A Review of Direct-Acting Oral Anticoagulants (DOACs) and Their Use in Special Populations
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Disclosure
- Allison Bernard does not have any actual or potential conflict of interests to disclose
- Off-label use of medications will be discussed during this presentation

Objectives
Following this one-hour presentation pharmacists and pharmacy technicians should be able to
1. Compare guideline recommendations to recent study outcomes for use of DOACs in patients with obesity and apply results to a patient case
2. Discuss efficacy evidence from recently published literature regarding DOAC dosing and safety for reduced renal function
3. Identify and discuss limitations with use of DOAC therapy in liver impairment
4. Recognize clinical situations when prescribing DOAC therapy is not recommended in the setting of extremes in weight, renal impairment, or hepatic impairment
5. Analyze the outcomes of the Hokusai VTE Cancer study
Background

- dabigatran (Pradaxa®)
- apixaban (Eliquis®)
- rivaroxaban (Xarelto®)
- edoxaban (Savaysa®)
- betrixaban (Bevyxxa®)

DOAC Selection

Indication

Dosing and adherence

Renal function

Liver function

Weight

Drug interactions

Insurance

Overview

- Obesity
- Reduced Renal Function
- Impaired Liver Function
- Malignancy Associated VTE
Pharmacokinetics in Obesity

- increased volume of distribution
- altered hepatic blood flow
- higher clearance
- altered elimination half-life


Patient Case

- History of Present Illness
  - DC is a 62 year old female on warfarin therapy for AFib
- Chief Complaint
  - She would like switch from warfarin to a DOAC
- Past Medical History
  - atrial fibrillation (diagnosed 2014) (CHADS₂-VASc=6)
  - stroke (2010)
  - unprovoked PE (2007) treated with warfarin x 6 months
  - type 2 diabetes
  - dyslipidemia
  - hypertension
  - obesity
Patient Case

- Pertinent Demographic and Laboratory Data

<table>
<thead>
<tr>
<th>9/2018</th>
<th>5/2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>172.7</td>
</tr>
<tr>
<td>Wt (kg)</td>
<td>120.6</td>
</tr>
<tr>
<td>Wt (lbs)</td>
<td>267</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>40.4</td>
</tr>
</tbody>
</table>

Would you recommend a DOAC for this patient?

DOAC Dosing in Obesity

International Society on Thrombosis and Hemostasis (ISTH) guidance recommendations

DOACs should NOT be used in patients with:
BMI > 40 kg/m²
or
Weight > 120 kg

If a DOAC is used, check a peak and trough drug level

Level within expected range: continue DOAC
Level below expected range: change to a Vitamin K antagonist (warfarin)

2014 American College of Cardiology/American Heart Association Guidelines

Dose adjustments may be warranted for extremes in body weight
**dabigatran (Pradaxa®)**

**RE-LY TRIAL**

- Studied dabigatran 100 mg (n=6015) or 150 mg (n=6076) versus warfarin (n=6022) in patients with Afib

<table>
<thead>
<tr>
<th>Weight Range</th>
<th>Percentage of Participants</th>
<th>Hazard Ratio (Stroke or Systemic Embolism)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-99 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥100 kg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


**Hazard Ratio of Primary Outcome (Stroke or Systemic Embolism) with Dabigatran 150 mg**

<table>
<thead>
<tr>
<th>Weight Range</th>
<th>Dabigatran Better</th>
<th>Warfarin Better</th>
<th>p=0.42</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-99 kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥100 kg</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Subgroup analysis

- Increasing body weight
- Decreasing dabigatran concentration

**RE-COVER TRIAL**

- Studied dabigatran (n=1273) versus warfarin (n=1266) for treatment of VTE

<table>
<thead>
<tr>
<th>BMI Range</th>
<th>Percentage of Participants</th>
<th>Hazard Ratio of Primary Outcome (Recurrent VTE) with Dabigatran 150 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI 25-&lt;30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI 30-&lt;35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI ≥35</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>BMI Range</th>
<th>Dabigatran Better</th>
<th>Warfarin Better</th>
<th>p=0.89</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI 25-&lt;30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI 30-&lt;35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI ≥35</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
dabigatran (Pradaxa®)

- Case Reports of obese patients on dabigatran who...
  - presented with a thromboembolic event
  - experienced a stroke
  - had dabigatran levels lower than the therapeutic levels

rivaroxaban (Xarelto®)

ROCKET-AF

- Studied rivaroxaban (n=7131) versus warfarin (n=7133) in patients with AFib

<table>
<thead>
<tr>
<th>BMI</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI &lt;25</td>
<td>HR=0.77 (0.56, 1.04)</td>
<td></td>
</tr>
<tr>
<td>BMI 25-35</td>
<td>HR=0.93 (0.76, 1.15)</td>
<td></td>
</tr>
<tr>
<td>BMI &gt;35</td>
<td>HR=0.99 (0.58, 1.68)</td>
<td>p=0.537</td>
</tr>
</tbody>
</table>

EINSTEIN-PE

- Studied rivaroxaban (n=2419) versus enoxaparin then warfarin (n=2413) for treatment of VTE

<table>
<thead>
<tr>
<th>BMI</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
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<td>HR=0.77 (0.56, 1.04)</td>
<td></td>
</tr>
<tr>
<td>BMI ≥30</td>
<td>HR=0.99 (0.58, 1.68)</td>
<td></td>
</tr>
</tbody>
</table>
rivaroxaban (Xarelto®)

- 2017 Review Conclusions
  - Pharmacokinetic profile of rivaroxaban was comparable in normal and high-weight groups
  - Time course of factor Xa activity inhibition was unaffected by weight
  - Dose adjustment likely unnecessary for weight extremes

apixaban (Eliquis®)
ARISTOTLE TRIAL

- Studied apixaban (n=9120) versus warfarin (9081) in patients with AFib

83.6% of participants had a weight >60-120 kg

5.4% of participants had a weight >120

apixaban (Eliquis®) - post-hoc analysis

- Results: Efficacy and Safety Outcomes Stratified by Weight Categories

<table>
<thead>
<tr>
<th>Weight &gt;60 to 120 kg (n=15,172)</th>
<th>Apixaban Rate (n)</th>
<th>Warfarin Rate (n)</th>
<th>Hazard Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy Endpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke or systemic embolism</td>
<td>1.23 (173)</td>
<td>1.44 (201)</td>
<td>0.853 (0.696 to 1.045)</td>
</tr>
<tr>
<td>All cause death</td>
<td>3.14 (451)</td>
<td>3.75 (535)</td>
<td>0.836 (0.738 to 0.948)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.54 (76)</td>
<td>0.86 (92)</td>
<td>0.619 (0.404 to 1.010)</td>
</tr>
<tr>
<td><strong>Safety Endpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any bleeding</td>
<td>18.15 (1987)</td>
<td>25.29 (2528)</td>
<td>0.732 (0.690 to 0.776)</td>
</tr>
</tbody>
</table>

*Rates per 100 patient years
Hazard Ratio <1 = Favors Apixaban
apixaban (Eliquis®)
ARISTOTLE TRIAL – post-hoc analysis

- Results: Efficacy and Safety Outcomes Stratified by Weight Categories

<table>
<thead>
<tr>
<th>Weight &gt;120 kg (n=982)</th>
<th>Apixaban Rate (n)</th>
<th>Warfarin Rate (n)</th>
<th>Hazard Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy Endpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke or systemic embolism</td>
<td>0.44 (4)</td>
<td>1.13 (11)</td>
<td>0.387 (0.123 to 1.215)</td>
</tr>
<tr>
<td>All cause death</td>
<td>3.00 (28)</td>
<td>2.52 (25)</td>
<td>1.190 (0.684 to 2.042)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.33 (3)</td>
<td>0.41 (4)</td>
<td>0.806 (0.180 to 3.600)</td>
</tr>
<tr>
<td><strong>Safety Endpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any bleeding</td>
<td>16.44 (119)</td>
<td>25.13 (176)</td>
<td>0.670 (0.531 to 0.846)</td>
</tr>
</tbody>
</table>

Rates per 100 patient years

Hazard Ratio <1 = Favors Apixaban

Fudim M et al. Poster presentation at ACC 2018, poster 1225M-09

apixaban (Eliquis®)
AMPLIFY TRIAL

- Studied apixaban (n=2691) versus conventional therapy (enoxaparin, then warfarin) (n=2704) in patients for treatment of VTE

Hazard Ratio of Primary Outcome (Recurrent VTE or Death Related to VTE)

71.8 PERCENT of participants were 61-99 kg

apixaban better enox/warfarin better
p=0.0639

19.4 PERCENT of participants were 2100 kg

apixaban better enox/warfarin better
p=0.0639

DOACs in Obesity Summary

- Limited evidence to support ISTH guidance recommendations to avoid DOAC therapy at levels of weight >120 kg and BMI >40

- Sub-group analysis of groups with BMI >35 and weight >100 kg demonstrate similar efficacy and safety compared to warfarin
  - Relatively few patients had body weight >120kg

- Apixaban and rivaroxaban have best efficacy

- Dabigatran may be less effective

- Clinical judgment is necessary to choose appropriate DOAC for patients

Patient Case

- History of Present Illness
  - DC is a 62 year old female on warfarin therapy for AFib

- Chief Compliant
  - She would like switch from warfarin to a DOAC

- Which agent would you recommend for DC?

<table>
<thead>
<tr>
<th></th>
<th>10/2018</th>
<th>9/2018</th>
<th>5/2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>172.7</td>
<td>172.7</td>
<td></td>
</tr>
<tr>
<td>Wt (kg)</td>
<td>121.7</td>
<td>120.6</td>
<td>122.5</td>
</tr>
<tr>
<td>Wt (lbs)</td>
<td>268</td>
<td>267</td>
<td>270</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>40.8</td>
<td>40.4</td>
<td>41.0</td>
</tr>
</tbody>
</table>

Reduced Renal Function
Pharmacokinetics/Pharmacodynamics in Renal Disease

- reduced drug clearance
- increased drug exposure (AUC)
- increased bleeding risk
- increased thromboembolism risk


Patient Case

- History of Present Illness
  - DC is a 62 year old female on warfarin therapy for AFib
- Chief Compliant
  - She would like switch from warfarin to a DOAC
- Past Medical History
  - atrial fibrillation (diagnosed 2014) (CHADS2-VASc=6)
  - stroke (2010)
  - type 2 diabetes
  - dyslipidemia
  - hypertension
  - chronic kidney disease (baseline serum creatinine 1.6-1.8)

Patient Case

- Pertinent Demographic and Laboratory Data

<table>
<thead>
<tr>
<th>10/8/2018</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>160.0</td>
</tr>
<tr>
<td>Wt (kg)</td>
<td>83</td>
</tr>
<tr>
<td>Wt (lbs)</td>
<td>183</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.4</td>
</tr>
<tr>
<td>BUN</td>
<td>24</td>
</tr>
<tr>
<td>Creatinine (stable)</td>
<td>1.6</td>
</tr>
<tr>
<td>CrCl (ml/min)</td>
<td>36.8</td>
</tr>
</tbody>
</table>

Would you recommend a DOAC for this patient?
DOAC Dosing in Renal Impairment

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal AFib</td>
<td>5 mg BID</td>
<td>10 mg BID</td>
<td>20 mg daily with evening meal</td>
<td>50 mg daily</td>
</tr>
<tr>
<td>Renal AFib</td>
<td>2.5 mg BID ONLY if ≥70 years old and CrCl 15-30</td>
<td>25 mg BID</td>
<td>15 mg with evening meal</td>
<td>60 mg daily</td>
</tr>
<tr>
<td>CrCl &lt;15 or Dialysis</td>
<td>AVOID</td>
<td>2.5 mg BID ONLY if &gt;2 of the following: Age &gt;80 years, Body weight &lt;60 kg, Serum Creatinine &gt;1.5 mg/dL</td>
<td>AVOID</td>
<td>AVOID</td>
</tr>
<tr>
<td>Normal VTE</td>
<td>150 mg BID</td>
<td>10 mg BID + 7 days</td>
<td>15 mg BID + 21 days</td>
<td>60 mg daily</td>
</tr>
<tr>
<td>Renal VTE</td>
<td>n/a</td>
<td>n/a</td>
<td>CrCl &gt;30 AVOID</td>
<td>n/a</td>
</tr>
<tr>
<td>Renal Elimination</td>
<td>80%</td>
<td>27%</td>
<td>33%</td>
<td>50%</td>
</tr>
<tr>
<td>Prodrug</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

DOACs

META-ANALYSIS

- Included trials of dabigatran, rivaroxaban, apixaban
- DOACs risk of major bleeding compared to warfarin
  - CrCl 50-80 mL/min and CrCl <50 mL/min
- Apixaban risk of major bleeding compared to other DOACs
  - CrCl <50 mL/min
- DOACs risk for hemorrhagic stroke compared to warfarin
  - CrCl 50-80 mL/min and CrCl <50 mL/min

Dabigatran, Rivaroxaban, Edoxaban in Renal Impairment

- Patients excluded from major trials: CrCl < 30 ml/min
- Except a few trials reported inclusion of such patients
- Dabigatran (77 patients RE-LY trial)
- Rivaroxaban (8 patients ROCKET AF trial)
- Edoxaban (121 patients ENGAGE AF trial)
Apixaban Dosing in Renal Impairment

Patients excluded from major trials:
- CrCl < 25 ml/min or
- SCr > 2.5 mg/dL

ARISTOTLE
(Apixaban vs. Warfarin in Patients with AFib)

AMPLIFY
(Oral Apixaban for Treatment of Acute VTE)

Apixaban vs. Warfarin in Severe Renal Impairment
- Retrospective, matched cohort study
- Inclusion Criteria: CrCl < 25 ml/min or SCr > 2.5 mg/dL
- Major bleeding and composite bleeding rates were similar


• Studied apixaban (n=9120) versus warfarin (n=9081) in patients with AFib

7587 patients
Mild impairment: >50 to 80 ml/min

2747 patients
Moderate impairment: >30 to 50 ml/min

270 patients
Severe impairment: ≤ 30 ml/min


Apixaban (Eliquis®) ARISTOTLE TRIAL

• Primary Efficacy Outcome: Stroke and Systemic Embolism

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Apixaban</th>
<th>Warfarin</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe or moderate</td>
<td>3357</td>
<td>14 (2.0)</td>
<td>19 (3.2)</td>
<td>0.72</td>
</tr>
<tr>
<td>No impairment</td>
<td>7118</td>
<td>16 (2.0)</td>
<td>19 (2.4)</td>
<td>0.92</td>
</tr>
</tbody>
</table>

• Primary Safety Outcome: Major Bleeding
Hemodialysis/ESRD

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Dalteparin</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Elimination</td>
<td>80%</td>
<td>21%</td>
<td>33%</td>
<td>50%</td>
</tr>
<tr>
<td>Dialyzable</td>
<td>Yes</td>
<td>Small</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

- **Apixaban**
  - Not dialyzable to minimally dialyzable (AUC ↓14% over 4 hours)
  - Limited available data, use with caution
  - Study in process: Renal Hemodialysis Patients Allocated Apixaban versus Warfarin in Atrial Fibrillation (RENAL-AF)

- **Rivaroxaban**
  - Not dialyzable. No dosage adjustments in manufacturer’s labeling
  - Limited available data, use extreme caution and monitor for bleeding

Dosing Dabigatran Apixaban Rivaroxaban Edoxaban
Renal Elimination 80% 27% 33% 50%
Dialyzable Yes Small No No

- Clinical trials excluded most patients with reduced creatinine clearance (<30 mL/min or <25 mL/min apixaban)
- The risk of clinical stroke or systemic embolization between DOACs and warfarin is similar
- The risk of major bleeding or clinically relevant non-major bleeding is similar between DOACs and warfarin
- Apixaban is associated with a lower risk of bleeds
- Apixaban is the only DOAC with FDA approval for hemodialysis dosing, despite limited supporting evidence

DOACs in Renal Impairment Summary

<table>
<thead>
<tr>
<th>Normal AFib</th>
<th>Dosing</th>
<th>150 mg BID</th>
<th>5 mg BID</th>
<th>20 mg daily with evening meal</th>
<th>90 mg daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal AFib</td>
<td>Dosing</td>
<td>75 mg BID</td>
<td>3 mg BID</td>
<td>30 mg daily with evening meal</td>
<td>30 mg daily</td>
</tr>
<tr>
<td>Dosing</td>
<td>C/Cr &lt;15</td>
<td>30 mg daily</td>
<td>C/Cr &lt;15</td>
<td>AVOID</td>
<td>C/Cr &lt;15</td>
</tr>
</tbody>
</table>

Patient Case

<table>
<thead>
<tr>
<th>Dosing</th>
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<table>
<thead>
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<tbody>
<tr>
<td>Height(cm)</td>
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<tr>
<td>Wt (kg)</td>
</tr>
<tr>
<td>Wt (lbs)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>BUN</td>
</tr>
<tr>
<td>Creatinine (stable)</td>
</tr>
<tr>
<td>Cr/Cr</td>
</tr>
</tbody>
</table>

Patient DC: A: Age = 62 B: Weight = 1.24 kg C: SrCr = 1.6 Meets criteria for normal dosing of apixaban
Impaired Liver Function

Pharmacokinetics/Pharmacodynamics in Liver Disease

- altered hepatic metabolism
- increased drug exposure (AUC)?
- changes in protein binding
- decreased procoagulant factors

Hepatic Impairment Assessment

- Child Pugh score for severity of liver disease

   Encephalopathy:
   - Grade 1: Minimally altered (1 point)
   - Grade 2: Moderate (2 points)
   - Grade 3: Markedly altered (3 points)

   Bilirubin:
   - ≤ 2.0 mg/dl (0 points)
   - > 2.0 mg/dl but ≤ 3.0 mg/dl (2 points)
   - > 3.0 mg/dl (3 points)

   Albumin:
   - > 3.5 g/dl (0 points)
   - 3.0-3.5 g/dl (2 points)
   - ≤ 3.0 g/dl (3 points)

   Platelet count:
   - ≥ 100,000/µl (0 points)
   - 50,000-99,999/µl (2 points)
   - < 50,000/µl (3 points)

   Ascites:
   - None (0 points)
   - Transient (1 point)
   - Persistent (2 points)

   Portal hypertension:
   - None (0 points)
   - Portal vein thrombosis (2 points)
   - Esophageal varices (3 points)

Score:
- 5 to 6 points: Child class A
- 7 to 9 points: Child class B
- 10 to 15 points: Child class C

Calculation:
Child Pugh score is severity of liver disease. Up to three.

Patient Case

- **History of Present Illness**
  - KB is a 52 year old male on warfarin therapy for history of unprovoked DVT. Last week he was admitted for a PE. He was started on enoxaparin and warfarin on discharge from hospital.

- **Chief Complaint**
  - He would like switch from warfarin to a DOAC

- **Past Medical History**
  - Heartburn occasionally

- **Social History**
  - Drinks ~6-10 beers per day

---

**Patient Case**

- **Pertinent Demographic and Laboratory Data**

<table>
<thead>
<tr>
<th></th>
<th>10/19/2018</th>
<th>10/18/2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>179</td>
<td></td>
</tr>
<tr>
<td>WH (kg)</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>2.2 (baseline 1.2 on 10/1/18)</td>
<td></td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>ROS</td>
<td>No ascites, no encephalopathy</td>
<td></td>
</tr>
</tbody>
</table>

Liver ultrasound

Cirrhotic

---

**DOAC Dosing in Liver Impairment**

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP450</td>
<td>Metabolism</td>
<td>No recommendations</td>
<td>No moderate disease (Child-Pugh class B)</td>
<td>Avoid in moderate and severe disease (Child-Pugh class B or C)</td>
</tr>
<tr>
<td>Pharmacokinetic Studies (Moderate impairment)</td>
<td>AUC</td>
<td>AUC</td>
<td>AUC</td>
<td>AUC</td>
</tr>
</tbody>
</table>

DOACs in Liver Impairment Summary

- Subjects with active liver disease were excluded from landmark approval trials
- Unique recommendations for each DOAC in liver impairment
- Limited clinical info for DOAC use in Child-Pugh Class C

**Mild (Child-Pugh A)**
- dabigatran
- apixaban
- rivaroxaban
- edoxaban

**Moderate (Child-Pugh B)**
- dabigatran
- apixaban

**Severe (Child-Pugh C)**
- NONE

Patient Case

<table>
<thead>
<tr>
<th>Date</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>INR</th>
<th>Albumin (g/L)</th>
<th>Bilirubin (mg/L)</th>
<th>ALP (U/L)</th>
<th>AST (U/L)</th>
<th>ALT (U/L)</th>
<th>ROS</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/18</td>
<td>179</td>
<td>80</td>
<td>2.2</td>
<td>2.9</td>
<td>1.5</td>
<td>77</td>
<td>52</td>
<td>24</td>
<td>None</td>
</tr>
</tbody>
</table>

**Removalalcy:**
1. INR > 2.0
2. INR > 3.0
3. INR > 4.0
4. INR > 5.0
5. INR > 6.0
6. INR > 7.0
7. INR > 8.0
8. INR > 9.0
9. INR > 10.0

**Malignancy**
1. INR > 2.0
2. INR > 3.0
3. INR > 4.0
4. INR > 5.0
5. INR > 6.0
6. INR > 7.0
7. INR > 8.0
8. INR > 9.0
9. INR > 10.0

**VTE**
1. INR > 2.0
2. INR > 3.0
3. INR > 4.0
4. INR > 5.0
5. INR > 6.0
6. INR > 7.0
7. INR > 8.0
8. INR > 9.0
9. INR > 10.0

**Malignancy Associated VTE**
In patients with cancer thrombosis is a leading cause of \textbf{MORBIDITY and MORTALITY}. The occurrence of VTE in cancer has been observed as high as \textbf{1 in 3 PERSONS}.

**Background**

- **High Risk for VTE**
  - Cancer is an acquired thrombophilic condition
  - Frequent hospital admissions
  - Immobilization
  - Indwelling central catheters
  - Chemotherapy
  - Erythropoiesis-stimulating agents

- **Treatment for VTE and no cancer**
  - 1st
    - Direct Oral Anticoagulants (dabigatran, rivaroxaban, apixaban, edoxaban)
  - 2nd
    - Vitamin K antagonist therapy (warfarin)
  - 3rd
    - Low molecular weight heparin (enoxaparin)
Guidelines

- Treatment of VTE in patients with malignancy

<table>
<thead>
<tr>
<th>ASCO Guidelines</th>
<th>ACCP Guidelines (CHEST)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMWH &gt; UFH for first 5-10 days</td>
<td>LMWH &gt; warfarin</td>
</tr>
<tr>
<td>LMWH for at least 6 months</td>
<td>LMWH for an extended duration</td>
</tr>
<tr>
<td>Warfarin if LMWH not possible</td>
<td>Warfarin if LMWH not possible</td>
</tr>
<tr>
<td>No recommendations for DOACs</td>
<td>LMWH &gt; VKA and DOACs</td>
</tr>
</tbody>
</table>


Most commonly prescribed anticoagulants

- Vitamin K antagonist therapy (warfarin) 50%
- Low molecular weight heparin (enoxaparin) 40%
- Direct Oral Anticoagulants (dabigatran, rivaroxaban, apixaban, edoxaban) 10%


Background

180 Shots

Pain
Dose
$$$

10/22/2018
DOACs in Malignancy

• Randomized Clinical Trials (RCT) DOAC vs. warfarin:
  • Subgroup analyses in cancer population:
    1. Dabigatran = RECOVER
    2. Apixaban = AMPLIFY
    3. Rivaroxaban = EINSTEIN-DVT/PE
    4. Edoxaban = HOKUSAI

• Outcomes
  • Primary Efficacy Outcome: Recurrent VTE% (vs. VKA%)
  • Primary Safety Outcome: Major bleeding% (vs. VKA%)

DOAC RCT Subgroup Analysis

Dabigatran (Pradaxa®)
RECOVER study

221 Patients with active cancer in the study

- Recurrent VTE % (vs. VKA%)
  • 3.5% (vs. 4.7%)
  • Risk: 0.74 (0.20-2.70)

- Major Bleeding % (vs. VKA%)
  • 3.8% (vs. 4.0%)
  • Risk: 1.23 (0.28-5.50)

Apixaban (Eliquis®)
AMPLIFY study

169 Patients with active cancer in the study

- Recurrent VTE % (vs. VKA%)
  • 3.7% (vs. 6.4%)
  • Risk: 0.56 (0.13-2.37)

- Major Bleeding % (vs. VKA%)
  • 2.3% (vs. 5.0%)
  • Risk: 0.45 (0.08-2.46)
DOAC RCT Subgroup Analysis

**Rivaroxaban (Xarelto®)**

**EINSTEIN-DVT/PE study**

- **462 Patients**
  - with active cancer in the study
  - Recurrent VTE % (vs. VKA%):
    - 2.3% (vs. 3.9%)
    - Risk: 0.62 (0.21-1.79)
  - Major Bleeding % (vs. VKA %):
    - 1.9% (vs. 2.9%)
    - Risk: 0.47 (0.15-1.45)


---

**Do Trials of DOAC vs. LMWH therapy exist?**

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**Edoxaban (Savaysa®)**

**HOKUSAI study**

- **208 Patients**
  - with active cancer in the study
  - Recurrent VTE % (vs. VKA%):
    - 3.7% (vs. 7.1%)
    - Risk: 0.55 (0.16-1.85)
  - Major Bleeding % (vs. VKA %):
    - 4.6% (vs. 3.0%)
    - Risk: 1.52 (0.36-6.43)

---
Literature Review

- **Objective:** evaluate edoxaban versus dalteparin for the treatment of cancer-associated VTE

- **Primary Outcome:** composite of recurrent VTE or major bleeding during the 12 months after randomization

525 patients assigned to edoxaban group

LMWH given for ≤5 days then edoxaban 60 mg once daily

525 patients assigned to dalteparin group

Dalteparin 200 units/kg once daily for 30 days then 150 units/kg once daily

Literature Review

- Results: recurrent VTE or major bleeding

12.8% 13.5%
edoxaban group dalteparin group

HR, 0.97 [95% CI, 0.70-1.36]
p=0.006


- Results: recurrent VTE

7.9% 11.3%
edoxaban group dalteparin group

difference in risk, -3.4 [95% CI, -7.0-0.2]
HR, 0.71 [95% CI, 0.48-1.06]
p=0.09


- Results: major bleeding

6.9% 4.0%
edoxaban group dalteparin group

difference in risk, +2.9% [95% CI, 0.1-5.6]
HR, 1.77 [95% CI, 1.03-3.04]
p=0.04

Literature Review

- Results: **major bleeding**

<table>
<thead>
<tr>
<th>Category</th>
<th>Edoxaban Group (%)</th>
<th>Dalteparin Group (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 2 bleeding</td>
<td>66.7%</td>
<td>38.1%</td>
</tr>
<tr>
<td>Category 3 bleeding</td>
<td>33.3%</td>
<td>57.1%</td>
</tr>
</tbody>
</table>

- Results: **clinically relevant non-major bleeding**

<table>
<thead>
<tr>
<th>Category</th>
<th>Edoxaban Group (%)</th>
<th>Dalteparin Group (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>14.6%</td>
<td>11.1%</td>
</tr>
</tbody>
</table>

HR, 1.38 [95% CI, 1.03-1.89]

- Treatment group differences

<table>
<thead>
<tr>
<th>Avg. duration of therapy (days)</th>
<th>Gastrointestinal Cancer (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edoxaban 211</td>
<td>Edoxaban 33</td>
</tr>
<tr>
<td>Dalteparin 184</td>
<td>Dalteparin 21</td>
</tr>
</tbody>
</table>
Ongoing Studies

- **SELECT-D Trial** – rivaroxaban vs. dalteparin
  - Pilot Study results
  - Reduction in 6 month VTE recurrence rate (4% vs. 11%)
  - Rate of major bleeding (6% vs. 4%)
  - Randomized Phase III Study ongoing

- **CARAVAGGIO** – apixaban vs. dalteparin
  - Ongoing

---

**DOAC use in Malignancy Associate VTE Summary**

- The results of this study support the use of edoxaban for cancer-associated VTE treatment
- Using DOAC therapy would likely reduce cost, may improve adherence, and improved quality of life
- LMWH may still be preferred in patients with reduced renal function, GI cancer, or higher bleeding risk
- Additional ongoing studies will provide evidence regarding use of other DOAC therapy

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**Thank you!**

Questions?