Debate:
Warfarin Versus the Rest of the World for Stroke Prevention in Non-valvular Atrial Fibrillation

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Debate Outline

• Introduction
• **Novel oral anticoagulants should be used for stroke prevention in non-valvular atrial fibrillation**
  – Matthew Wanat
• **Warfarin should be used for stroke prevention in non-valvular atrial fibrillation**
  – Henry Bussey
• Patient case application
• Q & A with audience

Pharmacist Objectives

1. Explain why warfarin is more efficacious, safer, and more cost-effective than the new oral anticoagulants

2. Explain why the new oral anticoagulants are more efficacious, safer, and more cost-effective than warfarin

3. Evaluate a given patient to determine if warfarin or a new oral anticoagulant is the most appropriate treatment option for stroke prevention in atrial fibrillation
Technician Objectives

1. List reasons why warfarin is more efficacious, safer, and more cost-effective than the new oral anticoagulants.

2. List reasons why the new oral anticoagulants are more efficacious, safer, and more cost-effective than warfarin.

3. Evaluate a given patient to determine if warfarin or a new oral anticoagulant is the most appropriate treatment option for stroke prevention in atrial fibrillation.

Lets set a few things straight…..

• Debate only covers stroke prevention in non-valvular AF
  – Valvular disease → use warfarin!!
  – Not discussing literature with VTE treatment

• Anticoagulation is NOT a one-sized fits all approach
  – Clinicians should individualize treatment based on patient specific characteristics
  – Hopefully we can help guide your decisions

• Two men enter, one man survives….

Novel Oral Anticoagulants Should be Used for Stroke Prevention in Patients with Non-Valvular Atrial Fibrillation

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Disclosures

I have NO disclosures concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.

Prevention of Cardioembolic Stroke

• Most devastating effect of AF
• Blood stasis in fibrillating atria increases risk for clot formation
• Left atrial appendage responsible for > 90% LA thrombus
• Clot dislodges
  – LA → LV → aorta → brain

History of Agents

• Warfarin FDA approved in 1954
• Dabigatran FDA approved in 2010
• Rivaroxaban FDA approved in 2011
• Apixaban FDA approved in 2012
• Ximelagatran withdrawn from European markets
  – Hepatotoxicity
• Idraparinux withdrawn after phase III trial
  – Excessive bleeding
Comparison of oral anticoagulants

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Vitamin K antagonist</th>
<th>Direct thrombin inhibitor</th>
<th>Factor Xa inhibitor</th>
<th>Direct factor Xa inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Dosing</td>
<td>Oral administration</td>
<td>Oral administration</td>
<td>Oral administration</td>
<td>Oral administration</td>
</tr>
<tr>
<td>Laboratory Monitoring</td>
<td>APTT, INR, PT</td>
<td>APTT, INR, PT</td>
<td>APTT, INR</td>
<td>APTT, INR, PT</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Quick and effective</td>
<td>Slow and effective</td>
<td>Quick and effective</td>
<td>Slow and effective</td>
</tr>
<tr>
<td>Renal/Hepatic</td>
<td>No dosage adjustment</td>
<td>No dosage adjustment</td>
<td>No dosage adjustment</td>
<td>No dosage adjustment</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>None</td>
<td>No specific interactions</td>
<td>No specific interactions</td>
<td>No specific interactions</td>
</tr>
<tr>
<td>Major Clinical Indications</td>
<td>Atrial fibrillation</td>
<td>Atrial fibrillation</td>
<td>Atrial fibrillation</td>
<td>Atrial fibrillation</td>
</tr>
</tbody>
</table>

The cold, hard truth

“Warfarin is not a bad drug, but it is a/an ____________ drug”

Struggles with Warfarin

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Warfarin baits</th>
<th>INR</th>
<th>Warfarin tablets</th>
<th>Warfarin</th>
<th>Anticoagulant levels</th>
<th>Warfarin dose adjustment</th>
</tr>
</thead>
<tbody>
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</tbody>
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TSHP 2014 Annual Seminar
Benefits of new oral anticoagulants (NOAC)

- Predictable pharmacokinetics
  - Fast onset, no bridging
- Do not require therapeutic drug monitoring
- Similar/better efficacy and bleeding profiles
- No drug-food interactions
  - Less clinically significant drug-drug interactions
- No known genetic variations

Let's take a close look at the clinical trials data......

RE-LY Trial

- 18,113 patients with AF and additional risk factor for stroke randomized to dabigatran 110mg or 150 mg BID versus warfarin (INR adjusted)
- Primary outcome => stroke(any) or systemic embolism
- Safety => major hemorrhage

### RE-LY Trial

#### Efficacy Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dabigatran 150mg (N=6076) (n, %/year)</th>
<th>Warfarin (n=6022) (n, %/year)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolism</td>
<td>136 (1.11%)</td>
<td>195 (1.63%)</td>
<td>0.66 (0.53-0.82)</td>
<td>&lt;0.001 for non-inferiority and superiority</td>
</tr>
<tr>
<td>Stroke (any)</td>
<td>122 (1.01%)</td>
<td>185 (1.57%)</td>
<td>0.64 (0.51-0.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>12 (0.10%)</td>
<td>45 (0.38%)</td>
<td>0.26 (0.14-0.49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>83 (0.74%)</td>
<td>63 (0.52%)</td>
<td>1.38 (1.03-1.81)</td>
<td>0.048</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>438 (3.64%)</td>
<td>487 (4.13%)</td>
<td>0.88 (0.77-1.00)</td>
<td>0.051</td>
</tr>
</tbody>
</table>

#### Safety Outcomes and Net Clinical Benefit

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dabigatran 150mg (n, %/year)</th>
<th>Warfarin (n, %/year)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>375 (3.11%)</td>
<td>397 (3.36%)</td>
<td>0.93 (0.81-1.07)</td>
<td>0.31</td>
</tr>
<tr>
<td>Life threatening</td>
<td>175 (1.45%)</td>
<td>212 (1.80%)</td>
<td>0.81 (0.66-0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>182 (1.51%)</td>
<td>120 (1.02%)</td>
<td>1.50 (1.19-1.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>36 (0.30%)</td>
<td>87 (0.74%)</td>
<td>0.40 (0.27-0.60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Net clinical benefit outcome</td>
<td>832 (6.91%)</td>
<td>901 (7.64%)</td>
<td>0.91 (0.82-1.00)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

### ROCKET-AF Trial

- Randomized, double-blind trial comparing rivaroxaban 20 mg daily versus warfarin (INR adjusted)
- 14,264 patients with AF with CHADS2 of ≥ 2
- Primary outcome → stroke (any) and/or systemic embolism
- Safety → composite of major and non-major clinically relevant bleeding events
**ROCKET-AF Trial**

<table>
<thead>
<tr>
<th>Efficacy Outcomes</th>
<th>Rivaroxaban (n=6958) (n, n/100 pt years)</th>
<th>Warfarin (n=7004) (n, n/100 pt years)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: Stroke (any) or systemic embolism (per-protocol)</td>
<td>188 (1.7)</td>
<td>241 (2.2)</td>
<td>0.79 (0.66-0.96)</td>
<td>&lt;0.001 for non-inferiority</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety Outcomes</th>
<th>Rivaroxaban (n=7111) (n, %)</th>
<th>Warfarin (n=7125) (n, %)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major and non-major clinically relevant bleeding</td>
<td>1475 (20.7)</td>
<td>1449 (20.3)</td>
<td>1.03 (0.96-1.11)</td>
<td>0.44</td>
</tr>
<tr>
<td>Any major bleed</td>
<td>395 (5.4)</td>
<td>386 (5.4)</td>
<td>1.04 (0.90-1.20)</td>
<td>0.58</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>55 (0.8)</td>
<td>84 (1.2)</td>
<td>0.67 (0.47-0.93)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**ARISTOTLE Trial**

- Randomized, double-blinded trial with apixaban 5 mg BID vs warfarin (INR adjusted)
- 18,201 patients with two documented AF episodes and ≥ 1 additional risk factor
- Primary outcome → Stroke (any) or systemic embolism
- Safety → Major bleeding events

<table>
<thead>
<tr>
<th>Efficacy Outcomes</th>
<th>Apixaban (n=9120) (n, %/year)</th>
<th>Warfarin (n=9081) (n, %/year)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: Stroke (any) or systemic embolism</td>
<td>212 (1.27%)</td>
<td>265 (2.0%)</td>
<td>0.79 (0.66-0.95)</td>
<td>0.01</td>
</tr>
<tr>
<td>Stroke</td>
<td>199 (1.13%)</td>
<td>235 (2.11%)</td>
<td>0.79 (0.65-0.95)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>45 (0.24%)</td>
<td>78 (0.47%)</td>
<td>0.51 (0.35-0.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>15 (0.08%)</td>
<td>17 (0.10%)</td>
<td>0.87 (0.44-1.75)</td>
<td>0.70</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>603 (3.52%)</td>
<td>689 (3.54%)</td>
<td>0.89 (0.81-0.98)</td>
<td>0.047</td>
</tr>
<tr>
<td>Stroke, embolism, MI or death from any cause</td>
<td>810 (4.53%)</td>
<td>906 (4.93%)</td>
<td>0.88 (0.80-0.97)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
### ARISTOTLE Trial

<table>
<thead>
<tr>
<th>Safety and net clinical outcomes</th>
<th>Apixaban (n=9088) (n, %/year)</th>
<th>Warfarin (n=9052) (n, %/year)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary safety outcome: ISTH major bleeding</td>
<td>327 (2.13%)</td>
<td>462 (3.00%)</td>
<td>0.69 [0.60-0.80]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intracranial</td>
<td>52 (0.33%)</td>
<td>122 (0.80%)</td>
<td>0.42 [0.30-0.58]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>105 (0.76%)</td>
<td>119 (0.86%)</td>
<td>0.89 [0.70-1.15]</td>
<td>0.37</td>
</tr>
<tr>
<td>Net Clinical Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke, systemic embolism or major bleeding</td>
<td>521 (3.17%)</td>
<td>666 (4.11%)</td>
<td>0.77 [0.69-0.86]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke, systemic embolism, major bleeding or death from any cause</td>
<td>1009 (6.13%)</td>
<td>1168 (7.20%)</td>
<td>0.85 [0.78-0.92]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Lets summarize the clinical data…….

- Dabigatran, rivaroxaban and apixaban all were non-inferior to warfarin for preventing stroke and/or systemic embolism
  - Dabigatran 150 mg dose and apixaban showed superiority
- Similar or less bleeding events with NOAC compared to warfarin
  - More ICH with warfarin compared to each of the NOAC’s

### What do the guidelines recommend?

**ACCF/AHA Guidelines for Atrial Fibrillation**

- Selection of agent should be based on risks of stroke and bleeding for a given patient (Class IA)

- Dabigatran useful as alternative to warfarin in patients with AF and risk factors, but without valvular disease, severe renal failure (CrCl < 15) or advanced liver disease (Level 1B)
CHEST Guidelines
Antithrombotic therapy for AF

- For patients where oral anticoagulation is recommended (non-valvular), suggest dabigatran 150 mg BID rather than warfarin (Grade 2B).

** The guidelines chose to not address rivaroxaban or apixaban in this version because they were not FDA approved at the time of writing.

European Society of Cardiology
Atrial Fibrillation Guidelines

- For patients where oral anticoagulation is recommended (non-valvular), a NOAC should be considered over warfarin based on net clinical benefit (Class IIaA).

- NOAC not recommended in CrCl < 30 (Class IIIA).

Renal disease

- Apixaban may be best choice
  - Can be used in ESRD (5 mg po BID)
  - Reduce to 2.5 mg BID if > 80 years old or weight < 60 kg

- Dosage adjustments required for dabigatran and rivaroxaban
  - Dabigatran - contraindicated if CrCl < 15 or CrCl 15-30 on p-glycoprotein inhibitor
  - Rivaroxaban - contraindicated if CrCl < 15 ml/min
  - Both contraindicated in ESRD
• NOAC drug cost significantly more expensive
  – Need to account for drug monitoring, patient satisfaction/QOL, cost of bleeding events….
  – What about from a hospital perspective?

Let's take a typical 70 kg patient with AF (CHADS2 3) admitted to the hospital for AF w/ RVR and started on one of these agents for AF.

<table>
<thead>
<tr>
<th>Hospital Costs (5 days inpatient)</th>
<th>Drug Costs AWP</th>
<th>Warfarin</th>
<th>NOAC (Rivaroxaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication</td>
<td>0.65 x 5 = 3.25</td>
<td>11.44 x 5 = 57.20</td>
<td></td>
</tr>
<tr>
<td>Enoxaparin bridge</td>
<td>52.80 x 5 = 264</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Therapeutic drug monitoring</td>
<td>~ 50</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Approximate total cost</td>
<td>317.25</td>
<td>57.20</td>
<td></td>
</tr>
</tbody>
</table>

So now that we know about the efficacy, safety and drug specific data, what do we do??

Patients who are GOOD candidates for NOAC

• Poorly controlled on warfarin
  – Consistently outside of therapeutic range
  – (TTR < 70%)  
• Compliant patients
  – Able to afford medication costs
• Varying medication and dietary changes
  – Drug-drug interactions
  – Varied vitamin k intake
• Patients who refuse warfarin therapy
Patients who are NOT good candidates for NOAC

• Adequately controlled, and stable on warfarin without bleeding events
  – TTR ~ 72% and greater
• History of GI bleeds
• Severe renal failure
• Mechanical heart valve
• Poor compliance
• Uninsured, unable to afford drug costs

Now lets hear the other side......

Patient Case

Discussion