Initial Therapy**

- **Rate arm**
  - Digoxin: 51%
  - Beta adrenergic blockers: 49%
  - Calcium channel blockers: 41%

- **Rhythm arm**
  - Amiodarone: 39%
  - Sotalol: 33%
  - Propafenone: 10%
  - Procainamide: 6%
  - Quinidine: 5%
  - Flecainide: 5%
  - Disopyramide: 2%
  - Moricizine: 1%
Primary Endpoint: All-Cause Mortality

\[ p = 0.058 \]

<table>
<thead>
<tr>
<th>Time (Years)</th>
<th>Rhythm N:</th>
<th>Rate N:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2033</td>
<td>2027</td>
</tr>
<tr>
<td>1</td>
<td>1932</td>
<td>1925</td>
</tr>
<tr>
<td>2</td>
<td>1807</td>
<td>1825</td>
</tr>
<tr>
<td>3</td>
<td>1316</td>
<td>1328</td>
</tr>
<tr>
<td>4</td>
<td>780</td>
<td>774</td>
</tr>
<tr>
<td>5</td>
<td>255</td>
<td>236</td>
</tr>
</tbody>
</table>
Stroke Risk Reduction in Atrial Fibrillation

Oral Anticoagulation and Left Atrial Appendage Occlusion
AF and Stroke

• AF is the most common cause of embolic stroke\(^1\)
• 15% of all strokes in the US can be attributed to AF\(^1\)
• AF is associated with an increase in mortality, from 1.3-2 times\(^2\)

AF and Stroke
Appropriate Prescription of OAC Across the Spectrum of Stroke Risk in AF

How are cardiovascular specialists in the United States doing in the real world?
Therapy Summary- The New

- **CHA2DS2-VASc ≥2**
  - Oral anticoagulation with warfarin or NOAC

- **CHA2DS2-VASc =1**
  - Oral anticoagulation with warfarin or NOAC or
  - ASA
  - Consider bleeding risk, compliance, patient preference

- **CHA2DS2-VASc =0**
  - No therapy or ASA
Lack of Appropriate OAC

Research

Original Investigation

Oral Anticoagulant Therapy Prescription in Patients With Atrial Fibrillation Across the Spectrum of Stroke Risk Insight

- >400,000 patients with AF
- Large, real-world population
- 2008-2012
- >100 practices, academic + private
- Treated by cardiologist
Oral Anticoagulant Use Does Not Top 50%, Even in the Highest Stroke Risk AF Patients

38-40% of patients at moderate to high risk of stroke treated with Aspirin alone, not OAC!
Underuse of Vitamin K Antagonist and Direct Oral Anticoagulants for Stroke Prevention in Patients With Atrial Fibrillation: A Contemporary Review

Jonathan C. Hsu and James V. Freeman

Atrial fibrillation (AF) is a leading cause of stroke. Oral anticoagulant (OAC) therapy can significantly reduce the risk of stroke in patients with AF, but underuse of OACs for stroke prevention continues to be a serious clinical problem, with significant deleterious impact on outcomes. We review the studies demonstrating OAC underutilization and evaluating strategies for promoting the increased use of OAC therapy for stroke prevention in nonvalvular AF (NVAF) patients, including in special patient populations.

STROKE PREVENTION FOR AF
AF is the most common cardiac arrhythmia, and worldwide prevalence continues to increase. As of 2010, AF affected an estimated 33.5 million individuals globally, with higher prevalence in the US and Europe compared with developing countries. AF significantly increases the risk and severity of stroke, which repre-
Left Atrial Appendage Occlusion Devices for Stroke Prevention in AF

An opportunity to fill treatment gaps in stroke risk reduction practices?
Role of LAA

Source of over 90% of thrombus in nonvalvular AF

One of the main goals with AF treatment:

- Reduce the rate of systemic embolism
  - Particularly stroke
- Most patients require chronic anticoagulation
  - Except those deemed to be at very low risk for embolic events

Not all AF patients can, or are willing to take oral anticoagulation despite risk of stroke
LAA Occlusion- WATCHMAN

- Manufactured by Boston Scientific
- Recent FDA approval 3/13/15
- Left atrial appendage occlusion device
  - Implanted with transseptal puncture and TEE guidance
- Goal
  - Reduce stroke risk
  - Comparator
    - Warfarin anticoagulation
Left atrial appendage closure

A device is placed in the left atrial appendage to close it off from the rest of the left atrium.
PROTECT-AF Long Term F/U

Original Investigation

Percutaneous Left Atrial Appendage Closure vs Warfarin for Atrial Fibrillation
A Randomized Clinical Trial

Vivek Y. Reddy, MD; Horst Sievert, MD; Jonathan Halperin, MD; Shephal K. Doshi, MD; Maurice Buchbinder, MD; Petr Neuzil, MD, PhD; Kenneth Huber, MD; Brian Whisenant, MD; Saibal Kar, MD; Vijay Swarup, MD; Nicole Gordon, BSEE; David Holmes, MD; for the PROTECT AF Steering Committee and Investigators

**IMPORANTACE** While effective in preventing stroke in patients with atrial fibrillation (AF), warfarin is limited by a narrow therapeutic profile, a need for lifelong coagulation monitoring, and multiple drug and diet interactions.

**OBJECTIVE** To determine whether a local strategy of mechanical left atrial appendage (LAA) closure was noninferior to warfarin.

### Table 2. Intention-to-Treat Primary Efficacy and Safety Outcomes According to Treatment Group by Bayesian Model

<table>
<thead>
<tr>
<th>Event</th>
<th>Device Group (n = 463)</th>
<th>Warfarin Group (n = 244)</th>
<th>Device/Warfarin Rate Ratio (95% Credible Interval)</th>
<th>Posterior Probabilities, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events/Patient-Years</td>
<td>Observed Rate(^a)</td>
<td>Events/Patient-Years</td>
<td>Observed Rate(^a)</td>
</tr>
<tr>
<td>Primary efficacy end point(^b)</td>
<td>39/1720.2</td>
<td>2.3 (1.7-3.2)</td>
<td>34/900.8</td>
<td>3.8 (2.5-4.9)</td>
</tr>
<tr>
<td>Stroke</td>
<td>26/1720.7</td>
<td>1.5 (1.0-2.2)</td>
<td>20/900.9</td>
<td>2.2 (1.3-3.1)</td>
</tr>
<tr>
<td>Ischemic</td>
<td>24/1720.8</td>
<td>1.4 (0.9-2.1)</td>
<td>10/904.2</td>
<td>1.1 (0.5-1.7)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>3/1774.2</td>
<td>0.2 (0.0-0.4)</td>
<td>10/916.2</td>
<td>1.1 (0.5-1.8)</td>
</tr>
<tr>
<td>Disabling(^c)</td>
<td>8/1771.3</td>
<td>0.5 (0.2-0.8)</td>
<td>11/912.7</td>
<td>1.2 (0.6-1.9)</td>
</tr>
<tr>
<td>Nondisabling(^c)</td>
<td>18/1723.7</td>
<td>1.0 (0.7-1.7)</td>
<td>9/907.7</td>
<td>1.0 (0.4-1.7)</td>
</tr>
<tr>
<td>Systemic embolization</td>
<td>3/1773.6</td>
<td>0.2 (0.0-0.4)</td>
<td>0/919.5</td>
<td>0</td>
</tr>
<tr>
<td>Cardiovascular or unexplained death</td>
<td>17/1774.3</td>
<td>1.0 (0.6-1.5)</td>
<td>22/919.4</td>
<td>2.4 (1.4-3.4)</td>
</tr>
<tr>
<td>Primary safety end point(^d)</td>
<td>60/1666.2</td>
<td>3.6 (2.8-4.6)</td>
<td>27/878.2</td>
<td>3.1 (2.0-4.3)</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

\(^a\) Events per 100 patient-years (95\% credible interval).

\(^b\) Primary efficacy defined as composite of stroke, systemic embolization, or cardiovascular/unexplained death.

\(^c\) Disabling or fatal strokes were those with a Modified Rankin Score of 3-6 after the stroke. Nondisabling strokes were those with Modified Rankin Scores of 0-2 after the stroke.

\(^d\) Safety defined as procedure-related events (pericardial effusion requiring intervention or prolonged hospitalization, procedure-related stroke, or device embolization) and major bleeding (intracranial or bleeding requiring transfusion).
WATCHMAN- FDA Approval

- Increased risk for stroke based on CHADS$_2$ or CHA$_2$DS$_2$-VASc scores and are recommended for anticoagulation therapy
- Are deemed by their physicians to be suitable for warfarin
- Have an appropriate rationale to seek a non-pharmacologic alternative to warfarin
Summary

• Two methods for approaching medical therapy of AF
  • Rate control
  • Rhythm control

• Need to consider stroke risk in patients with AF - OAC vs. LAAO

• Symptoms and patient/physician preference important
THANK YOU

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Twitter: @JonHsuMD