Anticoagulation Management

Learning Objectives
- Appreciate the pharmacokinetic differences between novel anticoagulants
- Tailoring anticoagulation therapy to patient needs
- Recent updates on the treatment of VTE

Case 1
- 89 year old retired physician
- May 2009
  - Paroxysmal atrial fibrillation
    CHADS-2 score: 3 (C, H, A)
  - Tachybrady syndrome
    - June 2009: AV sequential PPM
    - May 2010: AV node ablation
  - Mild cognitive impairment

Risk Assessment for Stroke in Atrial Fibrillation
CHADS-2 Score

<table>
<thead>
<tr>
<th>Points</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF (90 days)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt;75 years</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Stroke Prediction in AF
CHADS 2

Annual Adjusted

<table>
<thead>
<tr>
<th>Score</th>
<th>Stroke Rate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9</td>
<td>1.2-3.0</td>
</tr>
<tr>
<td>1</td>
<td>2.8</td>
<td>2.0-3.8</td>
</tr>
<tr>
<td>2</td>
<td>4.0</td>
<td>3.1-5.1</td>
</tr>
<tr>
<td>3</td>
<td><strong>5.9</strong></td>
<td><strong>4.6-7.3</strong></td>
</tr>
<tr>
<td>4</td>
<td>8.5</td>
<td>6.3-11.1</td>
</tr>
<tr>
<td>5</td>
<td>12.5</td>
<td>8.2-17.5</td>
</tr>
<tr>
<td>6</td>
<td>18.2</td>
<td>10.5-27.4</td>
</tr>
</tbody>
</table>
Atrial Fibrillation

Background

- \textbf{5-fold} increased risk of stroke
- Warfarin reduces this risk \textasciitilde70\%
- Aspirin reduces this risk \textasciitilde20\%

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{chart.png}
\caption{INR graph with dates and events.}
\end{figure}

Why Search for New Anticoagulants?

Warfarin

- Frequent monitoring with dose alteration
- Coexisting medications
- Coexisting illnesses
- Dietary variability
- Compliance

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{chart2.png}
\caption{Warfarin management chart.}
\end{figure}

Why Search for New Anticoagulants?

- Often not prescribed when indicated
- 35\% of "ideal candidates" with atrial fibrillation not offered warfarin
- Especially true for Blacks and Hispanics

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{chart3.png}
\caption{Anticoagulant effectiveness chart.}
\end{figure}

Quality Measures for Warfarin Management

- Meaningful Outcomes
  - Efficacy
  - Safety
  - Surrogate
    - Time in therapeutic range (TTR)
    - \textbf{Often averages 50\% or less}

\begin{align*}
\text{TTR} &= \frac{\text{Time in range (INR 2.0-3.0)}}{\text{Total time on warfarin}}
\end{align*}

Novel Oral Anticoagulants

- Dabigatran
  - Oral DTI
  - Renal clearance
  - Twice daily
- Rivaroxaban
  - Direct factor Xa inhibitor
  - Renal clearance
  - Once daily
- Apixaban
  - Direct factor Xa inhibitor
  - Hepatic clearance
  - Twice daily
- Edoxaban
  - Direct factor Xa inhibitor
  - Hepatic clearance
  - Once daily

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{chart4.png}
\caption{Anticoagulant comparison chart.}
\end{figure}
**Targets of New Inhibitors**

- IX → IXa
- X → Va
- Xa → Prothrombin
- Thrombin → Dabigatran
- Fibrinogen → Fibrin

**Why Target Thrombin**

- In contrast to heparin, DTIs have access to clot bound thrombin
- No local inhibitor of DTIs

**Dabigatran-Etexilate**

- Oral direct thrombin inhibitor
- MW: 684
- Prodrug with rapid in vivo activation
- 6% bioavailability
- Rapid onset: 2 hours post ingestion
- T1/2: ~17 hours
- Renal excretion (80%)

**Dabigatran**

- Twice daily dosing
- 150 mg tablet strength
  - Creatinine clearance >30 ml/min
- 75 mg tablet strength
  - Creatinine clearance 15-30 ml/min
- Based entirely on pharmacokinetic profiling

**Are There Drug Interactions?**

**P-Glycoproteins (PgP)**

- Efflux transporters
- Promote drug excretion

**FDA Approval**

- October 19, 2010
- First oral anticoagulant approved >50 years
- Approved indication
  - Non-valvular atrial fibrillation
- No dosing information
  - CrCl <15 mL/min
  - Pregnancy, nursing mothers
  - Pediatric patients

**Pharmacokinetics**


**Hematol. 2008;37:259-65**
Are There Drug Interactions?

P-Glycoproteins (PgP)

- Inducers
  - Reduce circulating drug levels
  - *e.g.*, Rifampin
- Inhibitors
  - Increase circulating levels
  - *e.g.*, Quinidine, Amiodarone

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.

**Peri-Procedural Recommendations for Dabigatran Based on Renal Function**

<table>
<thead>
<tr>
<th>Renal Function, CrCl, ml/min</th>
<th>Half-Life, Hours (Range)</th>
<th>Timing of Dabigatran Discontinuation Prior to Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>15 (12-34)</td>
<td>24 hours</td>
</tr>
<tr>
<td>30-50</td>
<td>18 (13-23)</td>
<td>At least 48 hours</td>
</tr>
<tr>
<td>≤30</td>
<td>27 (22-35)</td>
<td>2-5 days</td>
</tr>
</tbody>
</table>

*Both Cockcroft-Gault and MDRD over estimate creatinine clearance*

**Surgical Procedures at High Risk for Bleeding**

- Open heart surgery
- Abdominal vascular surgery
- Neurosurgery
- Major cancer surgery
- Urologic procedures
- Problem: Many procedures with low bleeding risk use neuraxial anesthesia

**Peak and Trough Plasma Concentration of Dabigatran**

<table>
<thead>
<tr>
<th>Dose</th>
<th>$C_{\text{max}}$ (ng/ml)</th>
<th>$C_{\text{tough}}$ (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 mg bid</td>
<td>184 (64-443)</td>
<td>90 (31-225)</td>
</tr>
</tbody>
</table>

*Both Cockcroft-Gault and MDRD over estimate creatinine clearance*
Pre-Procedural Recommendations
How do we do it?

- Define the surgical date
- Define the creatinine clearance
  - If ≥50, stop 5 days prior
  - If <50, stop 7 days prior
  - If high risk of hemorrhage, check pre-operative thrombin time to ensure complete elimination

Follow-Up Once Dabigatran is Initiated

- Initial consultation
- Clinical assessment
- Patient education
- Insurance analysis and prior authorization
- Individualized treatment recommendations
- Follow-up with referring provider
- Initiation of therapy if appropriate
- Follow-up phone call in 7-14 days to evaluate drug tolerance and adverse effects
- Follow-up phone call 1 month later, Rx, and refills
- Quarterly phone follow-up
  - Compliance
  - Education
  - SCr and CrCl annually or more frequently if needed
- Clinical assessment
  - Patient education
- Peri-procedural management

Targets of New Inhibitors

<table>
<thead>
<tr>
<th>Fibrinogen</th>
<th>Fibrin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombin</td>
<td>Xa</td>
</tr>
<tr>
<td>Prothrombin</td>
<td>Va</td>
</tr>
<tr>
<td>Xa</td>
<td>IX</td>
</tr>
<tr>
<td>VIIa</td>
<td>IXa</td>
</tr>
</tbody>
</table>

Rivaroxaban
Apixaban
Edoxaban

Dabigatran

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.

Cumulative Rates of the Primary End Point (Stroke or Systemic Embolism) in the Per-Protocol Population and in the Intention-to-Treat Population

AVERROES Trial

Vitamin K antagonists have been shown to prevent stroke in patients with atrial fibrillation. However, many patients are not suitable candidates for or are unwilling to receive vitamin K antagonist therapy, and those patients have a high risk of stroke. Apixaban, a novel factor Xa inhibitor, may be an alternative treatment for such patients.

Conclusions
In patients with atrial fibrillation for whom vitamin K antagonist therapy was unsuitable, apixaban reduced the risk of stroke or systemic embolism without significantly increasing the risk of major bleeding or intracranial hemorrhage. (Funded by Bristol-Myers Squibb and Pfizer; ClinicalTrials.gov number: NCT03496769.)
In patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.

**Novel Factor Xa Inhibitors**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mol Wt</td>
<td>436</td>
<td>460</td>
<td>548</td>
</tr>
<tr>
<td>Prodrug</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Time to peak, hrs</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>T1/2, hrs</td>
<td>10</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Antidote</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

**Thromb Res 2011;S2:S5**

**Drug Interactions**
- P-glycoprotein inhibitors
- CYP3A4 inhibitors
- Protease inhibitors
- Macrolide antibiotics
- Azole antifungals

**Laboratory Monitoring**
- Generally not indicated
- Not suitable for efficacy
- May be useful in bleeding patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>PT-INR</th>
<th>aPTT</th>
<th>Thrombin Time</th>
<th>Ecarin Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>↑</td>
<td>↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
</tr>
</tbody>
</table>

- aPTT
  - 2 x control after 1-2 hours
  - 1.5 x control at 12 hours


**Effect on Hemoclot Thrombin Time**

**Drug**
- Dabigatran
- Rivaroxaban
- Apixaban

**Trial**
- RE-LY
- ROCKET-AF
- ARISTOTLE

**NNT to prevent 1 ischemic event over warfarin per year**
- 77
- 88
- 135
- 167

**NNT to prevent 1 major bleeding episode over warfarin per year**
- 77
- 250
- -
- 67
**Magnitude of Benefit (CHADS score ignored)**

- Dabigatran 150 mg
- Apixaban
- Dabigatran 110 mg
- Rivaroxaban
- Warfarin

<table>
<thead>
<tr>
<th>Drug</th>
<th>Magnitude of Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>2.1</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>1.7</td>
</tr>
<tr>
<td>Dabigatran 150</td>
<td>1.53</td>
</tr>
<tr>
<td>Apixaban</td>
<td>1.27</td>
</tr>
<tr>
<td>Dabigatran 110</td>
<td>1.11</td>
</tr>
</tbody>
</table>

**Sub Group Analysis**

- Newer agents better
- Warfarin better

**Proposed Use of Anticoagulants in AF**

- Needs Warfarin based on CHADS2 Score
  - Avoid Dabigatran in patients with CAD
  - High dose PPI may inhibit absorption of Dabigatran

<table>
<thead>
<tr>
<th>CHADS2 Score</th>
<th>0-2</th>
<th>≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or TIA</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

**Cases**

**Case 1**
- 60 yr-old with diabetes, HTN and atrial fibrillation
- Home meds includes: Lisinopril 10mg daily, Metoprolol 50mg Bid, Rivaroxaban 20mg daily, Atrovastatin 10mg daily
- Admitted for chest pain
- Coronary angiogram showed 80% stenosis in the LAD
- What would be your recommendations for anticoagulation?
- What if he had no diabetes or HTN?

**Case 2**
- 85 yr-old with mild dementia, HTN and atrial fibrillation
- She had few falls over the past year
- What would be your choice for anticoagulation?
- What if her Cr 2.0
- What if she has used warfarin for 7 years?

**Managing Bleeding Complications**

- No suitable antidote
- Time is not the antidote

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>17</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>10</td>
</tr>
<tr>
<td>Apixaban</td>
<td>12</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>10</td>
</tr>
</tbody>
</table>

Managing Bleeding Complications

- Not plasma (FFP)
- Focused identification and correction of bleeding site(s)
  - Endoscopy
  - Surgery
  - Interventional radiology (coiling)
- Red cell transfusion, pressors, mechanical ventilation

Hemodialysis?

- Small molecule, ~60% dialyzable
- Problems
  - Volume distribution ~50 liters
  - Requires central venous catheter
  - If reasonable renal function, dialysis may not greatly augment clearance
  - Requires >2 hours
- Plasmapheresis and hemofiltration do not work

Bridging Therapy

Goals of Bridging Therapy

- Minimize:
  - Thromboembolism during anticoagulation interruption
  - Bleeding
  - Inconvenience
  - Economic burden

What is the Peri-Procedural Risk of Thromboembolism?

- Nonvalvular atrial fibrillation

“Bridging” Atrial Fibrillation Peri-Procedural Event Rates: Warfarin

<table>
<thead>
<tr>
<th>Author</th>
<th>No.</th>
<th>Clot, %</th>
<th>Bleed, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Douketis 2004</td>
<td>346</td>
<td>1.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Pengo 2009</td>
<td>653</td>
<td>0.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Kovacs 2004</td>
<td>112</td>
<td>2.7</td>
<td>6.3</td>
</tr>
<tr>
<td>Dunn 2007</td>
<td>76</td>
<td>2.3</td>
<td>3.5</td>
</tr>
<tr>
<td>Wysokinski 2008</td>
<td>345</td>
<td>1.1</td>
<td>2.7</td>
</tr>
<tr>
<td>Total</td>
<td>1,532</td>
<td>0.9</td>
<td>2.0</td>
</tr>
</tbody>
</table>
Warfarin is Fighting to “Stay Alive”

- Excellent efficacy
- Low cost of $.75 per day
- Long track record (1954)
- Centralized anticoagulation clinics that maintain TTRs >60%
- Rapid turnaround genetic testing
- Point-of-care testing

![Image of a monkey]

![Chart showing cost of AC]

![Image of a computer screen with text: Rivaroxaban approved for PE in Europe]

![Image of a government website: FDA]
VTE Prevention
Ortho: THR, TKR, Hip Fracture

Where Approved
- Dabigatran: EU, Canada
- Rivaroxaban: EU, Canada, US
- Apixaban: EU
- Edoxaban: Japan

VTE Prevention
Non-Ortho Surgery, Medical

Not Approved
- Dabigatran
- Rivaroxaban
- Apixaban
- Edoxaban

DVT and/or PE Treatment

- Dabigatran (recently approved in UK for DVT treatment only)
- Rivaroxaban (approved in EU and US)
- Apixaban
- Edoxaban

Take Home Points
- Novel oral anticoagulants, though expensive, will provide more choices and convenience for clinicians and patients to prevent and treat VTE
- Warfarin’s low price, efficacy, and long track record will prolong its life
- Look for 2016 updated guidelines for changes in the management of VTE

Questions and Discussion