Anticoagulation Updates in Special Populations

A. Josh Roberts, Pharm.D., BCPS-AQ Cardiology
Senior Clinical Pharmacist, UC Davis Medical Center
Associate Clinical Professor, UC San Francisco School of Pharmacy
Associate Clinical Professor, UC Davis School of Medicine
Conflicts of Interest Disclosure

I have no real or potential conflicts of interest related to the subject matter in this presentation.

(plan to make BIG 💰💰 the ol’ fashion way)
Case #1: BD is a 79yo M with CC of Dark Tarry Stools

ADMIT Dx:
• Possible GIB

LABS:
• Na 138 | K 4.8 | Cl 102 | Mg 2.0
• BUN 13 | SCr 1.13
• INR 7.5
• H/H 8.6/25.8 | Plts 210

VITALS:
• BP 106/68 | HR 101

PMH / PSH:
• Mechanical St Jude Aortic Valve (’14)
• HTN
• CAD s/p 3v-CABG

MEDICATIONS:
• Asa 81 daily
• Carvedilol 25mg BID
• Warfarin as directed

WEIGHT:
Prev Clinic Visit: 68 kg
Question: 1

What dose of Vitamin K would you give to BD?
A. Vitamin K 0.5 mg IV once
B. Vitamin K 2 mg IV once
C. Vitamin K 2.5 mg PO once
D. Vitamin K 10 mg PO once
What dose of Vitamin K would you give to BD?

A. Vitamin K 0.5 mg IV once

B. Vitamin K 2 mg IV once

C. Vitamin K 2.5 mg PO once

D. Vitamin K 10 mg PO once
Reversal Strategies

• What do you want out of your reversal agent?

• When do you plan on restarting anticoagulation?
  – Consider a few days into the future

• Consider level of correction needed
Reversal Strategies

• Time frame for establishing hemostasis?
  – Minutes - Urgent / Emergent
  – Hours
  – Days

• Consider Pharmaco-kinetics + dynamics of medication
  – time to onset of action & waning of effect

• Titrate to Effect
  – Time to procedure?
  – Visualization of bleeding or surrogate lab?
Vitamin K: Route & Dosing

• Onset of Action
  – IV faster than PO
    • 0.5mg IV vs 2.5mg PO
    – No difference at 48hrs

• No documented ADRs
  – Dilute IV & infuse over 30min

• Currently, PO $$$
  – IV cheaper

**Vitamin K: Dose Response**

- **Effectiveness**
  - Vitamin K 2mg IV
    - Essentially normalized INR

- **Take Home Points:**
  - 2mg IV – 10mg IV = No Difference
  - Larger doses = longer bridging back to Tx INR

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*Tsu L. Ann Pharmacother. 2012 Dec;46(12):1617-26*
Low-Dose Strategy

• Is Vitamin K 0.25mg IV enough?
  – Less likely to over-correct INR
  – Less likely to need parental anticoagulant bridging

Tsu L. Ann Pharmacother. 2012 Dec;46(12):1617-26
Roberts AJ – prelim data
Example: Vitamin K dosing for patients on WARFARIN

<table>
<thead>
<tr>
<th>Patient’s Daily Warfarin Dose</th>
<th>Target INR Goal</th>
<th>Bleeding</th>
<th>No Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Daily Dose</strong> (&lt; 2mg/day)</td>
<td>2-3 @ 12 hours</td>
<td>0.25mg – 1.25mg IV</td>
<td>1 - 2.5mg PO</td>
</tr>
<tr>
<td></td>
<td>1.5 @ 12 hours</td>
<td>/= 2mg IV</td>
<td>/= 5 mg PO</td>
</tr>
<tr>
<td></td>
<td>1.5 @ 24 – 48 hours</td>
<td>0.25 – 1.25mg IV</td>
<td>/= 3 mg PO</td>
</tr>
<tr>
<td></td>
<td>&lt;1.3 @ 24 – 48 hours*</td>
<td>/= 2mg IV</td>
<td>/= 5 mg PO</td>
</tr>
<tr>
<td><strong>Medium Daily Dose</strong> (2 – 4 mg/day)</td>
<td>2-3 @ 12 hours</td>
<td>0.25mg – 1.25mg IV</td>
<td>/= 2 mg PO</td>
</tr>
<tr>
<td></td>
<td>1.5 @ 12 hours</td>
<td>/= 2mg IV</td>
<td>/= 5 mg PO</td>
</tr>
<tr>
<td></td>
<td>1.5 @ 24 – 48 hours</td>
<td>0.25 – 1.25mg IV</td>
<td>/= 5 mg PO</td>
</tr>
<tr>
<td></td>
<td>&lt; 1.3 @ 24 – 48 hours*</td>
<td>/= 2mg IV</td>
<td>5 - 10 mg PO</td>
</tr>
<tr>
<td><strong>High Daily Dose</strong> (&gt; 4 mg/day)</td>
<td>2-3 @ 12 hours</td>
<td>0.25mg – 1.25mg IV</td>
<td>/= 2.5 mg PO</td>
</tr>
<tr>
<td></td>
<td>1.5 @ 12 hours</td>
<td>/= 2mg IV</td>
<td>/= 5 mg PO</td>
</tr>
<tr>
<td></td>
<td>1.5 @ 24 – 48 hours</td>
<td>0.25 – 1.25mg IV</td>
<td>/= 5 mg PO</td>
</tr>
<tr>
<td></td>
<td>&lt;1.3 @ 24 – 48 hours*</td>
<td>/= 2mg IV</td>
<td>5 - 10 mg PO</td>
</tr>
</tbody>
</table>
Vitamin K Summary

• IV works faster than PO

• Low-dose (0.25mg-0.5mg IV; 2.5mg PO) sufficient to reverse INR without over-correcting

• 2mg IV sufficient to reverse INR related to warfarin
  – Larger doses increase need and bridging length of time

• Consider 10mg IV when no plans for restarting warfarin in <7days
Case #2:  
BG 68yo M with CC: SOB & CP

ADMIT Dx:  
Bilateral Segmental Pulmonary Embolisms

LABS:  
• Na 138 | K 4.3 | Cl 102 | Mg 2.2  
• BUN 63 | SCr 5.13 | BNP 1227  
• INR 1.09  
• H/H 9.6/28.8 | Plts 210

VITALS:  
• BP 127/78 | HR 93

WEIGHT:  
• Prev Clinic Visit: 92 kg

PMH / PSH:  
• Recurrent PEs  
• DM2 c/b neuropathy  
• CAD  
• PAD  
• ESRD (HD MWF via HeRO Graft)

MEDICATIONS:  
• Asa 81 daily  
• Atorvastatin 80 daily  
• Aspart Insulin SS  
• Metoprolol 50mg BID  
• Renal Vitamins daily  
• Warfarin as directed
• BG needs a parenteral ‘bridge’ BG back to therapeutic warfarin

• BG is a ‘hard stick’ & now refuses further lab draws

• BG is stable & really wants to go home
  ✦ INR 1.39

• What options do you have...?
  1. Continue heparin drip
  2. Switch to Low molecular weight heparin injections
Question 2

What parenteral agent would you give to BD?
A. Enoxaparin 0.4 mg/kg SC Q24h
B. Enoxaparin 0.7 mg/kg SC Q24h
C. Enoxaparin 1 mg/kg SC Q24h
D. Dalteparin 39 units/kg SC Q24h
What parenteral agent would you give to BD?

A. Enoxaparin 0.4 mg/kg SC Q24h
B. Enoxaparin 0.7 mg/kg SC Q24h
C. Enoxaparin 1 mg/kg SC Q24h
D. Dalteparin 39 units/kg SC Q24h
LMWH In Dialysis?

- LMWH is contraindicated in dialysis, right?!
- Many RCTs omitted Dialysis Patients or CrCl <15 ml/min
**LMWH In Dialysis**

- No RCT evaluating LMWH & HD
  - Case Series + Observational Studies
- LMWH Dosing (IV Prior to Dialytic Session)
  - Dalteparin: 39 units/kg
  - Enoxaparin: 0.7 mg/kg
  - 1mg/kg = ↑ minor hemorrhaging

Enoxaparin & HD: In The Real World

- **Enoxaparin 0.7mg/kg SQ DAILY**
  - Dose range 0.4 - 1 mg/kg
  - Rounded to closest whole syringe size

- **Indications:**
  - VTE Treatment (45%)
  - AF (13%)
  - Other Events: HD catheter clotting, hypercoagulable state, mech valve, pulm-htn

- No sig diff in Bleeding or Thrombosis

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<table>
<thead>
<tr>
<th>1º Endpoints</th>
<th>Enox (n=82)</th>
<th>UFH (n=82)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Bleeding (30 day)</strong></td>
<td>5 (6.1%)</td>
<td>9 (11%)</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Thromboembolic or HD Catheter Clotting (30 day)</strong></td>
<td>0</td>
<td>2 (2.4%)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2º Endpoints</th>
<th>Enox (n=82)</th>
<th>UFH (n=82)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospital LOS Mean (±SD)</strong></td>
<td>20 ± 58</td>
<td>29 ± 45</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Mortality (30 Day)</strong></td>
<td>5 (6.1%)</td>
<td>12 (14.6%)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Readmission (30 Day)</strong></td>
<td>17 (20.7%)</td>
<td>20 (24.4%)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

*Pon T. Thromb Res. 2014 Jun;133(6):1023-8*
LMWH in Dialysis Summary

• Consider using when:
  – loss of IV access or extremely hard stick
  – facilitate discharge
  – promote patient compliance

• Dose 0.7 mg/kg SC Daily
  – Ranges 0.4 – 1 mg/kg SC Daily
  – Round up or down depending on risk of bleeding and thrombosis
  – Round to nearest syringe size
Case#3:
HK is a 78yo F with CC of Palpitations

ADMIT Dx:
New onset AFib + RVR

LABS:
Na 138 | K 4.3 | Cl 102 | Mg 2.2
BUN 58 | SCr 6.21 | BNP 1227
INR 1.12
H/H 9.6/28.8 | Plts 210

VITALS:
BP 127/82 | HR 134

WEIGHT:
Prev Clinic Visit: 68 kg

PMH / PSH:
DM2
HTN
ESRD (HD TTS via LUE-AVF)

MEDICATIONS:
Amlodipine 10 daily
Atorvastatin 80 daily
Carvedilol 25 BID
Renal Vitamins 1 tab daily
Question 3

Which of the following answers would be best for HK in preventing Stroke or Systemic Embolism given her newly diagnosed NVAF?

A. Rivaroxaban 10 mg PO Daily
B. Apixaban 2.5 mg PO BID
C. Apixaban 5 mg PO BID
D. Warfarin dosed to Therapeutic INR
Which of the following answers would be best for HK in preventing Stroke or Systemic Embolism given her newly diagnosed NVAF?

A. Rivaroxaban 10 mg PO Daily
B. Apixaban 2.5 mg PO BID
C. Apixaban 5 mg PO BID
D. Warfarin dosed to Therapeutic INR
<table>
<thead>
<tr>
<th>Agent</th>
<th>&gt;80 ml/min</th>
<th>50-80 ml/min</th>
<th>30-49 ml/min</th>
<th>&lt;30 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>14 hrs</td>
<td>17 hrs</td>
<td>19 hrs</td>
<td>28 hrs</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>8 hrs</td>
<td>9 hrs</td>
<td>9 hrs</td>
<td>10 hrs</td>
</tr>
<tr>
<td>Apixaban</td>
<td>15 hrs</td>
<td>14 hrs</td>
<td>18 hrs</td>
<td>17 hrs</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>9 - 11 hrs</td>
<td></td>
<td>10-14 hrs</td>
<td></td>
</tr>
</tbody>
</table>

Apixaban & Dialysis

• “No dosage adjustment is recommended... based on pharmacokinetic and pharmacodynamic (anti-FXa activity) data in subjects with ESRD maintained on dialysis.”

## Apixaban & Dialysis

<table>
<thead>
<tr>
<th>Dose</th>
<th>Cmax (ng/mL)</th>
<th>Cmin (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EMA</td>
<td></td>
</tr>
<tr>
<td>2.5mg BID</td>
<td>123 (69-221)</td>
<td>79 (34-162)</td>
</tr>
<tr>
<td>5mg BID</td>
<td>171 (91-321)</td>
<td>103 (41-230)</td>
</tr>
<tr>
<td></td>
<td>Wang</td>
<td></td>
</tr>
<tr>
<td>2.5mg BID</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5mg BID</td>
<td>114</td>
<td>–</td>
</tr>
</tbody>
</table>


DOAC’s & Dialysis

- CKD-4/5 & Dialysis patients excluded from Phase-3 studies

- Small Pharmacokinetetic and -dynamic studies
  - Single or Two dose administration → Flawed Concept
  - Does Montecarlo Modeling replace actual human studies?
Single Dose Studies: Dialysis v. Healthy

- **Apixaban 5mg**
  - 1st dose before & 2nd dose after HD
    - “…modest increase (36%) in apixaban AUC and no increase in Cmax…”

- **Rivaroxaban 15mg**
  - 1st dose before & 2nd dose after HD
    - 35% decrease in overall drug clearance
    - PK/PD “parameters were generally comparable to... patients with moderate-to-severe renal impairment”

Plasma (1st comp)

Tissue (2nd comp)

Deep Tissues (3rd comp)

Eliminated

↑ EXPOSURE = ↑ HALF-LIFE

Rx

Adapted: Dager WE. Semin Dial. 2010;23:466-9
## Apixaban & Dialysis

<table>
<thead>
<tr>
<th>Dose</th>
<th>EMA</th>
<th>Wang</th>
<th>Mavrakanas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cmax (ng/mL)</td>
<td>Cmin (ng/mL)</td>
<td></td>
</tr>
<tr>
<td>2.5mg BID</td>
<td>123 (69-221)</td>
<td>-</td>
<td>132</td>
</tr>
<tr>
<td>5mg BID</td>
<td>171 (91-321)</td>
<td>103 (41-230)</td>
<td>58</td>
</tr>
<tr>
<td>2.5mg BID</td>
<td>-</td>
<td>-</td>
<td>307</td>
</tr>
<tr>
<td>5mg BID</td>
<td>114</td>
<td>-</td>
<td>218</td>
</tr>
</tbody>
</table>

**References:**
Apixaban in Dialysis

- Retrospective Study (n=25,523)
  - Apixaban: n=2,351
  - Warfarin: n=23,172

- Apixaban > Warfarin
  - 5 BID = SSE + Death
  - 2.5 BID = warfarin

- Time-on-Treatment
  - Apixaban: 105 days
  - Warfarin: 157 days

- Does this hold true over longer ‘on-treatment’ therapy?

## Clinical Experience with Apixaban in Hemodialysis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population (n)</th>
<th>Embolic Events/yr</th>
<th>Major Bleeding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siontis et al [Medicare Beneficiaries] 2.5mg (56%) 5mg (44%)</td>
<td>AF: HD and ESRD Apixaban Warfarin (7053) Note: 2/3 not taking AC after 1 yr</td>
<td>Stroke 12.4  Death 23.7</td>
<td>Major 19.7  GI 23.8  ICH 3.1</td>
</tr>
<tr>
<td>Bowie et al [5 cohort studies] 2.5mg – 45% 5mg – 55%</td>
<td>ESRD/HD Apixaban (236) Warfarin (170) ESRD/HD + AKD Apixaban (235) Warfarin (193)</td>
<td>Stroke 11.8  Death 24.9</td>
<td>Major 22.9  GI 23.4  ICH 3.5</td>
</tr>
<tr>
<td>Chokesuwattanaskul et al [Meta-analysis – CKD 4/5/HD 5 trials]</td>
<td>AF (87%), Dose varied (3 in Bowie analysis)</td>
<td>No difference in thromboembolic events</td>
<td>Apixaban (8.2%) Warfarin (10.6%)</td>
</tr>
<tr>
<td>Schafer et al CKD 4 (65%) CKD 5 (35%) HD (30%)</td>
<td>Apixaban (302) 2.5mg (57%) 5mg (43%) Warfarin (302)</td>
<td>No difference in thrombotic events (8 vs 9)</td>
<td>0-3mo 8.3  3-6mo 1.4  6-12mo 1.5  Fatal n=2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3-6mo 9.9  6-12mo 4  Fatal n=10</td>
</tr>
</tbody>
</table>

### Pending trials: Apixaban vs Warfarin in ESRD: ASA-DIA and RENAL-AF

# Rivaroxaban in Hemodialysis

<table>
<thead>
<tr>
<th>Dose</th>
<th>CrCl &gt;50 ml/min</th>
<th>CrCl &lt;50 ml/min</th>
<th>Hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20mg daily</td>
<td>15 mg daily</td>
<td>10mg daily</td>
</tr>
<tr>
<td>C-trough (De Vriese)</td>
<td>44.7 (9-147)</td>
<td>44.4 (9-143)</td>
<td>20.2 (4-93)</td>
</tr>
<tr>
<td>C-trough (Buller)</td>
<td>32 (19-60)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>


DOACs in Dialysis Summary

• Apixaban dosing remains unclear
  – Consider other factors and medications that may tip the scale towards one dose over the other
  – Long term safety and efficacy unclear
    • Awaiting more robust prospective trial data

• Rivaroxaban shows initial promise as an OAC in HD though small numbers
  – Need more robust data before moving into prime-time
Case#4:
MD is a 45yo F with CC of Palpitations

ADMIT Dx: New LLE DVT

LABS:
Na 143 | K 3.9 | Cl 105 | Mg 2.1
BUN 13 | SCr 1.21
INR 1.09
H/H 13.0/39.1 | Plts 309

VITALS:
BP 139/92 | HR 134

WEIGHT: 169 kg

PMH / PSH:
DM2
HTN

MEDICATIONS:
Lisinopril 20 mg daily
Metformin 1000mg BID
Question 4

Which of the following agents would be best for treating MD’s new LLE DVT (weight 169kg)?

A. Enoxaparin 1 mg/kg SC Q12h
B. Fondaparinux 10 mg SC Q24hr
C. Rivaroxaban 15 mg PO BID x21 days; then 20mg PO Daily with Food
D. Apixaban 10mg PO BID x7 days; then 5mg PO daily
Which of the following agents would be best for treating MD’s new LLE DVT (weight 169kg)?

A. Enoxaparin 1 mg/kg SC Q12h
B. Fondaparinux 10 mg SC Q24hr
C. Rivaroxaban 15 mg PO BID x21 days; then 20mg PO Daily with Food
D. Apixaban 10mg PO BID x7 days; then 5mg PO daily
# Anticoagulants in Obesity

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>Actual (ABW) vs Adjusted Body weight unclear</td>
<td>Consider ABW as more likely to reach targets sooner in obesity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider Max bolus and infusion cap</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Higher BMI may require a lower “units/kg/hr” rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Excessive dosing on ABW increase rates of bleeding</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>1mg/kg q 12hr</td>
<td>Caution with capped dosing. TE risk &gt; bleeding risk</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>Max 18000 units for VTE</td>
<td>Caution Capping dose – Is once daily still OK?</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>2.5-10mg SC</td>
<td>May have therapeutic effects at lower doses. Flat dose response in phase II trials. BMI &gt; 30 kg/m2 - ↓ Bleeding (0.3 vs 1.5%) and no change in thrombosis (3.7% vs 3.9%)</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>Dose on total body weight</td>
<td></td>
</tr>
<tr>
<td>Argatroban</td>
<td>Dose on total body weight</td>
<td></td>
</tr>
<tr>
<td>DOACs</td>
<td>Max 120kg – total body weight</td>
<td>Changes in outcomes unclear (Variable findings)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ISTH: Recommend not using DOACs in patients with a BMI of &gt; 40 kg/m2 or a weight of &gt; 120 kg</td>
</tr>
</tbody>
</table>

LMWH Labeling in Obesity

Dalteparin
   - 18,000U/day max for VTE (~90 kg patient)

Enoxaparin
   - Marginal increase in anti-Xa exposure (1.5mg/kg SC once daily)
   - No recommended max dose

Fondaparinux
   - 10mg/day for VTE treatment in patients > 100kg
LMWH Pharmacokinetics in Obesity

- Heavy-weight subjects = 101 to 165 kg; BMI 26-61 kg/m²

http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020484s011lbl.pdf
Enoxaparin: Once-Daily vs Twice-Daily Dosing

- What’s the clinical significance?
- Does dosing frequency matter?

**Table 2** Anti-Xa activity measured 4 h post-dose on day 2 or 3 of treatment by body mass index

<table>
<thead>
<tr>
<th>Weight range:</th>
<th>Anti-Xa activity (IU/mL): mean (95% CI)</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (kg) min–max</td>
<td>Subtherapeutic</td>
<td>Therapeutic</td>
</tr>
<tr>
<td><strong>Once-daily administration</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td>&lt;1.00 IU/mL</td>
<td>1.00–2.00 IU/mL</td>
</tr>
<tr>
<td>Low weight: &lt;18 kg/m²</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Healthy weight: ≥18 and ≤30 kg/m²</td>
<td>62</td>
<td>1.13 (1.04–1.22)</td>
</tr>
<tr>
<td>Obese: &gt;30 kg/m²</td>
<td>30</td>
<td>1.15 (1.02–1.28)</td>
</tr>
<tr>
<td><strong>Twice-daily administration</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td>&lt;0.5 IU/mL</td>
<td>0.5–1.1 IU/mL</td>
</tr>
<tr>
<td>Low weight: &lt;18 kg/m²</td>
<td>2</td>
<td>1.40 (−0.45–3.24)</td>
</tr>
<tr>
<td>Healthy weight: ≥18 and ≤30 kg/m²</td>
<td>69</td>
<td>1.12 (1.03–1.20)</td>
</tr>
<tr>
<td>Obese: &gt;30 kg/m²</td>
<td>51</td>
<td>1.17 (1.08–1.25)</td>
</tr>
</tbody>
</table>

*Bazinet A. Thrombosis Research (2005) 116, 41—50*
Once vs Twice daily Enoxaparin Dosing

<table>
<thead>
<tr>
<th></th>
<th>UFH</th>
<th>Enoxaparin (1mg/kg q 12hr)</th>
<th>Enoxaparin (1.5mg/kg q day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH</td>
<td>(Bolus 5000 unit, 1250 unit/hr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>(1mg/kg q 12hr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>(1.5mg/kg q day)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 3. Recurrence of Venous Thromboembolism and Attendant Risk Factors for All Treated Patients and Evaluable Patients**

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Unfractionated Heparin Group</th>
<th>Once-Daily Enoxaparin Group</th>
<th>Twice-Daily Enoxaparin Group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>All treated patients, n</td>
<td>290</td>
<td>298</td>
<td>312</td>
<td>900</td>
</tr>
<tr>
<td>Recurrent venous thromboembolic event, n (%)†</td>
<td>12 (4.1)</td>
<td>13 (4.4)</td>
<td>9 (2.9)</td>
<td>34 (3.8)</td>
</tr>
<tr>
<td>Deep venous thrombosis (lower extremity), n</td>
<td>7</td>
<td>11</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>Deep venous thrombosis (upper extremity), n</td>
<td>1</td>
<td>11</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary embolism, n</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Deep venous thrombosis and pulmonary embolism, n</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Evaluable patients, n</td>
<td>235</td>
<td>247</td>
<td>258</td>
<td>740</td>
</tr>
<tr>
<td>Recurrent venous thromboembolic event, n (%)†</td>
<td>10 (4.3)</td>
<td>11 (4.5)</td>
<td>8 (3.1)</td>
<td>29 (3.9)</td>
</tr>
<tr>
<td>Obesity</td>
<td>3/122 (2.5)</td>
<td>10/137 (7.3)</td>
<td>5/146 (3.4)</td>
<td>18/405 (4.4)</td>
</tr>
<tr>
<td>Pulmonary embolism at baseline</td>
<td>4/88 (4.5)</td>
<td>5/94 (5.3)</td>
<td>5/105 (4.8)</td>
<td>14/287 (4.9)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>0/44 (0.0)</td>
<td>1/54 (1.9)</td>
<td>2/59 (3.4)</td>
<td>3/157 (1.9)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>4/44 (9.1)</td>
<td>4/40 (10.0)</td>
<td>3/46 (6.5)</td>
<td>11/130 (8.5)</td>
</tr>
<tr>
<td>Cancer</td>
<td>3/45 (6.7)</td>
<td>6/49 (12.2)</td>
<td>3/47 (6.4)</td>
<td>12/141 (8.5)</td>
</tr>
</tbody>
</table>

Fondaparinux

**TABLE 3. Details on Initial Treatment of All Patients**

<table>
<thead>
<tr>
<th></th>
<th>SR90107a/ORG31540</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 mg (n=103)</td>
</tr>
<tr>
<td>Mean duration of study drug, d (SD)</td>
<td>6.7 (1.5)</td>
</tr>
<tr>
<td>Mean AUC of SR90107a/ORG31540, mg · h · L⁻¹ (SD)</td>
<td>15.1 (6.07)</td>
</tr>
<tr>
<td>Early discontinuation of study drug, n (%)</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>INR at discontinuation of study drug (SD)</td>
<td>2.9 (0.7)</td>
</tr>
</tbody>
</table>

AUC indicates area under the curve as determined in steady state (day 4).

- Phase II Pharmacokinetics – medication dosing based on tiered weights

UFH/LMWH vs Fondaparinux

- n = 4418
  - Fonda – 2201
    - >100kg = 11%
    - BMI≥30 = 55%
  - LMWH/UFH – 2217

- Event Rates
  - VTE Recurrence: No Diff
    - Numerically lower w/ obesity
  - Major Bleeding: No Diff
    - Numerically lower w/ obesity

Davidson B. J Thromb Haemost. 2007;5:1191-4
UFH/LMWH vs Fondaparinux

- Large overlapping ranges
- No sig signals in comparing either group (non-obese vs obese)
- Sig values
  - Body Weights (i.e. 166kg)
  - BMI (kg/m²)
    - fonda = 46
    - lmwh/ufh = 58

Davidson B. J Thromb Haemost. 2007;5:1191-4
VTE Recurrence: DOACs vs VKA

- No significant difference between agents
  - DOACs non-inferior

DOAC Pharmacokinetics in Obesity

- Dabigatran (>100kg)
  - ↑ VTE
  - ↔ TIA, SSE

- Riva / Apix or Warf (Single Center; n=795, BMI ≥40)
  - No differences in bleeding or recurrent VTE or SSE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Outcome</th>
<th>Weights</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>C-ss</td>
<td>&gt;100 kg ↓41-60%</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>C-max AUC T1/2</td>
<td>&gt;120 kg ↔</td>
</tr>
<tr>
<td>Apixaban</td>
<td>C-max AUC T1/2</td>
<td>&gt;120 kg ↓41-60% ↓20-40%</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Total Exposure</td>
<td>??</td>
</tr>
</tbody>
</table>

ISTH Statement on Obesity

• Recommend not using DOACs in patients with a BMI of > 40 kg/m² or a weight of > 120 kg
• Due to limited data and pharmacokinetic data, the suggests it could be an issue
• If they are used, they suggest using drug specific calibrated levels
• Peak and trough
• Don’t adjust studied doses if low; switch to warfarin

Obesity Summary

• Observations when dosing LMWH based on total body weight (TBW) in obesity:
  – Anti-Xa activity is not significantly increased – may not be a reliable test
  – TBW predicts anti-Xa activity better than lean body weight
  – No increase in bleeding
  – Fondaparinux a potential option – 10mg capped dose

• Consider twice daily LMWH dosing

• DOACs and warfarin appear safer in moderate obesity in AF

• Few studies evaluated TBW > 150kg or BMI > 50kg/m²
Case #5: CK is a 76yo F with CC of SOB

**ADMIT Dx:**
Elective LHC/RHC/ Cors

**LABS:**
- Na 138 | K 4.3 | Cl 102 | Mg 2.2
- BUN 15 | SCr 1.2
- H/H 9.6/28.8 | Plts 210

**VITALS:**
- BP 127/78 | HR

**WEIGHT:**
- Prev Clinic Visit: 62 kg

**PMH / PSH:**
- Afib
- Mitral Stenosis - mod
- HFrEF
- CAD
- HTN

**MEDICATIONS:**
- Asa 81 daily
- Atorvastatin 80 daily
- Metoprolol 50mg BID
- Warfarin as Directed
Question 5

What dose of enoxaparin would be best for CK?

A. Enoxaparin 1 mg/kg SC Q24h
B. Enoxaparin 0.75 mg/kg SC Q24h
C. Enoxaparin 1 mg/kg SC Q12h
D. Enoxaparin 0.75 mg/kg SC Q12h
What dose of enoxaparin would be best for CK?

A. Enoxaparin 1 mg/kg SC Q24h
B. Enoxaparin 0.75 mg/kg SC Q24h
C. Enoxaparin 1 mg/kg SC Q12h
D. Enoxaparin 0.75 mg/kg SC Q12h
LMWH + Creatinine Clearance

• Dependence on Renal Function
  – Enoxaparin ≥ Dalteparin

• Meta-analysis (12 studies, 4971 patients)
  – Major bleeding
    • 5.0% v 2.4% (CrCl < 30mL/min vs CrCl ≥ 30mL/min)
    • OR = 2.25 [CI, 1.19 to 4.27]; p=0.013
Age Related Dosing: Interesting Numbers

STEMI s/p LMWH + Thrombolytic

- **≥75yo: 0.75mg/kg q12h**
  - Dose ↓25% (i.e. 75 yo = 75% of dose)
  - >75yo group
    - CrCl >60 ml/min: 33%
    - CrCl 30-60ml/min: 60.5%
  - ↓risk of [excess] bleeding (~UFH)
  - Similar benefits of UFH

- **Empiric dose-reduction in >75yo patients may ameliorate bleeding complications without compromising efficacy**
  - Would patients with CrCl 30-60ml/min benefit from this strategy?

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White HD. Eur Heart J. 2007 May;28(9):1066-71