Extended Venous Thromboembolism (VTE) Prophylaxis with Betrixaban in Acutely Ill Medical Patients

Ben Bredhold, PharmD
PGY2 Internal Medicine Pharmacy Resident
Eskenazi Health
September 30, 2017

The presenter has no actual or potential conflicts of interest in relation to this presentation.
Objectives

1. Describe the literature behind the approval of betrixaban use for VTE prophylaxis

2. Identify possible implications betrixaban may have on inpatient VTE prophylaxis
Extended VTE Prophylaxis in Medically Ill Patients

Benefits

• Increased risk for VTE for at least 1 month after discharge
• Patients with a high risk of VTE

Barriers

• Not supported by guidelines
• Lack of safety and efficacy data
• Resistance from providers and/or patients

FDA Approved Options for VTE Prophylaxis in Medical Patients

- Enoxaparin
- Heparin
- Fondaparinux

Betrixaban Basics

• Oral Factor Xa Inhibitor
• Substrate of P-gp
• Bioavailability 34%
• Peak serum concentration 3-4 hours
• Protein binding 60%
• Half-life 19-27 hours
• 11-18% excreted unchanged in urine
Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients (APEX) trial

<table>
<thead>
<tr>
<th>Population</th>
<th>Adults ≥ 40 years who were hospitalized with acute medical illness with reduced mobility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Subcutaneous enoxaparin 40 mg once daily for 10±4 days vs. oral betrixaban 80 mg once daily for 35-42 days</td>
</tr>
<tr>
<td>Primary Outcome</td>
<td>Composite of asymptomatic proximal deep-vein thrombosis (DVT) and symptomatic VTE</td>
</tr>
</tbody>
</table>

Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients (APEX) trial

<table>
<thead>
<tr>
<th>Results of Primary Outcome</th>
<th>Cohort 1: Elevated D-dimer level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Betrixaban 6.9% vs. enoxaparin 8.5% ([CI], 0.65-1.00; (p=0.054))</td>
</tr>
<tr>
<td></td>
<td>Cohort 2: Elevated D-dimer level or age at least 75 years</td>
</tr>
<tr>
<td></td>
<td>• Betrixaban 5.6% vs. enoxaparin 7.1% ([CI], 0.66-0.98; (p=0.03))</td>
</tr>
<tr>
<td></td>
<td>Overall patient cohort</td>
</tr>
<tr>
<td></td>
<td>• Betrixaban 5.3% vs. enoxaparin 7.0% ([CI], 0.63-0.92; (p=0.006))</td>
</tr>
</tbody>
</table>

| Major Bleeding | Betrixaban 0.7% vs. enoxaparin 0.6% ([CI], 0.67-2.12; \(p=0.55\)) |

## Safety and Efficacy of Full and Reduced Dose Betrixaban in the APEX Trial

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous enoxaparin 40 mg once daily for 10±4 days</td>
<td>vs. Oral betrixaban 80 mg once daily for 35-42 days or Oral betrixaban 40 mg once daily for 35-42 days in patients with severe renal impairment</td>
</tr>
</tbody>
</table>

## Safety and Efficacy of Full and Reduced Dose Betrixaban in the APEX Trial

<table>
<thead>
<tr>
<th></th>
<th>Betrixaban 80 mg</th>
<th>P-value</th>
<th>Betrixaban 40 mg</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort 1</td>
<td>6.27% vs. 8.39%</td>
<td>0.023</td>
<td>9.32% vs. 8.66%</td>
<td>0.80</td>
</tr>
<tr>
<td><strong>Cohort 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort 2</td>
<td>5.14% vs. 7.00%</td>
<td>0.009</td>
<td>7.46% vs. 7.41%</td>
<td>0.80</td>
</tr>
<tr>
<td><strong>Overall Population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Population</td>
<td>4.87% vs. 7.06%</td>
<td>0.001</td>
<td>6.97% vs. 6.73%</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>Major Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>0.50% vs. 0.53%</td>
<td>0.86</td>
<td>1.37% vs. 0.69%</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Betrixaban Approval

- FDA approved June 23, 2017
- Bevyxxa® (betrixaban)
- 40 mg and 80 mg capsules
- Available: End of 2017?
- Indication: prophylaxis of VTE in adult patients hospitalized for an acute medical illness
- Normal dosing
  - Initial single dose of 160 mg, followed by 80 mg once daily, taken at the same time each day with food for 35-42 days

Betrixaban Dosing Adjustments

Renal Dosing

- If CrCl $\geq$ 15 to < 30 mL/min
  - Initial single dose of 80 mg then 40 mg once daily for 35-42 days
- If CrCl < 15 mL/min
  - Use not recommended

Use with P-gp Inhibitors

- Initial single dose of 80 mg then 40 mg once daily for 35-42 days
For Your Consideration

• What patient population(s) would benefit?
• Oral product vs. injection
• No current antidote available
• Longer duration of use vs. current standard of care
  • Would patients take for 35-42 days?
  • Would providers prescribe for 35-42 days?
• How long to hold before a procedure?
• Dose adjustments for obesity?
• Cost
Conclusion

• Betrixaban is a new Factor Xa inhibitor approved for VTE prophylaxis in acutely medically ill patients

• First oral agent to carry indication for VTE prophylaxis in medical patients

• Approved for extended VTE prophylaxis for 35-42 days

• Many questions remain unanswered about its potential use
Extended Venous Thromboembolism (VTE) Prophylaxis with Betrixaban in Acutely Ill Medical Patients

Ben Bredhold, PharmD
PGY2 Internal Medicine Pharmacy Resident
Eskenazi Health
September 30, 2017