Anticoagulation in Atrial Fibrillation

Parag P. Patel, MD FACC

Disclosures

Eliquis Speakers Bureau
Clinical Scenario

- Ms. L is a 76F admitted to the stroke service with a dense right sided hemiparesis
- A workup for the CVA includes a TEE
- She later has paroxysmal Afib seen on telemetry for which she was asymptomatic
- No previous history of palpitations

Cornerstones of AFib Management

- Rate Control
- Rhythm Control
- Anticoagulation
- Control of symptoms
- Prevention of thromboembolism
- Treatment or prevention of Tachycardia Induced Cardiomyopathy (CMP)
- Reduction in Hospitalizations
- Minimization of bleeding risk
Stroke and cardioembolism prevention

Afib and Embolism/Stroke

- AF, whether paroxysmal, persistent, or permanent, and whether symptomatic or silent, significantly increases the risk of thromboembolic ischemic stroke
  - 69000/795000 yearly strokes in the USA are attributable to AFib
  - Nonvalvular AF increases the risk of stroke 5 times (MS related AF up to 20 fold)
  - Afib related CVA is associated with a greater risk of recurrent stroke, more severe disability and mortality
  - The appropriate use of antithrombotic therapy and the control of other risk factors including hypertension, and hypercholesterolemia substantially reduces stroke risk

January, CT et al. 2014 AHA/ACC/HRS Atrial Fibrillation Guideline
## Stroke Risk Stratification

### CHADS<sub>2</sub> -> CHA<sub>2</sub>D<sub>2</sub>VS<sub>c</sub>

<table>
<thead>
<tr>
<th>CHADS&lt;sub&gt;2&lt;/sub&gt; Risk</th>
<th>Score</th>
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<tbody>
<tr>
<td>CHF</td>
<td>1</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Age &gt; 75</td>
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<tr>
<td>Diabetes</td>
<td>1</td>
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<tr>
<td>Stroke/TIA</td>
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<tr>
<td>Age 65-74</td>
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<tr>
<td>Female</td>
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</table>

### CHA<sub>2</sub>D<sub>2</sub>VS<sub>c</sub> Score

<table>
<thead>
<tr>
<th>CHA&lt;sub&gt;2&lt;/sub&gt;D&lt;sub&gt;2&lt;/sub&gt;VS&lt;sub&gt;c&lt;/sub&gt; Score</th>
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**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

- **CHA.DS-VASc score of > 2 (class I)**
  - Oral anticoagulants are recommended
  - Options include warfarin (INR 2.0 to 3.0), dabigatran, rivaroxaban, or apixaban

- **CHA.DS-VASc score of 0 (class IIa)**
  - It is reasonable to omit antithrombotic therapy

- **CHA.DS-VASc score of 1 (class IIb)**
  - no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered
Stroke Risk Reduction

- Despite guidelines and tools anticoagulation is under prescribed, which exposes patients with AF to the risk of debilitating strokes

- National Anticoagulation Benchmark Outcomes Report (NABOR)
  - Risk factors indicated that 86% of patients had a high risk for stroke only 55% were anticoagulated

Perceived Fears

- Anticoagulants rank high in drugs associated with adverse outcomes
- “first do no harm”
- Patient apprehension and lack of compliance
- Concomitant medications
  - Antiplatelets, NSAIDs
- No clear guideline or risk stratification scheme to assess bleeding risk
Anticoagulants

• Warfarin

• NOACs – For NonValvular Afib
  ◦ Dabigatran
  ◦ Rivaroxaban
  ◦ Apixaban
  ◦ Edoxaban

Coagulation cascade.

Craig T. January et al. Circulation. 2014;130:e199-e267

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Warfarin

- Warfarin is a vitamin K antagonist in use since the 1950s as an oral anticoagulant for stroke prevention in patients with AF.

- Initially developed as rat poison

- Later developed at U of Wisconsin and given the name WARFarin

- Inhibits factors II, VII, IX and X

- 6 RCTs of 2,900 subjects in which adjusted-dose warfarin was compared with placebo or no treatment, the mean INR ranged from 2.0 to 2.9

  - Adjusted-dose warfarin resulted in a 64% RR reduction for ischemic and hemorrhagic stroke compared with the placebo.

  - The absolute risk reduction was 2.7% per year which yielded a NNT of 37 for 1 year to prevent 1 stroke and 12 for patients with prior stroke or TIA

  - Standard of care for decades for cardioembolism risk reduction in higher risk Afib patients.
Effects on all stroke (ischemic and hemorrhagic) of therapies for patients with atrial fibrillation

Adjusted-Dose Warfarin Compared with Placebo

<table>
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<th>Trial</th>
<th>N (Site)</th>
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<td>AFASAK I</td>
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<tr>
<td>SPAF I</td>
<td>57</td>
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<tr>
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<tr>
<td>EAFT</td>
<td>403</td>
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<td>All Trials</td>
<td>6</td>
</tr>
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</table>

Relative Risk Reduction (95% CI)

Adjusted odds ratios for ischemic stroke and intracranial bleeding in relation to intensity of anticoagulation

Fuster, V. et al. J Am Coll Cardiol 2006;48:e149-e246
Problems with Warfarin

- Dosing Varies
- Labor Intensive
- Food and Drug Interactions
- Unpredictability
- Bridging Issues

Novel Oral Anticoagulants

- Direct Thrombin Inhibitor
  - Dabigatran,
- Factor Xa Inhibitors
  - Rivaroxaban, Apixiban, Edoxaban
- Standardized dosing
- No INR monitoring
- Less labor intensive
- Minimal interactions
- Predictable pharmacokinetics
- Some concerns
  - Increased risk of thrombosis if drug is stopped?
  - No approved reversible agent
  - Not indicated for valvular atrial fibrillation
Unblinded for warfarin, Blinded for dabigatran dose
Noninferiority trial
Randomly assigned 18,113 patients who had NVAF and a risk of stroke to receive
- Dabigatran 110 mg BID
- Dabigatran 150 mg BID
- Warfarin

The median duration of the follow-up period was 2.0 years
The primary outcome was stroke or systemic embolism.


ANNUAL CVA OR EMBOLISM
Warfarin - 1.69%
Dabigatran 110mg - 1.53%
Dabigatran 150mg - 1.11%

The 110mg dose of dabigatran was noninferior to warfarin (P<0.001).
The 150-mg dose of dabigatran was superior to warfarin

ANNUAL BLEEDING RISK
Warfarin - 3.36%
Dabigatran 110mg - 2.71%
Dabigatran 150mg - 3.11%

Rates of life-threatening bleeding, intracranial bleeding, and major or minor bleeding were higher with warfarin (P<0.05 for all comparisons of dabigatran with warfarin).

There was a significantly higher rate of major gastrointestinal bleeding with dabigatran at the 150-mg dose than with warfarin.
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.

Based on this data the FDA approved Dabigatran 150mg bid on October 19th, 2010

The 110mg dose was NOT approved


**Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation**

- Randomized, double-blind trial
- 14,264 patients with nonvalvular atrial fibrillation who were at increased risk for stroke to receive either
  - Rivaroxaban 20 mg (15mg for reduced GFR)
  - Warfarin
- The per-protocol, as-treated primary analysis was designed to determine whether rivaroxaban was noninferior to warfarin for the primary end point of stroke or systemic embolism.

### Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

**ANNUAL CVA OR EMBOLISM**
- Warfarin – 2.2%
- Rivaroxaban – 1.7%

Rivaroxaban was noninferior to warfarin (P<0.001) for CVA/embolism

**ANNUAL MAJOR BLEEDING**
- Warfarin - 3.4%
- Rivaroxaban – 3.6%

Rates of critical site bleeding and intracranial bleeding were higher with warfarin

Transfusion rates and GI bleeding were higher for rivaroxaban

<table>
<thead>
<tr>
<th>Event</th>
<th>Warfarin</th>
<th>Rivaroxaban</th>
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</thead>
<tbody>
<tr>
<td>CVA or Embolism</td>
<td>2.2%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>3.4%</td>
<td>3.6%</td>
</tr>
</tbody>
</table>

*In patients with atrial fibrillation, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.*

- FDA approval Nov 4, 2011

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Randomized, double-blind trial

18,201 patients with atrial fibrillation and at least one additional risk factor for stroke to receive either
- Apixaban 5 mg bid (2.5mg in select patients)
- Warfarin

The primary outcome was ischemic or hemorrhagic stroke or systemic embolism.

Test for noninferiority, with key secondary objectives of testing for superiority with respect to the primary outcome and to the rates of major bleeding and death from any cause.

**ANNUAL CVA OR EMBOLISM**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Event Rate</th>
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<tbody>
<tr>
<td>Warfarin</td>
<td>1.6%</td>
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<tr>
<td>Apixaban</td>
<td>1.27%</td>
</tr>
</tbody>
</table>

Apixaban was superior to warfarin (P=0.01) for CVA/embolism

Mostly related to significant decrease in hemorrhagic CVA as pure ischemic CVA occurred at a similar rate

**ANNUAL MAJOR BLEEDING**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Event Rate</th>
</tr>
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<tbody>
<tr>
<td>Warfarin</td>
<td>3.09%</td>
</tr>
<tr>
<td>Apixaban</td>
<td>2.13%</td>
</tr>
</tbody>
</table>

Apixaban was superior to warfarin in bleeding endpoints (mostly related to reduction in IC and fatal bleeding, GI bleeding occurrences were equivalent)

Overall mortality from any cause were 3.52% for Eliquis and 3.94% for warfarin (P = 0.047)
“In patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.”

FDA Approval Dec 28, 2012

Randomized, double-blind, double-dummy trial

21,105 patients with moderate to high-risk atrial fibrillation followed for 2.8 years

- Edoxaban 30mg
- Edoxaban 60mg
- Warfarin

- Edoxaban doses were cut in half if creatinine clearance of 30-50 ml per minute, a body weight of 60 kg or less, or the concomitant use of verapamil, dronedarone

- The primary efficacy end point was stroke or systemic embolism
- Each edoxaban regimen was tested for noninferiority to warfarin during the treatment period
- The principal safety end point was major bleeding.
For the total primary endpoint of CVA or embolism, both doses were noninferior to warfarin.

Edoxaban 30mg was inferior to warfarin for pure ischemic stroke (1.77% vs. 1.25% P<0.001).

The annualized rate of major bleeding events:
- 3.43% warfarin
- 2.75% edoxaban 60mg
- 1.61% edoxaban 30mg

Consistently lower dose-related rates of all types of bleeding except for GI bleeding.

Significantly lower CV death.

FDA Approval Jan 8, 2015 of the 60mg dose.

"Both once-daily regimens of edoxaban were noninferior to warfarin for the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes."
Novel Oral Anticoagulants

- **Dabigatran (Pradaxa)**
  - 150mg BID & 75mg BID (for CrCl 15-30 ml/min) for afib

- **Rivaroxaban (Xarelto)**
  - 20mg QD & 15mg QD (for CrCl 15-50 ml/min) for afib

- **Apixaban (Eliquis)**
  - 5mg BID & 2.5mg for special circumstances (Combined P-gp and strong CYP3A4 inhibitors, or any 2 of the following (age >80, wt<60kg, Cr >1.5)
  - Can be used on ESRD patients on HD (although not clinically studied)

- **Edoxaban (Savaysa)**
  - 60mg dose for CrCl 50-95 ml/min (should not be used if CrCl >95 ml/min)
  - 30mg dose for CrCl 15-50 ml/min
Novel Oral Anticoagulants

BLACK BOX WARNINGS!!!!

- Premature discontinuation of any oral anticoagulant increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if the drug is discontinued for a reason other than pathological bleeding or completion of a course of therapy.

- Epidural or spinal hematomas may occur in patients treated with these agents who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Monitor patients frequently for signs and symptoms of neurological impairment and if observed, treat urgently. Consider the benefits and risks before neuraxial intervention in patients who are or who need to be anticoagulated.

Specific Black Box - SAVAYSA

- REDUCED EFFICACY IN NONVALVULAR ATRIAL FIBRILLATION PATIENTS WITH CRCL > 95 ML/MIN

- SAVAYSA should not be used in patients with CrCL > 95 mL/min

- In the ENGAGE AF-TIMI 48 study, nonvalvular atrial fibrillation patients with CrCL > 95 mL/min had an increased rate of ischemic stroke with SAVAYSA 60 mg once daily compared to patients treated with warfarin. In these patients another anticoagulant should be used.
Many, Many Questions…

- Are they safe?
- I take warfarin now, should I switch?
- What happens if I need surgery?
- What happens if I bleed?

Special Situations with Anticoags

- Transitioning
- Perioperative Management
- Bridging
- Bleeding
Warfarin

- In patients who require temporary interruption of a VKA before surgery, we recommend stopping VKAs approximately **5 days** before surgery instead of stopping VKAs a shorter time before surgery (Grade 1C)

- In patients who require temporary interruption of a VKA before surgery, we recommend resuming VKAs approximately 12 to 24 h after surgery (evening of or next morning) and when there is adequate hemostasis instead of later resumption of VKAs (Grade 2C)
Perioperative Management - NOACs

### Renal function

<table>
<thead>
<tr>
<th>Drug</th>
<th>High risk of bleeding</th>
<th>Low risk of bleeding</th>
<th>High risk of bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>24 h</td>
<td>2-4 days</td>
<td>3 days</td>
</tr>
<tr>
<td></td>
<td>59 h</td>
<td>4 days</td>
<td>6 days</td>
</tr>
<tr>
<td></td>
<td>≥69 h</td>
<td>≥5 days</td>
<td>≥8 days</td>
</tr>
</tbody>
</table>

Note: Adapted from van Ryn et al. (2016), Sympotropes and Dworkes (2012) and Kuiswetter et al. (2012).

### Drug

- **Dabigatran**: Resume on day after surgery (34 h postoperative), 150 mg twice daily.
- **Rivaroxaban**: Resume on day after surgery (24 h postoperative), 20 mg once daily.
- **Apixaban**: Resume on day after surgery (24 h postoperative), 5 mg twice daily.

### High bleeding risk surgery

- Resume 2-3 days after surgery (48-72 h postoperative), 150 mg twice daily.
- Resume 2-3 days after surgery (48-72 h postoperative), 20 mg once daily.
- Resume 2-3 days after surgery (48-72 h postoperative), 5 mg twice daily.

### Low bleeding risk surgery

- Resume on day after surgery (12 h postoperative), 10 mg once daily.
- Resume on day after surgery (24 h postoperative), 3.5 mg twice daily.
- Resume on day after surgery (24 h postoperative), 3 mg twice daily.

### Perioperative Management of Antithrombotic Therapy

#### Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

##### Table 1. (Introduction) Suggested Risk Stratification for Perioperative Thrombolysis

- **High risk patients should be bridged**
- **Low risk patients should not be bridged**
- **Moderate risk can be considered**
Mitigating bleeding risk

- Change in renal function/liver function
- Concomitant medications
  - Antiplatelets
  - NSAIDs
  - SSRI, SNRI
- Patient Education

Reversal strategies?

* Siegel et al. European Heart Journal (2013) 34, 489–500
Reversal Agents

- **Andexanet alfa: FXa Inhibitor Antidote**
  - Acts as a Factor Xa decoy that targets and sequesters with high specificity both direct and indirect Factor Xa inhibitors in the blood.
  - Phase 2 proof-of-concept studies
    - Immediately reversed the anticoagulation activity of apixaban, rivaroxaban and edoxaban
    - Well tolerated in clinical studies, with no thrombotic events or antibodies to Factor Xa or Factor X observed.
  - Phase 3 studies – ANNEXA studies ongoing
  - FDA designated orphan drug designation

Conclusions

- Cardioembolism and CVA is a significant cause of morbidity and mortality in patients with Afib
- Risk stratification with CHADS-VaSC2 score is important in approaching the patient with Afib
- Several options are now available for anticoagulation