Atrial Fibrillation

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Disclosure Statement of Financial Interest

I do not have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.
Objectives

• Common risk factors leading to atrial fibrillation
• Initial evaluation and management
• Strategies for thromboembolism prophylaxis
• Cardiology consultation
The estimated US prevalence of atrial fibrillation (AF) in the year 2050 ranges from 5.6 million to as high as 15.9 million individuals.

Lifetime risk for developing atrial fibrillation (AF) from the Framingham Heart Study

Implications of Increasing AF Prevalence

- Heart failure
  - AF → tripling of mortality

- Impaired cognitive function
  - 10% at 5 years
  - 3-fold mortality

- Stroke
  - Nonvalvular AF → ~ 5-fold increased risk of stroke
  - Greater severity → greater disability → greater mortality

- QOL limitations
  - Physical, mental, cognitive & social

- Healthcare cost
  - 73% higher medical costs → $8075 → $6-26 billion

Mechanisms of Atrial Fibrillation

J Am Coll Cardiol. 2014;64(21):2246-2280. doi:10.1016/j.jacc.2014.03.021
The population-attributable risk of atrial fibrillation in men and women determined from a community-based longitudinal study. For both men and women, a substantial portion of atrial fibrillation risk remains unexplained.

Risk Factors for Atrial Fibrillation

- Age
- Male sex
- Obesity
- Hypertension
- Diabetes mellitus
- Myocardial infarction
- Heart failure
- Valvular heart disease
- Cardiac surgery
ARIC: % “Optimal” Risk Factor Modification

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>White Women (5788)</th>
<th>White Men (5145)</th>
<th>Black Women (2266)</th>
<th>Black Men (1399)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (SD)</td>
<td>54.2 (5.8)</td>
<td>54.0 (5.7)</td>
<td>54.8 (5.7)</td>
<td>53.3 (5.7)</td>
<td>53.9 (6.0)</td>
</tr>
<tr>
<td>BP %</td>
<td>38.5</td>
<td>47.2</td>
<td>41.1</td>
<td>21.3</td>
<td>21.2</td>
</tr>
<tr>
<td>BMI %</td>
<td>33.3</td>
<td>46.3</td>
<td>27.0</td>
<td>17.5</td>
<td>30.2</td>
</tr>
<tr>
<td>DM %</td>
<td>51.8</td>
<td>61.7</td>
<td>43.6</td>
<td>48.7</td>
<td>46.1</td>
</tr>
<tr>
<td>Smoking %</td>
<td>41.6</td>
<td>50.8</td>
<td>28.0</td>
<td>57.6</td>
<td>28.2</td>
</tr>
<tr>
<td>Cardiac Dz %</td>
<td>91.8</td>
<td>94.2</td>
<td>89.7</td>
<td>90.4</td>
<td>92</td>
</tr>
</tbody>
</table>

BP: < 120/80 mmHg  
BMI: < 25 kg/m²  
DM: Fasting BG < 100 mg/dL  
Tobacco: Never  
Cardiac Disease: No HF or CAD
Survival curves adjusted for age, study center, education, and height showing time free from atrial fibrillation (AF) according to risk factor group (optimal, borderline, or elevated) in white women (A), white men (B), black women (C), and black men (D).

Age-adjusted incidence rates:
(Per 1000 person years)
White men – 7.45
White women – 4.59
Black men – 5.27
Black women – 3.67

Risk Factors:
1. Elevated BMI
2. DM
3. HTN
4. Prior cardiac disease

## ARIC: 1987 - 2007

<table>
<thead>
<tr>
<th>Risk Profile</th>
<th>Total</th>
<th>Incident AF</th>
<th>Incidence Rate</th>
<th>RH (95% C.I.)</th>
<th>PAF %</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal RFs</td>
<td>794</td>
<td>31</td>
<td>2.19</td>
<td>0.33 (0.23-0.47)</td>
<td>0.00</td>
<td>...</td>
</tr>
<tr>
<td>Borderline RFs Only</td>
<td>4064</td>
<td>288</td>
<td>3.68</td>
<td>0.50 (0.44-0.57)</td>
<td>6.53</td>
<td>1.28-11.3</td>
</tr>
<tr>
<td>Elevated RFs</td>
<td>9740</td>
<td>1201</td>
<td>6.59</td>
<td>1 (Reference)</td>
<td>50.0</td>
<td>37.5-58.5</td>
</tr>
</tbody>
</table>

**Incidence Rate**: The incidence rate of AF per 1000 person-years adjusted for age (mean 54.2)

**RH**: Relative hazard adjusted for age, study site, education, income and height

**PAF**: Population-attributable fraction for AF by race and gender
Prevention of Atrial Fibrillation

- Modification of cardiovascular risk factors (especially hypertension)
- Weight loss
- Physical activity
- Moderation of alcohol consumption
- Dietary modification
  - Mediterranean diet
  - Extra virgin olive oil
  - N-3 polyunsaturated fatty acids

Pathak, JACC 2014; 64(21):2222-31
Estruch, NEJM 2013; 368(14):1279
Initial Evaluation

• Types of atrial fibrillation
• History & physical
• ECG
• Presence of symptoms
• Association with diseases
Types of Atrial Fibrillation (A Progressive Disease)

• Paroxysmal atrial fibrillation
  • Terminates spontaneously or with intervention within 7 days of onset

• Persistent atrial fibrillation
  • Fails to terminate within 7 days

• Long-standing persistent atrial fibrillation
  • AF lasting more than 12 months

• Permanent atrial fibrillation
  • Persistent AF with decision to abandon rhythm control strategy
Valvular vs Non-valvular Atrial Fibrillation

• Distinction remains a matter of debate – determination of thromboembolic risk in AF

• Valvular AF
  • Mitral stenosis
  • Prosthetic heart valves
  • Anticoagulation with VKA

• Non-valvular AF
  • The remainder of AF
  • Valvular heart disease (aortic stenosis/regurgitation & mitral regurgitation) – normal flow in LA – responsive to thromboembolism prophylaxis with DOACs

History

• Symptoms
  • Palpitations, fatigue, dyspnea, lightheadedness, chest pain, declining stamina

• Precipitating factors
  • Exercise, emotion, alcohol

• Disease association
  • History of cardiac pathology
    • Coronary artery disease, valvular heart disease & congestive heart failure
  • Hypertension, DM, COPD, obstructive sleep apnea
  • Hyperthyroidism
  • Excessive alcohol ingestion
Physical Examination

- Valvular heart disease
  - Mitral stenosis
- Congestive heart disease
  - Elevated JVP
  - Pulmonary edema
  - Lower extremity edema
12-Lead ECG

- Documentation of atrial fibrillation – establish diagnosis
- ECGs for both atrial fibrillation & sinus rhythm
- ECG data
  - Nonelectrical cardiac disease (LVH & pathological Q waves)
  - Electrical cardiac disease (ventricular pre-excitation & infranodal conduction disease)
  - QT interval – potential risk of antiarrhythmic therapy
  - Severe bradycardia and sinus node dysfunction
Diagnostic Tests

- ECG
- Echocardiogram
  - Atrial dimensions
  - LV and RV size and function
  - Hypertensive heart disease (LVH & diastolic dysfunction)
  - Valvular heart disease (mitral stenosis)
  - Pulmonary hypertension
  - Pericardial disease
- TSH & free T4
  - Clinical/subclinical hyperthyroidism – < 5% of AF population
  - Patients with 1st episode of AF or increase in AF frequency
- Cardiac rhythm monitor
  - AF burden
  - Other arrhythmias (atrial flutter, bradycardia & heart block)
  - Ventricular rate control
What is the left atrial appendage (LAA)?

- An actual appendage that hangs off of the left atrium, lined with pectinate muscular ridges
- Area of slower flow in patients with atrial fibrillation
- From TEE and autopsy studies, > 90% of thrombi in nonvalvular atrial fibrillation come from the LAA
- Stroke, TIA, silent cerebral ischemia, MI, mesenteric/renal/splenic infarcts, peripheral arterial embolizations
Thrombus in the Left Atrial Appendage
Mitigation of Thromboembolic Risk

• For patients with AF and mechanical heart valves, warfarin is recommended.

• For patients with nonvalvular AF, CHA₂DS₂-VASc score is used:
  • CHF, HTN, Age (65-74 & ≥ 75), DM, TIA/CVA/thromboembolism, vascular disease & sex
  • 0 – Reasonable to omit antithrombotic Rx
  • 1 – No Rx vs oral anticoagulation (OAC) vs ASA
  • ≥ 2 – OAC

• Selection of OAC should be based on thromboembolic risk, irrespective of type of AF (paroxysmal, persistent or permanent).

• For patients undergoing cardioversion, OAC is recommended regardless of CHA₂DS₂-VASc score or the mode of cardioversion (DC or pharmacological).

J Am Coll Cardiol. 2014;64(21):2246-2280. doi:10.1016/j.jacc.2014.03.021
Direct Oral Anticoagulants: Indications

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonvalvular atrial fibrillation (AF)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>DVT &amp; PE treatment, prevent recurrence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (treatment only)</td>
</tr>
<tr>
<td>DVT prophylaxis, post hip or knee surgery</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (Japan)</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>Phase II</td>
<td>Pending (?)</td>
<td>Phase III</td>
<td>N/A</td>
</tr>
</tbody>
</table>
# Atrial Fibrillation Trial Review

<table>
<thead>
<tr>
<th></th>
<th>RE-LY (dabigatran)</th>
<th>ROCKET AF (rivaroxaban)</th>
<th>ARISTOTLE (apixaban)</th>
<th>ENGAGE-AF (edoxaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>n=18,113</td>
<td>n=14,264</td>
<td>n=18,201</td>
<td>n=21,105</td>
</tr>
<tr>
<td>Age (years)</td>
<td>71 (mean)</td>
<td>73 (median)</td>
<td>70 (median)</td>
<td>72 (median)</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>64%</td>
<td>60%</td>
<td>65%</td>
<td>62%</td>
</tr>
<tr>
<td>TTR (mean)</td>
<td>64%</td>
<td>55%</td>
<td>62%</td>
<td>68% (median)</td>
</tr>
<tr>
<td>CHADS₂ (mean)</td>
<td>2.1</td>
<td>3.5</td>
<td>2.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Prior stroke or TIA</td>
<td>20%</td>
<td>55%</td>
<td>19%</td>
<td>28%</td>
</tr>
<tr>
<td>Dosage notes</td>
<td>110 mg dose (n = 6,105)</td>
<td>15 mg dose (n = 1,474)</td>
<td>2.5 mg dose (n = 602)</td>
<td>30 mg dose (n = 7,034)</td>
</tr>
</tbody>
</table>

### Efficacy Outcomes

<table>
<thead>
<tr>
<th></th>
<th>RE-LY (dabigatran)</th>
<th>ROCKET AF (rivaroxaban)</th>
<th>ARISTOTLE (apixaban)</th>
<th>ENGAGE-AF (edoxaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic</td>
<td>1.11% (d)*</td>
<td>2.1% (r)</td>
<td>1.27% (a)*</td>
<td>1.18% (e)*</td>
</tr>
<tr>
<td>embolism (per year)</td>
<td>vs. 1.69% (w)</td>
<td>vs. 2.4% (w)</td>
<td>vs. 1.6% (w)</td>
<td>vs. 1.5% (w)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.1% (d)*</td>
<td>0.26% (r)*</td>
<td>0.24% (a)*</td>
<td>0.26% (e)*</td>
</tr>
<tr>
<td>(per year)</td>
<td>vs. 0.38% (w)</td>
<td>vs. 0.44% (w)</td>
<td>vs. 0.47% (w)</td>
<td>vs. 0.47% (w)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.92% (d)*</td>
<td>1.34% (r)</td>
<td>0.97% (a)</td>
<td>1.25% (e)</td>
</tr>
<tr>
<td>(per year)</td>
<td>vs. 1.2% (w)</td>
<td>vs. 1.42% (w)</td>
<td>vs. 1.05% (w)</td>
<td>vs. 1.25% (w)</td>
</tr>
</tbody>
</table>

* = statistically significant (p < 0.05)
## Safety Outcomes

<table>
<thead>
<tr>
<th></th>
<th>RE-LY (dabigatran)</th>
<th>ROCKET AF (rivaroxaban)</th>
<th>ARISTOTLE (apixaban)</th>
<th>ENGAGE-AF (edoxaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>3.11% (d) vs. 3.36% (w)</td>
<td>3.6% (r) vs. 3.4% (w)</td>
<td>2.13% (a) vs. 3.09% (w)*</td>
<td>2.75% (e) vs. 3.43% (w)*</td>
</tr>
<tr>
<td>(per year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>0.3% (d) vs. 0.74% (w)*</td>
<td>0.5% (r) vs. 0.7% (w)*</td>
<td>0.33% (a) vs. 0.8% (w)*</td>
<td>0.26% (e) vs. 0.85% (w)*</td>
</tr>
<tr>
<td>(per year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>1.51% (d)* vs. 1.02% (w)</td>
<td>3.2% (r)* vs. 2.2% (w)</td>
<td>0.76% (a) vs. 0.86% (w)</td>
<td>1.51% (e)* vs. 1.23% (w)</td>
</tr>
<tr>
<td>(per year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* = statistically significant (p < 0.05)

References:
DOACs: Reversal

• Dabigatran\(^1\)
  • Idarucizumab (Praxbind) – monoclonal antibody to dabigatran
  • 88-98% patients with complete reversal of anticoagulant effects within minutes

• Factor Xa inhibitors (rivaroxaban & apixaban)\(^2\)
  • Andexanet alfa – recombinant protein to reverse the anticoagulant effects of oral & injectable Factor Xa inhibitors
  • Phase III trial complete
  • FDA evaluation pending

1. Pollack et al NEJM 2015 (373):511-20
2. Connolly et al NEJM 2016 (375):1131-41
## Discontinuation Rate & Major Bleeding

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study Drug Discontinuation Rate</th>
<th>Major Bleeding (Rate/Year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban(^1)</td>
<td>24%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Apixaban(^2)</td>
<td>25%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Dabigatran(^3)  (150 mg)</td>
<td>21%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Edoxaban(^4) (60 mg/30 mg)</td>
<td>33% / 34%</td>
<td>2.8% / 1.6%</td>
</tr>
<tr>
<td>Warfarin(^1)-(^4)</td>
<td>17% - 28%</td>
<td>3.1% - 3.6%</td>
</tr>
</tbody>
</table>

2. Patel, M. NEJM 2011; 365:883-891 – 1.9 yrs follow-up, ITT  
3. Granger, C NEJM 2011; 365:981-992 – 1.8 yrs follow-up,  
Catheter Ablation

• A therapeutic option for symptomatic drug-resistant atrial fibrillation

• Thromboembolism risk at time of ablation – 0.4-2%1,2,3
  • Catheter manipulation within LA
  • Catheter trauma to LA endothelium
  • Thrombus formation on ablation catheters or guide sheaths
  • Conversion to sinus rhythm during procedure
  • Withdrawal of OAC prior to procedure

• Most strokes occur within 24-48 hrs post procedure.3
• Embolic events have been reported for up to 1 week.4

Oral Anticoagulation Following Catheter Ablation

- 2-3 months following catheter ablation
  - CHA₂DS₂-VASc score = 0  Stop OAC
  - CHA₂DS₂-VASc score = 1 -> ???
    - Cardiac rhythm monitor
    - Stop OAC – untested approach
  - CHA₂DS₂-VASc score > 1 -> Maintain long-term OAC
- The desire to stop long-term anticoagulation is NOT an indication for catheter ablation of atrial fibrillation.¹,²

Poor Candidates for Chronic OAC

- Percutaneous left atrial appendage occlusion for patients with nonvalvular atrial fibrillation
- New percutaneous and surgical LAA closure technologies under investigation
Rate vs Rhythm Control
Cardiology (Electrophysiology) Consultation

• Rate control
  • Beta blockers
  • Non-dihydropyridine calcium channel blockers
  • Digoxin
  • AV node ablation and permanent pacer

• Rhythm control
  • Antiarrhythmic agents
  • Catheter ablation
  • Surgical ablation
  • DC cardioversion
Synergy Between Primary Care & Cardiology

- Initial diagnosis of atrial fibrillation
- Evaluation and management of risk factors
  - Tobacco smoking
  - Hypertension
  - Diabetes mellitus
  - Obesity
  - Obstructive sleep apnea
- Systemic embolism prophylaxis
- Long-term treatment strategy