New Oral Anticoagulants: Factor IIa and Xa Inhibitors

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Faculty Disclosure
Disclosure:
• Dr. Smith has no actual or potential conflict of interest associated with this presentation.

In the Beginning
“One snowy morning in February, 1933, Ed Carlson, a farmer from Deer Park, Wisconsin, came into Karl Paul Link’s laboratory carrying a milk-can full of blood that refused to coagulate. Outside he had a small heap of spoiled sweet clover hay and a dead heifer freezing in the back of his truck.”

http://www.warf.org/about/index.jsp?cid=26&scid=34

New Oral Anticoagulants
• Objectives
  – Discuss the mechanism of action, indications, contraindications and adverse effects of oral Factor IIa and Xa Inhibitors.
  – Identify patients that may benefit from the new agents over warfarin and those that may not.
  – Develop a monitoring plan for patients receiving oral Factor IIa and Xa Inhibitors.
New Oral Anticoagulants

- New Oral Anticoagulants - NOAC
- Target Specific Oral Anticoagulants - TSOA
- Direct Oral Anticoagulant - DOAC

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>FDA Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Pradaxa</td>
<td>A Fib, DVT/PE</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Xarelto</td>
<td>+ + +</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Eliquis</td>
<td>+ + +</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Savaysa</td>
<td>+ +</td>
</tr>
</tbody>
</table>

New Oral Anticoagulants

Question #1

- The DOACs are better than warfarin.
  - True
  - or
  - False

New Oral Anticoagulants

- General comparison with warfarin

<table>
<thead>
<tr>
<th>Warfarin</th>
<th>DOACs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>3-7 days</td>
</tr>
<tr>
<td>Return to baseline</td>
<td>3-7 days</td>
</tr>
<tr>
<td>Dosing</td>
<td>Variable</td>
</tr>
<tr>
<td>Food interactions</td>
<td>Yes</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Yes</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Yes</td>
</tr>
</tbody>
</table>

New Oral Anticoagulants

- Comparison to Warfarin for Non-Valvular Atrial Fibrillation (all results %/yr)

<table>
<thead>
<tr>
<th></th>
<th>Stroke/ Embolism</th>
<th>Bleeding Rate</th>
<th>Intracranial hemorrhage</th>
<th>Time In Therapeutic Range (TTR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>3.11</td>
<td>3.11</td>
<td>0.3</td>
<td>64%</td>
</tr>
<tr>
<td>Warfarin</td>
<td>3.66</td>
<td>3.66</td>
<td>0.74</td>
<td>55%</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>2.1</td>
<td>2.1</td>
<td>0.5</td>
<td>62.2%</td>
</tr>
<tr>
<td>Apixaban</td>
<td>2.1</td>
<td>2.1</td>
<td>0.7</td>
<td>68.4%</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>2.75</td>
<td>2.75</td>
<td>0.8</td>
<td>68.4%</td>
</tr>
<tr>
<td>Warfarin</td>
<td>2.75</td>
<td>2.75</td>
<td>0.8</td>
<td>68.4%</td>
</tr>
</tbody>
</table>
Dabigatran
• Direct thrombin inhibitor (DTI)
• Administer with or without food
• Renal clearance: 80%
• Drug interactions: P-glycoprotein
• Must be kept in original container
• Can not be crushed

Dabigatran
• Atrial fibrillation Dosing
  – 150mg BID for CrCl >30ml/min
  – 75mg BID for CrCl <30ml/min
  – If 30-50 and concomitant use of dronedarone of ketoconazole, consider 75mg twice daily
  – Avoid use co-administration with p-GP inhibitors if CrCl<30ml/min
  – Contraindicated in patients with CrCl<15

Rivaroxaban
• Direct Factor Xa inhibitor
• Should be taken with the largest meal of the day
• Renal clearance: 33%
• Drug interactions: CYP 3A4 and P-glycoprotein
• Not recommended in patients with moderate to severe hepatic impairment (Child-Pugh B or C)

Rivaroxaban
• Atrial fibrillation dosing
  – 20mg once daily with the evening meal for CrCl>50
  – 15mg once daily with the evening meal for CrCl 15-30
  – Contraindicated in patients with CrCl<15

Rivaroxaban
• Treatment of DVT/PE dosing
  – 15mg twice daily with food for the first 21 days
  – 20mg once daily with food for the remainder of the treatment/reduction in risk of recurrence
  – Contraindicated in patients with CrCl<30
• Prophylaxis of DVT following hip or knee replacement surgery dosing
  – Hip: 10mg once daily for 35 days
  – Knee: 10mg once daily for 12 days
  – Contraindicated in patients with CrCl<30
Apixaban
- Direct Factor Xa inhibitor
- Twice daily with or without food
- Renal clearance: 25%
- Drug interactions: CYP 3A4 and P-glycoprotein
- Not recommended in patients with severe hepatic disease
- Patient age and weight also a consideration for dose

Apixaban
- Atrial fibrillation dosing
  - 5mg BID
  - 2.5mg BID if patient has 2 or more of the following:
    - Age >80; SrCr ≥1.5; weight ≤60kg
  - 2.5mg BID if co-administered with strong dual inhibitors of 3A4 and P-gp, contraindicated if patient has 2 or more of the above + drug interactions.
  - Same recommendations for patients maintained on dialysis. No data if CrCl < 15ml/min

Apixaban
- Treatment of DVT/PE dosing
  - 10mg BID for the first 7 days, then 5mg BID for the remainder of the treatment.
  - Reduction in the risk of recurrence: 2.5mg BID after at least 6 months of the above treatment dose.
  - Prophylaxis of DVT following hip or knee replacement surgery dosing
    - 2.5mg BID, first dose taken 12-24 hours post surgery
    - Hip: 35 days
    - Knee: 12 days

Apixaban
- Direct Factor Xa inhibitor
- Once daily with or without food
- Renal clearance: 50%
- Drug interactions: P-glycoprotein
- Contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B or C)

Edoxaban
- Atrial fibrillation dosing
  - 60mg once daily in patients with CrCl >50 to ≤95ml/min
  - 30mg once daily in patients with CrCl 15-50 ml/min
  - Contraindicated in patients with a CrCl >95

Edoxaban
- Treatment of DVT/PE dosing
  - Following 5-10 days of a parenteral anticoagulant:
    - 60mg once daily
  - 30mg once daily for patients with a CrCl 15-50 OR weight ≤ 60kg or co-administration with strong P-gp inhibitors (verapamil, quinidine, azithromycin, clarithromycin, erythromycin, oral ketoconazole, oral itraconazole.
New Oral Anticoagulants

- A note about creatinine clearance determination with the Cockroft-Gault equation
- Everyone has their favorite way of calculating renal function.
  - Body weight: Actual vs Ideal vs Adjusted
  - Minimum value in the elderly: 0.6, 0.8, 1?
- The bottom line: use actual for DOAC dose determination.

New Oral Anticoagulants

- Question #2
- Outside of specific contraindications, the DOACs are appropriate for just about everyone.
  - Si
  - Or
  - No

Appropriate DOAC Patients

- Non-valvular Atrial Fibrillation
- History of good compliance
- Adequate and stable renal function
- Barriers to appropriate warfarin monitoring
- Unable to maintain a stable INR
- Avoidance of strong 3A4/P-gp medications
- Able to afford prescription costs
- Warfarin resistant disease/treatment failure

General Selection Guide

- Mechanical heart valves, valvular A-fib, moderate-severe hepatic disease, severe renal impairment-> Warfarin
- Upper GI discomfort-> avoid dabigatran
- History of recent GI bleed-> warfarin or apixaban
- Uses a pill box or need to crush the medication-> avoid dabigatran

New Oral Anticoagulants

- Question #3
- Converting a patient from one anticoagulant to another is simple because...
  A. The DOACs have a rapid onset of action
  B. Pharmacokinetics will not play a role
  C. We can always monitor the INR if warfarin is involved
  D. Votre fou

New Oral Anticoagulants

- Converting from Warfarin to a DOAC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Discontinue warfarin and start dabigatran when the INR is below 2.0</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Discontinue warfarin and start rivaroxaban when the INR is below 3.0</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Discontinue warfarin and start apixaban when the INR is below 2.0</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Discontinue warfarin and begin edoxaban when the INR is ≤ 2.5.</td>
</tr>
</tbody>
</table>
New Oral Anticoagulants

• Converting from parenteral anticoagulants
  – Enoxaparin: Discontinue enoxaparin and start the oral agent at the time the next dose of enoxaparin was due. (dabigatran and rivaroxaban, D-2 hrs before per the PPI)
  – Unfractionated heparin infusion: Administer the oral agent at the same time the infusion is stopped.
    • Except edoxaban: Administer 4 hours after the infusion is stopped.

New Oral Anticoagulants

• Converting to warfarin from dabigatran:
  – Because dabigatran can increase INR, the INR will better reflect warfarin’s effect only after dabigatran has been stopped for at least 2 days

<table>
<thead>
<tr>
<th>Renal function (CrCl)</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50</td>
<td>Start warfarin and overlap therapy for 3 days, discontinue dabigatran on day 4</td>
</tr>
<tr>
<td>31-50</td>
<td>Start warfarin and overlap therapy for 2 days, discontinue dabigatran on day 3</td>
</tr>
<tr>
<td>&lt;30</td>
<td>Start warfarin and overlap therapy for 1 day, discontinue dabigatran on day 2</td>
</tr>
</tbody>
</table>

New Oral Anticoagulants

• Converting to warfarin from rivaroxaban:
  – Rivaroxaban affects INR, so INR measurements made during co-administration with warfarin may not be useful for determining the appropriate dose of warfarin.
  – One approach is to discontinue rivaroxaban and begin both a parenteral anticoagulant and warfarin at the time the next dose of rivaroxaban would have been taken.

<table>
<thead>
<tr>
<th>Renal function (CrCl)</th>
<th>Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50</td>
<td>Start parenteral anticoagulant 12-24 hours after the last dose of rivaroxaban (consider 12 hours in patients at greater risk of stroke/thrombosis). Start warfarin if used at the next administration time.</td>
</tr>
<tr>
<td>&lt;50</td>
<td>Start parenteral anticoagulant 24 hours after the last dose of rivaroxaban. Start warfarin if used at the next administration time.</td>
</tr>
</tbody>
</table>

New Oral Anticoagulants

• Converting to warfarin from apixaban:
  – Due to the effect of apixaban on the INR, it is recommended to discontinue apixaban and start a parenteral anticoagulant plus warfarin at the time of the next apixaban dose.
  – Discontinue the parenteral anticoagulant when the INR reaches a therapeutic range

New Oral Anticoagulants

• Converting to warfarin from edoxaban
  – For patients on 60 mg of edoxaban, reduce dose to 30 mg and begin warfarin concomitantly.
  – For patients on 30 mg of edoxaban, reduce dose to 15 mg and begin warfarin concomitantly.
  – During transition, INR should be done at least weekly just prior to daily dose of edoxaban (to minimize influence on INR).
  – Discontinue edoxaban once a stable INR ≥ 2.0 is achieved.
New Oral Anticoagulants

• Question 4
• Unlike warfarin, there doesn’t need to be a concern when a patient needs an invasive procedure... just stop the day before.
  True
  Or
  Falsch

New Oral Anticoagulants

• Interruption of DOACs for scheduled procedures

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patient's Renal Function (ml/min)</th>
<th>Low Bleeding Risk Procedure (take last dose... 2-3 half lives)</th>
<th>High Bleeding Risk Procedure (take last dose... 3-4 half lives)</th>
<th>Resumption after Low Risk Procedure</th>
<th>Resumption after High Risk Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>CrCl &gt;50</td>
<td>2 days before</td>
<td>5 days before</td>
<td>Resume the day after procedure</td>
<td>Resume 2-3 days after procedure</td>
</tr>
<tr>
<td></td>
<td>CrCl 30-50</td>
<td>3 days before</td>
<td>4-5 days before</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>CrCl &gt;50</td>
<td>2 days before</td>
<td>3 days before</td>
<td>Resume after procedure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CrCl 15-30</td>
<td>3 days before</td>
<td>4 days before</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>CrCl &gt;50</td>
<td>2 days before</td>
<td>3 days before</td>
<td>Resume 2-3 days after procedure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CrCl 30-90</td>
<td>3 days before</td>
<td>4 days before</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edoxaban</td>
<td>CrCl &gt;50</td>
<td>2 days before</td>
<td>3 days before</td>
<td>Resume 2-3 days after procedure</td>
<td></td>
</tr>
</tbody>
</table>

New Oral Anticoagulants

• Final Question
• Because of their predictability and lack of significant food or drug interactions, there is no need for a monitoring plan for DOACs
  True
  Or
  Falsch

New Oral Anticoagulants

• Poor Adherence = Poor Outcomes
  – 28% of patients are non-adherent to dabigatran
    • 13% increase in all-cause mortality and stroke for each 10% decrease in adherence
  • Increased adherence demonstrated with pharmacist-led monitoring
    – Yes, monitoring for a DOAC
  • Warfarin clinic patients get regular, consistent monitoring and adherence education. Is this a ‘burden’?
    – Average 2-3 visits/month, up to 1 visit Q3 months!

Patient Monitoring

• Adherence Assessment and Counseling
• Bleeding Risk Assessment
• Creatinine Clearance
• Drug Interaction Assessment and Counseling
• Examination
• Final Assessment and Follow-up

Management Plan Flow Chart