Atrial Fibrillation Update: Focus on Anticoagulation

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Conflict of Interest

I have no conflicts of interest to disclose
Learning Objectives

- Review the pathophysiology of stroke in atrial fibrillation (AF)
- Identify appropriate assessment tools to determine risk of stroke and risk of bleeding in patients with atrial fibrillation
- Describe guideline recommendations for anticoagulation in atrial fibrillation
Outline

- Background
- Pathophysiology
- Stroke Risk Assessment
- Guideline Review
- Oral anticoagulation
- Bleeding Risk Assessment
- Antiplatelet agents
Case #1

- MM is a 68 year old female
- CC: Intermittent ‘fluttering’ feeling in her chest over the past 2-3 weeks. She is compliant with medications and has private health insurance.
- PMH: Hypertension, Hyperlipidemia, Obesity, Obstructive sleep apnea
- Home Medications:
  - Atorvastatin 40mg PO daily at bedtime
  - Lisinopril 20mg PO daily
  - Metoprolol tartrate 50mg PO twice daily
Case #1

- EKG: Irregular rate, irregular rhythm

- Vitals:
  - BP 130/78, P 68 bpm
  - Weight 140kg, Height 165 cm

- Labs – all within normal ranges
What is the most appropriate therapy for this patient?

- No antithrombotic therapy
- Aspirin + Clopidogrel
- Warfarin (goal INR 2-3)
- Rivaroxaban 20mg PO daily
Atrial fibrillation (AF) affects approximately 2.2 million patients in US

Most common arrhythmia requiring hospitalization
  - 416,000 hospital discharge per year

795,000 strokes annually, 691,650 ischemic strokes

71,000 patients die per year from AF or Atrial Flutter

Increases risk of stroke 5-fold

Electrophysiology of AF

- Abnormal electrical path leads to recirculation of blood in atrial chambers
- Stagnant blood promotes formation of embolus
Cardioembolic Stroke

- Embolus travels from left atrium to left ventricle, then to aorta
- Three primary arteries off aortic arch lead to brain

http://www.dwl.de/index.php?Right%252FLeft%2BShunt
AF-Related Ischemic Strokes

- More likely to have hospital complications such as ICU stay, infections, and ventilator therapy
- More likely to be disabled at discharge
- More likely to remain disabled
- Less likely to be discharged to home
- Associated with higher short- and long-term mortality

MM is a 68 year old female
CC: Intermittent ‘fluttering’ feeling in her chest over the past 2-3 weeks. She is compliant with medications and has private health insurance.
PMH: Hypertension, Hyperlipidemia, Obesity, Obstructive Sleep Apnea
Home Medications:
- Atorvastatin 40mg PO daily at bedtime
- Lisinopril 20mg PO daily
- Metoprolol tartrate 50mg PO twice daily
Question

- What is MM’s risk for stroke?
  - Low Risk
  - Moderate Risk
  - High Risk
CHADS$_2$

- JAMA, 2001
  - $n = 1,733$
  - Medicare chart review
- Easy to use
- Does not include all potential risk factors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive Heart Failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt; 75 yrs</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>2</td>
</tr>
</tbody>
</table>

### CHADS$_2$ Score

<table>
<thead>
<tr>
<th>CHADS2 Score</th>
<th>Adjusted Stroke Rate (%/yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9%</td>
</tr>
<tr>
<td>1</td>
<td>2.8%</td>
</tr>
<tr>
<td>2</td>
<td>4.0%</td>
</tr>
<tr>
<td>3</td>
<td>5.9%</td>
</tr>
<tr>
<td>4</td>
<td>8.5%</td>
</tr>
<tr>
<td>5</td>
<td>12.5%</td>
</tr>
<tr>
<td>6</td>
<td>18.2%</td>
</tr>
</tbody>
</table>

### Stroke Risk

<table>
<thead>
<tr>
<th>Risk</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>0</td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>1</td>
</tr>
<tr>
<td>High Risk</td>
<td>≥ 2</td>
</tr>
</tbody>
</table>

UPDATE — Stroke Risk Stratification

- Additional risk factors validated
  - Female gender
  - Age 65-74
  - Vascular disease

- More specific delineation of low, moderate, and high risk

- More accurate identification of truly low risk patients

**CHA\textsubscript{2}DS\textsubscript{2}VASc**

- Chest, 2010
  - n = 1,084
  - Comparison of 8 stroke risk stratification schemas
- More inclusive of common stroke risk factors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive Heart Failure or LVEF ≤ 40%</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</td>
<td>1</td>
</tr>
<tr>
<td>Stroke, TIA, or VTE</td>
<td>2</td>
</tr>
<tr>
<td>Vascular Disease (Prior MI, PAD, or aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>Age 65 - 74</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (female)</td>
<td>1</td>
</tr>
</tbody>
</table>

**CHA_{2}DS_{2}-VASc**

<table>
<thead>
<tr>
<th>CHA_{2}DS_{2}-VASc Score</th>
<th>Adjusted Stroke Rate (%/yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>1</td>
<td>0.7%</td>
</tr>
<tr>
<td>2</td>
<td>1.9%</td>
</tr>
<tr>
<td>3</td>
<td>4.7%</td>
</tr>
<tr>
<td>4</td>
<td>2.3%</td>
</tr>
<tr>
<td>5</td>
<td>3.9%</td>
</tr>
<tr>
<td>6</td>
<td>4.5%</td>
</tr>
<tr>
<td>7</td>
<td>10.1%</td>
</tr>
<tr>
<td>8</td>
<td>14.2%</td>
</tr>
<tr>
<td>9</td>
<td>100%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stroke Risk</th>
<th>Score</th>
</tr>
</thead>
<tbody>
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<tr>
<td>Moderate Risk</td>
<td>1</td>
</tr>
<tr>
<td>High Risk</td>
<td>≥ 2</td>
</tr>
</tbody>
</table>

## Stroke Risk Stratification

<table>
<thead>
<tr>
<th>Total Score</th>
<th>Annual Risk of Stroke (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CHADS$_2$</td>
</tr>
<tr>
<td>0</td>
<td>1.9</td>
</tr>
<tr>
<td>1</td>
<td>2.8</td>
</tr>
<tr>
<td>2</td>
<td>4.0</td>
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<td>3</td>
<td>5.9</td>
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<td>4</td>
<td>8.5</td>
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<td>5</td>
<td>12.5</td>
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<tr>
<td>6</td>
<td>18.2</td>
</tr>
<tr>
<td>7</td>
<td>--</td>
</tr>
<tr>
<td>8</td>
<td>--</td>
</tr>
<tr>
<td>9</td>
<td>--</td>
</tr>
</tbody>
</table>

Stroke Risk Stratification

- ATRIA
- Qstroke
- RCHADS2
- Euro Heart Survey
- Swedish Cohort
- UK General Practice
- AF Registry of Denmark
- Olmsted County Cohort
- SPORTIF Cohorts

Wang et al. JAMA 2003; 290:1049-1056
Singer et al. J Am Heart Assoc 2013
Fang et al. J Am Coll Card 2008; 51:81607
MM is a 68 year old female

CC: Intermittent ‘fluttering’ feeling in her chest over the past 2-3 weeks. She is compliant with medications and has private health insurance.

PMH: Hypertension, Hyperlipidemia, Obesity, Obstructive Sleep Apnea

Home Medications:
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- Metoprolol tartrate 50mg PO twice daily
Question

What is MM’s risk for stroke?
  - Low Risk
  - Moderate Risk
  - High Risk
Guideline Review

- ACCP (Chest) Guidelines 2012
- ACCF/AHA/HRS Guidelines 2014
- AHA/ASA Guidelines 2014
### ACCP (Chest) Guidelines

<table>
<thead>
<tr>
<th>CHADS$_2$ Score</th>
<th>Antithrombotic Recommendations</th>
<th>Additional Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No therapy rather than antithrombotic therapy (2B)</td>
<td>For patients who choose antithrombotic therapy, we suggest Aspirin (2B)</td>
</tr>
<tr>
<td>1</td>
<td>Oral anticoagulation (OAC) rather than no therapy or antiplatelet therapy (1B)</td>
<td>For patients who are unsuitable or choose not to take OAC, we suggest combination therapy with Aspirin and Clopidogrel (2B)</td>
</tr>
<tr>
<td>$&gt; 2$</td>
<td>OAC rather than no therapy or antiplatelet therapy (1A)</td>
<td>For patients who are unsuitable for or choose not to take an oral anticoagulant, we recommend combination therapy with Aspirin and Clopidogrel (1B)</td>
</tr>
</tbody>
</table>

You JJ et al. Chest 2012; 141: e531s-575s
<table>
<thead>
<tr>
<th>CHA₂DS₂-VASc Score</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Omit antithrombotic therapy (2B)</td>
</tr>
<tr>
<td>1</td>
<td>No antithrombotic therapy or treatment with OAC or Aspirin may be considered (2C)</td>
</tr>
<tr>
<td>&gt; 2</td>
<td>Oral anticoagulants are recommended (Class 1A/1B)</td>
</tr>
</tbody>
</table>

**AHA/ASA Guidelines**

<table>
<thead>
<tr>
<th>CHA$_2$DS$_2$-VASc Score</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Omit antithrombotic therapy (2B)</td>
</tr>
<tr>
<td>1</td>
<td>No antithrombotic therapy, anticoagulant therapy, or aspirin therapy may be considered (2C)</td>
</tr>
<tr>
<td>≥ 2</td>
<td>Oral anticoagulants are recommended (1A/B)</td>
</tr>
</tbody>
</table>

# Comparison of Guideline Recommendations

<table>
<thead>
<tr>
<th>CHA$_2$DS$_2$VASc Score = 0</th>
<th>CHA$_2$DS$_2$VASc Score = 1</th>
<th>CHA$_2$DS$_2$VASc Score &gt; 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCP (Chest) Guidelines</td>
<td>No therapy</td>
<td>OAC</td>
</tr>
<tr>
<td>ACCF/AHA/HRS Guidelines</td>
<td>No therapy</td>
<td>No therapy, OAC, or ASA</td>
</tr>
<tr>
<td>AHA/ASA Guidelines</td>
<td>No therapy</td>
<td>No therapy, OAC, or ASA</td>
</tr>
</tbody>
</table>

You JJ et al. Chest 2012; 141: e531s-575s
What is the most appropriate therapy for MM?

- No antithrombotic therapy
- Aspirin + Clopidogrel
- Warfarin (goal INR 2-3)
- Rivaroxaban 20mg PO daily
Oral Anticoagulants
Warfarin

- FDA Approved 1954
- Vitamin K Antagonist (VKA)
- Dosing
  - Dosing titration based on INR values
  - Goal INR 2-3 (Atrial Fibrillation)
  - Hepatic metabolism
- Monitoring
  - Frequent INR values required
  - Weekly to every 3 months

Coumadin ® [Package Insert]. USA: Bristol-Myers Squibb; 2011
## Warfarin

<table>
<thead>
<tr>
<th>Group</th>
<th>AF Investigators Meta Analysis Strokes (%/yr)</th>
<th>Albers Meta Analysis Strokes (%/yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>1.4%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Control</td>
<td>4.5%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Relative Risk</td>
<td>68% (p&lt;0.001)</td>
<td>83% (p&lt;0.001)</td>
</tr>
<tr>
<td>Reduction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Suboptimal Time in Therapeutic Range (TTR)

- **ORBIT-AF**
  - n = 5210
  - Duration = 18 months
  - Average 20 INRs/pt
  - Only 59% of all INRs drawn within therapeutic range
  - Goal TTR for stroke reduction is > 70%

![Graph showing distribution of INR measurements with median TTR and median time above/below therapeutic range]

Warfarin advantages

- Sixty years of experience in various populations
- Cost is ~ $4/month
- Acute reversal available
- Monitor therapeutic effectiveness
Warfarin disadvantages

- **Monitoring**
  - Weekly INRs initially until therapeutic, then monthly. May consider Q3 month monitoring if stable.

- **Drug Interactions**

- **Food Interactions**
  - Asparagus, Avocado, Bananas, Blueberries, Broccoli, Cabbage, Celery, Coconut, Cooking oils, Cranberry, Cucumber, Collard greens, Seaweed, Energy bars, Garlic, Gnocchi, Grapefruit, Greek yogurt, licorice, Mangoes, Oatmeal, Olestra, Papaya, Parsley, Pomegranate, Salmon, Soy, Spinach, Lettuce, Mayonnaise, Salad dressings, enteral feeding

Coumadin® [Package Insert]. USA: Bristol-Myers Squibb; 2011
Dabigatran

- FDA Approved October, 2010
- Direct Thrombin Inhibitor
- Renal Dosing
  - CrCl > 30 ml/min = 150mg twice daily
  - CrCl 15-30 ml/min = 75mg twice daily
  - < 15 ml/min = avoid
- No monitoring required
Dabigatran

- Onset 1-2 hours
- Half life 12-17 hours
- May falsely elevate INR
- DO NOT CRUSH
  - Increase bioavailability by 70%
- Brand Name: Pradaxa

- Cost
  - $377/month
RE-LY Trial
Dabigatran vs. Warfarin

- $n = 18,113$ patients
- Duration = 2 years
- Non-valvular AF + $\geq 1$ of the following:
  - History of CVA/TIA, LVEF $< 40\%$, HF
  - NYHA Class $\geq$ II, Age $> 75$ years, Age $65-74$ years + DM, HTN, CAD

# RE-LY Trial
Dabigatran vs. Warfarin

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Warfarin Risk %/yr</th>
<th>Dabigatran 150mg Risk %/yr</th>
<th>Dabigatran 150mg vs. Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or Systemic Embolus</td>
<td>1.69%</td>
<td>1.11%</td>
<td>p&lt;0.001 non-inferior</td>
</tr>
<tr>
<td>Stroke (all types)</td>
<td>1.57%</td>
<td>1.01%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Fatal Stroke</td>
<td>1.0%</td>
<td>0.66%</td>
<td>p = 0.005</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>4.13%</td>
<td>3.64%</td>
<td>NS</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>0.38%</td>
<td>0.10%</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

# RE-LY Trial
Dabigatran vs. Warfarin

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Warfarin Risk/yr</th>
<th>Dabigatran 150mg Risk/yr</th>
<th>Dabigatran 150mg vs. Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>3.36%</td>
<td>3.11%</td>
<td>NS</td>
</tr>
<tr>
<td>Life threatening bleeding</td>
<td>1.8%</td>
<td>1.45%</td>
<td>p=0.04</td>
</tr>
<tr>
<td>Minor Bleeding</td>
<td>16.37%</td>
<td>14.84%</td>
<td>p=0.005</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>0.74%</td>
<td>0.3%</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

Major Bleeding: HGB drop of > 20g/L, Transfusion of > 2 units PRBC, symptomatic bleeding in critical area or organ
Life-Threatening Bleeding: fatal bleeding, symptomatic intracranial bleeding, HGB drop of > 50g/L, Transfusion of > 4 units PRBC, inotropes, surgery

RE-LY Conclusions

- Dabigatran is non-inferior to warfarin for prevention of stroke and systemic embolism
- No difference in rates of major bleeding between Dabigatran and Warfarin
- Lower rates of hemorrhagic stroke and minor bleeding with Dabigatran over warfarin

Rivaroxaban

- FDA Approved November, 2011
- Factor Xa Inhibitor
- Renal Dosing
  - CrCl > 50 ml/min = 20mg once daily
  - CrCl 15-50 ml/min = 15mg once daily
  - CrCl < 15 ml/min = avoid
- No monitoring required

Xarelto ® [Package Insert], Titusville, NJ: Janssen Pharmaceuticals, Inc; 2011
Rivaroxaban

- Onset 2-4 hours
- Half life 5-9 hours
- Administer with meal
- May falsely elevate INR
- Coupons offered by manufacturer
- Brand Name: Xarelto ©

Cost
- $400/month

Xarelto © [Package Insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2011
ROCKET-AF
Rivaroxaban vs. Warfarin

- n = 14,264 patients
- Duration = 1.94 years
- Non-valvular AF +
  - CVA/TIA/Embolism or
  - > 2 of the following
    - HF, HTN, Age ≥ 75 years, DM
- Mean CHADS$_2$ Score = 3.5

Patel MR et al. NEJM 2011; 365:833-891
## ROCKET-AF
**Rivaroxaban vs. Warfarin**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban No./100pt yr</th>
<th>Warfarin No./100pt yr</th>
<th>Rivaroxaban vs. Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolism – per protocol</td>
<td>1.7</td>
<td>2.2</td>
<td>p&lt;0.001 Non-inferior</td>
</tr>
<tr>
<td>Stroke or systemic embolism – ITT</td>
<td>2.1</td>
<td>2.4</td>
<td>p&lt;0.001 Non-inferior</td>
</tr>
</tbody>
</table>

*Patel MR et al. NEJM 2011; 365:833-891*
## ROCKET-AF

**Rivaroxaban vs. Warfarin**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban No./100pt yr</th>
<th>Warfarin No./100pt yr</th>
<th>Rivaroxaban vs. Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleeding</td>
<td>3.6</td>
<td>3.4</td>
<td>NS</td>
</tr>
<tr>
<td>Fatal Bleeding</td>
<td>0.2</td>
<td>0.5</td>
<td>p=0.003</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.5</td>
<td>0.7</td>
<td>p=0.02</td>
</tr>
</tbody>
</table>

Major bleeding defined as decrease in hgb > 2 g/dl, PRBC transfusion, critical bleeding, fatal bleeding

Patel MR et al. NEJM 2011; 365:833-891
ROCKET-AF Conclusions

- Rivaroxaban is non-inferior to warfarin for prevention of stroke or systemic embolism
- No difference in rates of major and clinically relevant nonmajor bleeding between two groups
- Lower rates of intracranial and fatal bleeding with Rivaroxaban
Apixaban

- FDA Approved December, 2012
- Factor Xa Inhibitor
- Dosing
  - CrCl > 15 ml/min = 5mg BID
  - Reduce dose to 2.5mg BID for patients with ≥ 2 of the following:
    - Age ≥ 80 years
    - Weight ≤ 60kg
    - SCr ≥ 1.5
  - No monitoring required

Apixaban

- Onset 3-4 hours
- Half life 12 hours
- May falsely elevate INR
- Pregnancy category B
- Brand Name: Eliquis®

Cost
- $400/month
ARISTOTLE
Apixaban vs Warfarin

- n = 18,201 patients
- Duration = 1.8 years
- Non-valvular AF + ≥ 1:
  - CVA/TIA/Embolism, Age ≥ 75 years, History of HF or LVEF ≤ 40%, HTN, DM
- Mean CHADS2 Score = 2.1
- Average TTR for warfarin 62%

Granger C, et al. NEJM 365: 981-992
### ARISTOTLE

**Apixaban vs Warfarin**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Apixaban Risk %/yr</th>
<th>Warfarin Risk %/yr</th>
<th>Apixaban vs. Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolism</td>
<td>1.27%</td>
<td>1.60%</td>
<td>0.01</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.97%</td>
<td>1.05%</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Granger C, et al. NEJM 365: 981-992
ARISTOTLE
Apixaban vs Warfarin

<table>
<thead>
<tr>
<th>Outcome</th>
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<th>Warfarin Risk %/yr</th>
<th>Apixaban vs. Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleeding</td>
<td>2.13%</td>
<td>3.09%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>0.33%</td>
<td>0.80%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major or clinically relevant non-major bleeding</td>
<td>4.07%</td>
<td>6.01%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Granger C, et al. NEJM 365: 981-992
ARISTOTLE Conclusions

- Lower rates of stroke or systemic embolism with Apixaban than warfarin
- Lower rates of major bleeding and intracranial bleeding with Apixaban over warfarin

Granger C, et al. NEJM 365: 981-992
Edoxaban

- FDA Approved January, 2015
- Factor Xa Inhibitor
- Renal Dosing
  - CrCl > 95 ml/min - Avoid
  - CrCl 51-94 ml/min: 60mg PO daily
  - CrCl 15-50 ml/min: 30mg PO daily
  - CrCl < 15 ml/min: Avoid
- No monitoring required

Sayasa ® [Package Insert]. Tokyo, Japan: Daiichi Sankō Co, LTD; 2015
Edoxaban

- Onset 1-2 hours
- Half life 10-14 hours
- Boxed Warning:
  - Dosing CrCl > 95ml/min
- May falsely elevate INR
- Brand Name: Savaysa ©

Cost
- $664/month
ENGAGE AF Timi-48
Edoxaban vs. Warfarin

- n = 21,105
- Duration = 2.8 years
- Non-valvular Atrial Fibrillation + ≥ 2
  - CVA/TIA/Embolism, Age ≥ 75 years, History of HF or LVEF ≤ 40%, HTN, DM
- Mean CHADS2 Score = 2.8

### ENGAGE AF Timi-48
#### Edoxaban vs. Warfarin

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Edoxaban Pts/yr (%)</th>
<th>Warfarin Pts/yr (%)</th>
<th>Edoxaban vs. Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolism – ITT</td>
<td>1.57%</td>
<td>1.8%</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke or systemic embolism – modified ITT</td>
<td>1.18%</td>
<td>1.5%</td>
<td>p&lt;0.001 Non-inferior</td>
</tr>
<tr>
<td>Stroke (all)</td>
<td>1.49%</td>
<td>1.69%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>1.25%</td>
<td>1.25%</td>
<td>NS</td>
</tr>
</tbody>
</table>

ENGAGE AF Timi-48
Edoxaban vs. Warfarin

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Edoxaban Pts/yr (%)</th>
<th>Warfarin Pts/yr (%)</th>
<th>Edoxaban vs. Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic Stroke</td>
<td>1.26%</td>
<td>0.47%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Death or intracranial hemorrhage</td>
<td>4.24%</td>
<td>4.61%</td>
<td>p=0.004</td>
</tr>
<tr>
<td>Death (any cause)</td>
<td>3.99%</td>
<td>4.35%</td>
<td>NS</td>
</tr>
</tbody>
</table>

ENGAGE AF Timi-48
Conclusions

- Edoxaban is non-inferior to warfarin for prevention of stroke or systemic embolism
- Edoxaban is associated with lower rates of bleeding and death from cardiovascular causes
- For patients with CrCl > 95ml/min, edoxaban was associated with higher rates of stroke

New OAC

- **Advantages**
  - No monitoring required
  - Data suggests lower rates of stroke and bleeding compared to VKA
  - Short half life

- **Disadvantages**
  - High cost
  - No reversal agent available
  - Lack of data in special populations
Choose warfarin if:

- Mechanical Heart Valve
- Renal insufficiency
- Cost/Insurance a concern
- High risk of bleeding (reversal available)
- Coronary Artery Disease/Myocardial Infarction

You JJ et al. Chest 2012; 141: e531s-575s
MM is a 68 year old female

CC: Intermittent ‘fluttering’ feeling in her chest over the past 2-3 weeks. She is compliant with medications and has private health insurance.

PMH: Hypertension, Hyperlipidemia, Obesity, Obstructive Sleep Apnea

Home Medications:
- Atorvastatin 40mg PO daily at bedtime
- Lisinopril 20mg PO daily
- Metoprolol tartrate 50mg PO twice daily
What is the most appropriate therapy for MM?

- No antithrombotic therapy
- Aspirin + Clopidogrel
- Warfarin (goal INR 2-3)
- Rivaroxaban 20mg PO daily
Case #2

- JD is an 85 yr old female who presents to clinic after hospital stay for Right MCA Stroke secondary to undiagnosed Afib.
- PMH: Gout, Hypertension, CKD (baseline SCr 1.2)
- Medications:
  - Aspirin 81mg Daily
  - Atorvastatin 80mg Daily
  - Metoprolol 25mg BID
  - Allopurinol 300mg Daily
Case #2

- ECG: Currently in NSR
- Labs:
  - SCr 1.2
  - LFTs wnl
- Vitals
  - BP 140/90
  - Pulse 75
Question

What is the most appropriate therapy for this patient?

- No Anticoagulation
- Aspirin
- Aspirin + Clopidogrel
- Oral anticoagulant
Balancing Risk to Benefit

http://cliparts.co/balance-scale-clipart
Bleeding Risk Stratification

- HAS-BLED
  - Euro Heart Study
- ORBIT
  - ORBIT-AF Study
- ATRIA
  - Kaiser Permanente Study
- HEMORR2HAGES
  - AF National Registry
HAS-BLED
Euro Heart Survey

- Chest, 2010
  - n=3,978
  - Follow up 1 year
- Fast and Simple
- Data elements not easily accessible

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (SBP&gt;160)</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal renal or liver function (1 point each)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>• SCr&gt;2, dialysis, transplant</td>
<td></td>
</tr>
<tr>
<td>• LFTs &gt;3-fold; Bili &gt;2-fold</td>
<td></td>
</tr>
<tr>
<td>Stroke history</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding history</td>
<td>1</td>
</tr>
<tr>
<td>Labile INRs (TTR &lt; 60%)</td>
<td>1</td>
</tr>
<tr>
<td>Elderly (Age &gt; 65 yrs)</td>
<td>1</td>
</tr>
<tr>
<td>Drugs or alcohol (1 point each) - Antiplatelets, NSAIDS</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

## HAS-BLED

### Euro Heart Survey

<table>
<thead>
<tr>
<th>Score</th>
<th>Bleeds per 100 pt yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.13</td>
</tr>
<tr>
<td>1</td>
<td>1.02</td>
</tr>
<tr>
<td>2</td>
<td>1.88</td>
</tr>
<tr>
<td>3</td>
<td>3.74</td>
</tr>
<tr>
<td>4</td>
<td>8.70</td>
</tr>
<tr>
<td>5</td>
<td>12.5</td>
</tr>
<tr>
<td>6-9</td>
<td>Insufficient Data</td>
</tr>
</tbody>
</table>

### Bleeding Risk

<table>
<thead>
<tr>
<th>Bleeding Risk</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
</tr>
<tr>
<td>Moderate</td>
<td>1-2</td>
</tr>
<tr>
<td>High</td>
<td>&gt; 3</td>
</tr>
</tbody>
</table>

HAS-BLED

- Predictive of intracranial bleeding
- Will not predict bleeding with non-warfarin anticoagulants
- Validated in AF and non-AF populations
- Predict bleedin in those undergoing bridging
ORBIT
ORBIT-AF Study

- n = 7,411 patients
- ORBIT-AF registry of 176 US sites
- Simple to use
- Newest scoring system – needs validation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age (Age &gt; 75 years)</td>
<td>1</td>
</tr>
<tr>
<td>Reduced hgb (&lt;13 mg/dL), hematocrit (&lt;40% men, &lt;36% women), or history of anemia</td>
<td>2</td>
</tr>
<tr>
<td>Bleeding history</td>
<td>2</td>
</tr>
<tr>
<td>Insufficient kidney function (eGFR &lt;60 mg/dL/1.73m²)</td>
<td>1</td>
</tr>
<tr>
<td>Treatment with antiplatelets (aspirin, ticagrelor, clopidogrel, prasugrel, aggrenox)</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Bleeds per 100 pt yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.7</td>
</tr>
<tr>
<td>1</td>
<td>2.3</td>
</tr>
<tr>
<td>2</td>
<td>2.9</td>
</tr>
<tr>
<td>3</td>
<td>4.7</td>
</tr>
<tr>
<td>4</td>
<td>6.8</td>
</tr>
<tr>
<td>5</td>
<td>9.0</td>
</tr>
<tr>
<td>6</td>
<td>12.3</td>
</tr>
<tr>
<td>7</td>
<td>14.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bleeding Risk</th>
<th>Score</th>
<th>Bleeds per 100 pt yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0-2</td>
<td>2.4</td>
</tr>
<tr>
<td>Moderate</td>
<td>3</td>
<td>4.7</td>
</tr>
<tr>
<td>High Risk</td>
<td>≥ 4</td>
<td>8.1</td>
</tr>
</tbody>
</table>

JD is an 85 yr old female who presents to clinic after hospital stay for Right MCA Stroke secondary to undiagnosed Afib

PMH: Gout, Hypertension, CKD (baseline SCr 1.2)

Medications:
- Aspirin 81mg Daily
- Atorvastatin 80mg Daily
- Metoprolol 25mg BID
- Allopurinol 300mg Daily
Question

- What is JD’s Stroke Risk?
  - CHA2DS2-VASc Score

- What is JD’s Bleeding Risk?
  - HAS-BLED Score
Danish National Cohort
Risk vs. Benefit

- n = 132,372
- Real-world cohort that assessed stroke risk and bleeding risk to identify net clinical benefit
- Outcomes – Rates of ischemic and hemorrhagic stroke based on CHADS$_2$, CHA$_2$DS$_2$-VASc, and HAS-BLED Scores

Olesen J, et al. Thromb and Haem 2011; 106:739-749
Conclusions:
- Positive net clinical benefit of VKA in patients with CHADS$_2$ ≥ 1 or CHA$_2$DS$_2$-VASc ≥ 2
- Net clinical benefit of VKA higher in patients with high risk of bleeding - HAS-BLED Score ≥ 3

Olesen J, et al. Thromb and Haem 2011; 106:739-749
Question

What is the most appropriate therapy for this patient?
- No Anticoagulation
- Aspirin
- Aspirin + Clopidogrel
- Oral anticoagulant
Antiplatelets
Aspirin
BAFTA Study

- Aspirin Alone vs. Warfarin
- n = 973
- Afib + age > 75 years

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Warfarin Risk/yr</th>
<th>Aspirin Risk/yr</th>
<th>Warfarin vs. Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke (all types)</td>
<td>1.6%</td>
<td>3.4%</td>
<td>P = 0.003</td>
</tr>
<tr>
<td>Fatal Stroke</td>
<td>1.0%</td>
<td>1.6%</td>
<td>NS</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>0.8%</td>
<td>2.5%</td>
<td>P = 0.0004</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>0.5%</td>
<td>0.4%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Aspirin + Clopidogrel
ACTIVE-W Study

- Aspirin + Clopidogrel vs. Warfarin
- n = 6706
- Afib + ≥ 1 risk factor for stroke

Conclusions:
- Study stopped early due to clear superiority of OAC for stroke and systemic embolism (p = 0.0003)

## Aspirin + Clopidogrel

### ACTIVE-W Study

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Aspirin + Clopidogrel Risk (%/yr)</th>
<th>Warfarin Risk (%/yr)</th>
<th>Warfarin vs. Aspirin + Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net benefit (stroke vs major bleed)</td>
<td>7.56%</td>
<td>5.45%</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Stroke (all)</td>
<td>2.39%</td>
<td>1.40%</td>
<td>p = 0.001</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>2.15%</td>
<td>1.00%</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.12%</td>
<td>0.36%</td>
<td>p = 0.036</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>0.33%</td>
<td>0.36%</td>
<td>NS</td>
</tr>
<tr>
<td>Major bleed</td>
<td>2.42%</td>
<td>2.21%</td>
<td>NS</td>
</tr>
</tbody>
</table>

ACTIVE-W Conclusions

- Warfarin is superior to Aspirin + Clopidogrel for stroke and systemic embolism and ischemic stroke
- Lower rates of hemorrhagic stroke with Aspirin + Clopidogrel
- Net clinical benefit for stroke vs. major bleed superior with warfarin

JD is an 85 yr old female who presents to clinic after hospital stay for Right MCA Stroke secondary to undiagnosed Afib

PMH: Gout, Hypertension, CKD (baseline SCr 1.2)

Medications:
- Aspirin 81mg Daily
- Atorvastatin 80mg Daily
- Metoprolol 25mg BID
- Allopurinol 300mg Daily
Question

- What is the most appropriate therapy for this patient?
  - No Anticoagulation
  - Aspirin
  - Aspirin + Clopidogrel
  - Oral anticoagulant
Conclusions

- Use CHA₂DS₂-VASc for stroke risk stratification
- Use an appropriate bleeding risk stratification tool (HAS-BLED or ORBIT) to identify high risk patients
- For patients with CHA₂DS₂-VASc = 0, no therapy is recommended
- For patients with CHA₂DS₂-VASc ≥ 2, OAC is recommended
- Discuss risk vs. benefit with patients when choosing antithrombotic therapy
- High bleeding risk score should not be an excuse to avoid OAC