New Approaches to Anticoagulation in Atrial Fibrillation

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Outline

• Overview of Atrial Fibrillation
• Treatment Strategies
• Stroke Risk
• Anticoagulation Options
• Rate and Rhythm Control
• Conclusion
Disclosures

- Consultant, Research Support, or Honoraria
- Biosense Webster, CryoCor, ProRhythm, Ablation Frontiers,
- Medtronic, Boston Scientific, AtriCure, Sanofi Adventis
Epidemiology of AF

- Most common sustained cardiac arrhythmia\(^1\)
- Currently affects 5.1 million Americans\(^2\)
- Prevalence expected to increase to 12.1 million by 2050 (15.9 million if increase in incidence continues)\(^2\)
- Preferentially affects men and the elderly\(^1,2\)
- Lifetime risk of developing AF: \(~1\) in 4 for adults \(\geq\)40 years of age\(^3\)

AF Is Associated With Increased Thromboembolic Risk

- Major cause of stroke in elderly
- 5-fold ↑ in risk of stroke
- 15% of strokes in US are attributable to AF
- Stroke severity (and mortality) is worse with AF than without AF
- Incidence of all-cause stroke in patients with AF: 5%
- Stroke risk persists even in asymptomatic AF

AF Is the Leading Cause of Hospitalizations for Arrhythmia

Hospital Admissions in US

- AF
- AFL
- Cardiac arrest
- Conduction disease
- Junctional
- Premature beats
- Sick sinus
- Unspecified
- VF
- VT

Hospital Days (thousands)

N=517,699 (representing 10% of CV admissions).

VF, ventricular fibrillation; VT, ventricular tachycardia.

Mortality After Diagnosis of AF

4-month HR, 9.62
Post-4 months HR, 1.66

Survival, %

Years From AF Dx

Years After 4 Mo From AF Dx

MN-white expected
Observed

P<.0001

Impact on QoL: AF vs Other CV Illness

*Higher numbers indicate higher QoL.
SF-36 = Medical Outcomes Study Short Form 36.

Pathogenesis of AF

- Multiple-wavelet hypothesis\(^1\)
- Focal mechanism with fibrillatory conduction\(^2\)
- “Autonomic” hypothesis\(^3\)

Conditions Frequently Associated With Nonvalvular AF$^{1-4}$

- Hypertension
- Aging
- Male sex
- Obesity/metabolic syndrome/diabetes
- Ischemic heart disease
- Heart failure/diastolic dysfunction
- Obstructive sleep apnea
- Physical inactivity
- Thyroid disease
- Inflammation?

Prevalence of AF Increases With Severity of HF
Classification of AF

Recurrent AF* (≥2 episodes)

Paroxysmal
- Arrhythmia terminates spontaneously
- AF is sustained ≤7 days

Persistent
- Arrhythmia does not terminate spontaneously
- AF is sustained >7 days

Permanent
- Both paroxysmal and persistent AF can become permanent

*Termination with pharmacologic therapy or direct-current cardioversion does not change the designation.

Treatment
Treatment Goals and Strategies

**Rate control**
- Pharmacologic
  - Ca$^{2+}$ blockers
  - β-blockers
  - Digitalis
  - Amiodarone
- Nonpharmacologic
  - Ablate and pace

**Maintenance of SR**
- Pharmacologic
  - Class IA
  - Class IC
  - Class III
  - β-blocker
- Nonpharmacologic
  - Catheter ablation
  - Pacing
  - Surgery
  - Implantable devices

**Stroke prevention**
- Pharmacologic
  - Warfarin
  - Aspirin
  - Thrombin Inhibitor
- Nonpharmacologic
  - Removal/isolation
  - LA appendage

**Prevent Remodeling**
- CCB
- ACE-I, ARB
- Statins
- Fish oil
### CHADS<sub>2</sub> Risk Criteria for Stroke in Nonvalvular AF

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 y</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>History of stroke or transient ischemic attack</td>
<td>2</td>
</tr>
</tbody>
</table>

Stroke Risk in Patients With Nonvalvular AF Not Treated With Anticoagulation Based on the CHADS$_2$ Index

- **CHADS$_2$** refers to Congestive heart failure, Hypertension, Age $>$ 75, Diabetes mellitus, and prior Stroke or transient ischemic attack.
## Risk Stratification for AF: Antithrombotic Therapy

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Risk</strong></td>
<td>Aspirin, 81-325 mg a day</td>
</tr>
<tr>
<td>No moderate-risk factors</td>
<td>CHADS₂ = 0</td>
</tr>
<tr>
<td><strong>Moderate Risk</strong></td>
<td>Aspirin, 81-325 mg a day or warfarin (INR 2.0-3.0)</td>
</tr>
<tr>
<td>One moderate-risk factor</td>
<td>CHADS₂ = 1</td>
</tr>
<tr>
<td><strong>High Risk</strong></td>
<td>Warfarin (INR 2.0-3.0*)</td>
</tr>
<tr>
<td>Any high-risk factor or ≥2 moderate-risk factors</td>
<td>CHADS₂ ≥2</td>
</tr>
</tbody>
</table>

*INR 2.5-3.5 for prosthetic valves. What to do about “weaker” risk factors?

# Risk factor-based point-based scoring system - 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 ans</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>
<tr>
<td><strong>Maximum score</strong></td>
<td><strong>9</strong></td>
</tr>
</tbody>
</table>

*Prior myocardial infarction, peripheral artery disease, aortic plaque. Actual rates of stroke in contemporary cohorts may vary from these estimates.
## Adjusted stroke rate according to CHA$_2$DS$_2$-VASc score

<table>
<thead>
<tr>
<th>CHA$_2$DS$_2$-VASc score</th>
<th>Patients (n = 7329)</th>
<th>Adjusted stroke rate (%/y)</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>
Use of oral anticoagulation for stroke prevention in AF

CHADS\textsubscript{2} score ≥ 2\textsuperscript{+} →
- No
  - Consider other risk factors\textsuperscript{*}
    - Age ≥ 75 years
      - No
        - ≥ 2 others risk factors\textsuperscript{*}
          - No
            - 1 other risk factor\textsuperscript{*}
              - No
                - OAC
              - Yes
                - OAC (or aspirin)
          - Yes
            - Nothing (or aspirin)
      - Yes
        - OAC
- Yes

\textsuperscript{+}Congestive heart failure, hypertension, Age 75 years, Diabetes, Stroke/TIA/thromboembolism (doubled)

\textsuperscript{*}Other clinically relevant non-major risk factors: age 65-74, female sex, vascular disease

AF = atrial fibrillation; OAC = oral anticoagulant; TIA = transient ischaemic attack

www.escardio.org/guidelines
## Limitations of Warfarin

<table>
<thead>
<tr>
<th>Limitations</th>
<th>Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow onset of action</td>
<td>Overlap with parenteral anticoagulant</td>
</tr>
<tr>
<td>Genetic variation in metabolism</td>
<td>Variable dose requirements</td>
</tr>
<tr>
<td>Multiple food and drug interactions</td>
<td>Frequent coagulation monitoring</td>
</tr>
<tr>
<td>Narrow therapeutic window</td>
<td>Frequent coagulation monitoring</td>
</tr>
</tbody>
</table>


Courtesy of PR Kowey, MD.
**Limitations of Warfarin**

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<td>Narrow therapeutic window</td>
<td>Frequent coagulation monitoring</td>
</tr>
</tbody>
</table>


Courtesy of PR Kowey, MD.
Targets of New Anticoagulant Agents

- **ORAL**
  - TTP889
  - Rivaroxaban
  - Apixaban
  - Edoxaban
  - Betrixaban
  - Darexaban
  - LY517717
  - TAK 42
  - Dabigatran
  - AZD0837

- **PARENTERAL**
  - TFPI (tifacogin)
  - APC (drotrecogin alfa)
  - sTM (ART-123)
  - Fondaparinux
  - Semuloparin
  - Idrabiotaparinux
  - DX-9065a
  - Otamixaban

- **Pathway**
  - TFA/VIIa
  - X
  - IX
  - IXa
  - VIIa
  - Va
  - AT
  - Xa
  - II
  - Ila
  - Fibrinogen
  - Fibrin

Becattini Throm Res 2012 23
# Main Features of New Anticoagulant Agents

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
<th>Edoxaban</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversible</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Absolute availability, %</td>
<td>60</td>
<td>80</td>
<td>50</td>
<td>7</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Pro-drug</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Mean half-life, h (t1/2)</td>
<td>8-15 h</td>
<td>7-11 h</td>
<td>9-11 h</td>
<td>12-17 h</td>
</tr>
<tr>
<td>Tmax, h</td>
<td>3-4 h</td>
<td>2-4 h</td>
<td>1-2 h</td>
<td>0.5-2 h</td>
</tr>
<tr>
<td>Protein binding, %</td>
<td>87%</td>
<td>&gt; 90%</td>
<td>55%</td>
<td>35%</td>
</tr>
<tr>
<td>Potential for drug drug interaction</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
<td>P-GP-inhibit</td>
</tr>
<tr>
<td>Renal excretion, %</td>
<td>25</td>
<td>66</td>
<td>35</td>
<td>80</td>
</tr>
<tr>
<td>Drug or food interaction</td>
<td>Clarithromycin</td>
<td>Ritonavir Ketokonazole</td>
<td>NR</td>
<td>Amiodarone, Quinidine, Verapamil</td>
</tr>
</tbody>
</table>

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Clinical Trials and new Anticoagulant Agents  
- A Summary -

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Drug</th>
<th>Comparator</th>
<th>CHADS2</th>
<th>Patients</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>RELY</td>
<td>Open label</td>
<td>Dabigatran 110 mg or 150 mg t.d.</td>
<td>Warfarin</td>
<td>≥2</td>
<td>18113</td>
<td>Stroke or systemic embolism</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>Double blind</td>
<td>Rivaroxaban 20 mg o.d.</td>
<td>Warfarin</td>
<td>≥2</td>
<td>14266</td>
<td></td>
</tr>
<tr>
<td>AVERROES</td>
<td>Double blind</td>
<td>Apixaban 5 mg t.d.</td>
<td>Aspirin</td>
<td>≥1</td>
<td>5599</td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>Double blind</td>
<td>Apixaban 5 mg t.d.</td>
<td>Warfarin</td>
<td>≥1</td>
<td>18201</td>
<td></td>
</tr>
<tr>
<td>ENGAGE (Phase II)</td>
<td>Double blind</td>
<td>Edoxaban 30 mg o.d., 60 mg o.d., 30 mg t.d. or 60 mg t.d.</td>
<td>Warfarin</td>
<td>≥2</td>
<td>1146</td>
<td>Major and/or clinically relevant non-major bleeding and elevated hepatic enzymes and/or bilirubin</td>
</tr>
<tr>
<td>ENGAGE AF</td>
<td>Double blind</td>
<td>Edoxaban 30 mg o.d. or 60 mg o.d.</td>
<td>Warfarin</td>
<td>≥2</td>
<td>21105</td>
<td>Stroke or systemic embolism</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trial/drug</th>
<th>Primary Outcome</th>
<th>Major Bleeding</th>
<th>Ischemic Stroke</th>
<th>AMI</th>
<th>Intracranial Bleeding</th>
<th>Overall death</th>
</tr>
</thead>
<tbody>
<tr>
<td>RELY (110)</td>
<td>Drug (%)year vs Comparator (%)year, p-value</td>
<td>1.53 vs 1.69 P&lt;0.001</td>
<td>2.71 vs 3.36 p = 0.003</td>
<td>1.34 vs 1.20 p = 0.35</td>
<td>0.72 vs 0.53 p = 0.07</td>
<td>0.23 vs 0.74 p &lt; 0.001</td>
</tr>
<tr>
<td>(150)</td>
<td></td>
<td>1.11 vs 1.69 P&lt;0.001</td>
<td>3.11 vs 3.36 p = 0.31</td>
<td>0.92 vs 1.20 p = 0.03</td>
<td>0.74 vs 0.53 p = 0.048</td>
<td>0.30 vs 0.74 p &lt; 0.001</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td></td>
<td>2.12 vs 2.42 p = 0.117</td>
<td>3.6 vs 3.45 p = 0.576</td>
<td>1.34 vs 1.42 p = 0.58</td>
<td>0.91 vs 1.12 p = 0.121</td>
<td>0.49 vs 0.74 p = 0.019</td>
</tr>
<tr>
<td>AVERROES</td>
<td></td>
<td>1.6 vs 3.7 p&lt;0.001</td>
<td>1.4 vs 1.2 p = 0.57</td>
<td>1.1 vs 3.0 p&lt;0.001</td>
<td>0.8 vs 0.9 p = 0.59</td>
<td>0.4 vs 0.4 p = 0.69</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td></td>
<td>1.27 vs 1.60 P = 0.01</td>
<td>2.13 vs 3.09 P&lt;0.001</td>
<td>0.97 vs 1.05 p = 0.42</td>
<td>0.53 vs 0.61 p = 0.37</td>
<td>0.33 vs 0.80 p&lt;0.001</td>
</tr>
<tr>
<td>ENGAGE AF</td>
<td></td>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AMI = acute myocardial infarction.
In patients with atrial fibrillation, dabigatran given at a dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage.

Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage.

In this trial, 14,264 patients with atrial fibrillation were randomly assigned to receive either rivaroxaban or warfarin.

In a per-protocol, as-treated analysis, rivaroxaban was noninferior to warfarin with respect to the primary end point of stroke or systemic embolism.

In this trial, the factor Xa inhibitor apixaban was shown to reduce the risk of stroke or systemic embolism, as compared with aspirin, without a significant increase in the risk of major bleeding.

Apixaban is an alternative to aspirin for patients who cannot take warfarin.

Apixaban versus Warfarin in Patients with Atrial Fibrillation (ARISTOTLE)

Apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and lowered mortality.

Which New Agent Should We Recommend?

- Raise the issue / Pop the question
- Variables to consider:
  - coumadin experience
  - approach to new drugs
  - cost considerations
  - h/o GI symptoms
  - compliance issues
Treatment Goals and Strategies

Rate control

Pharmacologic
- Ca\textsuperscript{2+} blockers
- β-blockers
- Digitalis
- Amiodarone

Nonpharmacologic
- Ablate and pace

Prevent Remodeling

Maintenance of SR

Pharmacologic
- Class IA
- Class IC
- Class III
- β-blocker

Nonpharmacologic
- Catheter ablation
- Pacing
- Surgery
- Implantable devices

Stroke prevention

Pharmacologic
- Warfarin
- Aspirin
- Thrombin Inhibitor

Nonpharmacologic
- Removal/isolation
- LA appendage

Prevent Remodeling

CCB
- ACE-I, ARB
- Statins
- Fish oil
Rate Control

● **End point**
  - Resting and ambulatory ventricular rates similar to those expected in sinus rhythm
  - Best assessed with Holter monitoring
  - *Determining pulse on exam and heart rate on ECG are not sufficient*

● **Methods**
  - Digitalis: in sedentary patients or CHF
  - β-blockers and/or CCBs (verapamil, diltiazem): needed in most active individuals
  - AVN ablation plus pacemaker: in resistant patients

● **Special considerations**
  - Brady-tachy syndrome (pindolol, or pacer plus drugs)
  - Preexcitation (focus on the BT as well as the AVN)
# Current Efficacy of AF Ablation: Estimates

<table>
<thead>
<tr>
<th>Surgical Ablation</th>
<th>Single Procedure</th>
<th>Multiple</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal patient</td>
<td>70%-90%</td>
<td></td>
</tr>
<tr>
<td>Less optimal patient</td>
<td>60%-80%</td>
<td></td>
</tr>
<tr>
<td>Poor candidate</td>
<td>50%-60%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Catheter Ablation</th>
<th>Single Procedure</th>
<th>Multiple</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal patient</td>
<td>60%-80%</td>
<td>80%-90%</td>
</tr>
<tr>
<td>Less optimal patient</td>
<td>50%-70%</td>
<td>70%-80%</td>
</tr>
<tr>
<td>Poor candidate</td>
<td>≤40%</td>
<td>40%-60%</td>
</tr>
</tbody>
</table>

# Indications for Catheter Ablation Of Atrial Fibrillation

## TABLE 2: CONSENSUS INDICATIONS FOR CATHETER AND SURGICAL ABLATION of AF

<table>
<thead>
<tr>
<th>INDICATIONS FOR CATHETER ABLATION of AF</th>
<th>CLASS</th>
<th>LEVEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic AF refractory or intolerant to at least one Class 1 or 3 antiarrhythmic medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal: Catheter ablation is recommended *</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Persistent: Catheter ablation is reasonable</td>
<td>Ila</td>
<td>B</td>
</tr>
<tr>
<td>Longstanding Persistent: Catheter ablation may be considered</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Symptomatic AF prior to initiation of antiarrhythmic drug therapy with a Class 1 or 3 antiarrhythmic agent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal: Catheter ablation is reasonable</td>
<td>Ila</td>
<td>B</td>
</tr>
<tr>
<td>Persistent: Catheter ablation may be considered</td>
<td>IIb</td>
<td>C</td>
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<tr>
<td>Longstanding Persistent: Catheter ablation may be considered</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>

* Catheter ablation of symptomatic paroxysmal AF is considered a Class 1 indication only when performed by an electrophysiologist who has received appropriate training and is performing the procedure in an experienced center.
# Patient Selection for Ablation

**Variable**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Highly symptomatic</th>
<th>Minimally symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I and III drugs failed</td>
<td>≥1</td>
<td>0</td>
</tr>
<tr>
<td>AF type</td>
<td>Paroxysmal</td>
<td>Long-standing persistent</td>
</tr>
<tr>
<td>Age</td>
<td>Younger (&lt;70 years)</td>
<td>Older (≥70 years)</td>
</tr>
<tr>
<td>LA size</td>
<td>Smaller (&lt;5.0 cm)</td>
<td>Larger (≥5.0 cm)</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>Normal</td>
<td>Reduced</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Other cardiac disease</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Obesity</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Prior stroke/TIA</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Courtesy of Hugh Calkins, MD.
Treatment Goals and Strategies

Rate control
- Pharmacologic
  - Ca\textsuperscript{2+} blockers
  - \(\beta\)-blockers
  - Digitalis
  - Amiodarone
- Nonpharmacologic
  - Ablate and pace

Prevent Remodeling
- CCB
- ACE-I, ARB
- Statins
- Fish oil

Maintenance of SR
- Pharmacologic
  - Class IA
  - Class IC
  - Class III
  - \(\beta\)-blocker
- Nonpharmacologic
  - Catheter ablation
  - Pacing
  - Surgery
  - Implantable devices

Stroke prevention
- Pharmacologic
  - Warfarin
  - Aspirin
  - Thrombin Inhibitor
- Nonpharmacologic
  - Removal/isolation
  - LA appendage
Conclusions

- Atrial fibrillation is common
- Atrial fib is an important risk factor for stroke.
- Stroke risk can be determined using CHADS and CHADSvasc
- Patients at increased risk of stroke should be anticoagulated.
- Aspirin does little.
- The era of new anticoagulants is here and now.
Thank You