Anticoagulation Updates in Special Populations: Weighing the Evidence & Filtering the Data in Obesity and Renal Impairment

Jared Sheley, Pharm.D., BCPS

Objectives

Pharmacists
- Identify limitations in applying weight-based dosing of parenteral anticoagulants in obese patients and when alterations may be necessary
- Describe current recommendations and existing data for direct oral anticoagulant (DOAC) use in obese patients
- Explain the limitations in data with direct oral anticoagulants (DOAC) use in patients with renal impairment

Technicians
- Discuss why obese patients require different dosing strategies of parenteral anticoagulants than non-obese patients
- Describe why there are concerns with direct oral anticoagulants (DOAC) in obese patients
- Identify patients, by history or laboratory measures, in whom there may be concern for using direct oral anticoagulants (DOAC)

Technician Question

Why would obese patients require different dosing strategies of parenteral anticoagulants than non-obese patients?

A. Parenteral anticoagulants are given at fixed doses, so obese patient may be underdosed
B. Parenteral anticoagulants are given at fixed doses, so obese patients may be overdosed
C. Parenteral anticoagulants are given at weight-based doses, so obese patients may be underdosed
D. Parenteral anticoagulants are given at weight-based doses, so obese patients may be overdosed

Technician Question

Describe why there are concerns with direct oral anticoagulants (DOAC) in obese patients

A. DOAC are given at fixed doses, so obese patient may be underdosed
B. DOAC are given at fixed doses, so obese patients may be overdosed
C. DOAC are given at weight-based doses, so obese patients may be underdosed
D. DOAC are given at weight-based doses, so obese patients may be overdosed

Technician Question

Which of the following would be a reason for concern with DOAC use?

A. Feeding tube status
B. Hemodialysis status
C. Tricare prescription insurance
D. Elevated blood glucose

Pharmacist Question

Which of the following scenarios likely requires intervention by the pharmacist upon receiving the medication order?

A. 90 kg patient (BMI = 31) with new proximal DVT ordered enoxaparin 1 mg/kg subQ BID
B. 180 kg patient (BMI = 55) with new PE ordered enoxaparin 1 mg/kg subQ BID
C. 90 kg patient (BMI = 31) with A Fib started on unfractionated heparin w/ IV bolus dose 80 units/kg/hr and IV infusion rate 18 unit/kg/hr
D. 180 kg patient (BMI = 55) with ACS started on unfractionated heparin w/ IV bolus dose 4,000 units and IV infusion rate 1,000 unit/hr
Pharmacist Question

Which of the following is consistent with the guidance from the International Society of Thrombosis and Haemostasis (ISTH) on use of the direct oral anticoagulants (DOAC) in obese patients?

A. DOACs are recommended to be used at standard doses for all patients due to data suggesting obesity does not affect drug concentrations
B. DOACs are recommended to be used at double the dose for patients with extreme obesity due to data suggesting similar drug concentrations
C. DOACs are suggested to be avoided in patients with BMI > 30 kg/m² or weight > 90 kg due to exclusion from trials
D. DOACs are suggested to be avoided in patients with BMI > 40 kg/m² or weight > 120 kg due to data suggesting decreased drug concentrations

Pharmacist Question

Which of the following is true regarding data on DOAC in patients with renal impairment?

A. Some DOAC with labeled indications for patients on dialysis now have robust data showing safety and efficacy in this patient population
B. Patients with ESRD on dialysis or CrCl < 25 ml/min were excluded from all clinical trials of DOAC
C. Patients with CrCl < 50 ml/min were excluded from all clinical trials of DOAC
D. Renal function is not a relevant consideration w/ DOAC use

Obesity in the US

- Obesity prevalence in adults (BMI > 30 kg/m²) = 40%
- Extreme / morbid obesity in adults (BMI > 40 kg/m²) = 8%
- Increasing annually for > 20 years
- Obesity known to be an independent risk factor for many conditions that require anticoagulation
  - Venous Thromboembolism (VTE)
  - Atrial Fibrillation (A Fib)

Parenteral Anticoagulants in Obesity

- Normally recommended dosing

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Findings in Obese Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barletta J, et al. 2008</td>
<td>Compared initial aPTT values BMI &gt; 40 vs BMI &lt; 40</td>
<td>Higher aPTT, BMI &gt; 40 independent RF for elevated aPTT</td>
</tr>
<tr>
<td>Gerlach A, et al. 2013</td>
<td>Omitted bolus dose, use reduced infusion rate 16 unit/kg/hr in obese, 12 unit/kg/hr in morbidly obese</td>
<td>Similar times to reach therapeutic range Avg. dose 11 unit/kg/hr in obese vs 16 unit/kg/hr in non-obese</td>
</tr>
<tr>
<td>Nehrer E, et al. 2015</td>
<td>Retrospective review of therapeutic doses</td>
<td>Lower weight-based dosing &gt;130 kg, 13 unit/kg/hr vs 16 unit/kg/hr</td>
</tr>
<tr>
<td>Shin S, et al. 2015</td>
<td>Retrospective review of therapeutic doses</td>
<td>Longer time to therapeutic range Lower doses needed for therapeutic level Avg. dose for &gt;150 kg = 11 unit/kg/hr vs 16 unit/kg/hr for &lt;100 kg</td>
</tr>
</tbody>
</table>

Parenteral Anticoagulants in Obesity

- Normally recommended dosing

<table>
<thead>
<tr>
<th>“Full anticoagulation” (DVT, PE, Valve)</th>
<th>Acute Coronary Syndromes (ACS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated Heparin (UFH)</td>
<td>Bolus: 80 unit/kg IV Infusion: 18 unit/kg/hr IV</td>
</tr>
<tr>
<td>Enoxaparin (Lovenox)</td>
<td>1 mg/kg BID</td>
</tr>
</tbody>
</table>

- Obesity Recommendations

<table>
<thead>
<tr>
<th>“Full anticoagulation” (DVT, PE, Valve)</th>
<th>Acute Coronary Syndromes (ACS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated Heparin (UFH)</td>
<td>None</td>
</tr>
<tr>
<td>Enoxaparin (Lovenox)</td>
<td>None</td>
</tr>
</tbody>
</table>

Unfractionated Heparin Data in Obesity

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Findings in Obese Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barletta J, et al. 2008</td>
<td>Compared initial aPTT values BMI &gt; 40 vs BMI &lt; 40</td>
<td>Higher aPTT, BMI &gt; 40 independent RF for elevated aPTT</td>
</tr>
<tr>
<td>Gerlach A, et al. 2013</td>
<td>Omitted bolus dose, use reduced infusion rate 16 unit/kg/hr in obese, 12 unit/kg/hr in morbidly obese</td>
<td>Similar times to reach therapeutic range Avg. dose 11 unit/kg/hr in obese vs 16 unit/kg/hr in non-obese</td>
</tr>
<tr>
<td>Nehrer E, et al. 2015</td>
<td>Retrospective review of therapeutic doses</td>
<td>Lower weight-based dosing &gt;130 kg, 13 unit/kg/hr vs 16 unit/kg/hr</td>
</tr>
<tr>
<td>Shin S, et al. 2015</td>
<td>Retrospective review of therapeutic doses</td>
<td>Longer time to therapeutic range Lower doses needed for therapeutic level Avg. dose for &gt;150 kg = 11 unit/kg/hr vs 16 unit/kg/hr for &lt;100 kg</td>
</tr>
</tbody>
</table>

Unfractionated Heparin Data in Obesity

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Findings in Obese Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barletta J, et al. 2008</td>
<td>Compared initial aPTT values BMI &gt; 40 vs BMI &lt; 40</td>
<td>Higher aPTT, BMI &gt; 40 independent RF for elevated aPTT</td>
</tr>
<tr>
<td>Gerlach A, et al. 2013</td>
<td>Omitted bolus dose, use reduced infusion rate 16 unit/kg/hr in obese, 12 unit/kg/hr in morbidly obese</td>
<td>Similar times to reach therapeutic range Avg. dose 11 unit/kg/hr in obese vs 16 unit/kg/hr in non-obese</td>
</tr>
<tr>
<td>Nehrer E, et al. 2015</td>
<td>Retrospective review of therapeutic doses</td>
<td>Lower weight-based dosing &gt;130 kg, 13 unit/kg/hr vs 16 unit/kg/hr</td>
</tr>
<tr>
<td>Shin S, et al. 2015</td>
<td>Retrospective review of therapeutic doses</td>
<td>Longer time to therapeutic range Lower doses needed for therapeutic level Avg. dose for &gt;150 kg = 11 unit/kg/hr vs 16 unit/kg/hr for &lt;100 kg</td>
</tr>
</tbody>
</table>
Low Molecular Weight Heparin Data in Obesity

- **Enoxaparin**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Methods</th>
<th>Findings in Obese Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deal E, et al. 2011</td>
<td>BMI &gt; 40</td>
<td>Retrospective</td>
<td>Avg dose for therapeutic level was 0.74 mg/kg 0 below goal, 38% above goal</td>
</tr>
<tr>
<td>Thompson-Moore N, et al. 2015</td>
<td>BMI &gt; 40 or Wt &gt; 140 kg</td>
<td>Retrospective</td>
<td>Median therapeutic dose 0.83 mg/kg Median supratherapeutic dose 0.98 mg/kg</td>
</tr>
<tr>
<td>Lee Y, et al. 2015</td>
<td>BMI &gt; 40</td>
<td>Retrospective</td>
<td>&gt; 50% were supratherapeutic</td>
</tr>
<tr>
<td>Lalama J, et al. 2015</td>
<td>BMI &gt; 40</td>
<td>Prospective study</td>
<td>48% therapeutic, 36% above goal, 16% below Avg dose therapeutic dose 0.71 mg/kg</td>
</tr>
</tbody>
</table>

**Technician Question**

Why would obese patients require different dosing strategies of parenteral anticoagulants than non-obese patients?

A. Parenteral anticoagulants are given at fixed doses, so obese patient may be underdosed
B. Parenteral anticoagulants are given at fixed doses, so obese patients may be overdosed
C. Parenteral anticoagulants are given at weight-based doses, so obese patients may be underdosed
D. Parenteral anticoagulants are given at weight-based doses, so obese patients may be overdosed

**Pharmacist Question**

Which of the following scenarios likely requires intervention by the pharmacist upon receiving the medication order?

A. 90 kg patient (BMI = 31) with new proximal DVT ordered enoxaparin 1 mg/kg subQ BID
B. 180 kg patient (BMI = 55) with new PE ordered enoxaparin 1 mg/kg subQ BID
C. 90 kg patient (BMI = 31) with A Fib started on unfractionated heparin w/ IV bolus dose 80 units/kg/hr and IV infusion rate 18 unit/kg/hr
D. 180 kg patient (BMI = 55) with ACS started on unfractionated heparin w/ IV bolus dose 4,000 units and IV infusion rate 1,000 unit/hr

**Direct Oral Anticoagulants (DOAC) in Obesity**

- **Drug Mechanism Indications**
  - **Dabigatran (Pradaxa)** Direct Thrombin Inhibitor NVAF, VTE treatment, Post-orthosurg VTE prevention
  - **Rivaroxaban (Xarelto)** Factor Xa Inhibitor NVAF, VTE treatment, Post-orthosurg VTE prevention
  - **Apixaban (Eliquis)** Factor Xa Inhibitor NVAF, VTE treatment, Post-orthosurg VTE prevention
  - **Edoxaban (Savaysa)** NVAF, VTE treatment
  - **Betrixaban (Bevyxxa)** VTE prevention

**Direct Oral Anticoagulants (DOAC) in Obesity**

- **Drug Volume of Distribution (L) Protein Binding (%)**
  - **Dabigatran (Pradaxa)** 50 - 70 35
  - **Rivaroxaban (Xarelto)** 50 92
  - **Apixaban (Eliquis)** 21 87
  - **Edoxaban (Savaysa)** 107 55
  - **Betrixaban (Bevyxxa)** 32 60

**Direct Oral Anticoagulants (DOAC) in Obesity**

- **Data from normal weight patients**
  - Concerns with DOAC in obese patients
    - Prescribed at fixed doses
    - Would expect increased Vd and clearance → decreased drug exposure → ?? efficacy
    - No monitoring to determine level of anticoagulation
Pharmacokinetic Data

<table>
<thead>
<tr>
<th>Drug</th>
<th>PK Data in &quot;Obesity&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>21 – 35% decrease in mean concentration</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Cmax &amp; AUC relatively unchanged, slight decrease half-life</td>
</tr>
<tr>
<td>Apixaban</td>
<td>30-45% decrease in Cmax, 23-36% decrease in AUC, slight decrease half-life</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>No data exists</td>
</tr>
<tr>
<td>Betrixaban</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Data - Dabigatran

- No significant differences in weight/BMI subgroups in reported data
- RE-LY highest BMI group >28 kg/m², highest weight >100 kg
  - Peak and trough levels for 76% & 70% of patients
  - 21-35% decrease in mean drug concentration in >100 kg
  - Risk of ischemic stroke inversely related to trough plasma concentrations (p=0.045)

Clinical Data - Dabigatran

- VTE rates numerically increasing with increasing weight & BMI

<table>
<thead>
<tr>
<th>Trial</th>
<th>Weight threshold reported (kg)</th>
<th>% Patients (%)</th>
<th>BMI Threshold Reported (kg/m2)</th>
<th>% Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>&gt;100</td>
<td>17.1</td>
<td>&gt;28</td>
<td>49.5</td>
</tr>
<tr>
<td>RE-COVER I &amp; II (pooled data)</td>
<td>&gt;100</td>
<td>17.2</td>
<td>&gt;35</td>
<td>12.3</td>
</tr>
<tr>
<td>RE-MEDY</td>
<td>&gt;100</td>
<td>20.9</td>
<td>&gt;35</td>
<td>12.3</td>
</tr>
<tr>
<td>RE-SOLVE</td>
<td>&gt;100</td>
<td>17.9</td>
<td>&gt;35</td>
<td>12.3</td>
</tr>
</tbody>
</table>

Clinical Data - Dabigatran

- Clinical outcomes in VTE prevention studies (orthosurg)

<table>
<thead>
<tr>
<th>BMI</th>
<th>VTE/VTE death Dabigatran</th>
<th>VTE/VTE death Enoxaparin</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-25 kg/m²</td>
<td>2.1%</td>
<td>4.3%</td>
<td>0.48 (0.24-0.97)</td>
</tr>
<tr>
<td>25-30 kg/m²</td>
<td>3.0%</td>
<td>4.5%</td>
<td>0.67 (0.41-1.09)</td>
</tr>
<tr>
<td>&gt;30 kg/m²</td>
<td>2.7%</td>
<td>2.9%</td>
<td>0.92 (0.49-1.74)</td>
</tr>
</tbody>
</table>

Clinical Data - Rivaroxaban

<table>
<thead>
<tr>
<th>Trial</th>
<th>Weight threshold reported (kg)</th>
<th>% Patients (%)</th>
<th>BMI Threshold Reported (kg/m2)</th>
<th>% Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROCKET-AF</td>
<td>&gt;90</td>
<td>28.5%</td>
<td>&gt;35</td>
<td>13.6%</td>
</tr>
<tr>
<td>EINSTEIN DVT</td>
<td>&gt;90</td>
<td>28.3%</td>
<td>&gt;35</td>
<td>13.6%</td>
</tr>
<tr>
<td>EINSTEIN PE</td>
<td>&gt;90</td>
<td>14.2%</td>
<td>&gt;35</td>
<td>13.6%</td>
</tr>
<tr>
<td>RECORD 1-4</td>
<td>Not reported</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Clinical Data - Rivaroxaban

- No significant differences in weight/BMI subgroups in reported data
  - Highest weight group > 90 kg
  - Highest BMI group > 30 kg/m² for VTE
    > 35 kg/m² for A Fib

Clinical Data - Apixaban

- Higher BMI correlated w/ lower major bleeding in ARISTOTLE (p=0.039)
  - 1.38%/year for BMI > 40 vs. 2.04-2.26% for other BMI subgroups
- No other significant differences in weight/BMI subgroups in reported data
  - Highest weight group > 100 kg, highest BMI group > 35 kg/m² for efficacy data
    (> 30 kg/m² for A Fib and VTE pm)

Clinical Data - Edoxaban

- No significant differences in weight/BMI subgroups in reported data
  - Not reported for A Fib
  - Highest weight group > 100 kg for VTE

  Note CrCl > 95 ml/min = Contraindication due to increased stroke risk in A Fib

Clinical Data - Betrixaban

- No reporting of outcome data by weight or BMI

Clinical Data - Apixaban

<table>
<thead>
<tr>
<th>Trial</th>
<th>Weight threshold reported (kg)</th>
<th>% Patients (%)</th>
<th>BMI Threshold Reported (kg/m²)</th>
<th>% Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARISTOTLE</td>
<td>≥ 30</td>
<td>40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 40</td>
<td>5.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVERROES</td>
<td>Not reported</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMPLIFY</td>
<td>≥ 100</td>
<td>19.4%</td>
<td>&gt; 35</td>
<td>11.0%</td>
</tr>
<tr>
<td>ADVANCE trials (pooled)</td>
<td>≥ 30</td>
<td>16.9%</td>
<td></td>
<td>(1149)</td>
</tr>
</tbody>
</table>

> 30 kg/m² for A Fib and VTE ppx

Clinical Data - Edoxaban

<table>
<thead>
<tr>
<th>Trial</th>
<th>Weight threshold reported (kg)</th>
<th>% Patients (%)</th>
<th>BMI Threshold Reported (kg/m²)</th>
<th>% Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENGAGE AF-TIMI 48</td>
<td>Not Reported</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOKUSAI VTE</td>
<td>&gt; 100</td>
<td>14.8%</td>
<td></td>
<td>(111)</td>
</tr>
</tbody>
</table>

Obesity Paradox in Atrial Fibrillation

- Obese patients with Atrial Fibrillation have shown better prognosis vs. normal weight patients
  - Lower rate of stroke / systemic embolism
  - Lower rate of major bleeding
  - Lower rate of CV death / all-cause death


ISTH SSC Guidance Statement

- We recommend appropriate standard dosing of the DOACs in patients with a BMI less than or equal to 40 kg m⁻² and weight less than or equal to 120 kg for VTE treatment, VTE prevention, and prevention of ischemic stroke and systemic arterial embolism in non-valvular AF
  - We suggest that DOACs should not be used in patients with a BMI of > 40 kg m⁻² or a weight of > 120 kg
    - Limited clinical data available for patients at the extreme of weight
    - Available PK/PD evidence suggests that decreased drug exposures, reduced peak concentrations and shorter half-lives with increasing weight
    - Concerns about underdosing


Technician Question

Describe why there are concerns with direct oral anticoagulants (DOAC) in obese patients

A. DOAC are given at fixed doses, so obese patient may be underdosed
B. DOAC are given at fixed doses, so obese patients may be overdosed
C. DOAC are given at weight-based doses, so obese patients may be underdosed
D. DOAC are given at weight-based doses, so obese patients may be overdosed

Pharmacist Question

Which of the following is consistent with the guidance from the International Society of Thrombosis and Haemostasis (ISTH) on use of the direct oral anticoagulants (DOAC) in obese patients?

A. DOACs are recommended to be used at standard doses for all patients due to data suggesting obesity does not effect drug concentrations
B. DOACs are recommended to be used at double the dose for patients with extreme obesity due to data suggesting similar drug concentrations
C. DOACs are suggested to be avoided in patient with BMI >30 kg/m² or weight > 90 kg due to exclusion from trials
D. DOACs are suggested to be avoided in patients with BMI > 40 kg/m² or weight > 120 kg due to data suggesting decreased drug concentrations

DOAC in Renal Impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>% Renal Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran (Pradaxa ®)</td>
<td>80%</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto ®)</td>
<td>36%</td>
</tr>
<tr>
<td>Apixaban (Eliquis ®)</td>
<td>27%</td>
</tr>
<tr>
<td>Edoxaban (Savaysa ®)</td>
<td>50%</td>
</tr>
<tr>
<td>Betrixaban (Bevyxxa ®)</td>
<td>11%</td>
</tr>
</tbody>
</table>

**DOAC in Renal Impairment**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran (Pradaxa®)</td>
<td>AFib: No dose adjustment CrCl &gt;30, 50% reduction in CrCl 15-30 VTE: Avoid CrCl &lt;30</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto®)</td>
<td>AFib: CrCl 15-50 reduce dose from 20 mg to 15 mg daily VTE: Avoid in CrCl &lt;30</td>
</tr>
<tr>
<td>Apixaban (Eliquis®)</td>
<td>AFib: Reduce dose 50% if 2 of 3: Age ≥ 80, Wt ≤ 60 kg, SCr ≥ 1.5 AFib &amp; VTE No dose adjustment recommended for renal impairment including those w/ ESRD on dialysis</td>
</tr>
<tr>
<td>Edoxaban (Savaysa®)</td>
<td>A Fib &amp; VTE: 50% dose reduction in CrCl 15-50 ml/min</td>
</tr>
<tr>
<td>Betrixaban (Bevyxxa®)</td>
<td>VTE prevention: 50% dose reduction in CrCl 15-30 ml/min</td>
</tr>
</tbody>
</table>

**DOAC in Renal Impairment- Manufacturer vs. Data**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran (Pradaxa®)</td>
<td>AFib: 50% reduction in CrCl 15-30</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto®)</td>
<td>AFib: Reduce dose 20 mg to 15 mg in CrCl 15-50</td>
</tr>
<tr>
<td>Apixaban (Eliquis®)</td>
<td>AFib &amp; VTE: 50% dose reduction in CrCl 15-50 ml/min</td>
</tr>
<tr>
<td>Edoxaban (Savaysa®)</td>
<td>A Fib &amp; VTE: 50% dose reduction in CrCl 15-50 ml/min</td>
</tr>
</tbody>
</table>

---

**Dabigatran in Renal Impairment**

So if they weren’t included in clinical trials, what data do we have?

- Single dose PK data
  
<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>AUC Increase</th>
<th>Cmax Increase</th>
<th>Half-life (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 80</td>
<td>1 X</td>
<td>1 X</td>
<td>13</td>
</tr>
<tr>
<td>50-80</td>
<td>1.5 X</td>
<td>1.1 X</td>
<td>15</td>
</tr>
<tr>
<td>30-50</td>
<td>2.2 X</td>
<td>1.7 X</td>
<td>18</td>
</tr>
<tr>
<td>15-30</td>
<td>3.3 X</td>
<td>2.3 X</td>
<td>27</td>
</tr>
</tbody>
</table>

- APTT time curve
  - 75 mg dose in CrCl 15-30 higher than 150 mg dose in CrCl 30-50
  - PK simulation test – estimated 12% ↑ peak & 39% ↑ trough

**Rivaroxaban in Renal Impairment**

So if they weren’t included in clinical trials, what data do we have?

- CrCl 30-50 ml/min received 15 mg daily in ROCKET-AF
  - No difference in outcomes
- CrCl 15-30: AUC increase 64%, Factor Xa inhibition increase 100%
- HD patients:
  - Single 15 mg dose in 8 patients → 56% increased AUC vs. normal renal function
  - 10 mg single dose → “similar drug exposure” to 20 mg in normal renal function
  - 10 mg x 7 days → “no accumulation”

**Apixaban in Renal Impairment**

So if they weren’t included in clinical trials, what data do we have?

- Single dose PK study in 8 patients on hemodialysis
  - After HD: AUC ↑ 38%
  - Before HD: AUC ↑ 17%
- Repeated dosing in 7 patients on hemodialysis x 8 days showed accumulation
  - Suggests 5 mg BID should be avoided
  - 2.5 mg BID reasonable ?
  - 4-7% of drug removed w/ HD session
- Single dose PK study → regression showed AUC ↑ 44% with CrCl 15 ml/min

**Apixaban in Renal Impairment**

So if they weren’t included in clinical trials, what data do we have?

- Retrospective review of patients on apixaban or warfarin with CrCl <25, SCr >2.5, or on dialysis at single hospital (n= 73 each)
  - 27% on dialysis, 10% ESRD not on dialysis, 63% non-ESRD
  - 46% apixaban new starts, 0% warfarin new starts
- No difference in major bleeding (9.6% vs. 17.8%)
- No difference in composite bleeding (21.9% vs. 27.4%)
- No difference in stroke rate (7.5% vs. 7.5%) or VTE (0%)
Apixaban in Renal Impairment

So if they weren't included in clinical trials, what data do we have?
• Retrospective review of ESRD pts- 40 apixaban vs. 120 warfarin
  • 58% on 2.5 mg dose (all qualified for 5 mg dose per labeling)
  • No differences in bleeding events
    • 0% vs. 5.8% major
    • 12.5% vs. 5.8% clinical relevant nonmajor
  • Relied mostly on paper chart documentation for bleeding events


Apixaban in Renal Impairment

So if they weren't included in clinical trials, what data do we have?
• Retrospective review of hospitalized ESRD pts on apixaban (n=114)
  • 46% new starts
  • 15% bleeding rate over average LOS 6 days
    • 6% ISTH major bleeding, 11% ISTH major or clinically relevant
  • Risk Factors for bleeding:
    • Higher cumulative apixaban exposure
    • Hospital LOS
    • Total daily dose (OR 1.72)
    • Total number of HD sessions (OR 2.04)
    • Continuation of outpatient apixaban (OR 13.07)


Edoxaban in Renal Impairment

So if they weren't included in clinical trials, what data do we have?
• Manufacturer PK data – CrCl <30 had 93% increase drug exposure vs normal renal function


Betrixaban in Renal Impairment

So if they weren't included in clinical trials, what data do we have?
• Manufacturer PK data – eGFR (MDRD) 15‐30 ml/min/1.73 m2 had 2.63 fold increase drug exposure vs normal renal function


Technician Question

Which of the following would be a reason for concern with DOAC use?

A. Feeding tube status
B. Hemodialysis status
C. Tricare prescription insurance
D. Elevated blood glucose

Pharmacist Question

Which of the following is true regarding data on DOAC in patients with renal impairment?

A. Some DOAC with labeled indications for patients on dialysis now have robust data showing safety and efficacy in this patient population
B. Patients with ESRD on dialysis or CrCl < 25 ml/min were excluded from all clinical trials of DOAC
C. Patients with CrCl < 50 ml/min were excluded from all clinical trials of DOAC
D. Renal function is not a relevant consideration w/ DOAC use
Anticoagulation Updates in Special Populations:
Weighing the Evidence & Filtering the Data in Obesity and Renal Impairment

Jared Sheley, Pharm.D., BCPS