Epidemiology
Scope of the Problem

- More than 2 million patients in the US with AF
- Major impact on the elderly
- Prevalence increase as population ages
- Substantial morbidity due to symptoms
- Associated with stroke, heart, failure, and death
- Most common arrhythmia requiring hospitalization

Atrial Fibrillation Demographics by Age

Prevalence of AF in the United States


Consequences of Atrial Fibrillation

**Embolic**
- TIA
- Stroke
- Systemic emboli

**Hemodynamic**
- Loss of atrial systole
- Increased heart rate
- Decrease in diastolic time
Management of Atrial Fibrillation

**Stroke Prevention**
- Risk assessment
- Role of anticoagulation

**Control of symptoms**
- Rate vs Rhythm
- Role of cardioversion

Types of Atrial Fibrillation

- Episode of AF
  - Paroxysmal
  - Persistent
  - Permanent
Atrial Fibrillation: Definitions

- **Paroxysmal**
  - AF that terminates spontaneously within 7 days
- **Persistent**
  - AF that requires cardioversion for termination
- **Permanent**
  - Sinus rhythm cannot be restored

Atrial Fibrillation is Associated with Stroke

Ischemic Strokes and AF: More Likely Disabling

Framingham Heart Study


Stroke in AF
Paroxysmal vs Chronic

Anticoagulation in AF

Stroke Risk Reductions

- Warfarin Better
- Control Better

<table>
<thead>
<tr>
<th>Study</th>
<th>Reduction of stroke RRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFASAK</td>
<td>62%</td>
</tr>
<tr>
<td>SPAF</td>
<td></td>
</tr>
<tr>
<td>BAATAF</td>
<td>62%</td>
</tr>
<tr>
<td>CAFA</td>
<td></td>
</tr>
<tr>
<td>SPINAF</td>
<td></td>
</tr>
<tr>
<td>EAFT</td>
<td></td>
</tr>
<tr>
<td>Aggregate</td>
<td>62%</td>
</tr>
</tbody>
</table>

Reduction of all-cause mortality RRR 26%

INR Control: Target 2-3

How Well Do We Do?

Randomized Clinical Trials

- SPORTIF 3 66%
- SPORTIF 5 68%
- ACTIVE W 65% (previous OAC)
- 60% (OAC naïve)
- RELY 64%
- Meta analysis 66%

Community Practice

- Meta analysis 57%


Lancet 2003; 362: 1691-98
JAMA 2005; 293(6): 690-98
Chest 2006; 129: 1155-66
Ischemic Stroke and Intracranial Bleeding


Issues and Challenges for Stroke Prevention in AF Patients

- Warfarin is effective but difficult to use
- Not all patients take or tolerate warfarin
- Time in therapeutic range often low
- Risk of bleeding
SPAF: Risk vs Benefit of Anticoagulation

Risk of stroke
Risk of bleeding

Stroke and Nonvalvular AF

The CHADS\textsubscript{2} Score
Stroke Risk Score for Atrial Fibrillation

<table>
<thead>
<tr>
<th>Score (points)</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive Heart failure 1</td>
<td>32</td>
</tr>
<tr>
<td>Hypertension 1</td>
<td>65</td>
</tr>
<tr>
<td>Age &gt; 75 years 1</td>
<td>28</td>
</tr>
<tr>
<td>Diabetes mellitus 1</td>
<td>18</td>
</tr>
<tr>
<td>Stroke or TIA 2</td>
<td>10</td>
</tr>
</tbody>
</table>

- Moderate-High risk >2
- Low risk 0-1


CHADS2 Score: Targeted Therapy

<table>
<thead>
<tr>
<th>CHADS\textsubscript{2} Score</th>
<th>Adjusted Stroke Rate\textsuperscript{†} (95% CI)</th>
<th>CHADS\textsubscript{2} Risk Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9 (1.2-3.0)</td>
<td>Low</td>
</tr>
<tr>
<td>1</td>
<td>2.8 (2.0-3.8)</td>
<td>Low</td>
</tr>
<tr>
<td>2</td>
<td>4.0 (3.1-5.1)</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>5.9 (4.6-7.3)</td>
<td>Moderate</td>
</tr>
<tr>
<td>4</td>
<td>8.5 (6.3-11.1)</td>
<td>High</td>
</tr>
<tr>
<td>5</td>
<td>12.5 (8.2-17.5)</td>
<td>High</td>
</tr>
<tr>
<td>6</td>
<td>18.2 (10.5-27.4)</td>
<td>High</td>
</tr>
</tbody>
</table>

\textsuperscript{†}Expected rate of stroke per 100 patient-years.

The CHA²DS²-VASc Score
Stroke Risk Score for Atrial Fibrillation

- Congestive heart failure or LVEF ≤ 35% (1 point)
- Hypertension (1 point)
- Age > 75 years (2 points)
- Diabetes mellitus (1 point)
- Stroke/TIA/systemic embolism (2 points)
- Vascular Disease (MI/PAD/Aortic plaque) (1 point)
- Age 65-74 years (1 point)
- Sex category (female) (1 point)

Moderate-High risk: > 2 points
Low risk: 0-1 points


Canadian Cardiovascular Society
AF Guidelines 2012 Update

Assess Thromboembolic Risk (CHADS²)

- CHADS₂ = 0
  - No anti-thrombotic
  - No additional risk factors of stroke

- CHADS₂ = 1
  - ASA
  - Either female sex or vascular disease
  - OAC*
  - Age > 65 y or combination of female sex and vascular disease

- CHADS₂ > 2
  - OAC*
  - *Aspirin is a reasonable alternative in some as indicated by risk/benefit
  - OAC
**Risk of Bleeding: HAS-BLED Score**

Risk Score for Predicting Bleeding in Anticoagulated Patients with Atrial Fibrillation

<table>
<thead>
<tr>
<th>Condition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (&gt; 160 mm Hg systolic)</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal renal or hepatic function</td>
<td>1-2</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding history or anemia</td>
<td>1</td>
</tr>
<tr>
<td>Labile INR (TTR &lt; 60%)</td>
<td>1</td>
</tr>
<tr>
<td>Elderly (age &gt; 75 years)</td>
<td>1</td>
</tr>
<tr>
<td>Drugs (antiplatelet, NSAID) or alcohol</td>
<td>1-2</td>
</tr>
</tbody>
</table>

- **High risk** (> 4%/year) ≥ 4
- **Moderate risk** (2-4%/year) 2-3
- **Low risk** (< 2%/year) 0-1

---

**CHADS\textsubscript{2} vs CHADS\textsubscript{2}-VASc**

2012 focused update of the ESC Guidelines for the management of atrial fibrillation

- Guideline recommends a shift towards focus on low risk
- No recommendation on composite bleeding stroke risk score

2012 focused update of the ESC Guidelines for the management of atrial fibrillation: Europace. 2012 Aug 24
Subclinical AF and Risk of Stroke

Atrial tachyarrhythmia > 6 min ≤ 3 months after pacemaker or defibrillator implantation

Progression of Atrial Fibrillation

Paroxysmal
Self-Terminating

Persistent
Lasts > 7 Days

Permanent
Cardioversion Failed or Not Attempted

Paroxysmal AF is as likely to cause stroke as persistent or permanent AF
SPAF: The Challenge of Assessing Stroke Risk

- Paroxysmal AF is difficult to detect.
- 24h Holter is often insufficient. Prolonged monitoring may be necessary.
- Many strokes are misclassified as “cryptogenic”.
- The misclassified strokes are really thromboembolic and warrant anticoagulation.
- Patients with PAF and risk factors need OAC.

SPAF: Challenges for the Future

- Better risk-stratification
  - Balancing stroke vs bleeding
- Methods to better predict events and guide therapy
- Successful rhythm control over time (?)
- Safer treatments for the highest risk patients
  - Role of new anticoagulants
Anticoagulants

VIIa

Intrinsic Pathway

XIIa

XIa

Extrinsic Pathway

Warfarin
II, VII, IX, X

Apixaban
Rivaroxaban
Endoxaban

IIa (thrombin)

FIBRIN

Major Advances In Oral Anticoagulation for SPAF

6 Trials of Warfarin vs Placebo
1989-1993

ROCKET AF
(Rivaroxaban)
2010

ENGAGE AF
(Edoxaban)
2013

RE-LY
(Dabigatran)
2009

ARISTOTLE
(Apixaban)
2011

## Comparative Pharmacokinetics/Pharmacodynamics of Novel Agents

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>IIa (thrombin)</td>
<td>Xa</td>
<td>Xa</td>
<td>Xa</td>
</tr>
<tr>
<td><strong>Hrs to Cmax</strong></td>
<td>2</td>
<td>1-3</td>
<td>2-4</td>
<td>1-2</td>
</tr>
<tr>
<td><strong>CYP metabolism</strong></td>
<td>None</td>
<td>15%</td>
<td>32%</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>7%</td>
<td>66%</td>
<td>80%</td>
<td>&gt; 45%</td>
</tr>
<tr>
<td><strong>Transporters</strong></td>
<td>P-gp</td>
<td>P-gp</td>
<td>P-gp/BCRP</td>
<td>P-gp</td>
</tr>
<tr>
<td><strong>Protein binding</strong></td>
<td>35%</td>
<td>87%</td>
<td>&gt;90%</td>
<td>55%</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>12-14h</td>
<td>8-15h</td>
<td>9-13h</td>
<td>8-10h</td>
</tr>
<tr>
<td><strong>Renal elimination</strong></td>
<td>80%</td>
<td>25%</td>
<td>33%</td>
<td>35%</td>
</tr>
<tr>
<td><strong>Linear PK</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

BCRP = breast cancer resistance protein; CYP = cytochrome P450; P-gp = P-glycoprotein


## Pivotal AF Trials: Dose Comparison

<table>
<thead>
<tr>
<th></th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
<th>ENGAGE AF-TIMI 48</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
<td>Edoxaban</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>18,113</td>
<td>14,266</td>
<td>18,201</td>
<td>21,105</td>
</tr>
<tr>
<td><strong>Dose (mg)</strong></td>
<td>150, 110 bid</td>
<td>20 qd</td>
<td>5 bid</td>
<td>60, 30 qd</td>
</tr>
<tr>
<td><strong>Initial Dose adj</strong></td>
<td>No</td>
<td>20 → 15 mg</td>
<td>5 → 2.5 mg</td>
<td>60 → 30 mg 30 → 15 mg</td>
</tr>
<tr>
<td><strong>Dose adj (%)</strong></td>
<td>0</td>
<td>21</td>
<td>4.7</td>
<td>&gt; 25</td>
</tr>
<tr>
<td><em><em>Dose adj</em> after randomization</em>*</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>PROBE</td>
<td>2 x blind</td>
<td>2 x blind</td>
<td>2 x blind</td>
</tr>
</tbody>
</table>

* Dose adjusted in patients with ↓drug clearance

Ruff CR et al. Am Heart J 2010; 160:635-41
## Pivotal AF Trials: Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>RE-LY (Dabigatran)</th>
<th>ARISTOTLE (Apixaban)</th>
<th>ENGAGE AF (Edoxaban)</th>
<th>ROCKET-AF (Rivaroxaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong># Enrolled</strong></td>
<td>18,113</td>
<td>18,201</td>
<td>21,105</td>
<td>14,264</td>
</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>72 ± 9</td>
<td>70 [63-76]</td>
<td>72 [64-77]</td>
<td>73 [65-78]</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>36%</td>
<td>35%</td>
<td>38%</td>
<td>40%</td>
</tr>
<tr>
<td><strong>CHADS₂ score ≥3</strong></td>
<td>32%</td>
<td>30%</td>
<td>52%</td>
<td>87%</td>
</tr>
<tr>
<td><strong>VKA naive</strong></td>
<td>50%</td>
<td>43%</td>
<td>41%</td>
<td>38%</td>
</tr>
<tr>
<td><strong>Paroxysmal AF</strong></td>
<td>33%</td>
<td>15%</td>
<td>25%</td>
<td>18%</td>
</tr>
<tr>
<td><strong>Prior stroke/TIA</strong></td>
<td>20%</td>
<td>19%</td>
<td>18% / 12%</td>
<td>55%*</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>23%</td>
<td>25%</td>
<td>36%</td>
<td>40%</td>
</tr>
<tr>
<td><strong>Prior CHF</strong></td>
<td>32%</td>
<td>35%</td>
<td>56%</td>
<td>62%</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>79%</td>
<td>87%</td>
<td>90%</td>
<td>91%</td>
</tr>
</tbody>
</table>

*Includes prior systemic embolism

Ruff CR et al. Am Heart J 2010; 160:635-41

## Pivotal AF Trials: Results

<table>
<thead>
<tr>
<th>Drug Dose (mg)</th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dabigatran 110 bid</td>
<td>Rivaroxaban 20 mg qd</td>
<td>Apixaban 5 mg bid</td>
</tr>
<tr>
<td>Stroke + SEE</td>
<td>non-infer.</td>
<td>ITT cohort: non-infer. On Rx cohort: Superior</td>
<td>Superior</td>
</tr>
<tr>
<td>ICH</td>
<td>Superior</td>
<td>Superior</td>
<td>Superior</td>
</tr>
<tr>
<td>Bleeding</td>
<td>Lower</td>
<td>similar</td>
<td>Lower</td>
</tr>
<tr>
<td>Mortality</td>
<td>similar</td>
<td>P = 0.051</td>
<td>similar</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>similar</td>
<td>similar</td>
<td>similar</td>
</tr>
<tr>
<td>Mean TTR</td>
<td>64%</td>
<td>55%</td>
<td>62%</td>
</tr>
<tr>
<td>Stopped drug</td>
<td>21%</td>
<td>23%</td>
<td>23%</td>
</tr>
<tr>
<td>WD consent</td>
<td>2.3%</td>
<td>8.7%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

TTR = time in therapeutic range
WD consent = withdrawal of consent, no further data available
Novel Oral Anticoagulant: Efficacy

Ischemic Stroke

Hemorrhagic Stroke

Novel Oral Anticoagulant: Safety

Bleeding

Major

ICH

GI

Novel Oral Anticoagulant: Bleeding

**Fatal Bleeding**
- 40%

**Major Bleeding**
- 20%

**GI Bleeding**
- 30%


AVERROES:
Comparison of Apixaban and Aspirin

**Stroke or Systemic Embolic Event**

- Aspirin
- Apixaban

P < 0.001

HR 0.45 (0.32-0.62)

**Major Bleeding**

- Aspirin
- Apixaban

P < 0.001

HR 1.13 (0.74-1.75)

Summary of SPAF Guidelines

- The CHADS$_2$-VASc is probably best for identifying low-risk patients
- The HAS-BLED score assesses bleeding risk.
  - Correct the correctable
  - HAS-BLED>3 - caution and regular review advised
- NOACs offer better efficacy, and convenience compared to VKAs
  - No data to recommend one over the other
- Efficacy of ASA is weak
  - Risk of bleeding same as OAC

Atrial Fibrillation: Management

Rate control ----------- Rhythm control
Why Are There No New Drugs for Rhythm Control??

Definition:

Antiarrhythmic Drugs=
Poisons with beneficial side effects

Drugs for Rhythm Control

- **Class I Drugs** - Na⁺ Blockers (slow conduction)
  - IA Quinidine or Disopyramide
  - IC (avoid in pts with CAD, CM)
    - Flecainide 100-225mg bid
    - Propafenone 150-225 mg tid or bid

- **Class III Drugs** - K⁺ Blockers (prolong repolarization)
  - Sotalol 80-160 mg bid (may not be tolerated in CHF)
  - Dofetilide 0.125-0.500 mg bid (may be used in CHF, but must watch QTc, K⁺, creatinine)
  - Dronedarone 400 mg BID (avoid CHF or permanent AF)
  - Amiodarone 100-200 mg daily (drug of choice in pts with CHF)
Canadian Trial of Atrial Fibrillation (CTAF): Rhythm Control

Rate of recurrence lowest with amiodarone


AFFIRM: Rate control versus Rhythm control


<table>
<thead>
<tr>
<th>No. of deaths</th>
<th>Number, percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhythm control</td>
<td>0  80 (4)  175 (9)  257 (13)  314 (18)  352 (24)</td>
</tr>
<tr>
<td>Rate control</td>
<td>0  78 (4)  148 (7)  210 (11)  275 (16)  306 (21)</td>
</tr>
</tbody>
</table>

p=0.058
## Rhythm or Rate Control in AF

### Mortality

<table>
<thead>
<tr>
<th></th>
<th>Rate Control</th>
<th>Rhythm Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIAF</td>
<td>1 (0.8%)</td>
<td>2 (1.6%)</td>
<td>ns</td>
</tr>
<tr>
<td>STAF</td>
<td>8 (8%)</td>
<td>4 (4%)</td>
<td>ns</td>
</tr>
<tr>
<td>AFFIRM</td>
<td>306 (26%)</td>
<td>356 (27%)</td>
<td>.058</td>
</tr>
<tr>
<td>RACE</td>
<td>18 (7.0%)</td>
<td>18 (6.7%)</td>
<td>ns</td>
</tr>
</tbody>
</table>

### Cerebrovascular Events

<table>
<thead>
<tr>
<th></th>
<th>Rhythm Control</th>
<th>Rate Control</th>
<th>Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFFIRM (n=4060)</td>
<td>1.28 (0.95 – 1.72)</td>
<td>1.28 (0.95 – 1.72)</td>
<td>1.28 (0.95 – 1.72)</td>
<td>.04</td>
</tr>
<tr>
<td>RACE (n=522)</td>
<td>2.25 (1.88 – 5.75)</td>
<td>2.25 (1.88 – 5.75)</td>
<td>2.25 (1.88 – 5.75)</td>
<td>.04</td>
</tr>
<tr>
<td>STAF (n=200)</td>
<td>3.01 (0.35 – 25.30)</td>
<td>3.01 (0.35 – 25.30)</td>
<td>3.01 (0.35 – 25.30)</td>
<td>.04</td>
</tr>
<tr>
<td>PIAF (n=252)</td>
<td>4.92 (0.58 – 41.50)</td>
<td>4.92 (0.58 – 41.50)</td>
<td>4.92 (0.58 – 41.50)</td>
<td>.04</td>
</tr>
<tr>
<td>TOTAL (n=5034)</td>
<td>1.36 (1.03 – 1.78)</td>
<td>1.36 (1.03 – 1.78)</td>
<td>1.36 (1.03 – 1.78)</td>
<td>.04</td>
</tr>
</tbody>
</table>
**Relationship between NSR, Treatment, and Survival in AFFIRM: AFFIRM substudy**

**Time-Dependent Co-variates Associated with Survival**

<table>
<thead>
<tr>
<th>Covariate</th>
<th>p-value</th>
<th>H.R.</th>
<th>99% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus rhythm</td>
<td>&lt;0.0001</td>
<td>0.53</td>
<td>0.39-0.72</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>&lt;0.0001</td>
<td>0.50</td>
<td>0.37-0.69</td>
</tr>
<tr>
<td>Digoxin use</td>
<td>0.0007</td>
<td>1.42</td>
<td>1.09-1.86</td>
</tr>
<tr>
<td>AAD use</td>
<td>0.0005</td>
<td>1.49</td>
<td>1.11-2.01</td>
</tr>
</tbody>
</table>

Toxicity of antiarrhythmic drugs counterbalances the benefits of SR

AFFIRM Investigators: Circulation 2004;109:1509-1513

**AF Clinical Trials: Rhythm vs Rate Control**

- Mortality is similar, regardless of treatment strategy
- Lenient control (mean rate <110 bpm) as good as strict control (mean rate <80 bpm)
  - RACE II: NEJM 2010;362:1363
- Anticoagulation in patients at high risk for stroke is important, regardless of rate or rhythm treatment strategy
What AFFIRM did not answer:

- Is NSR associated with an improved outcome in high-risk, symptomatic patients?
- Is NSR preferable in young patients?
- Is rhythm control superior if patients receive OAC?
Choose antiarrhythmic drug according to underlying pathology

Treatment of AF: Non-pharmacologic Options

- Rate control
  - Ablate and pace
- Surgical
  - Cox-MAZE procedure
- Radiofrequency catheter ablation
  - Pulmonary vein isolation
  - Extended LA ablation
Surgical procedure for AF: Standard Maze-III

Angiogram of a Left Inferior Pulmonary Vein Depicting the Source and Exit of Ectopic Activity.

Initiation of Focal AF

Haissaguerre et al., NEJM 1998;389:659-66

AF Ablation: Targeting and isolating pulmonary veins

Ames A, Stevenson W G Circulation 2006;113:e666-e668a
Electroanatomic map with an integrated computed tomographic image of the left atrium and pulmonary veins (viewed from the back) showing the lesion set created for ablation of paroxysmal atrial fibrillation.

Calkins H Circulation. 2012;125:1439-1445

AF Ablation: Creating PVI

Tung R et al. Circulation 2012;126:223-229
Ablation of Persistent AF: Additional lesions required

Tung R et al. Circulation 2012;126:223-229

Efficacy of Antiarrhythmic Drugs versus Catheter Ablation

Calkins H: Circ Arrhy Electrophysiol 2009;2:349
AF Ablation Complications

- Mortality
  - Death overall: 0.7%
  - Procedure-related: 0%
- Vascular access: <1%
- Periprocedural events
  - TIA/Stroke: 0.5%
  - Cardiac tamponade: 0.8%
  - Pericardial effusion: 0.6%
  - PV stenosis: 1.6%
  - LA-esophageal fistula: 0%
- Total: 4.9%

Calkins H: Circ Arrhy Electrophysiol 2009;2:349
Summary

- AF is a common disorder whose incidence is expected to rise dramatically
- Stroke prevention is a critical component of management in patients with AF
- Anticoagulation is underutilized
- Even when utilized, current anticoagulant characteristics limit the ability to maintain patients within target range
- Emerging anticoagulant agents without some of these limitations may improve stroke prevention
- Rate control vs rhythm management based on clinical assessment
- AF ablation is a Rx option for highly symptomatic patients