Weighing the Options for Anticoagulation in Obesity

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Pharmacy Grand Rounds
May 24, 2016
Objectives

• Review pharmacokinetic changes in obesity

• Discuss dosing and monitoring strategies when using low molecular weight heparin

• Outline evidence and recommendations for utilization of direct oral anticoagulants
Overweight Adults in the United States

BMI ≥ 25kg/m²: 69%
BMI < 25kg/m²: 31%

BMI = Body mass index

Overweight & Obesity. CDC. http://www.cdc.gov/obesity/.
Obese Adults in the United States

1 in 3 adults you take care of will be obese

BMI ≥30kg/m²

BMI <30kg/m²

Overweight & Obesity. CDC. http://www.cdc.gov/obesity/.
What Will Obesity in the U.S. Be In The Future?

Obese Individuals

Year

2010 2015 2020 2025 2030

32% 37% 41% 46% 51%

Pharmacokinetics in Obesity

- Volume of Distribution ($V_d$)
- Clearance (CL)
- Elimination Half-Life ($T_{1/2}$)
Drugs with High $V_d$

130kg patient

Intravascular

60kg patient

Extravascular

$V_d = \text{Volume of distribution}$
Drugs with Low $V_d$

130kg patient

Intravascular

Fat

Extravascular

60kg patient

Fat
Clearance

- Defined as the volume of blood cleared of drug in a given time

- In obese patients:
  - Altered hepatic blood flow
  - Higher absolute clearance

Elimination Half-Life

- Defined as time it takes for concentration to fall to half its original concentration

\[ T_{\frac{1}{2}} = \frac{(\ln 2 \times V_d)}{CL} \]

\( CL = \text{Clearance} \)

Which of the following statements is true?

A. Obese and non-obese patients have similar PK profiles
B. $V_d$ is increased in obese patients
C. $T_{1/2}$ is equivalent in obese and non-obese patients
D. Compared to non-obese patients, obese patients have equivalent CL
Venous Thromboembolism Prophylaxis
**What Does the Package Insert Say?**

<table>
<thead>
<tr>
<th>Indication</th>
<th>eCrCl ≥ 30mL/min</th>
<th>eCrCl &lt; 30mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis of VTE</td>
<td>40mg daily</td>
<td>30mg daily</td>
</tr>
<tr>
<td>Treatment of VTE</td>
<td>1mg/kg Q12H</td>
<td>1mg/kg daily</td>
</tr>
</tbody>
</table>

“The safety and efficacy of prophylactic doses of Lovenox in obese patients (BMI >30 kg/m²) has not been fully determined and there is no consensus for dose adjustment”

VTE = Venous thromboembolism
VTE Prophylaxis in Obesity

- Standard fixed prophylactic doses suboptimal
- Relationship between BMI and thrombosis

Stasis of Blood Flow
Vessel Wall Injury
Hypercoagulability

Virchow’s Triad

# Unfractionated Heparin and Low Molecular Weight Heparin for VTE Prophylaxis

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Retrospective cohort study at 3 hospitals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Adult obese (&gt; 100kg) inpatients (&gt; 48 hours) who received thromboprophylaxis with UFH or enoxaparin</td>
</tr>
<tr>
<td>Intervention</td>
<td>Standard - UFH 5,000 units BID/TID or enoxaparin 40mg daily vs High-dose - UFH 7,500 units TID or enoxaparin 40mg BID</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>Rates of VTE in the standard vs high-dose groups</td>
</tr>
<tr>
<td>Secondary Endpoints</td>
<td>- VTE rates stratified by BMI - Hemorrhage</td>
</tr>
</tbody>
</table>

UFH = Unfractionated heparin

Did High-Dose Prophylaxis Reduce VTE?

Standard Dosing Regimen: 1.5%

High-dose Dosing Regimen: 0.8%

p = 0.05

Did High-Dose Prophylaxis Increase Hemorrhage?

- Standard Dosing Regimen: 8.4%
- High-Dose Dosing Regimen: 7.2%

$p = 0.15$

VTE Prophylaxis Recommendations

- **Weight ≥ 100kg**
  - **BMI ≥ 40 kg/m²**

- **eCrCl < 30mL/min**
  - Heparin 7,500 units TID

- **eCrCl ≥ 30mL/min**
  - Heparin 7,500 units TID
  - Enoxaparin 40mg BID
Treatment Dosing of Low Molecular Weight Heparin
46F admitted with unilateral LLE swelling and redness, found to have a DVT on ultrasound. Initiated on enoxaparin for bridging to warfarin treatment.

Hgb: 11g/dL
Platelets: 368 x 10⁹ L
INR: 1.2
Wt: 200 kg
BMI: 39.1 kg/m²
eCrCl = 96 mL/min

LLE = Left lower extremity
DVT = Deep vein thrombosis
eCrCl = Estimated creatinine clearance
Which dosing strategy would you chose for this patient?

200kg, eCrCl=96mL/min

A. 150mg BID
B. 150mg BID and check anti-Xa
C. 200mg BID
D. 200mg BID and check anti-Xa
Anti-Xa Monitoring

- Peak levels drawn 3 – 5 hours after steady state

- LMWH therapeutic range
  - 0.5 – 1.00 IU/mL for BID dosing
  - 1.00 – 2.00 IU/mL for once daily dosing

- Low antithrombin III (AT III) levels can decrease the efficacy of heparins

Pharmacokinetics of Enoxaparin

# VTE Treatment Dosing with Enoxaparin

**Study Design**
- Retrospective case series

**Population**
- Received enoxaparin with a corresponding anti-Xa and BMI \( \geq 40\text{kg/m}^2 \)
  - 26 patients
  - Median weight 162kg (58% > 150kg)
  - 27% ICU patients

**Primary Endpoint**
- Achievement of goal anti-Xa level (0.5-1 IU/mL)

**Secondary Endpoints**
- Bleeding events
- No patient had subtherapeutic levels
- No thrombotic events occurred in the study
- 40% of patients with a supratherapeutic level had bleeding events
- Median starting dose was 0.8mg/kg
  - Doses ranged from 80mg – 150mg BID

Enoxaparin Algorithm

Weight $\geq 100$kg and/or
BMI $\geq 40$ kg/m$^2$

- eCrCl<30mL/min
  - 1mg/kg Q24H
  - Max: 150mg
  - Check anti-Xa 3-5 hours after 4th dose

- eCrCl>30mL/min
  - 0.8mg/kg Q12H
  - Max: 150mg
  - Check anti-Xa 3-5 hours after 4th dose
46F admitted with unilateral LLE swelling and redness, found to have a DVT on ultrasound. Initiated on enoxaparin for bridging to warfarin treatment.

Hgb: 11g/dL
Platelets: 368 x 10^9 L
INR: 1.2
Wt: 200 kg
BMI: 39.1 kg/m²
eCrCl = 96 mL/min
Which dosing strategy would you choose for this patient?

200kg, eCrCl=96mL/min

A. 150mg BID
B. 150mg BID and check anti-Xa
C. 200mg BID
D. 200mg BID and check anti-Xa
Direct Oral Anticoagulants (DOACS)
# Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixiban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Volume of Distribution</strong></td>
<td>60-70 L</td>
<td>50L</td>
<td>20-70L</td>
</tr>
<tr>
<td><strong>Protein Binding</strong></td>
<td>35%</td>
<td>&gt;90%</td>
<td>87%</td>
</tr>
</tbody>
</table>

# Obese Patients in Dabigatran Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Weight (kg)</th>
<th>BMI*</th>
<th>Number (%) ≥100kg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RE-LY</strong> Atrial Fibrillation</td>
<td>Dabigatran 110mg BID</td>
<td>82.0±19.9*</td>
<td>N/A</td>
<td>3,099 patients (17%)</td>
</tr>
<tr>
<td></td>
<td>Dabigatran 150mg BID</td>
<td>82.5±19.4*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>82.7±19.7*</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RE-COVER VTE</strong></td>
<td>Heparin/dabigatran 150mg BID</td>
<td>84 (38-175)**</td>
<td>28.9±5.7</td>
<td>438 patients (17.1%)</td>
</tr>
<tr>
<td></td>
<td>Heparin/warfarin</td>
<td>82 (39-161)**</td>
<td>28.4±5.5</td>
<td></td>
</tr>
<tr>
<td><strong>RE-COVER II VTE</strong></td>
<td>Heparin/dabigatran 150mg BID</td>
<td>80 (36-184)**</td>
<td>28.4±5.8</td>
<td>394 patients (15.4%)</td>
</tr>
<tr>
<td></td>
<td>Heparin/warfarin</td>
<td>81 (35-210)**</td>
<td>28.4±5.8</td>
<td></td>
</tr>
</tbody>
</table>

*mean±standard deviation
**median (range)
Dabigatran

- RE-LY subgroup analysis

- Case reports of stroke in obese patients
  - 153kg (BMI 44.7kg/m²) peak level was less than the 25th percentile of therapeutic trough

Dabigatran Pharmacokinetics in Obesity

Plasma Level of Dabigatran (ng/mL)

Daytime Hours

- 8 a.m.
- 10 a.m.
- Noon
- 2 p.m.
- 4 p.m.
- 6 p.m.
- 8 p.m.
<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>BMI*</th>
<th>Number (%) &gt;90kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROCKET-AF</td>
<td>Rivaroxaban 20mg daily</td>
<td>28.3 (25-32)</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>28.1 (25-32)</td>
<td></td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td>Rivaroxaban 15mg BID → 20mg daily</td>
<td>N/A</td>
<td>491 patients (28.4%)</td>
</tr>
<tr>
<td></td>
<td>Enoxaparin 1.0mg/kg → warfarin</td>
<td></td>
<td>486 patients (28.3%)</td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>Rivaroxaban 15mg BID → 20mg daily</td>
<td>N/A</td>
<td>683 patients (28.2%)</td>
</tr>
<tr>
<td></td>
<td>Enoxaparin 1.0mg/kg → warfarin</td>
<td></td>
<td>672 patients (27.8%)</td>
</tr>
</tbody>
</table>

*median (interquartile range)
Rivaroxaban

- Post-hoc analysis comparing stroke outcomes in normal weight, overweight, and obese patients with AF
  - 5,206 patients in the obese group

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight</td>
<td>0.77</td>
<td>0.62-0.95</td>
<td>0.013</td>
</tr>
<tr>
<td>Obese</td>
<td>0.62</td>
<td>0.50-0.78</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

AF = Atrial fibrillation
CI = Confidence interval

# Obese Patients in Apixaban Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Weight (kg)*</th>
<th>BMI*</th>
<th>Number (%) of Obese Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARISTOLE Atrial Fibrillation</td>
<td>Apixaban 5mg BID</td>
<td>N/A</td>
<td>28±5</td>
<td>BMI ≥30kg/m² 7,159 patients (40%)</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td></td>
<td>28±5</td>
<td></td>
</tr>
<tr>
<td>AMPLIFY VTE</td>
<td>Apixaban 10mg BID → 5mg BID</td>
<td>84.6±19.8</td>
<td>N/A</td>
<td>≥100kg 522 patients (19.4%)</td>
</tr>
<tr>
<td></td>
<td>Enoxaparin → warfarin</td>
<td></td>
<td>84.6±19.8</td>
<td>≥100kg 518 patients (19.2%)</td>
</tr>
</tbody>
</table>

*Mean±standard deviation

ARISTOTLE
Subgroup Analysis Based on BMI

<table>
<thead>
<tr>
<th>BMI Range</th>
<th>Events per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.5-25 kg/m²</td>
<td>Stroke/SE: 2%</td>
</tr>
<tr>
<td></td>
<td>Death: 3.4%</td>
</tr>
<tr>
<td></td>
<td>Major Bleeding: 2.4%</td>
</tr>
<tr>
<td>25-30 kg/m²</td>
<td>Stroke/SE: 1.4%</td>
</tr>
<tr>
<td></td>
<td>Death: 2.9%</td>
</tr>
<tr>
<td></td>
<td>Major Bleeding: 2.3%</td>
</tr>
<tr>
<td>≥30 kg/m²</td>
<td>Stroke/SE: 1.5%</td>
</tr>
<tr>
<td></td>
<td>Death: 3.4%</td>
</tr>
<tr>
<td></td>
<td>Major Bleeding: 2.3%</td>
</tr>
</tbody>
</table>

p < 0.0001

SE = Systemic embolism

How Does Apixaban Compare to Warfarin in Obese Patients with Atrial Fibrillation?

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI ≥30kg/m²</td>
<td></td>
</tr>
<tr>
<td>Stroke/SE</td>
<td>0.76 (0.55-1.05)</td>
</tr>
<tr>
<td>Death</td>
<td>0.81 (0.67-0.99)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>0.84 (0.67-1.07)</td>
</tr>
</tbody>
</table>

DOACS for VTE
DOAC vs Warfarin for VTE

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-COVER I&amp;II</td>
<td>1.16 (0.58, 2.29)</td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td>0.99 (0.43, 2.26)</td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>1.28 (0.56, 2.90)</td>
</tr>
<tr>
<td>AMPLIFY</td>
<td>0.61 (0.29, 1.28)</td>
</tr>
<tr>
<td>Total</td>
<td>0.98 (0.72, 1.35)</td>
</tr>
</tbody>
</table>

DOACs Recommendations in Obesity

• Avoid dabigatran in obese patients

• Rivaroxaban may be considered in obese patients

• Apixaban has the best evidence for utilization of DOACs in obese patients
In a post-hoc analysis comparing apixaban vs warfarin in obese patients (BMI≥30kg/m²) with atrial fibrillation, warfarin prevented more strokes and systemic embolism?

A. True  
B. False
Summary

• Evaluate pharmacokinetics when dosing medications in obese patients

• For VTE prophylaxis “high-dose” heparin or LMWH is recommended for patients ≥100kg and BMI ≥40kg/m²

• For VTE treatment dose adjustments are warranted and anti-Xa levels should be monitored

• Apixiban may be considered for anticoagulation in obese patients
Questions & Discussion
Dose Capping with Unfractionated Heparin

- **NSTEMI**
  - Obese patients took longer to reach goal aPTT
  - No dose cap
  - Higher doses achieves therapeutic anticoagulation more rapidly

- **VTE**
  - Weight-based nomograms with no cap
  - Studies have shown relationship between patients’ weight and heparin requirement

Fondaparinux

- $V_d = 8.2\text{L}$

- Largely resides in the intravascular space
  - $>94\%$ protein bound

- Treatment of VTE based on the MATISSE trials
  - 10mg if $>100\text{kg}$

Anti-Xa Monitoring Cost

• Mayo Clinic Hospital – Rochester
  • $207.50

• Vancomycin trough level cost $150.00
<table>
<thead>
<tr>
<th>Anti-Xa Level (U/mL)</th>
<th>Hold Next Dose</th>
<th>Dosage Change</th>
<th>Next Anti-Xa Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.35</td>
<td>No</td>
<td>Increase by 25%</td>
<td>4 hour after next dose</td>
</tr>
<tr>
<td>0.35-0.49</td>
<td>No</td>
<td>Increase by 10%</td>
<td>4 hour after next dose</td>
</tr>
<tr>
<td>0.5-1.0</td>
<td>No</td>
<td>No</td>
<td>Next day, then weekly, then monthly</td>
</tr>
<tr>
<td>1.1-1.5</td>
<td>No</td>
<td>Decrease by 20%</td>
<td>Before next dose</td>
</tr>
<tr>
<td>1.6-2.0</td>
<td>3 hours</td>
<td>Decrease by 30%</td>
<td>Before next dose and 4 hour after next dose</td>
</tr>
<tr>
<td>&gt;2.0</td>
<td>Until anti-Xa &lt;0.5</td>
<td>Decrease by 40%</td>
<td>Before next dose and 4h after next dose</td>
</tr>
</tbody>
</table>

ARISTOTLE
Subgroup Analysis Based on BMI

SE = Systemic embolism