ATRIAL FIBRILLATION 2014

Ronald L Walsh, D.O.
FSACOFP Meeting
August 2, 2014
DEFINITION OF ATRIAL FIBRILLATION-AF

AF is a supraventricular arrhythmia characterized by rapid disorganized atrial depolarizations resulting in rapid conduction to the ventricles that cause a drop in cardiac output and are associated with highly variable clinical symptoms or present even asymptomatically.

AF in early stages is triggered by random electrical activity in and around the pulmonary veins that creates the disorganized atrial electrical activity in susceptible patients.

AF when long-lasting can lead to electrical remodeling within the atria that helps to maintain the AF and eventually make it chronic and self-perpetuating.
ELECTROCARDIOGRAM OF ATRIAL FIBRILLATION
ATRIAL FIBRILLATION TALK GOALS

- Describe etiology of Atrial fibrillation
- Treatment Goals for Atrial Fibrillation
  - Novel Anticoagulants
  - Rate Control/ Rhythm Control
- Advances in Therapy for Atrial fibrillation
Projected Number of Adults with Atrial Fibrillation in the United States Between 1995 and 2050

Adults with AFib (millions)

Year:
- 1990: 2.08
- 1995: 2.26
- 2000: 2.44
- 2005: 2.66
- 2010: 2.94
- 2015: 3.33
- 2020: 3.80
- 2025: 4.34
- 2030: 4.79
- 2035: 5.15
- 2040: 5.42
- 2045: 5.61
- 2050: 5.61

Proportion of over 65s aged ≥80 yrs:
- 2000: 37%
- 2025: 36%
- 2050: 53%

Go: JAMA, 2000
ATRIAL FIBRILLATION ACCOUNTS FOR 1/3 OF ALL PATIENT DISCHARGES WITH ARRHYTHMIA AS PRINCIPAL DIAGNOSIS.

Mortality and AF

With AF (n=13,558)  Without AF (n=13,195)

% Mortality Over 3 Years

Men
Women
Men
Women
Men
Women

38.6
30.2*
25.4
36.1*
71.3
65.1*

47.4*
47.5

75-84

51.1*

62.4

* Significantly different from patients with AF at P<.05.

THE HALLMARK OF AF IS CHAOTIC ATRIAL IMPULSES LEADING TO IRREGULARLY IRREGULAR VENTRICULAR CONTRACTION, USUALLY WITH INCESSANT TACHYCARDIA
MECHANISMS OF ATRIAL FIBRILLATION: MULTIWAVELET REENTRY, RAPID ROTORS AND FOCAL TRIGGERS
The Scope of the Problem

- AF is the most common tachyarrhythmia requiring therapy and the most common arrhythmia leading to hospitalization.
- The AF population has a mortality risk and impaired quality of life (QOL).
  - Associated with the arrhythmia
  - Associated with its therapy
- Economic and healthcare cost burden is in the billions of dollars/year range.
- Limited resource availability.
OVERVIEW

- Atrial fibrillation is a progressive disease
- Atrial fibrillation has hemodynamic and myocardial consequences (i.e., reduced cardiac output and heart failure)
- There is significant morbidity and mortality consequences
  - increased hospitalizations
  - reduced quality of life
  - increased risk of thromboembolism and stroke (accounts for 75,000 strokes per year in the United States alone)
  - decreased survival (AF is associated with increased mortality, but whether it is the cause or an innocent bystander is not well established)\(^1\)-\(^8\)

- Atrial fibrillation is a treatable disorder, especially with early intervention
- What’s new in atrial fibrillation treatment

CLASSIFICATION AND PATTERNS OF AF

- **Paroxysmal**: terminates spontaneously, typically duration is < 7 days (most < 24 hours). May be recurrent.

- **Persistent**: medication or electrical intervention is required to restore sinus rhythm; does not self-terminate. Typically lasts > 7 days. May be recurrent.

- **Permanent**: sinus rhythm cannot be restored or maintained despite intervention.

* Evaluate for thrombotic risk each of these situations.*
CONDITIONS ASSOCIATED WITH ATRIAL FIBRILLATION

- Hypertension
- Heart attacks/ CAD
- Valvular Heart Disease
- Congenital heart defects
- Hyperthyroid or other metabolic imbalance
- Exposure to stimulants such as medications, caffeine or tobacco, or to alcohol (holiday heart)
- Sick sinus syndrome — improper functioning of the heart's natural pacemaker
- Emphysema or other lung diseases
- CABG/ Previous heart surgery
- Viral infections /Pericarditis
- Stress due to pneumonia, surgery or other illnesses (Catecholamine)

- Pulmonary Embolus
- Pneumonia
- Sleep Apnea
- Pericarditis
- Lone A fib (younger people)
- Left ventricular Hypertrophy
- Cardiomyopathy
- CHF –Systolic or Diastolic
- Idiopathic – mostly in younger people – Lone Atrial Fib
- Familial Predisposition.
- Glucocorticoids
- Electrolyte abnormalities (especially Low Mg+2)
- Atrial fibrosis from Sarcoid, collagen vascular disease, infiltrating diseases
**Simplifying Your Atrial Fibrillation Treatment Plan**

Encourage your patients to take an active role in their healthcare by using this tool to help them understand appropriate treatment options available for them.

**How will I prevent* stroke?**

Based on the following

**Does my heart rhythm or rate need treatment?**

If yes, there are 2 basic treatment considerations

**What are my C.H.A.D.S. risk factors?**


**Will I Need**

**Aspirin?**

Aspirin for patients without risk factors other than AFib

**FDA Approved Anticoagulants?**

**Follow up**

Follow up and regular checkups are important for preventing congestive heart failure and stroke.

**Yes, we will pursue keeping the heart in normal rhythm**

**Yes, we will pursue heart rate control**

**Healthy Lifestyle**

**Medications**

**Catheter Ablation**

**Cardioversion**

**Surgery**

Usually combined with other treatments

**Medications**

*It is very important to take risk reduction measures even though no method or treatment can guarantee prevention. Know the warning signs for stroke and call 9-1-1 immediately if you experience them.*
**Risk Assessment Megatrend**

- CHA$_2$DS$_2$-VASc has replaced CHADS$_2$ as the predominant assessment tool to predict stroke risk (ESC 2012 AF Guidelines Update).

- HAS-BLED has gained dominance as the most predictive bleeding index. It is best used as a cautionary “yellow flag” rather than as a reason to withhold anticoagulation (ESC 2012).
SYMPTOMS

- Inappropriate heart rate response: palpitations, dyspnea
- Tachymyopathy: CHF symptoms
- Loss of atrial systolic function: Low cardiac output, fatigue, dizziness
- Thromboembolism: Stroke, Major organ embolic event
DEFINITIONS AND MECHANISMS OF ATRIAL FIBRILLATION

- Paroxysmal Atrial Fibrillation - recurrent, spontaneously converting AF, <7 days, due to focal premature atrial contractions triggering AF or focal atrial tachycardia

- Persistent Atrial Fibrillation - recurrent, sustained AF, > 7 days, requiring electrical or pharmacological cardioversion, may be focally triggered but is due to multiple wavelet reentry

- Permanent (Accepted) Fibrillation - permanent AF due to multiple wavelet reentry, abnormal atrial substrate
**RATE VERSUS RHYTHM CONTROL**

- Benefits of rhythm control include: decreased hospitalizations, improved cardiac function, improved exercise tolerance, and improvement in quality of life.

- Consequences of failure to maintain sinus rhythm: Atrial remodeling and permanent atrial fibrillation.

- The goals of anti-arrhythmic therapy to maintain normal sinus rhythm should be:
  1. To reduce the frequency, severity, and duration of AF to a degree acceptable to the patient
  2. To do so with the lowest likelihood of adverse effects
If clinicians do not try to maintain normal sinus rhythm in the present, it becomes more difficult over time. Patients converted to normal sinus rhythm within 3 months have a 69% chance of remaining in sinus rhythm at 6 months compared to only 27% if they are allowed to remain in AF for > 12 months.²

Therapeutic Goals in the Treatment of AF

- Prevent Stroke/TE
- Prevention of CHF
- Relief of symptoms
- Improved quality of life
- Reduction in cost of care to medical system

**TABLE 1. Some Measurable End Points or Outcomes Associated With AF**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Rhythm End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpitation</td>
<td>Measures of rhythm control</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Measures of rate control</td>
</tr>
<tr>
<td>Fatigue/asthenia</td>
<td>Others</td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
</tr>
<tr>
<td>Many others less commonly</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Events</th>
<th>Other Clinical Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/thromboembolism</td>
<td>Functional capacity</td>
</tr>
<tr>
<td>Death</td>
<td>Quality of life</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Cognitive function</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Ventricular function (when reduced)</td>
</tr>
<tr>
<td>Others</td>
<td>Others</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Composite End Points</th>
<th>Cost and cost-effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate composites of those listed above</td>
<td></td>
</tr>
</tbody>
</table>


ATRIAL FIBRILLATION: A UNIFYING THEORY

- Focal triggering initiation
- Multiple wavelets for AF maintenance
- Parasympathetic effects on atrial substrate
- Varying importance among population of lone, vagally-mediated, PAF, persistent, and permanent atrial fibrillation.
The role of pulmonary veins in the perpetuation and initiation of paroxysmal AF have been demonstrated; hence the effectiveness of pulmonary vein isolation techniques in this cohort of patients.

As atrial fibrillation progresses to persistent and permanent, the role of “muscle, scar, and fibrosis”, that is structural disease, becomes more prominent, hence a hybrid approach is more effective both targeting the substrate and the triggers.
2014 AHA/ACC/HRS GUIDELINE FOR THE MANAGEMENT OF PATIENTS WITH ATRIAL FIBRILLATION: MAJOR CHANGES FROM 2011 UPDATE

1. Increased use of Radiofrequency Ablation Techniques (RFA) in treatment of Non-Valvular Atrial Fibrillation (NVAF).

2. Decreased emphasis on the use of aspirin for lower risk patients.

3. Incorporation of the 3 New Oral Anticoagulants (NOAC’s) into stroke reduction guidelines.

4. Endorsement of the CHADS2VA2SC Scoring system for risk stratification of stroke risk.
January, CT et al.

2014 AHA/ACC/HRS Atrial Fibrillation Guideline

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society

Developed in Collaboration With the Society of Thoracic Surgery
THINGS TO KEEP IN MIND ABOUT THE GUIDELINES

1. “Guidelines” are just that—GUIDELINES

2. Individualize treatment options for each patient.

3. Rhythm control option continues to improve in both efficacy and safety.
APPROACH TO NEW FINDING OF ATRIAL FIBRILLATION

1. Determine duration and severity of episode—Duration assessment may be difficult especially with lack of symptoms in many patients (elderly frequently without symptoms)

2. Assess treatment options: Rhythm vs Rate Control

3. Assess immediate need for Rate Control if pt presents in Atrial Fibrillation/Flutter (may even need immediate cardioversion if severe symptoms or hemodynamic compromise.

4. Assess Stroke Risk to determine need for Anticoagulation (CHA2DS2-VASc)

5. Decide timing of interventions which will be guided by the above decisions.
RHYTHM CONTROL

1. Generally considered with new onset/discovery of Atrial Fibrillation (Only with symptoms?)

2. **Less than 48 hours duration**: Can go right to cardioversion: Pharmacologic and/or Electrical

3. **Greater than 48 hours duration**: Need TEE to exclude LAA thrombus before immediate cardioversion attempt. Can also begin anticoagulation for 3 weeks with rate control only and then begin cardioversion attempt in less urgent situations. Debate over whether chronic antiarrhythmic drug therapy is needed post-cardioversion.

4. If recurrent episodes, then rhythm control options depend on frequency and severity of recurrences. Range from “Pill in the Pocket” to full Pulmonary Vein Ablation/Isolation procedure.
RATE CONTROL

1. Generally required when average resting ventricular response exceeds 90-100 bpm or pharmacologic cardioversion with Ic agents is attempted to avoid increased rates with conversion to atrial flutter.

2. A patient with new onset atrial fibrillation does not mandate hospitalization or immediate ER evaluation if they are stable.

3. Outpatient rate control medications are Beta-Blockers, Non-dihydropyridine CCB’s ie, verapamil / diltiazem, Digoxin. All can be given IV if needed in hospital/ER settings. May require 2 or more agents.—Decision of which one to start depends on the clinical circumstances at the time of therapy including comorbidities/allergies/structural heart disease.

4. If drug(s) fail or not tolerated in chronic accepted AF then AV Junctional ablation with implantation of a single RV or BiV pacemaker is indicated. Usually in more elderly pts that are not good candidates for rhythm control.

5. Adequate rate control with exercise is accepted as <150 bpm.
STROKE IN ATRIAL FIBRILLATION

- AF/PAF pts have 5x the stroke risk as compared to age/health matched individuals without AF/PAF. There is NO DIFFERENCE in risk with AF vs PAF.

- The occurrence of stroke is **NOT** temporally related to the actual occurrence of atrial fibrillation.

- *This suggests that the presence of atrial fibrillation is a marker for an atrial myopathy associated with increased thrombogenicity with embolization risk but the actual stroke may occur without atrial fibrillation occurrence for days or weeks.*

- *Recent data on Cryptogenic stroke indicates that up to 30% of these pts will be found to have AF on prolonged cardiac rhythm monitoring (24-36 mths) with an ILR. Most frequently the AF is 90-120 days after the event. Possibly as little as 1 episode of 30 secs of AF or average of 5 min/24 hrs predict an increased risk of stroke. NEJM 2014;370:2478-86.*

- 15-25% of all strokes are related to AF. Strokes that occur in association with AF have a higher mortality and are more severely debilitating.
FUTURE POSSIBILITIES?

All patients that have unexplained stroke have a CHA2DS2-VASc score done and anticoagulate the highest risk patients (ie, >3) while looking for AF/PAF—Study needs to be done. In the works???

In patients unable to tolerate anticoagulation therapy left atrial appendage closure will be standard of care for stroke prevention.

Ablation procedures will be used to prevent recurrent AF that will absolutely reduce stroke risk regardless of AF recurrence.---Not likely but more data will become available in the future.
Atrial fibrillation
A COMPARISON OF RATE CONTROL AND RHYTHM CONTROL IN PATIENTS WITH ATRIAL FIBRILLATION

The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators*
Primary Endpoint: All-Cause Mortality

\[ p = 0.058 \]

Rhythm N: 2033 1932 1807 1316 780 255
Rate N: 2027 1925 1825 1328 774 236
IMMEDIATE EVALUATION

- History, Physical, Labs
  - Underlying heart disease, thyroid, alcohol
- ECG
  - LVH, WPW, MI
- CXR
  - Pneumonia, CHF
- Echo
  - Cardiomyopathy, Valve disease, Effusion
- ETT/Holter
  - Rate assessment
< 24 HRS DURATION

- Minimally symptomatic with rate control
- Observe for another 24 hrs (may be paroxysmal)
  - Anticoagulate if indicated
< 48HRS BUT > 24HRS

- Cardiovert if NSR is desirable
  - Most patients with new onset atrial fibrillation regardless of age
- Rate control and anticoagulation if appropriate
  - Hx or recurrent paroxysmal with minimal sx’s usually in the elderly
CASE: 2

- 50 yr old female hasn’t felt well for 3 days
- Otherwise healthy
- ECG atrial fib rate 140
  - Rx’d beta blocker: HR 105
  - Still feels terrible
A  Left Atrium

B  Left Atrial Appendage Clot

CASE:

- 83 yr old noted to be in atrial fibrillation on routine office visit - asymptomatic
- Otherwise healthy except for HTN
- Wonders what all the fuss is about
- Evaluation for underlying causes is negative
WHAT NEXT?

• 1: If it ain’t broke don’t fix it
• 2: Anticoagulate, rate control and cardiovert 1 month later
• 3: Anticoagulate and rate control
• 4: Rate control
CASE: 4

- 38 yr old with atrial fib noted on routine physical asymptomatic
- Otherwise healthy
- Evaluation unremarkable
WHAT NEXT?

1: If it ain’t broke don’t fix it
2: Anticoagulate, rate control and cardiovert 1 month later
3: Anticoagulate and rate control
4: Rate control
5: Immediate TEE and ECV if no thrombus
6: Refer for primary pulmonary vein ablation/isolation procedure
RATE CONTROL : A NEW PARADIGM

- 5 Randomized trails of Rhythm vs. Rate
  - PIAF - 252
  - PAF2 - 141
  - RACE - 522
  - STAF - 200
  - AFFIRM - 4060 patients
    - 3.5 yrs
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
Warfarin Use

% Using Warfarin at Follow-up Visit

Rate N:
2027 1942 1934 1852 1726 1229 735 248

Rhythm N:
2033 1950 1933 1851 1718 1241 737 268
Secondary Endpoint - Death, Disabling Stroke or Anoxic Encephalopathy, Major Bleed, or Cardiac Arrest

p = 0.283
Implications

- AFFIRM results pertain to patients with AF:
  - and risk factors for stroke / death
  - for whom drug therapy – either rate or rhythm control – was thought to be necessary
- AFFIRM has demonstrated that rate control is an acceptable primary therapy
- Continuous anticoagulation seems warranted in all patients with risk factors for stroke
ANTICOAGULATION: THE GOLD STANDARD

- 5 large prospective randomized trials
- All comparing warfarin to placebo while utilizing rate control.
- All with the same highly significant result
- Embolic risk decreases to 1.4% (68% reduction)
Stroke Prevention in Atrial Fibrillation: Warfarin Data

- AFASAK: 27 events, 811 patient-years
- BAATAF: 15 events, 922 patient-years
- CAFA: 14 events, 478 patient-years
- SPAF: 23 events, 508 patient-years
- SPINAF: 29 events, 972 patient-years
- Combined: 108 events, 3691 patient-years

Atrial Fibrillation Investigators. 
PREVENTING Atrial Fibrillation Related STROKES with Anticoagulants
STROKE AND ATRIAL FIBRILLATION: ANTICOAGULATION ISSUES

• Prevalence and incidence of AF
• Risk stratification for stroke and bleeding
• New oral anticoagulants
• Guidelines
• Practical considerations for choosing an anticoagulant
PREVALENCE OF DIAGNOSED AF

Stratified by Age and Sex

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;55</td>
<td>530</td>
<td>1529</td>
</tr>
<tr>
<td>55-59</td>
<td>310</td>
<td>634</td>
</tr>
<tr>
<td>60-64</td>
<td>566</td>
<td>934</td>
</tr>
<tr>
<td>65-69</td>
<td>896</td>
<td>1426</td>
</tr>
<tr>
<td>70-74</td>
<td>1498</td>
<td>1907</td>
</tr>
<tr>
<td>75-79</td>
<td>1572</td>
<td>1886</td>
</tr>
<tr>
<td>80-84</td>
<td>1291</td>
<td>1374</td>
</tr>
<tr>
<td>&gt; 85</td>
<td>1132</td>
<td>759</td>
</tr>
</tbody>
</table>

QUESTION #1

An 82 year old man is in your office for an annual Medicare physical. What is the chance he has atrial fibrillation?

1. 1%
2. 5%
3. 10%
4. 25%
QUESTION #2

A 46 year old male patient is in for an annual physical exam. What is his lifetime risk of developing AF?

1. 1%
2. 5%
3. 10%
4. 25%
INCIDENCE OF AF

Lifetime Risk for AF at Selected Index Ages by Sex

<table>
<thead>
<tr>
<th>Index Age, yrs</th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>26.0% (24.0 – 27.0)</td>
<td></td>
<td>23.0% (21.0 – 24.0)</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>25.9% (23.9 – 27.0)</td>
<td></td>
<td>23.2% (21.3 – 24.3)</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>25.8% (23.7 – 26.9)</td>
<td></td>
<td>23.4% (21.4 – 24.4)</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>24.3% (22.1 – 25.5)</td>
<td></td>
<td>23.0% (20.9 – 24.1)</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>22.7% (20.1 – 24.1)</td>
<td></td>
<td>21.6% (19.3 – 22.7)</td>
<td></td>
</tr>
</tbody>
</table>

Prevalence and incidence of AF

Risk stratification for stroke and bleeding

New oral anticoagulants

Guidelines

Practical considerations for choosing an anticoagulant
QUESTION #3

68 year old female with atrial fibrillation and no other co-morbidities. How would you classify her stroke risk?

1. Low
2. Moderate
3. High
SCORING SYSTEMS IN STROKE RISK

• A variety of systems have been published
  – Outlined on next slide

• All use selected clinical characteristics to predict the risk of stroke

• Most widely used is the CHADS$_2$ score but being replaced by the CHA2DS2-VASc score

• All scores provide a rough estimate of risk of thrombosis in a population at similar risk as patient being reviewed
# CHADS<sub>2</sub>: RISK OF STROKE

National Registry of Atrial Fibrillation Participants (NRAF)

<table>
<thead>
<tr>
<th>CHADS&lt;sub&gt;2&lt;/sub&gt; Score</th>
<th># Patients (n = 1733)</th>
<th># Strokes (n = 94)</th>
<th>NRAF Crude Stroke Rate per 100 Patient-yrs</th>
<th>NRAF Adjusted Stroke Rate (95% CI)&lt;sup&gt;†&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>120</td>
<td>2</td>
<td>1.2</td>
<td>1.9 (1.2-3.0)</td>
</tr>
<tr>
<td>1</td>
<td>463</td>
<td>17</td>
<td>2.8</td>
<td>2.8 (2.0-3.8)</td>
</tr>
<tr>
<td>2</td>
<td>523</td>
<td>23</td>
<td>3.6</td>
<td>4.0 (3.1-5.1)</td>
</tr>
<tr>
<td>3</td>
<td>337</td>
<td>25</td>
<td>6.4</td>
<td>5.9 (4.6-7.3)</td>
</tr>
<tr>
<td>4</td>
<td>220</td>
<td>19</td>
<td>8.0</td>
<td>8.5 (6.3-11.1)</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>6</td>
<td>7.7</td>
<td>12.5 (8.2-17.5)</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>2</td>
<td>44.0</td>
<td>18.2 (10.5-27.4)</td>
</tr>
</tbody>
</table>

**Scoring:**
1 point: Congestive heart failure, HTN, < 75 years, and DM
2 points: Stroke history or transient ischemic attack
† Expected stroke rate per 100 pt-yrs from the exponential survival model, assuming aspirin not taken

### CHA$_2$DS$_2$-VASc

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure/LV dysfunction</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age $\geq$ 75 y</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td>2</td>
</tr>
<tr>
<td><strong>Vascular disease</strong></td>
<td>1</td>
</tr>
<tr>
<td><em>myocardial infarction, peripheral artery disease, or aortic plaque</em></td>
<td></td>
</tr>
<tr>
<td>Age 65-74 y</td>
<td>1</td>
</tr>
<tr>
<td><strong>Sex category</strong></td>
<td>1</td>
</tr>
<tr>
<td><em>(i.e. female gender)</em></td>
<td></td>
</tr>
</tbody>
</table>

LV = left ventricular; TE = thromboembolism

# CHA\textsubscript{2}DS\textsubscript{2}-VASC

## Stroke or Other TE at One Year

<table>
<thead>
<tr>
<th>CHA\textsubscript{2}DS\textsubscript{2}-VASC Score</th>
<th>#</th>
<th>#TE Events</th>
<th>TE Rate During 1 yr (95% CI)</th>
<th>1 TE Rate During 1 yr, Adjusted for Aspirin RX</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>103</td>
<td>0</td>
<td>0% (0-0)</td>
<td>0%</td>
</tr>
<tr>
<td>1</td>
<td>162</td>
<td>1</td>
<td>0.6% (0.0-3.4)</td>
<td>0.7%</td>
</tr>
<tr>
<td>2</td>
<td>184</td>
<td>3</td>
<td>1.6% (0.3-4.7)</td>
<td>1.9%</td>
</tr>
<tr>
<td>3</td>
<td>203</td>
<td>8</td>
<td>3.9% (1.7-7.6)</td>
<td>4.7%</td>
</tr>
<tr>
<td>4</td>
<td>208</td>
<td>4</td>
<td>1.9% (0.5-4.9)</td>
<td>2.3%</td>
</tr>
<tr>
<td>5</td>
<td>95</td>
<td>3</td>
<td>3.2% (0.7-9.0)</td>
<td>3.9%</td>
</tr>
<tr>
<td>6</td>
<td>57</td>
<td>2</td>
<td>3.6% (0.4-12.3)</td>
<td>4.5%</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>2</td>
<td>8.0% (1.0-26.0)</td>
<td>10.1%</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>1</td>
<td>11.1% (0.3-48.3)</td>
<td>14.2%</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>1</td>
<td>100% (2.5-100)</td>
<td>100%</td>
</tr>
<tr>
<td>Total</td>
<td>1,084</td>
<td>25</td>
<td></td>
<td>P Value for trend 0.003</td>
</tr>
</tbody>
</table>

### CHA$_2$DS$_2$-VASC AND CHADS$_2$ SCORE 0–1

Refines stroke risk stratification in AF patients: nationwide cohort

<table>
<thead>
<tr>
<th></th>
<th>1 Year Follow-up</th>
<th>12 Years Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Person Yrs</td>
<td>Events</td>
</tr>
<tr>
<td>CHA$_2$DS$_2$-VAsc = 0</td>
<td>6,919</td>
<td>58</td>
</tr>
<tr>
<td>CHA$_2$DS$_2$-VAsc = 1</td>
<td>8,880</td>
<td>159</td>
</tr>
<tr>
<td>CHA$_2$DS$_2$-VAsc = 2</td>
<td>11,863</td>
<td>435</td>
</tr>
<tr>
<td>CHA$_2$DS$_2$-VAsc = 3</td>
<td>11,473</td>
<td>660</td>
</tr>
<tr>
<td>CHA$_2$DS$_2$-VAsc = 4</td>
<td>1,137</td>
<td>93</td>
</tr>
</tbody>
</table>

| CHADS$_2$ score = 0 | 17,327 | 275 | 1.59 (1.41–1.79) | 92,531 | 1,182 | 1.28 (1.21–1.35) |
| CHA$_2$DS$_2$-VAsc = 0 | 6,919 | 58 | 0.84 (0.65–1.08) | 39,500 | 299 | 0.76 (0.68–0.85) |
| CHA$_2$DS$_2$-VAsc = 1 | 6,811 | 119 | 1.75 (1.46–2.09) | 35,079 | 504 | 1.44 (1.32–1.57) |
| CHA$_2$DS$_2$-VAsc = 2 | 3,347 | 90 | 2.69 (2.19–3.31) | 16,710 | 353 | 2.11 (1.90–2.34) |
| CHA$_2$DS$_2$-VAsc = 3 | 250 | 8 | 3.20 (1.60–6.40) | 1,242 | 26 | 2.09 (1.43–3.07) |
| CHA$_2$DS$_2$-VAsc = 4 | 2,069 | 40 | 1.93 (1.42–2.64) | 10,847 | 158 | 1.46 (1.25–1.70) |
| CHA$_2$DS$_2$-VAsc = 2 | 8,516 | 345 | 4.05 (3.65–4.50) | 34,885 | 1136 | 3.26 (3.07–3.45) |
| CHA$_2$DS$_2$-VAsc = 3 | 11,223 | 652 | 5.81 (5.38–6.27) | 44,557 | 1907 | 4.28 (4.09–4.48) |
| CHA$_2$DS$_2$-VAsc = 4 | 1,137 | 93 | 8.18 (6.68–10.02) | 4,380 | 216 | 4.93 (4.32–5.64) |

QUESTION #4

78 year old male with atrial fibrillation and hypertension (CHADS2 score = 2 [4% stroke rate per year]). What is his annual major bleeding rate?

1. 1%
2. 2%
3. 3%
4. 5%
5. 10%
BLEEDING RISK SCORES WIDELY USED IN AF

- HAEMORRHAGES\(^1\)
- HASBLED\(^2\)
- ATRIA Score\(^3\)

## BLEEDING RISK SCORES IN AF

<table>
<thead>
<tr>
<th>ATRIA</th>
<th>HAS-BLED</th>
<th>HEMORR₂HAGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia¹</td>
<td>Hypertension⁴</td>
<td>Hepatic¹⁰ or Renal disease²</td>
</tr>
<tr>
<td>Severe renal disease²</td>
<td>Abnormal Renal⁵ or Liver function⁶</td>
<td>Ethanol abuse</td>
</tr>
<tr>
<td>Age ≥75 yrs</td>
<td>Stroke</td>
<td>Malignancy</td>
</tr>
<tr>
<td>Any prior hemorrhage</td>
<td>Bleeding</td>
<td>Older Age (&gt;75 yrs)</td>
</tr>
<tr>
<td>Hypertension³</td>
<td>Labile INR⁸</td>
<td>Reduced platelet number or function¹¹</td>
</tr>
<tr>
<td></td>
<td>Elderly (&gt;65 yrs)</td>
<td>Rebleeding¹²</td>
</tr>
<tr>
<td></td>
<td>Drugs⁹ or Alcohol</td>
<td>Hypertension⁴</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anemia¹³</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Genetic factors¹⁴</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Excessive fall risk¹⁵</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stroke</td>
</tr>
</tbody>
</table>

1. Hemoglobin <13 g/dl men; <12 g/dl woman
2. Estimated glomerular filtration rate <30 ml/min or dialysis-dependent
3. Diagnosed hypertension
4. Systolic blood pressure >160 mmHg
5. Presence of chronic dialysis or renal transplantation or serum creatinine ≥200 mmol/L
6. Chronic hepatic disease (eg cirrhosis) or biochemical evidence of significant hepatic derangement (eg bilirubin 2 x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3 x upper limit normal, etc.)
7. Unstable/high INRs or poor time in therapeutic range (eg <60%)
8. Concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse etc.
9. Chronic, two-fold or greater elevation of AST or APT, or albumin <3.8 g/dl
10. Platelets <75,000, use of antiplatelet therapy (eg daily aspirin) or NSAID therapy; or blood dyscrasia
11. Cirrhosis, two-fold or greater elevation of AST or APT, or albumin <3.8 g/dl
12. Prior hospitalization for bleeding
13. Most recent hematocrit <30 or hemoglobin <10 g/dl
14. CYP2C9*2 and/or CYP2C9*3
15. Excessive fall risk
16. Alzheimer's dementia, Parkinson's disease, schizophrenia, or any condition predisposing to repeated falls

### AMADEUS COHORT

Stratified by the HEMORR$^2$HAGES, HAS-BLED, and ATRIA Schemes

<table>
<thead>
<tr>
<th>Scheme</th>
<th>All Patients</th>
<th>Clinically Relevant Bleeding</th>
<th>Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HEMORR$^2$HAGES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (≤1) Risk</td>
<td>1,738 (76.6)</td>
<td>182 (10.5)</td>
<td>25 (1.4)</td>
</tr>
<tr>
<td>Intermediate Risk (2–3)</td>
<td>517 (22.8)</td>
<td>63 (12.2)</td>
<td>13 (2.5)</td>
</tr>
<tr>
<td>High Risk (&gt;3)</td>
<td>13 (0.5)</td>
<td>3 (23.1)</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>2,268</td>
<td>248 (10.9)</td>
<td>39 (1.7)</td>
</tr>
<tr>
<td><strong>HAS-BLED</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Risk (&lt;3)</td>
<td>1,739 (75.9)</td>
<td>159 (9.1)</td>
<td>22 (1.3)</td>
</tr>
<tr>
<td>High Risk (≥3)</td>
<td>553 (24.1)</td>
<td>92 (16.6)</td>
<td>17 (3.1)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>2,292</td>
<td>251 (11.0)</td>
<td>39 (1.7)</td>
</tr>
<tr>
<td><strong>ATRIA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Risk (&lt;4)</td>
<td>2,038 (90)</td>
<td>220 (10.8)</td>
<td>31 (1.5)</td>
</tr>
<tr>
<td>Intermediate Risk (4)</td>
<td>102 (4.4)</td>
<td>13 (12.7)</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>High Risk (&gt;4)</td>
<td>128 (5.6)</td>
<td>18 (14.1)</td>
<td>5 (3.9)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>2,268</td>
<td>248 (10.9)</td>
<td>39 (1.7)</td>
</tr>
</tbody>
</table>
- Prevalence and incidence of AF
- Risk stratification for stroke and bleeding
- **New oral anticoagulants = NOACS**
- Guidelines
- Practical considerations for choosing an anticoagulant
# PHARMACOKINETICS OF NOACS

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct factor inhibition</td>
<td>Xa</td>
<td>IIa</td>
<td>Xa</td>
</tr>
<tr>
<td>Bioavailability ($F_{rel}$)</td>
<td>80%</td>
<td>6%</td>
<td>80%</td>
</tr>
<tr>
<td>Peak action ($t_{max}$)</td>
<td>1–3 hr</td>
<td>1–3 hr</td>
<td>1–3 hr</td>
</tr>
<tr>
<td>Protein binding</td>
<td>84%</td>
<td>35%</td>
<td>92–95%</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>25%</td>
<td>80%</td>
<td>33%</td>
</tr>
<tr>
<td>Elimination half life with creatinine clearance &gt; 80 ml/min</td>
<td>15.1 hr</td>
<td>13.8 hr</td>
<td>8.3 hr</td>
</tr>
<tr>
<td>Elimination half life with creatinine clearance 50–79 ml/min</td>
<td>14.6 hr</td>
<td>16.6 hr</td>
<td>8.7 hr</td>
</tr>
<tr>
<td>Elimination half life with creatinine clearance 30–49 ml/min</td>
<td>17.6 hr</td>
<td>18.7 hr</td>
<td>9.0 hr</td>
</tr>
<tr>
<td>Elimination half life with creatinine clearance &lt; 30 ml/min</td>
<td>17.3 hr</td>
<td>27.5 hr</td>
<td>9.5 hr</td>
</tr>
</tbody>
</table>

# MEASURING THE EFFECT OF NOACS

<table>
<thead>
<tr>
<th>Coagulation Assays</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>Not useful</td>
<td>Qualitative</td>
<td>Not useful</td>
</tr>
<tr>
<td>-dilute PT</td>
<td>Data n/a</td>
<td>Data n/a</td>
<td>Data n/a</td>
</tr>
<tr>
<td>-modified PT</td>
<td>Qualitative</td>
<td>Data n/a</td>
<td>Data n/a</td>
</tr>
<tr>
<td>aPTT</td>
<td>Not useful</td>
<td>Not useful</td>
<td>Qualitative</td>
</tr>
<tr>
<td>TT</td>
<td>No effect</td>
<td>No effect</td>
<td>Qualitative</td>
</tr>
<tr>
<td>-dTT/HEMOCLOT</td>
<td>No effect</td>
<td>No effect</td>
<td>Quantitative</td>
</tr>
<tr>
<td>Chromogenic Assays</td>
<td>Quantitative</td>
<td>Quantitative</td>
<td>No effect</td>
</tr>
<tr>
<td>-Anti-Xa</td>
<td>No effect</td>
<td>No Effect</td>
<td>Quantitative</td>
</tr>
<tr>
<td>-Anti-lla</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n/a = not available

# REVERSAL OF NOACS

## Types of Studies Evaluating Reversal of New Oral Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral activated charcoal</td>
<td>No data</td>
<td>In vitro</td>
<td>No data</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>No data</td>
<td>Human volunteers</td>
<td>No data</td>
</tr>
<tr>
<td>Hemoperfusion with activated charcoal</td>
<td>No data</td>
<td>In vitro</td>
<td>No data</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>No data</td>
<td>Mouse model</td>
<td>No data</td>
</tr>
<tr>
<td>Activated factor VIIa</td>
<td>No data</td>
<td>Rat model</td>
<td>Rat and baboon model</td>
</tr>
<tr>
<td>3-factor PCC</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>4-factor PCC</td>
<td>No data</td>
<td>Human volunteers and rat model</td>
<td>Human volunteers</td>
</tr>
</tbody>
</table>

META-ANALYSIS OF EFFICACY AND SAFETY OF NEW ORAL ANTICOAGULANTS

Dabigatran, Rivaroxaban, Apixaban vs. Warfarin in AF patients

### All cause stroke/SEE

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>n/N, NOA</th>
<th>n/N, Warfarin</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>0.66 (0.53, 0.82)</td>
<td>134/6076</td>
<td>202/6022</td>
<td>28.57</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>0.88 (0.75, 1.03)</td>
<td>269/7081</td>
<td>306/7090</td>
<td>37.22</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>0.80 (0.67, 0.95)</td>
<td>212/9120</td>
<td>265/9081</td>
<td>34.20</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.78 (0.67, 0.92)</td>
<td>615/22277</td>
<td>773/22193</td>
<td>100.00</td>
</tr>
</tbody>
</table>

#### Ischemic and unspecified stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>n/N, NOA</th>
<th>n/N, Warfarin</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>0.77 (0.61, 0.99)</td>
<td>111/6076</td>
<td>142/6022</td>
<td>27.29</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>0.91 (0.73, 1.13)</td>
<td>156/7061</td>
<td>172/7082</td>
<td>35.93</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>0.92 (0.75, 1.14)</td>
<td>162/9120</td>
<td>175/9081</td>
<td>36.78</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.87 (0.77, 0.99)</td>
<td>429/22257</td>
<td>489/22185</td>
<td>100.00</td>
</tr>
</tbody>
</table>

#### Hemorrhagic stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>n/N, NOA</th>
<th>n/N, Warfarin</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>0.26 (0.14, 0.50)</td>
<td>12/6076</td>
<td>45/6022</td>
<td>24.45</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>0.58 (0.37, 0.92)</td>
<td>29/7061</td>
<td>50/7082</td>
<td>34.94</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>0.51 (0.35, 0.75)</td>
<td>40/9120</td>
<td>78/9081</td>
<td>40.60</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.45 (0.31, 0.68)</td>
<td>81/22257</td>
<td>173/22185</td>
<td>100.00</td>
</tr>
</tbody>
</table>
META-ANALYSIS OF EFFICACY AND SAFETY OF NEW ORAL ANTICOAGULANTS

Dabigatran, Rivaroxaban, Apixaban vs. Warfarin in AF patients

HIGHLIGHTS

- Prevalence and incidence of AF
- Risk stratification for stroke and bleeding
- New oral anticoagulants
- Guidelines
- Practical considerations for choosing an anticoagulant
QUESTION #5

78 year old female with atrial fibrillation, hypertension and CHF.
CHADS$_2$ = 3
CHA$_2$DS$_2$-VASc = 5
HAS-BLED = 2

What would you use for stroke prevention?
1. No anticoagulation
2. Aspirin
3. Aspirin + clopidogrel
4. VKA antagonist
5. Dabigatran, Rivaroxaban or Apixaban
## Risk Factors

For Stroke and Thrombo-embolism in Non-valvular AF

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure/LV dysfunction*</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt;75**</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes Mellitus*</td>
<td>1</td>
</tr>
<tr>
<td>Stroke / TIA / Thrombo-embolism**</td>
<td>2</td>
</tr>
<tr>
<td>Vascular Disease*</td>
<td>1</td>
</tr>
<tr>
<td>Age 65-74*</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (i.e. female sex)*</td>
<td>1</td>
</tr>
</tbody>
</table>

**Note:** maximum score is 9 since age may contribute 0,1, or 2 points

* ‘Clinically relevant non-major’ risk factor

** “Major” risk factor
## EUROPEAN SOCIETY OF CARDIOLOGY GUIDELINES

### Approach to Thromboprophylaxis in Patients with AF

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>CHA&lt;sub&gt;2&lt;/sub&gt;DS&lt;sub&gt;2&lt;/sub&gt;-VASc Score</th>
<th>Recommended Antithrombotic Therapy&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>One ‘major’ risk factor or &gt; 2 ‘clinically relevant non-major’ risk factors</td>
<td>≥ 2</td>
<td>OAC</td>
</tr>
<tr>
<td>One ‘clinically relevant non-major’ risk factor</td>
<td>1</td>
<td>• Either OAC or aspirin 75-325 mg daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Preferred: OAC rather than aspirin</td>
</tr>
<tr>
<td>No risk factors</td>
<td>0</td>
<td>• Either aspirin 75-325 mg daily or no antithrombotic therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Preferred: no antithrombotic therapy rather than aspirin</td>
</tr>
</tbody>
</table>

### Risk of Bleeding

<table>
<thead>
<tr>
<th>Risk of Bleeding</th>
<th>HAS-BLED Score</th>
<th>Dabigatran Dosage&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>0–2</td>
<td>150 mg b.i.d.</td>
</tr>
<tr>
<td>Measurable risk, or 1 clinically-relevant non-major risk factor</td>
<td>≥3</td>
<td>110 mg b.i.d.</td>
</tr>
</tbody>
</table>

ACCP GUIDELINES

For patients with Nonrheumatic AF, including those with Paroxysmal AF

<table>
<thead>
<tr>
<th>Level of Risk</th>
<th>ACCP Recommendation</th>
<th>Alternative*</th>
<th>Not Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk (CHADS₂ = 0)</td>
<td>No Therapy</td>
<td>Aspirin</td>
<td>Oral anticoagulation or combination therapy with aspirin and clopidogrel</td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>Oral anticoagulation</td>
<td>Aspirin with clopidogrel</td>
<td>Aspirin</td>
</tr>
<tr>
<td>(CHADS₂ = 1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Risk (CHADS₂ = 2)</td>
<td>Oral anticoagulation (dabigatran 150 mg b.i.d. vs. VKA**)</td>
<td>Aspirin with clopidogrel</td>
<td>Aspirin</td>
</tr>
</tbody>
</table>

*For patients with AF unsuitable for, or who refuse, oral anticoagulant (for reasons other than concerns about major bleeding)

**VKA = adjusted-dose vitamin K antagonist

PREVENTING Atrial Fibrillation Related STROKES with Anticoagulants

HIGHLIGHTS

- Prevalence and incidence of AF
- Risk stratification for stroke and bleeding
- New oral anticoagulants
- Guidelines
- Practical considerations for choosing an anticoagulant
OPTIMAL CANDIDATES FOR NEW DRUGS

Patients who:

• Find **INR testing burdensome**

• Despite adherence to provider recommendations, have **low ‘time-in-range’**

• Can **afford** (or arrange to get) the new drugs

• Have **normal renal function**
OPTIMAL CANDIDATES FOR WARFARIN

Patients who:

- Have (borderline) renal insufficiency
- Are taking stable dose of warfarin and do not find INR testing burdensome
- Have access to self-testing machine
- Are concerned about the lack of an evidence-based reversal strategy
STROKE AND SYSTEMIC EMBOLISM

By Center TTR in RELY


- TTR=optimum therapeutic range
- cTTR=Center’s mean TTR
MAJOR BLEEDING

By Center TTR in RELY

- TTR=optimum therapeutic range
- cTTR=Center’s mean TTR

# StROKE AND SYSTEMIC EMBOLIZATION BY CENTER PROPORTION OF INR IN THERAPEUTIC RANGE IN ROCKET AF

<table>
<thead>
<tr>
<th>Center TTR‡</th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
<th>Rivaroxaban vs. Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rivaroxaban</td>
<td>Warfarin</td>
<td>Rivaroxaban vs. Warfarin</td>
</tr>
<tr>
<td></td>
<td>Event Rate (100 Pt Yrs)$</td>
<td>Total</td>
<td>Event Rate (100 Pt Yrs)$</td>
</tr>
<tr>
<td>0.00-50.6%</td>
<td>45/1735 (2.59)</td>
<td>1.77</td>
<td>62/1689 (3.67)</td>
</tr>
<tr>
<td>50.7%-58.5%</td>
<td>53/1746 (3.04)</td>
<td>1.94</td>
<td>63/1807 (3.49)</td>
</tr>
<tr>
<td>58.6-65.7%</td>
<td>54/1734 (3.11)</td>
<td>1.90</td>
<td>62/1758 (3.53)</td>
</tr>
<tr>
<td>65.7-100.0%</td>
<td>37/1676 (2.21)</td>
<td>1.33</td>
<td>55/1826 (3.01)</td>
</tr>
</tbody>
</table>

N=7061 rivaroxaban  N=7082 warfarin
P value for interaction=0.736
Time in therapeutic range-2-3 inclusive
‡Center TTR calculated using total INR values in target range from all warfarin subjects within center, divided by total INR values from all warfarin subjects within center
§Number of events per 100 patient-years of follow-up
II Hazard ratio from Cox proportional hazard model with treatment as a covariate

SUMMARY

- Prevalence and incidence of AF
- Risk stratification for stroke and bleeding
- New oral anticoagulants
- Guidelines
- Practical considerations for choosing an anticoagulant
HAS BLED SCORE

- Hypertension History (Uncontrolled, >160 mmHg systolic)
- Renal Disease: Dialysis, transplant, Cr > 2.6 mg/dL or > 200 µmol/L
- Liver Disease: Cirrhosis, Bilirubin > 2x Normal, AST/ALT/AP > 3x Normal
- Stroke History
- Prior Major Bleeding or Predisposition to Bleeding
- Labile INR (Unstable/high INRs), Time in Therapeutic Range < 60%
- Age > 65
- Medication Usage Predisposing to Bleeding (Antiplatelet agents, NSAIDs)
- Alcohol Usage History ≥ 8 drinks/week

- Risk was 0.9% in one validation study and 1.13 bleeds per 100 patient-years in another validation study.
Action Plan When OAC is Indicated and Patient Has High HAS-BLED Index

- Modify bleeding risk factors.
- Intensify surveillance for bleeding and for triggers that cause bleeding.
- Consider “renal dose” for NOAC, especially in the presence of some renal dysfunction or frailty or age ≥ 80 years.
- Monitor renal function with vigilance.
- Prescribe PPI when indicated.
Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group

PRIMARY OUTCOME IN ARISTOTLE
STROKE (ISCHEMIC OR HEMORRHAGIC) OR SYSTEMIC EMBOLISM

Apixaban 212 patients, 1.27% per year
Warfarin 265 patients, 1.60% per year
HR 0.79 (95% CI, 0.66–0.95); P (superiority)=0.011
P (non-inferiority)<0.001
21% RRR

No. at Risk
Apixaban 9120 8726 8440 6051 3464 1754
Warfarin 9081 8620 8301 5972 3405 1768
MAJOR BLEEDING IN ARISTOTLE
ISTH DEFINITION

Apixaban 327 patients, 2.13% per year
Warfarin 462 patients, 3.09% per year
HR 0.69 (95% CI, 0.60–0.80); P<0.001

31% RRR

No. at Risk
Apixaban  9088  8103  7564  5365  3048  1515
Warfarin  9052  7910  7335  5196  2956  1491

Percent with Event
0  2  4  6  8

Months
0  6  12  18  24  30
New Anticoagulant Therapies Compared to Warfarin: All-cause Mortality

- Dabigatran 150 mg b.i.d.
- Dabigatran 110 mg b.i.d.
- Rivaroxaban 20 mg o.d.
- Abixaban 5 mg b.i.d.

References:
Connolly S et al NEJM 2009; Patel M et al NEJM 2011; Granger CB et al NEJM 2011
<table>
<thead>
<tr>
<th></th>
<th>RE-LY (Dabigatran)</th>
<th>ARISTOTLE (Apixaban)</th>
<th>ENGAGE AF-TIM 48* (Edoxaban)</th>
<th>ROCKET-AF (Rivaroxaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#Enrolled</td>
<td>18,113</td>
<td>18,201</td>
<td>21,105</td>
<td>14,264</td>
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<tr>
<td>Age (yrs)</td>
<td>72 ± 9</td>
<td>70 [63-76]</td>
<td>72 [64-77]</td>
<td>73 [65-78]</td>
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<tr>
<td>Female</td>
<td>36%</td>
<td>35%</td>
<td>38%</td>
<td>40%</td>
</tr>
<tr>
<td>CHADS2 score ≥3</td>
<td>32%</td>
<td>30%</td>
<td>52%</td>
<td>87%</td>
</tr>
<tr>
<td>VKA naive</td>
<td>50%</td>
<td>43%</td>
<td>41%</td>
<td>38%</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>33%</td>
<td>15%</td>
<td>25%</td>
<td>18%</td>
</tr>
<tr>
<td>Prior stroke/TIA</td>
<td>20%</td>
<td>19%</td>
<td>18% / 12%</td>
<td>55%**</td>
</tr>
<tr>
<td>Diabetes</td>
<td>23%</td>
<td>25%</td>
<td>36%</td>
<td>40%</td>
</tr>
<tr>
<td>Prior CHF</td>
<td>32%</td>
<td>35%</td>
<td>56%</td>
<td>62%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>79%</td>
<td>87%</td>
<td>90%</td>
<td>91%</td>
</tr>
</tbody>
</table>

*Preliminary data

**includes prior systemic embolism

Ruff CR et al. Am Heart J 2010; 160:635-41
# Pivotal Atrial Fibrillation Trials
## Results to Date

<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>150 BID</td>
<td>Rivaroxaban 20 mg qd</td>
</tr>
<tr>
<td>Stroke + SEE</td>
<td>non-infer</td>
<td>Superior</td>
<td>ITT cohort: non-infer. On Rx cohort: 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>similar</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>Lower</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 ANTICOAGULANTS IN RENAL FAILURE.

- **Apixaban (ELIQUIS)** (25% Renal 75% Hepatic metabolism)
  - In Apixaban (Eliquis) if two of the following present reduce the dose to 2.5 bid. (Creatinine >1.5, age ≥80 years or body weight ≤60 kg)
  - The recommended dose for patients with end-stage renal disease (ESRD) maintained on hemo dialysis is 5 mg twice daily. Reduce dose to 2.5 mg twice daily if one of the following patient characteristics (age ≥80 years or body weight ≤60 kg) is present.

- **Xarelto** (51% Renal 49% hepatic metabolism)
  - Patients with CrCl 30 to 50 mL/min were administered XARELTO 15 mg once daily resulting in serum concentrations of rivaroxaban and clinical outcomes similar to those in patients with better renal function administered XARELTO 20 mg once daily. (Patients with Cr Cl <30 ml/min not studied).

- **Dabigantran (Pradaxa)** (80% renal cleared)
  - For patients with creatinine clearance (CrCl) >30 mL/min, the recommended dose of PRADAXA is 150 mg taken orally, twice daily. For patients with severe renal impairment (CrCl 15-30 mL/min), the recommended dose of PRADAXA is 75 mg twice daily. Dosing recommendations for patients with a CrCl <15 mL/min or on dialysis cannot be provided.
AF triggers

Right Atrium
- Superior Vena Cava
- Some triggers here in crista, SVC junction, etc
- Inferior Vena Cava

Left Atrium
- Localization of the PV foci
  % based on the analysis of 69 foci identified in the PVs from 45 patients
- RSPV 26%
- LSPV 48%
- RIPV 9%
- LIPV 17%

Some triggers non-venous - mitral annulus, LAA, CS etc

>90% of AF triggers found in PVs

Haissaguerre et al NEJM 1998
ELECTROPHYSIOLOGIC MECHANISMS OF AF

- Autonomic Influence
- Wavelets and Rotors
- PV and LA Triggers
- Focal Triggers leading to initiation of reentry and wavelets
WHICH STRATEGY IS BETTER IN HEART FAILURE PATIENTS?

RHYTHM CONTROL VERSUS RATE CONTROL FOR ATRIAL FIBRILLATION AND HEART FAILURE TRIAL

NEJM 358:2667-2677  JUNE 19, 2008
Common practice is to restore and maintain sinus rhythm in patients with AF and heart failure. This approach is based in part on data indicating that AF is a predictor of death in patients with heart failure and suggesting that the suppression of AF may favorably affect the outcome.

Methods A multicenter, randomized trial comparing the maintenance of sinus rhythm (rhythm control) with control of the ventricular rate (rate control) in patients with EF 35% or less, symptoms of congestive heart failure, and a history of AF. The primary outcome was the time to death from cardiovascular causes, as compared with a rate-control strategy.
RESULTS OF AF CHF

*Results* A total of 1376 patients were enrolled (682 in the rhythm-control group and 694 in the rate-control group) and were followed for a mean of 37 months. Of these patients, 182 (27%) in the rhythm-control group died from cardiovascular causes, as compared with 175 (25%) in the rate-control group (hazard ratio in the rhythm-control group, 1.06; 95% confidence interval, 0.86 to 1.30; *P*=0.59 by the log-rank test).

- Secondary outcomes also did not differ significantly between the two treatment strategies:
  - All-cause death: 32% and 33%, *P*= 0.73
  - Stroke: 3% and 4%, *P*= 0.32
  - Worsening heart failure: 28% and 31%, *P*= 0.17
  - Composite of CV death, stroke, worsening heart failure: 43% and 46%, *P*= 0.20

There were also no significant differences favoring either strategy in any predefined subgroup.
The Mortality Issue: Does Normal Sinus Rhythm (NSR) Increase Survival?

Five prospective rate vs rhythm trials have been reported:
STAF (n=200), PIAF (n=252), HOT CAFÉ (n=205), RACE (n=522), AFFIRM (n=4060)

In all 5, there was no survival benefit associated with a rhythm-control strategy.

RACE and AFFIRM demonstrated a slight risk with a rhythm-control approach.
WHY HASN’T RHYTHM CONTROL WORKED IN TRIALS?

- Drugs used in trials don’t guarantee rhythm control
- Toxicity of Antiarrythmic drugs contribute to lack of benefit of rhythm control groups.
- AF may be a marker of poor prognosis, in which the primary problem is poor ventricular function, neurohormonal activation, or inflammation, with no independent effect of atrial fibrillation on outcome.
IF DRUGS DON’T WORK, WILL ABLATION?

• AF Ablation
  • eliminates confounding contributions of low efficacy and high toxicity associated with antiarrhythmic drug therapy
  • may better determine the desirability of maintaining sinus rhythm in patients with atrial fibrillation.
  • Clinical Trials are in progress comparing catheter ablation of atrial fibrillation to conventional antiarrhythmic drug therapy.
  • AF Ablation has yet to be proven to be better than rate control.
RATE VERSUS RHYTHM CONTROL

Favors rate control or limited intervention

Cautious DC of AC?

Favors rhythm control

Frequent

Not A/C

Rapid HR

No significant symptoms

Slow

Infrequent

Significant symptoms
Medication for Atrial Fibrillation

<table>
<thead>
<tr>
<th>Medication Type</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
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</thead>
<tbody>
<tr>
<td>Cardiac Glycosides</td>
<td>500</td>
<td>600</td>
<td>700</td>
<td>800</td>
<td>900</td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td>100</td>
<td>150</td>
<td>200</td>
<td>250</td>
<td>300</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>200</td>
<td>250</td>
<td>300</td>
<td>350</td>
<td>400</td>
</tr>
<tr>
<td>Antiarrhythmic Agents</td>
<td>100</td>
<td>150</td>
<td>200</td>
<td>250</td>
<td>300</td>
</tr>
</tbody>
</table>

Number of AF Rx


IMS data.
DRUGS USED FOR ATRIAL FIB

- Flecanide
- Dofetilide
- Propafenone
- Sotolol
- Amiodarone
- Dronedarone
Outpatient Maintenance of Sinus Rhythm: Promising Role of the “Pill-in-Pocket” Approach

- For patients with sporadic episodes of AF, intermittent rather than daily administration of antiarrhythmics is an acceptable treatment option.
ACC/AHA/ESC Guidelines For The Management Of Patients With AF

Class 1: Before initiating antiarrhythmic drug therapy, treatment of precipitating or reversible causes of AF is recommended. (no change)

Class 2a:
1) Pharmacologic therapy can be useful in patients with AF to maintain sinus rhythm and prevent tachycardia-induced cardiomyopathy. (nc)

2) Infrequent, well-tolerated recurrence of AF is reasonable as a successful outcome of antiarrhythmic drug therapy. (nc)

ACC/AHA/ESC Guidelines For The Management Of Patients With AF

Class 2a:
3) Outpatient initiation of antiarrhythmic drug therapy is reasonable in patients with AF who have no associated heart disease when the agent is well tolerated.

3) Outpatient initiation of antiarrhythmic drug treatment is appropriate in selected patients (01).

Class 2b:
1) Administer pharm agents to maintain sinus rhythm in asymptomatic patients to prevent atrial remodeling.
2) Administer pharm agents to maintain sinus rhythm to prevent thromboembolism or HF in selected patients.
3) Administer combinations of AA agents to maintain sinus rhythm when single drug therapy fails.

ACC/AHA/ESC Guidelines For The Management Of Patients With AF

Class 2a:

4) In patients with lone AF without structural heart disease, initiation of propafenone or flecainide can be beneficial on an outpatient basis in patients with paroxysmal AF who are in sinus rhythm at the time of drug initiation.

5) Sotalol can be beneficial in outpatients in sinus rhythm with little or no heart disease, prone to paroxysmal AF, if the baseline uncorrected QT interval is less than 460 msec, serum electrolytes are normal, and risk factors associated with class 3 drug-related proarrhythmia are not present.

ACC/AHA/ESC Guidelines For The Management Of Patients With AF

Class 3:
1) Antiarrhythmic therapy with a particular drug is not recommended for maintenance of sinus rhythm in patients with AF who have well-defined risk factors for proarrhythmia with that agent. (nc)

2) Pharmacologic therapy is not recommended for maintenance of sinus rhythm in patients with advanced sinus node disease or AV node dysfunction unless they have a functioning electronic cardiac pacemaker. (nc)

Does the treatment of AF improve survival, improve QOL, both, or neither?
For the most part, the efficacy IA, IC, and III AADs for the suppression of AF are similar. Amiodarone has been considered as more potent, but this has not been a uniform finding.
AMIODARONE SIDE EFFECTS

- Skin toxicity
- Cataracts
- Lung fibrosis
- Liver damage
- Hypo/hyperthyroid

Paul Karason and his girlfriend, Jackie Northrup.
INDICATIONS FOR CATHETER ABLATION OF ATRIAL FIBRILLATION

Indications for Catheter AF Ablation
- Symptomatic AF refractory or intolerant to at least one Class 1 or 3 antiarrhythmic medication.
- In rare clinical situations, it may be appropriate to perform AF ablation as first line therapy.
- Selected symptomatic patients with heart failure and/or reduced ejection fraction.
- The presence of a LA thrombus is a contraindication to catheter ablation of AF.

Indications for Surgical AF Ablation
- Symptomatic AF patients undergoing other cardiac surgery.
- Selected asymptomatic AF patients undergoing cardiac surgery in whom the ablation can be performed with minimal risk.
- Stand-alone AF surgery should be considered for symptomatic AF patients who prefer a surgical approach, have failed one or more attempts at catheter ablation, or are not candidates for catheter ablation.
Left Atrial Circumferential Ablation

(1) PV isolation for trigger initiation of AF
(2) Ablation of areas of potential reentry rotors/wavelets
(3) Transect the vein of Marshall
(4) Vagal denervation altering electrophysiologic substrate
AF triggers

Right Atrium

- Superior Vena Cava
- Some triggers here in crista, SVC junction, etc
- Inferior Vena Cava

Left Atrium

- Septum
- Localization of the PV foci % based on the analysis of 69 foci identified in the PVs from 45 patients
- RSPV 26%
- LSPV 48%
- RIPV 9%
- LIPV 17%

Some triggers non-venous - mitral annulus, LAA, CS etc

>90% of AF triggers found in PVs

Haissaguerre et al NEJM 1998
BALLOON CATHETER TECHNOLOGY IN AF ABLATION

- **HIFU (High-frequency Ultrasound)**: noncontact technique with tissue heating

- **Cryoablation**: tissue contact and freezing

- **Laser (infrared)**: tissue contact and heating
CATHETER ABLATION

*Ablation strategies target the PVs and or PV antrum.

*Complete electrical isolation should be the goal.
IMAGE INTEGRATION AND IMAGE-GUIDED MAPPING AND ABLATION

- 3-Dimensional Electroanatomical Mapping (EAM) systems are used to construct image of the left atrium
- This image is merged into a LA CT or MRI scan
- Using intracardiac ultrasound, the antrum of the pulmonary veins can be reliably determined
- The location and delivery of radiofrequency energy can be monitored and tracked with the 3-D EAM system
COMMON LESION SETS USED IN AF ABLATION
ICE IMAGES

[Image of an ultrasound scan with technical details and a screen capture of the imaging equipment.]
Observational Trials of AF Ablation:
% Pts Free of AF (6-30 months)

modified from Packer Boston AFS 2005
Controlled Trials of AF Ablation: Pts Free of AF (% at 1 year)

- RAAFT: 87%
- CACAF: 56%
- A4: 75%
- APAF: 86%
- Milan/NR*: 79%
- PABA CHF*: 86%
Pooled Studies: Observational and RCTs
% Patients Free of AF at 1-2 Years

OBS: N=1,965; 8 Studies

RCT: N=517; 4 Studies
Predictors of Clinical Outcome with Catheter Ablation for AF

Predictors of Favorable Outcome
- Paroxysmal > persistent
- % area of left atrium encircled (Pappone)
- Intra-procedural vagal response (Pappone)
- Reduced HRV post procedure (Pappone)
- Increased resting heart rate post ablation (Nilssen)
- Non-inducibility at end of ablation (Oral, Haissaguerre)
- No atrial tachyarrhythmia in blanking period

Predictors of Unfavorable Outcome
- Extensive fibrosis – left atrial scar (Verma)
- Extreme left atrial enlargement
- Hypertrophic cardiomyopathy
Adverse Outcomes of AF Ablation

- Death
- Atrio-esophageal fistula
- Stroke
- Tamponade
- Pulmonary vein stenosis
- Phrenic nerve palsy
- Retroperitoneal hematoma
- Femoral Vascular Complications
- Pericarditis
- Catheter entrapment
- Delayed gastric emptying
- Repeat catheter ablation
AF Ablation: Major Complication Rates

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Complication Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>WW Survey</td>
<td>5.9</td>
</tr>
<tr>
<td>European Reg.</td>
<td>4.8</td>
</tr>
<tr>
<td>CACAF</td>
<td>4.4</td>
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<tr>
<td>A4</td>
<td>3.3</td>
</tr>
<tr>
<td>RAAFT</td>
<td>3</td>
</tr>
<tr>
<td>APAF</td>
<td>2</td>
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<tr>
<td>Average-All</td>
<td>3.9</td>
</tr>
<tr>
<td>Average-RCT</td>
<td>3.2</td>
</tr>
</tbody>
</table>
What do we know about Catheter Ablation of AFib?

- It is effective for many patients with AF that is paroxysmal, persistent and permanent
- The success rate seems to decline over time, particularly for persistent or permanent AF
- The success rate is lower for more advanced AF
- It seems to markedly improve quality of life for many (most) patients with drug refractory and symptomatic AF
- Carries significant risks
- No trial has addressed whether this strategy improves mortality or stroke risk
- No trial has addressed whether it is safe to stop anticoagulation
Which Therapy Should We Employ?

AF Treatment Pathways

Rate control

- Pharmacologic: Ca²⁺ blockers, β-blockers, Digitalis, Amiodarone
- Nonpharmacologic: Ablate and pace

Prevent Remodeling

Maintainance of SR

Class IA
Class IC
Class III
β-blocker

Pharmacologic

- CCB
- ACE-I, ARB
- Statins?
- Fish oil?

Nonpharmacologic

- Catheter ablation
- Pacing
- Surgery
- Implantable devices

Stroke prevention

Pharmacologic: Warfarin, Aspirin, Thrombin inhibitor
Nonpharmacologic: Removal/isolation, LA appendage

From Prystowsky, Modified by Reiffel

Substrate modification: Many Patients
Rhythm control: Selected Patients
Rate control: All Patients
Anticoagulation: Many Patients
AFFIRM: Prevalence of Sinus Rhythm at Follow-up

<table>
<thead>
<tr>
<th>Time</th>
<th>Rate N:</th>
<th>Rhythm N:</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>1957</td>
<td>1960</td>
</tr>
<tr>
<td>2 Mo</td>
<td>1927</td>
<td>1945</td>
</tr>
<tr>
<td>4 Mo</td>
<td>1913</td>
<td>1920</td>
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<td>1692</td>
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<tr>
<td>3 Yr</td>
<td>1194</td>
<td>1213</td>
</tr>
<tr>
<td>4 Yr</td>
<td>710</td>
<td>713</td>
</tr>
<tr>
<td>5 Yr</td>
<td>231</td>
<td>262</td>
</tr>
</tbody>
</table>

Even With Ablation....

Even with ablation, choices need to be made with regard to technique (which is still evolving) and acceptability of risks.

- Perforation
- Embolic
- Fistula
- Valvular/coronary
- Radiation
- Vascular
- “Re-Do’s”
- etc

Modified from J. Ruskin, M.D.
Increasing Role for Catheter Ablation

- Initial Guidelines (2001): limited data
- Included in the AF treatment algorithm as an alternative for patients who fail therapy with AADs
- Radiofrequency ablation may be preferred in young patients who are very symptomatic
- May be an effective adjunct procedure for patients undergoing cardiac surgery (e.g., bypass, valve repair)

ATRIAL ARRHYTHMIA-RELATED HOSPITALIZATIONS IN THE U.S.

Atrial Fibrillation - 21%
Ventricular Fibrillation - 2%
Ventricular Tachycardia - 10%
Miscellaneous - 21%
Conduction Abnormalities - 8%
Sick Sinus Syndrome - 9%
Premature beats - 6%
Paroxysmal Supraventricular Tachycardia - 6%
Atrial Flutter - 4%
Atrial Fibrillation - 21%

Stroke rate is approximately 1-3% without anticoagulation

Adapted from Bialy et al.
WHY RESTORE SINUS RHYTHM?

- Reduce symptoms
- Decrease stroke risk - Unproven
- Preserve ventricular function
- Reduce mortality - Unproven
Age and Risk of Stroke in Atrial Fibrillation
Framingham Study

<table>
<thead>
<tr>
<th>Age group (yrs)</th>
<th>Estimated RR</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>50–59</td>
<td>4.1</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>60–69</td>
<td>2.6</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>70–79</td>
<td>4.0</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>80–89</td>
<td>4.8</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

RR = relative risk
Annual Event Rates per Age Groups

According to Risk Factors (Warfarin vs Control)

- Control
- Warfarin

Event Rate (%)

Age
<65
65-75
>75

no risk factors
≥1 risk factor

Adapted from Arch Int Med 1994;154:1454
ANTIARRHYTHMIC DRUGS FOR TREATMENT OF ATRIAL FIBRILLATION

• Class I Drugs
  • IA (avoid in patients with CAD, LVH, CM)
    • Disopyramide for vagally mediated AF
  • IC (avoid in pts with CAD, LVH, CM)
    • Flecainide 100-225mg bid
    • Propafenone 150-225 mg tid or bid

• Class III Drugs
  • Sotalol 80-160 mg bid (may not be tolerated in CHF)
  • Dofetilide 0.125-0.625 mg bid (may be used in CHF, but must watch QTc, K+, creatinine)
  • Amiodarone 100-200 mg daily (drug of choice in pts with CHF)
INADEQUATE HEART RATE CONTROL IN ATRIAL FIBRILLATION

• Average resting heart rate in excess of 100 bpm
• Maximum or peak heart rate in excess of 150 bpm during exercise
CLINICAL CONSEQUENCES OF INADEQUATE HEART RATE CONTROL IN ATRIAL FIBRILLATION

- Symptoms including palpitations, fatigue, weakness, shortness of breath, chest pain, lightheadedness or syncope
- Adverse hemodynamic effects include hypotension, provocation of ischemia, and aggravation of congestive heart failure
- Development of a tachycardia mediated cardiomyopathy
LV DYSFUNCTION DUE TO RVR IN PATIENTS WITH ATRIAL FIBRILLATION

CHRONIC PHARMACOLOGIC RATE CONTROL IN ATRIAL FIBRILLATION

• Calcium Channel Blockers:
  • Verapamil: 180 - 360 mg daily
  • Diltiazem: 180 - 360 mg daily

• Beta Blockers:
  • Metoprolol: 25 - 100 mg once or twice daily
  • Cardevolol: 3.125 – 50 mg twice daily

• Digoxin: Oral dose 0.125 - 0.5 mg once daily

• Combination of above

(Assess rate control with continuous ambulatory monitoring)
AV Node Ablation
AV NODE ABLATION
AV NODE ABLATION WITH COMPLETE AV BLOCK AND VVIR PACEMAKER
EFFECT OF AV NODE ABLATION AND PACEMAKER ON LVEF IN A PT

ICE TO GUIDE TRANSEPTAL PUNCTURE TO REDUCE RISK OF PERFORATION
Lasso Catheter Mapping of PV
3D CT ANGIOGRAM IMPORTED INTO CARTO™ MAPPING SYSTEM
QOL Following Ablation vs. Medical Therapy for AF

Adverse Event Rates Following Ablation vs. Medical Therapy for AF

LV Function after AF Ablation in Patients with or Without CHF

Hsu LF, et. al., NEJM 351:2372-83, 2004
Observed and Expected Survival After Ablation vs. Medical Therapy for AF

SUMMARY

• The treatment of atrial fibrillation is a rapidly evolving area of cardiac electrophysiology, which may be indicated for prevention of symptoms, alleviation of CHF, and reduction of risk of stroke, and mortality.

• Innovations in ablation therapy of atrial fibrillation in the future, including advances in mapping and ablation techniques and possibly alternative energy sources such as microwave ablation, may improve success rates and reduce risk of complications.
Thrombo-embolic risk stratification

- Newly devised HAS-BLED score predictive tool for bleeding AF patients on warfarin

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>H Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A Abnormal liver/renal function</td>
<td>1-2</td>
</tr>
<tr>
<td>S Stroke</td>
<td>1</td>
</tr>
<tr>
<td>B Prior major bleeding or predisposition</td>
<td>1</td>
</tr>
<tr>
<td>L Labile INRs</td>
<td>1</td>
</tr>
<tr>
<td>E Elderly (&gt;65yrs)</td>
<td>1</td>
</tr>
<tr>
<td>D Drugs/alcohol concomitantly</td>
<td>1-2</td>
</tr>
</tbody>
</table>
Thrombo-embolic risk stratification

Balancing the risks and benefits of warfarin:

No warfarin if:

HAS-BLED > CHADS\(_2\) or
HAS-BLED >2 in CHADS\(_2\) 0/1
HAS-BLED >3 in CHADS\(_2\) 2

Using this algorithm would reduce >10% of major bleeds
High stroke risk but high bleeding risk - stop thrombus forming in appendage

Sievert et al *Circulation* 2002;105:1887-1889
Percutaneous closure of appendage

Left atrial angiogram:
(a) after trans-septal puncture and LAA cannulation, contrast injection outlines LAA from which an ostial diameter can be measured;
(b) contrast injection via a lumen through the implant reveals hang up of dye behind the sealing surface, indicating proper position and occlusion;
(c) after device release, contrast injection in the LA establishes complete seal.
Ablation: a cure for AF?

Substrate evolution leads to a change in ablation technique

<table>
<thead>
<tr>
<th>AF type:</th>
<th>Paroxysmal</th>
<th>Persistent</th>
<th>Permanent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Role of pulmonary veins:</td>
<td>PVI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Role of muscle &amp; scar:</td>
<td>Substrate &amp; hybrid</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ablation:
Stroke Prevention in Atrial Fibrillation

- Etiology of Stroke in Atrial Fibrillation
- The ACTIVE-I Study

- Ischemic 80%
- Hemorrhagic 20%
- Other 5%
- Lacunar 20%
- Thromboembolic 10%
- Cardioembolic 20%
- Unknown 25%
- SAH 10%
- ICH 10%

*Stroke 2006; 37: 2493-8.*
Stroke Prevention in Atrial Fibrillation

-Efficacy of Warfarin
-Meta-Analysis of Antithrombotic Therapy in A Fib

Adjusted-dose warfarin compared with placebo or control

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFASAK I</td>
<td>1989; 1990</td>
</tr>
<tr>
<td>SPAF I</td>
<td>1991</td>
</tr>
<tr>
<td>BAATAF</td>
<td>1990</td>
</tr>
<tr>
<td>CAFA</td>
<td>1991</td>
</tr>
<tr>
<td>SPINAF</td>
<td>1992</td>
</tr>
<tr>
<td>EAFT</td>
<td>1993</td>
</tr>
</tbody>
</table>

All trials (n=6) N=2,900

Relative Risk Reduction (95% CI)

- Favors Warfarin
- Favors Placebo or Control

Stroke Prevention in Atrial Fibrillation

-Limitations of Warfarin Therapy in Atrial Fibrillation

Warfarin therapy has several limitations that make it difficult to use in practice:

- Unpredictable response
- Slow onset/offset of action
- Narrow therapeutic window (INR range 2-3)
- Numerous food-drug interactions
- Routine coagulation monitoring
- Numerous drug-drug interactions
- Frequent dose adjustments
- Risk of Bleeding Complications

- Warfarin was #1 in 2003 and 2004 in the number of mentions of “deaths for drugs causing adverse effects in therapeutic use”
- Warfarin caused 6% of the 702,000 ADEs treated in the ED/year; 17% required hospitalization
Stroke Prevention in Atrial Fibrillation

- Limitations of Warfarin Therapy in Atrial Fibrillation
- Narrow Therapeutic Window

The anticoagulant effect of warfarin is optimized when therapeutic doses are maintained within a very narrow range.

International Normalized Ratio (INR)


Target INR
(2.0-3.0)
Analyzed 597 patients with a first ischemic stroke who had known atrial fibrillation, were classified as high risk for stroke, and who had no known contraindications to anticoagulation.


Stroke Prevention in Atrial Fibrillation
-Limitations of Warfarin Therapy in Atrial Fibrillation
-Preventable Strokes in Patients with Atrial Fib

- No warfarin: 61%
- INR at Target: 10%
- Subtherapeutic INR: 29%

Analyzed 597 patients with a first ischemic stroke who had known atrial fibrillation, were classified as high risk for stroke, and who had no known contraindications to anticoagulation.

• Analyzed 323 patients with a second ischemic stroke who had known atrial fibrillation at the time of their first stroke, and who had no known contraindications to anticoagulation
Lack of Concordance Between Empirical Scores and Physician Assessment of Stroke and Bleeding Risk in Atrial Fibrillation: A Clinical Perspective

by Benjamin A. Steinberg, Sunghee Kim, Laine Thomas, Gregg C. Fonarow, Marc A. Hylek, Jack Ansell, Alan S. Go, Paul Chang, Peter Kowey, Bernard J. Gersh, Kenneth W. Mahaffey, Daniel E. Singer, Jonathan P. Piccini, and Eric D. Peterson

Circulation
Volume 129(20):2005-2012
May 20, 2014
Categorization of physician-assigned and empirical risk of stroke (A)
CHA2DS2-VASC SCORING SYSTEM

- Congestive Heart Failure
- Hypertension
- Age (65-74 years = 1; 75 years + = 2)
- Diabetes
- Stroke/TIA/Thromboembolism = 2
- VAscular Disease (CAD,PVD)
- Sex (gender) Female
AF Stroke Risk Evaluation

<table>
<thead>
<tr>
<th>CHADS2 score</th>
<th>Patients ((n = 1733))</th>
<th>Adjusted stroke rate %/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>120</td>
<td>1.9</td>
</tr>
<tr>
<td>1</td>
<td>463</td>
<td>2.8</td>
</tr>
<tr>
<td>2</td>
<td>523</td>
<td>4.0</td>
</tr>
<tr>
<td>3</td>
<td>337</td>
<td>5.9</td>
</tr>
<tr>
<td>4</td>
<td>220</td>
<td>8.5</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>12.5</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>18.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHA2DS2-VASc score</th>
<th>Patients ((n = 7329))</th>
<th>Adjusted stroke rate %/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>422</td>
<td>1.3</td>
</tr>
<tr>
<td>2</td>
<td>1230</td>
<td>2.2</td>
</tr>
<tr>
<td>3</td>
<td>1730</td>
<td>3.2</td>
</tr>
<tr>
<td>4</td>
<td>1718</td>
<td>4.0</td>
</tr>
<tr>
<td>5</td>
<td>1159</td>
<td>6.7</td>
</tr>
<tr>
<td>6</td>
<td>679</td>
<td>9.8</td>
</tr>
<tr>
<td>7</td>
<td>294</td>
<td>9.6</td>
</tr>
<tr>
<td>8</td>
<td>82</td>
<td>6.7</td>
</tr>
<tr>
<td>9</td>
<td>14</td>
<td>15.2</td>
</tr>
</tbody>
</table>

From ESC AF Guidelines. (http://www.ehj-euorg/guidelines/neantageguidelines/)
GuidelineECHoMenEGCGuidelines2011AF.pdf

37
HAS-BLED SCORING SYSTEM

- Hypertension
- Abnormal Renal and/or Liver Function
- Stroke history
- Bleeding history
- Labile INR measurements (warfarin)
- Elderly (age 65 and up)
- Drug and/or Alcohol use
AF Bleeding Risk Evaluation

<table>
<thead>
<tr>
<th>HAS-BLED Score</th>
<th>1 year Bleeding risk</th>
<th>Bleeds/100 pt-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.9%</td>
<td>1.13</td>
</tr>
<tr>
<td>1</td>
<td>3.4%</td>
<td>1.02</td>
</tr>
<tr>
<td>2</td>
<td>4.1%</td>
<td>1.88</td>
</tr>
<tr>
<td>3</td>
<td>5.8%</td>
<td>3.72</td>
</tr>
<tr>
<td>4</td>
<td>8.9%</td>
<td>8.70</td>
</tr>
<tr>
<td>5</td>
<td>9.1%</td>
<td>12.50</td>
</tr>
<tr>
<td>6 – 9</td>
<td>Insufficient data</td>
<td>Insufficient data</td>
</tr>
</tbody>
</table>
The Promise of New Anticoagulants
ATRIAL FIBRILLATION 2014
NEWER ORAL ANTICOAGULANTS (NOAC)

Dabigatran
- RE-LY Published 2009
  - Dabigatran Approved

Rivaroxaban
- ROCKET AF Published August 2011
  - Rivaroxiban Approved
- ARISTOTLE Published August 2011
- Apixiban Approved

Apixaban
- YOU ARE HERE!
- AVERROES Published February 2011
- You are here!
THE CLOTTING FACTORS

- Coagulation cascade
  - Initiation
    - TF/VIIa
  - Propagation
    - IX
    - IXa
    - VIIa
  - Thrombin activity
    - Xa
    - Va
    - II
    - IIa
- Fibrinogen
  - Fibrin
WARFARIN AFFECTS CLOTTING FACTORS

- Coagulation cascade
  - Initiation
    - TF/VIIa
  - Propagation
    - X
    - IX
    - VIIa
    - IXa
  - Thrombin activity
    - Xa
    - Va
    - II
    - IIa
- Fibrinogen → Fibrin
NEWER ANTICOAGULANTS

Coagulation cascade

- Initiation
  - TF/VIIa

- Propagation
  - X
  - Xa
  - IXa
  - IX
  - VIIa

- Thrombin activity
  - II
  - Va
  - Va
  - IIa
  - IIa

- Fibrinogen
  - Fibrin

Dabigatran
NEWER ANTICOAGULANTS

- Coagulation cascade
  - Initiation
    - TF/VIIa
    - VIIa
  - Propagation
    - IX
    - IXa
    - IIa
  - Thrombin activity
    - Va
    - II
    - Xa
- Fibrinogen
- Fibrin

Rivaroxaban, Apixaban
NEWER ANTICOAGULANTS

Coagulation cascade

Initiation

TF/VIIa

IX

IXa

X

Xa

II

Va

IIa

Fibrinogen

Fibrin
Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*
TIME TO FIRST STROKE OR SSE

**Dabigatran 150 mg BID**  **Dabigatran 110 mg BID**  **Warfarin**

- **RR 0.90**  (95% CI: 0.74–1.10)  
  - P<0.001 (NI)  
  - P=0.30 (Sup)

- **RR 0.65**  (95% CI: 0.52–0.81)  
  - P<0.001 (NI)  
  - P<0.001 (Sup)

RR = relative risk; RRR = relative risk reduction; SSE = systemic embolism.

Dabigatran etexilate is not approved for clinical use in stroke prevention in atrial fibrillation outside the US and Canada.

MAJOR BLEEDING RATES

**RR 0.80 (95% CI: 0.70–0.93)**

P=0.003 (superiority)

---

**RR 0.93 (95% CI: 0.81–1.07)**

P=0.32 (superiority)

---

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rate per year (%)</th>
<th>Relative Risk (RR)</th>
<th>95% CI</th>
<th>P-value</th>
<th>Superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>D150 mg BID</td>
<td>3.32</td>
<td>0.80</td>
<td>0.70–0.93</td>
<td>0.003</td>
<td>yes</td>
</tr>
<tr>
<td>D110 mg BID</td>
<td>2.87</td>
<td>0.93</td>
<td>0.81–1.07</td>
<td>0.32</td>
<td>no</td>
</tr>
<tr>
<td>Warfarin</td>
<td>3.57</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

D = dabigatran; RR = relative risk; RRR = relative risk reduction.

Dabigatran etexilate is not approved for clinical use in stroke prevention in atrial fibrillation outside the US and Canada.

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*
ROCKET AF – PRIMARY EFFICACY ENDPOINT

**Stroke or systemic embolism**

- **HR=0.79 (0.66, 0.96)**
- *p*<0.001 (non-inferiority)

### Number of subjects at risk

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6,958</td>
<td>7,004</td>
</tr>
<tr>
<td>120</td>
<td>8,211</td>
<td>8,327</td>
</tr>
<tr>
<td>240</td>
<td>5,786</td>
<td>5,911</td>
</tr>
<tr>
<td>360</td>
<td>5,488</td>
<td>5,542</td>
</tr>
<tr>
<td>480</td>
<td>4,406</td>
<td>4,481</td>
</tr>
<tr>
<td>600</td>
<td>3,407</td>
<td>3,478</td>
</tr>
<tr>
<td>720</td>
<td>2,472</td>
<td>2,539</td>
</tr>
<tr>
<td>840</td>
<td>1,496</td>
<td>1,538</td>
</tr>
</tbody>
</table>

Per-protocol population – as treated

Apixaban in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., John Eikelboom, M.B., B.S., Campbell Joyner, M.D., Hans-Christoph Diener, M.D., Ph.D., Robert Hart, M.D., Sergey Golitsyn, M.D., Ph.D., Greg Flaker, M.D., Alvaro Avezum, M.D., Ph.D., Stefan H. Hohnloser, M.D., Rafael Diaz, M.D., Mario Talajic, M.D., Jun Zhu, M.D., Prem Pais, M.B., B.S., M.D., Andrzej Budaj, M.D., Ph.D., Alexander Parkhomenko, M.D., Ph.D., Petr Jansky, M.D., Patrick Commerford, M.B., Ch.B., Ru San Tan, M.B., B.S., Kui-Hian Sim, M.B., B.S., Basil S. Lewis, M.D., Walter Van Mieghem, M.D., Gregory Y.H. Lip, M.D., Jae Hyung Kim, M.D., Ph.D., Fernando Lanas-Zanetti, M.D., Antonio Gonzalez-Hermosillo, M.D., Antonio L. Dans, M.D., Muhammad Munawar, M.D., Ph.D., Martin O’Donnell, M.B., Ph.D., John Lawrence, M.D., Gayle Lewis, Rizwan Afzal, M.Sc., and Salim Yusuf, M.B., B.S., D.Phil., for the AVERROES Steering Committee and Investigators*

N Engl J Med 2011;364(9): 806-17
AVERROES - Primary Efficacy Outcome

A Stroke or Systemic Embolism

Hazard ratio with apixaban, 0.45 (95% CI, 0.32–0.62)

Aspirin

Apixaban

P<0.001

No. at Risk
Aspirin 2791 2716 2530 2112 1543 628
Apixaban 2808 2758 2566 2125 1522 615

N Engl J Med 2011;364(9): 806-17
Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Geraldes, Ph.D., Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D., Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D., Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D., Jun Zhu, M.D., and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators*
**Primary Outcome**

*Stroke (ischemic or hemorrhagic) or systemic embolism*

- **Apixaban**:
  - 212 patients
  - 1.27% per year
  - HR 0.79 (95% CI, 0.66–0.95); P (superiority)=0.011
  - No. at Risk:
    - 9120
    - 8726
    - 8440
    - 6051
    - 3464
    - 1754

- **Warfarin**:
  - 265 patients
  - 1.60% per year
  - P (non-inferiority)<0.001
  - No. at Risk:
    - 9081
    - 8620
    - 8301
    - 5972
    - 3405
    - 1768

- 21% RRR

---

**N Engl J Med 2011**
## NOVEL ORAL ANTICOAGULANT COMPARISON

<table>
<thead>
<tr>
<th></th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Dabigatran 150mg BID vs. warfarin</td>
<td>Rivaroxaban 20mg daily vs. warfarin</td>
<td>Apixaban 5mg BID vs. warfarin</td>
</tr>
<tr>
<td><strong>Study Design</strong></td>
<td>RCT Open blinded assessment</td>
<td>RCT DB DD</td>
<td>RCT DB DD</td>
</tr>
<tr>
<td><strong>Sample size (n)</strong></td>
<td>18,000+</td>
<td>14,000+</td>
<td>18,000+</td>
</tr>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td>AF and selected risk factor(s) for embolization</td>
<td>AF and CHADS2 ≥2</td>
<td>AF or flutter and CHADS2 ≥1</td>
</tr>
<tr>
<td><strong>Key exclusion criteria</strong></td>
<td>Valvular AF; Use of ASA ≥100 mg/day CrCl &lt;30 ml/min</td>
<td>Valvular AF; Use of ASA &gt;100 mg/day CrCl &lt;30 ml/min</td>
<td>Valvular AF; Need for ASA &gt;165 mg/day Scr &gt;2.5mg/dL or CrCl &lt;25ml/min</td>
</tr>
<tr>
<td><strong>Follow-up (mean)</strong></td>
<td>2 yr</td>
<td>1.9 yr</td>
<td>1.8 yr</td>
</tr>
</tbody>
</table>

### Outcome Definitions
- **Primary Efficacy**: Composite of systemic embolism and stroke (ischemic or hemorrhagic)
- **Major Bleeding**: ISTH: fatal/critical organ bleed; decrease ≥2g/dL Hgb or transfusion of ≥2U blood
- **Mortality**: All causes

### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>71 (mean)</td>
<td>73 (median)</td>
<td>70 (median)</td>
</tr>
<tr>
<td><strong>Female (%)</strong></td>
<td>36.4%</td>
<td>39.7%</td>
<td>35.2%</td>
</tr>
<tr>
<td><strong>CHADS2 (mean)</strong></td>
<td>2.1</td>
<td>3.5</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>Previous embolic episode (%)</strong></td>
<td>20% (stroke or TIA only)</td>
<td>55% (stroke, TIA, systemic embolism)</td>
<td>19% (stroke, TIA, systemic embolism)</td>
</tr>
<tr>
<td><strong>TTR (%)</strong> (Standard 60-65%)</td>
<td>64%</td>
<td>55%</td>
<td>62%</td>
</tr>
</tbody>
</table>
## NOVEL ORAL ANTICOAGULANT COMPARISON

### Comparison of Efficacy Results

<table>
<thead>
<tr>
<th>Outcome (%)/year</th>
<th>RE-LY</th>
<th>ROCKETAFT</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dabigatran 150mg BID vs. warfarin</td>
<td>Rivaroxaban 20mg daily vs. warfarin</td>
<td>Apixaban 5mg BID vs. warfarin</td>
</tr>
<tr>
<td><strong>Primary Outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke or systemic embolism</td>
<td>1.1 vs. 1.7% p&lt;0.001 NNT 88</td>
<td>2.1 vs. 2.4% p=0.12</td>
<td>1.3 vs. 1.6% p=0.01 NNT 167</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.0 vs. 1.6% p&lt;0.001 NNT 88</td>
<td>1.65 vs. 1.96% p=0.09</td>
<td>1.2 vs. 1.5% p=0.01 NNT 175</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.9 vs. 1.3% p=0.03 NNT 132</td>
<td>1.3 vs. 1.4 p=0.58</td>
<td>0.97 vs. 1.05% p=0.42</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.1 vs. 0.4% p&lt;0.001 NNT 182</td>
<td>0.26 vs. 0.44% p=0.02 NNT 333</td>
<td>0.24 vs. 0.47% p&lt;0.001 NNT 238</td>
</tr>
<tr>
<td>All cause death</td>
<td>3.6 vs. 4.1% p=0.051</td>
<td>4.5 vs. 4.9% p=0.15</td>
<td>3.5 vs. 3.9 p=0.047 NNT 132</td>
</tr>
<tr>
<td>MI/ACS</td>
<td>0.7 vs. 0.5% p=0.048 NNH 239</td>
<td>0.9 vs. 1.1% p=0.12</td>
<td>0.5 vs. 0.6% p=0.37</td>
</tr>
</tbody>
</table>
# Novel Oral Anticoagulant Comparison

## Comparison of Safety Results

<table>
<thead>
<tr>
<th></th>
<th>RE-LY</th>
<th>ROCKETAF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major bleed</strong></td>
<td>3.1 vs. 3.36%</td>
<td>3.6 vs. 3.4%</td>
<td>2.1 vs. 3.1%</td>
</tr>
<tr>
<td><strong>Intracranial bleed</strong></td>
<td>p&lt;0.001 NNT 116</td>
<td>0.5 vs. 0.7%</td>
<td>0.3 vs. 0.8%</td>
</tr>
<tr>
<td><strong>GI bleed</strong></td>
<td>1.5 vs. 1.0%</td>
<td>3.2%**</td>
<td>0.76 vs. 0.86%</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.001 NNH 100</td>
<td>p=0.001 NNH 100</td>
<td></td>
</tr>
</tbody>
</table>
ATRIAL FIBRILLATION 2014
NEWER ORAL ANTICOAGULANTS (NOAC)

Dabigatran
RE-LY
Published 2009

Apixaban
ROCKET AF
Published August 2011

Rivaroxaban
Published 2009

YOU ARE HERE!

2009 2010 2011 2012 2013 2014

Dabigatran
Approved *

Rivaroxiban
Approved *

Apixiban
Approved *

AVERROES
Published February 2011

ARISTOTLE
Published August 2011

Apixaban
Approved

YOU ARE HERE!
AF LENGTH OF STAY EXAMINED

- ER presentation: Diltiazem drip
- Admit to primary physician: telemetry
  - Consult Cardiology
  - Echocardiogram
  - Decision for anticoagulation (CHADS2 score)
  - Decision for rate vs. rhythm control treatment
  - Initiate treatment… Response to treatment… etc.
- Consult EP for possible ablation
AF LENGTH OF STAY EXAMINED

• ER presentation: Protocol Driven
  • Decision for anticoagulation (CHADS2 score)
  • Decision for rhythm vs. rate control
  • Drug vs. electrical cardioversion

• Admit with “AF Expert” consultation
  • Echocardiogram
  • Initiate treatment… Response to treatment… etc.
  • Discharge
WHO ARE THE ATRIAL FIBRILLATION EXPERTS?

Fellowship in the Heart Rhythm Society is a mark of distinction. It says that your health care provider has special training and experience in the treatment of heart rhythm disorders. In particular, your provider is:

- Recognized by his or her peers for excellence and skill in medical practice, teaching, or research.
- Committed to improving the care of patients, promoting research and education, striving for the highest ethical and treatment standards, and advocating for optimal health care policies.
- In addition, 88 percent of U.S. physicians who have been promoted to FHRS status are electrophysiologists currently certified by the American Board of Internal Medicine (ABIM) in Clinical Cardiac Electrophysiology.

http://www.hrsonline.org/Find-a-Specialist/Designations/FHRS#axzz32Bsp70vl
1. Increased use of Radiofrequency Ablation Techniques (RFA) in treatment of Non-Valvular Atrial Fibrillation (NVAF).

2. Decreased emphasis on the use of aspirin for lower risk patients.

3. Incorporation of the 3 New Oral Anticoagulants (NOAC’s) into stroke reduction guidelines.

4. Endorsement of the CHA2DS2-VA2Sc Scoring system for risk stratification of stroke risk.
• January, CT et al.
• 2014 AHA/ACC/HRS Atrial Fibrillation Guideline
• 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation
• A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society
• Developed in Collaboration With the Society of Thoracic Surgery
THINGS TO KEEP IN MIND ABOUT THE GUIDELINES

1. “Guidelines” are just that—GUIDELINES

2. Individualize treatment options for each patient.

3. Rhythm control option continues to improve in both efficacy and safety.
APPROACH TO NEW FINDING OF ATRIAL FIBRILLATION

1. Determine duration and severity of episode—Duration assessment may be difficult especially with lack of symptoms in many patients (elderly frequently without symptoms)

2. Assess treatment options: Rhythm vs Rate Control

3. Assess immediate need for Rate Control if pt presents in Atrial Fibrillation/Flutter (may even need immediate cardioversion if severe symptoms or hemodynamic compromise.

4. Assess Stroke Risk to determine need for Anticoagulation (CHA2DS2-VASc)

5. Decide timing of interventions which will be guided by the above decisions.
RHYTHM CONTROL

1. Generally considered with new onset/discovery of Atrial Fibrillation (Only with symptoms?)

2. Less than 48 hours duration: Can go right to cardioversion: Pharmacologic and/or Electrical

3. Greater than 48 hours duration: Need TEE to exclude LAA thrombus before immediate cardioversion attempt. Can also begin anticoagulation for 3 weeks with rate control only and then begin cardioversion attempt in less urgent situations. Debate over whether chronic antiarrhythmic drug therapy is needed post-cardioversion.

4. If recurrent episodes, then rhythm control options depend on frequency and severity of recurrences. Range from “Pill in the Pocket” to full Pulmonary Vein Ablation/Isolation procedure.
RATE CONTROL

1. Generally required when average resting ventricular response exceeds 90-100 bpm or pharmacologic cardioversion with Ic agents is attempted to avoid increased rates with conversion to atrial flutter.

2. A patient with new onset atrial fibrillation does not mandate hospitalization or immediate ER evaluation if they are stable.

3. Outpatient rate control medications are Beta-Blockers, Non-dihydropyridine CCB’s ie, verapamil / diltiazem, Digoxin. All can be given IV if needed in hospital/ER settings. May require 2 or more agents.—Decision of which one to start depends on the clinical circumstances at the time of therapy including comorbidities/allergies/structural heart disease.

4. If drug(s) fail or not tolerated in chronic accepted AF then AV Junctional ablation with implantation of a single RV or BiV pacemaker is indicated. Usually in more elderly pts that are not good candidates for rhythm control.

5. Adequate rate control with exercise is accepted as <150 bpm.
STROKE IN ATRIAL FIBRILLATION

- AF/PAF pts have 5x the stroke risk as compared to age/health matched individuals without AF/PAF. There is NO DIFFERENCE in risk with AF vs PAF.
- The occurrence of stroke is NOT temporally related to the actual occurrence of atrial fibrillation.
  - *This suggests that the presence of atrial fibrillation is a marker for an atrial myopathy associated with increased thrombogenicity with embolization risk but the actual stroke may occur without atrial fibrillation occurrence for days or weeks.
  - *Recent data on Cryptogenic stroke indicates that up to 30% of these pts will be found to have AF on prolonged cardiac rhythm monitoring (24-36 mths) with an ILR. Most frequently the AF is 90-120 days after the event. Possibly as little as 1 episode of 30 secs of AF or average of 5 min/24 hrs predict an increased risk of stroke. NEJM 2014;370:2478-86.
- 15-25% of all strokes are related to AF. Strokes that occur in association with AF have a higher mortality and are more severely debilitating.
FUTURE POSSIBILITIES?

All patients that have unexplained stroke have a CHA2DS2-VASc score done and anticoagulate the highest risk patients (ie, >3) while looking for AF/PAF—Study needs to be done. In the works???

In patients unable to tolerate anticoagulation therapy left atrial appendage closure will be standard of care for stroke prevention.

Ablation procedures will be used to prevent recurrent AF that will absolutely reduce stroke risk regardless of AF recurrence.---Not likely but more data will become available in the future.