MANAGEMENT OF ANTICOAGULATION IN THE HOSPITALIZED PATIENT

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Disclosures

• none
Cases

- Should this patient be bridged perioperatively?
- How do I manage this new oral anticoagulant perioperatively?
- Should this patient on warfarin with GI bleed restart anticoagulation and if so when?
- How do I manage this patient who is bleeding on anticoagulation?
- Which anticoagulant can I use if my patient is morbidly obese?

Case #1
Which of these patients should receive bridge therapy postoperatively

1. 75 yo man AFIB CHADS2=4 (HTN, CHF, DM) on warfarin s/p L hip fx repair.
2. 50 year old man on warfarin for recurrent VTE, last event June 2012 s/p bowel resection
3. 65 year old man on warfarin with mechanical mitral valve s/p bowel resection
4. All of the above
Perioperative Anticoagulation

- Does anticoagulation need to be stopped?
- How many days prior does anticoagulation need to be stopped?
  - Which agent
  - What is renal function
- Should this patient be bridged?

ACCP Guidelines

- In patients with a mechanical heart valve, atrial fibrillation, or VTE at high risk for thromboembolism, we suggest
  Bridging anticoagulation instead of no bridging during interruption of VKA therapy (Grade 2C)
- In patients with a mechanical heart valve, atrial fibrillation, or VTE at low risk for thromboembolism, we suggest
  No bridging instead of bridging anticoagulation during interruption of VKA therapy (Grade 2C)
- In patients with a mechanical heart valve, atrial fibrillation, or VTE at moderate risk for thromboembolism,
  The bridging or no-bridging approach chosen is based on an assessment of individual patient- and surgery-related factors

Douketis JD. Chest. 2012 Feb;141(2 Suppl):e326S-50S. PMID: 22315266
### AF Risk Stratification for Perioperative Thromboembolism

<table>
<thead>
<tr>
<th>Risk Stratum</th>
<th>Indication for VKA Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>• CHADS$_2$ score of 5 or 6</td>
</tr>
<tr>
<td></td>
<td>• Recent (within 3 mo) stroke or transient ischemic attack</td>
</tr>
<tr>
<td></td>
<td>• Rheumatic valvular heart disease</td>
</tr>
<tr>
<td>Moderate</td>
<td>• CHADS$_2$ score of 3 or 4</td>
</tr>
<tr>
<td>Low</td>
<td>• CHADS$_2$ score of 0 to 2 (assuming no prior stroke or transient ischemic attack)</td>
</tr>
</tbody>
</table>

### VTE Risk Stratification

<table>
<thead>
<tr>
<th>Risk Stratum</th>
<th>VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>• Recent (within 3 mo) VTE</td>
</tr>
<tr>
<td></td>
<td>• Severe thrombophilia (eg, deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities)</td>
</tr>
<tr>
<td>Moderate</td>
<td>• VTE within the past 3-12 mo</td>
</tr>
<tr>
<td></td>
<td>• Nonevere thrombophilia (eg, heterozygous factor V Leiden or prothrombin gene mutation)</td>
</tr>
<tr>
<td></td>
<td>• Recurrent VTE</td>
</tr>
<tr>
<td></td>
<td>• Active cancer (treated within 6 mo or palliative)</td>
</tr>
<tr>
<td>Low</td>
<td>• VTE &gt; 12 mo previous and no other risk factors</td>
</tr>
</tbody>
</table>
**Risk Stratification for Perioperative Thromboembolism**

<table>
<thead>
<tr>
<th>Risk Stratum</th>
<th>Mechanical Heart Valve</th>
</tr>
</thead>
</table>
| High*        | Any mitral valve prosthesis  
               Any caged-ball or tilting disc aortic valve prosthesis  
               Recent (within 6 mo) stroke or transient ischemic attack |
| Moderate     | Bileaflet aortic valve prosthesis and one or more of the  
               of following risk factors: atrial fibrillation, prior stroke  
               or transient ischemic attack, hypertension, diabetes  
              , congestive heart failure, age > 75 y |
| Low          | Bileaflet aortic valve prosthesis without atrial  
               fibrillation and no other risk factors for stroke |

**Systematic Review of Bridging Cohort Studies**

### Table 4. Pooled Incidence Rates of Thromboembolic and Bleeding Events in Studies With and Without Bridging Comparator Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>TE Events, % (95% CI) and Events/ Patients at Risk</th>
<th>ATE Events, % (95% CI) and Events/ Patients at Risk</th>
<th>VTE Events, % (95% CI) and Events/ Patients at Risk</th>
<th>Major Bleeding, % (95% CI) and Events/ Patients at Risk</th>
<th>Overall Bleeding, % (95% CI) and Events/ Patients at Risk</th>
<th>Mortality, % (95% CI) and Events/ Patients at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bridged cohort</td>
<td>16 (9-24) 21400</td>
<td>16 (9-24) 21400</td>
<td>21 (10-36) 21400</td>
<td>21 (10-36) 21400</td>
<td>21 (10-36) 21400</td>
<td>21 (10-36) 21400</td>
</tr>
<tr>
<td>LMWH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full dose</td>
<td>14 (8-20) 6000</td>
<td>14 (8-20) 6000</td>
<td>14 (8-20) 6000</td>
<td>14 (8-20) 6000</td>
<td>14 (8-20) 6000</td>
<td>14 (8-20) 6000</td>
</tr>
<tr>
<td>Low dose</td>
<td>12 (8-17) 2400</td>
<td>12 (8-17) 2400</td>
<td>12 (8-17) 2400</td>
<td>12 (8-17) 2400</td>
<td>12 (8-17) 2400</td>
<td>12 (8-17) 2400</td>
</tr>
</tbody>
</table>

Bridge therapy associated with 3 fold increased risk of bleeding  
No ↓ in TE with heparin bridge regardless of dose of LMWH used  
Low int dose of LMWH associated with lower risk of bleed
The BRIDGE Trial

Mean CHADS2=2.3
Very few high risk

Table 3. Study Outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No Bridging (N=918)</th>
<th>Bridging (N=895)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>number of patients</td>
<td>number of patients</td>
<td></td>
</tr>
<tr>
<td>Arterial thromboembolism</td>
<td>4 (0.4)</td>
<td>3 (0.3)</td>
<td>0.01* 0.73</td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (0.2)</td>
<td>3 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>2 (0.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>12 (1.3)</td>
<td>29 (3.2)</td>
<td>0.005†</td>
</tr>
</tbody>
</table>

Secondary

Death                     | 5 (0.5)             | 4 (0.4)         | 0.81†  |
Myocardial infarction      | 7 (0.8)             | 14 (1.6)        | 0.10†  |
Deep vein thrombosis       | 0                   | 1 (0.1)         | 0.25†  |
Pulmonary embolism         | 0                   | 1 (0.1)         | 0.25†  |
Minor bleeding             | 110 (12.9)          | 187 (20.9)      | <0.001† |

* P value for noninferiority.
† P value for superiority.

Table 1. Baseline Characteristics of the Patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Bridging (N=918)</th>
<th>Bridging (N=895)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – yr</td>
<td>71.6±8.8</td>
<td>71.6±8.8</td>
<td></td>
</tr>
<tr>
<td>Male sex – no. (%)</td>
<td>566 (73.3)</td>
<td>566 (71.4)</td>
<td></td>
</tr>
<tr>
<td>Race – no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>860 (94.5)</td>
<td>849 (96.9)</td>
<td></td>
</tr>
<tr>
<td>Nonwhite</td>
<td>38 (3.3)</td>
<td>22 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (0.2)</td>
<td>3 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Weight – kg</td>
<td>96.2±24.87</td>
<td>95.4±23.50</td>
<td></td>
</tr>
<tr>
<td>CHADS2 score 2</td>
<td>1.3±1.18</td>
<td>2.4±1.97</td>
<td></td>
</tr>
<tr>
<td>Distribution – no. (%)</td>
<td>0</td>
<td>3 (0.3)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>216 (22.7)</td>
<td>212 (23.7)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>382 (41.8)</td>
<td>351 (39.0)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>229 (24.1)</td>
<td>222 (24.8)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>96 (10.5)</td>
<td>100 (11.3)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>21 (2.4)</td>
<td>27 (2.9)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3 (0.3)</td>
<td>5 (0.6)</td>
<td></td>
</tr>
<tr>
<td>CHF or left ventricular dysfunction – no. (%)</td>
<td>288 (31.2)</td>
<td>310 (34.4)</td>
<td></td>
</tr>
<tr>
<td>Hypertension – no. (%)</td>
<td>833 (87.7)</td>
<td>886 (98.0)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus – no. (%)</td>
<td>390 (41.0)</td>
<td>352 (38.9)</td>
<td></td>
</tr>
<tr>
<td>Stroke – no. (%)</td>
<td>79 (8.3)</td>
<td>99 (11.0)</td>
<td></td>
</tr>
<tr>
<td>Transient ischemic attack – no. (%)</td>
<td>79 (8.5)</td>
<td>77 (8.6)</td>
<td></td>
</tr>
<tr>
<td>Mitral valve disease – no. (%)</td>
<td>135 (14.9)</td>
<td>145 (16.0)</td>
<td></td>
</tr>
</tbody>
</table>
BRIDGING IN VTE

Table 8. Outcomes at 30 Days Overall and by Bridging Status and VTE Risk Category*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No./Total No. (%)</th>
<th>Bridge Therapy (n = 555)</th>
<th>No Bridge Therapy (n = 1257)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically Relevant Bleeding Risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>3/17 (17.6)</td>
<td>1/36 (2.8)</td>
<td>2/135 (1.5)</td>
<td>.19</td>
</tr>
<tr>
<td>Moderate</td>
<td>5/124 (4.0)</td>
<td>0/104 (0.0)</td>
<td>5/120 (4.2)</td>
<td>.85</td>
</tr>
<tr>
<td>Low</td>
<td>3/1431 (0.2)</td>
<td>2/1031 (0.2)</td>
<td>1/1400 (0.1)</td>
<td>.001</td>
</tr>
<tr>
<td>Overall</td>
<td>17/1812 (0.9)</td>
<td>5/555 (0.9)</td>
<td>12/1257 (0.9)</td>
<td>.01</td>
</tr>
<tr>
<td>Recurrent VTE Risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>0/57</td>
<td>0/36</td>
<td>0/21</td>
<td>.97</td>
</tr>
<tr>
<td>Moderate</td>
<td>1/124 (0.8)</td>
<td>0/104 (0.0)</td>
<td>1/120 (0.8)</td>
<td>.48</td>
</tr>
<tr>
<td>Low</td>
<td>2/1431 (0.1)</td>
<td>0/410</td>
<td>2/1021 (0.2)</td>
<td>.13</td>
</tr>
<tr>
<td>Overall</td>
<td>3/1812 (0.2)</td>
<td>0/555</td>
<td>3/1257 (0.2)</td>
<td>.56</td>
</tr>
</tbody>
</table>

- Use of bridge therapy was associated with hazard ratio of 17.2 for clinically-relevant bleeding (95% CI 3.9–75.1)
- No difference in recurrent VTE even with high risk patients
- No difference in bleed between full dose and prophylactic dose

To Bridge or Not to Bridge

- Bridge therapy is associated with marked ↑risk of bleeding-risk benefit unclear DESPITE guidelines recommending its use
- We no longer bridge AFIB routinely and only consider it in CHADs2=5/6 or recent stroke
- We no longer bridge VTE unless recent VTE, recurrent on while on AC, active cancer or very high risk thrombophilia
- For now still bridging mechanical mitral and high risk aortic valves
- THIS DOES NOT APPLY TO ACUTE INTERRUPTIONS DURING TREATMENT OF ACUTE THROMBOSIS
Case #1
Which of these patients should receive bridge therapy perioperatively?

- 75 yo man CHADS2=4 on warfarin s/p left hip fracture repair.
- 50 year old man on warfarin for recurrent VTE. last event June 2012 s/p bowel resection
- 65 year old man with mechanical mitral valve on warfarin s/p bowel resection

Case 1a

- 65 year old man on mechanical mitral on warfarin s/p bowel resection. You restart full dose bridge therapy
- 1. on POD#0 with IV heparin, no bolus
- 2. on POD#1 with IV heparin, no bolus
- 3. no sooner than POD#2 with IV heparin, no bolus
- 4. Why did this issue have to come up on my shift?
4.4. In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH and are undergoing high-bleeding-risk surgery

We suggest resuming therapeutic-dose LMWH 48 to 72 h after surgery instead of resuming LMWH within 24 h after surgery (Grade 2C)

Risk of Bleeding with Bridging after Major Surgery

<table>
<thead>
<tr>
<th>Invasive Procedure</th>
<th>Minor Surgery</th>
<th>Major Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.7 % (0.02-3.7%)</td>
<td>0% (0-5.0%)</td>
<td>20% (9.1-35.7%)</td>
</tr>
</tbody>
</table>
Case 1a

- 65 year old man on with mechanical mitral on warfarin s/p bowel resection. You restart full dose bridge therapy
- 1. on POD#0 with IV heparin, no bolus
- 2. on POD#1 with IV heparin, no bolus
- 3. no sooner than POD#2 with IV heparin, no bolus

Case #2

76 yo female with atrial fibrillation with a history of hypertension, remote CVA, CKD (CrCl=40s), on dabigatran in the pre op area for an elective hip replacement. What would be the appropriate anticoagulation regimen pre op for her?

a. Last dose dabigatran 5 days before surgery and use LMWH bridging in the usual manner
b. Last dose dabigatran 5 days before surgery, no LMWH
c. Last dose 1-2 days prior to surgery
d. Was that the code pager? Sorry, gotta run.
Peri-Procedural Management: DOACs

- When to stop DOAC
  - Dependent on type of procedure
    - Low bleed risk: hold for 2-3 half-lives
    - High bleed risk: hold for 4-5 half lives
  - Dependent on patient’s renal function and half-life of DOAC
    - Half-life ranges from 6-17 hours among agents
    - Will be prolonged with renal impairment – may almost double in severe impairment


Peri-op Management of DOACs

<table>
<thead>
<tr>
<th>Renal function (mL/min)</th>
<th>Estimated half-life (hours)</th>
<th>Low bleeding risk surgery (allow 2-3 t½ between last dose and surgery)</th>
<th>High bleeding risk surgery (allow 4-5 t½ between last dose and surgery)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalteparin (BID dosing)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCl &gt; 80</td>
<td>t½ 24</td>
<td>Hold time: 28-42 hr # doses to hold: 2</td>
<td>Hold time: 56-70 hr # doses to hold: 5-6</td>
</tr>
<tr>
<td>CCl &gt; 50-79</td>
<td>t½ 17</td>
<td>Hold time: 34-53 hr # doses to hold: 3-4</td>
<td>Hold time: 68-85 hr # doses to hold: 6-7</td>
</tr>
<tr>
<td>CCl 30-49</td>
<td>t½ 19</td>
<td>Hold time: 38-57 hr # doses to hold: 4-5</td>
<td>Hold time: 76-90 hr # doses to hold: 7-8</td>
</tr>
<tr>
<td>CCl 15-29</td>
<td>t½ 28</td>
<td>Hold time: 52-68 hr # doses to hold: 5-7</td>
<td>Hold time: 92-110 hr # doses to hold: 9-12</td>
</tr>
<tr>
<td>CCl &lt;15</td>
<td>unknown</td>
<td>Hold until resolved (e.g. if acute kidney injury) or consider transition to warfarin or UFH</td>
<td>1 day after procedure (~24 h post-op)</td>
</tr>
</tbody>
</table>

Rivaroxaban (Once daily dosing)

<table>
<thead>
<tr>
<th>Renal function (mL/min)</th>
<th>Estimated half-life (hours)</th>
<th>Low bleeding risk surgery (allow 2-3 t½ between last dose and surgery)</th>
<th>High bleeding risk surgery (allow 4-5 t½ between last dose and surgery)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCl &gt; 80</td>
<td>t½ 24</td>
<td>Hold time: 16-24 hr # doses to hold: 1</td>
<td>Hold time: 32-40 hr # doses to hold: 2</td>
</tr>
<tr>
<td>CCl &gt; 50-79</td>
<td>t½ 19</td>
<td>Hold time: 18-27 hr # doses to hold: 1</td>
<td>Hold time: 36-45 hr # doses to hold: 2</td>
</tr>
<tr>
<td>CCl 15-29</td>
<td>t½ 10</td>
<td>Hold time: 20-30 hr # doses to hold: 1</td>
<td>Hold time: 40-50 hr # doses to hold: 2</td>
</tr>
<tr>
<td>CCl &lt;15</td>
<td>unknown</td>
<td>Hold until resolved (e.g. if acute kidney injury) or consider transition to warfarin or UFH</td>
<td>1 day after procedure (~24 h post-op)</td>
</tr>
</tbody>
</table>

Apixaban (BID dosing)

<table>
<thead>
<tr>
<th>Renal function (mL/min)</th>
<th>Estimated half-life (hours)</th>
<th>Low bleeding risk surgery (allow 2-3 t½ between last dose and surgery)</th>
<th>High bleeding risk surgery (allow 4-5 t½ between last dose and surgery)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCl &gt;50</td>
<td>t½ 7-8</td>
<td>Hold time: 16-24 hr # doses to hold: 1</td>
<td>Hold time: 28-40 hr # doses to hold: 4</td>
</tr>
<tr>
<td>CCl 15-49</td>
<td>t½ 17-18</td>
<td>Hold time: 34-54 hr # doses to hold: 1</td>
<td>Hold time: 66-90 hr # doses to hold: 4</td>
</tr>
<tr>
<td>CCl &lt;15</td>
<td>unknown</td>
<td>Hold until resolved (e.g. if acute kidney injury) or consider transition to warfarin or UFH</td>
<td>1 day after procedure (~24 h post-op)</td>
</tr>
</tbody>
</table>

Edoxaban (Once daily dosing)

<table>
<thead>
<tr>
<th>Renal function (mL/min)</th>
<th>Estimated half-life (hours)</th>
<th>Low bleeding risk surgery (allow 2-3 t½ between last dose and surgery)</th>
<th>High bleeding risk surgery (allow 4-5 t½ between last dose and surgery)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCl &gt;50</td>
<td>t½ 8-9</td>
<td>Hold time: 16-27 hr # doses to hold: 1</td>
<td>Hold time: 32-45 hr # doses to hold: 2</td>
</tr>
<tr>
<td>CCl 30-49</td>
<td>t½ 9-10</td>
<td>Hold time: 18-30 hr # doses to hold: 1</td>
<td>Hold time: 36-50 hr # doses to hold: 2</td>
</tr>
<tr>
<td>CCl 15-29</td>
<td>t½ 17</td>
<td>Hold time: 34-51 hr # doses to hold: 1</td>
<td>Hold time: 68-85 hr # doses to hold: 2</td>
</tr>
<tr>
<td>CCl &lt;15</td>
<td>unknown</td>
<td>Hold until resolved (e.g. if acute kidney injury) or consider transition to warfarin or UFH</td>
<td>1 day after procedure (~24 h post-op)</td>
</tr>
</tbody>
</table>
### Procedure and Interruption Data from RCTs

#### 30-day event rates (%)

<table>
<thead>
<tr>
<th>Trial</th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>dabigatran</td>
<td>warfarin</td>
<td>rivaroxaban</td>
</tr>
<tr>
<td>Stroke or Systemic Embolism</td>
<td>0.5</td>
<td>0.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>5.1</td>
<td>4.6</td>
<td>0.99</td>
</tr>
</tbody>
</table>

*Subgroup analysis of RELY trial*

Bridge therapy did not ↓ TE rate but did bleeding↑

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### Case #2

76 yo female with atrial fibrillation with a history of CHF, hypertension, diabetes, CKD (CrCl=40s), previous stroke and normal renal function on a dabigatran, scheduled for an elective hip replacement. What would you do?

a. Last dose dabigatran 5 days before surgery and use LMWH bridging in the usual manner

b. **Last dose dabigatran 5 days before surgery, no LMWH**

c. Last dose 1-2 days prior to surgery

d. Don’t interrupt DOAC
Case #2a

When would you resume her full intensity anticoagulation therapy post operatively for stroke prevention?

a. Evening of surgery  
b. Post op day #1  
c. No sooner than post op day #2 or 3  
d. I know you just told us this. I wish I had more coffee this morning.

Resumption of DOACs post operatively

- DOACs have rapid onset of anticoagulant effect (~1-4 hours)
  - Analogous to using LMWH
  - Caution with resuming too soon
- Timing of resumption dependent on type of procedure
  - Low bleed risk: resume 24 hours post-op
  - High bleed risk: resume NO SOONER THAN 48-72 hours post-op
- May consider “step-up” approach
  - Lower or prophylactic dose of DOAC for initial 24-48+ hours; if/when tolerated, increase to treatment dose DOAC

Case #2a

When would you resume her full intensity anticoagulation therapy for stroke prevention?

a. Evening of surgery
b. Post op day #1
c. No sooner than post op day #2 or 3**

** remember if you restarted warfarin without a bridge post op pateint would not be fully anticoagulated until POD# 5-10. risks of full dose anticoagulation on POD#2-3 may outweigh benefits. May opt to wait until 5+ days post op in many cases.

Take Home Points BRIDGING

- Periprocedural bridge therapy is associated with marked increased risk of bleeding
- Consider on a case by case basis for highest risk patients
- Early resumption of full dose anticoagulation after major surgery associated with higher bleed rates
- Periop DOAC management dictated by renal function and procedure bleeding risk
Case #3

76 y/o man with AFIB CHADS2=3 on anticoagulation with warfarin is admitted with UGIB. INR is 3.0. He requires 3u PRBCs, vit K and FFP. EGD shows peptic ulcer disease. He is started on high dose PPI therapy, bx for H Pylori done. When should his anticoagulation be restarted?

a) Never  
b) In one week  
c) In one month  
d) Let the primary provider deal with this one

90 day Follow up

Risk of death 3x lower if restart  
↑ GIB (ns)-none fatal  
Highest risk time day 1-7

Nearly 50% of pts with GIB on ASA also  
↓ TE 0.4% vs 5.5% -3 fatal  
If resumed within 14 days no thrombosis

WITT et al Arch Intern Med. 2012
Recurrent GIB: Warfarin restart vs no

For each figure:
- dotted line: restarted
- solid line: not restarted

Outcomes stratified by duration of warfarin interruption

---- < 7 days

no warfarin
Case #3

76 y/o man with AFIB CHADS2=3 on anticoagulation with warfarin is admitted with UGIB. INR is 3.2. He requires 3u PRBCs and FFP. EGD shows peptic ulcer disease. He is started on high dose PPI therapy, bx for H Pylori done. When should his anticoagulation be restarted?

a) Never
b) In one week
c) In one month
d) Let the primary provider deal with this one

Take Home Points-GIB on AC

- reassess risk benefit of anticoagulation
- is TE risk high enough to restart?
- assess risk of rebleeding
- identifiable source, treatable lesion?
- reconsider need for concomitant aspirin/interacting meds
- what is TTR?
- spurious elevation in INR v. poor TTR/?DOAC
- if ongoing strong indication for anticoagulation determine best time to restart therapy with inpatient team-restarting after one week may provide reasonable risk benefit profile in carefully selected patients after GI bleed
Case #4

- A 65 year old man with AFIB CHADS2=2 (DM/HTN) on rivaroxaban for stroke prevention presents with melena, BP 120/80, HR 90, HCT 30 (baseline 40). PT 18. How do you manage his anticoagulation?

1. hold rivaroxaban and transfuse PRBCs & IV fluids as needed
2. hold rivaroxaban and administer PCC
3. hold rivaroxaban and transfuse FFP
4. I knew we should have had a protocol for this. Didn’t she mention at last years conference??

Major bleeding events comparing target-specific anticoagulants with VAKs.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>TROACs</th>
<th>VKAs</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
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<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Events</td>
<td>M-H, Random, 95% CI</td>
<td>M-H, Random, 95% CI</td>
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<td>1.1 Major bleeding</td>
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<td>EINSTEIN-ADHESION 2013</td>
<td>14</td>
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<td>RE-MEDY, 2013</td>
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<td>RE-COVER II, 2014</td>
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<td>RE-COVER II, 2009</td>
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<td>AMPLIFY, 2013</td>
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<td>JARRIET, 2012</td>
<td>26</td>
<td>630</td>
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<td>BAYTEN, 2013</td>
<td>26</td>
<td>2412</td>
<td>0.86 [0.69, 1.06]</td>
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<td>KOGAN TES, 2013</td>
<td>66</td>
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<td>ANDROMEDA, 2011</td>
<td>327</td>
<td>9360</td>
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<td>ROCKSTAR, 2011</td>
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<td>RE-LY, 2009</td>
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<td>ENSMAGE-AF-TTR, 2013</td>
<td>672</td>
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<td>0.68 [0.57, 0.82]</td>
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<td>Subtotal [95% CI]</td>
<td>57839</td>
<td>44757</td>
<td>0.73 [0.62, 0.86]</td>
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</tbody>
</table>

Total events: 2320

Heterogeneity: $I^2 = 56.4$ $Q$-value = 48.66, df = 11 ($P < 0.0001$); $I^2 = 78$

Test for overall effect: $Z = 3.98$ ($P = 0.0001$)

Total [95% CI]: 57839

Heterogeneity: $I^2 = 56.4$ $Q$-value = 48.66, df = 11 ($P < 0.0001$); $I^2 = 78$

Test for overall effect: $Z = 3.98$ ($P < 0.0001$)

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GI BLEEDING in DOAC v warfarin in AFIB

< 65-lower risk of GIB
> 65 higher risk of GIB
➢ > 75 particularly high risk GI bleeding

Neena S Abraham et al. BMJ 2015;350:bmj.h1857

NOACS and Major Bleeding Fatality

All cause mortality

Caldeira et al HEART 2015
Reversal Question

- **Is drug present in significant quantities?**
  
  Generally – but not guaranteed
  - If PT/INR is long there are significant amounts of rivaroxaban present
  - If PTT is long there are significant amounts of dabigatran present
  - There is no way to detect apixaban/edoxaban

  If TT normal dabigatran is not present in significant quantities
  If Xa heparin level less than lower limit of detection Xa inhibitors not present in significant quantities

---

Reversal Question

- **Does agent need to be reversed?**

  If bleeding is minor or easily addressed with interventions OR if surgery can be delayed
  - Drugs have short half-lives in patients with normal renal function
  - Waiting is the preferred option
Evidence for DOAC Reversal

- Evidence base for use of any reversal agent with DOACS is poor and not using a reversal agent is consistent with the standard of practice
  - PCC or aPCC corrects the anticoagulant effect rivaroxaban in animal models
  - In human plasma incubated with dabigatran aPCC
    - Reduced clot initiation time
    - Corrected thrombin generation
Isn’t there a specific reversal agent on the way?

- Dabigatran – monoclonal antibody derived specific reversal agent-Idarucizumab
- Xa inhibitors – Xa “clone target”
  Adexanet alpha
  Arizapine

Emergent Reversal of Warfarin

- Administer intravenous vitamin K
  Comment on anaphylaxis
- Administer coagulation factor concentrates
  Fresh frozen plasma
  Prothrombin complex concentrates
- Administer “pro-coagulants”
  rfVIIa
Within 1 hr 2/3 PCC patients with INR ≤ 1.3 vs 0 in plasma group.

PCC-II, VII, IX, X, C, S, Heparin

Case #4

- A 65 year old man with AFIB CHADS2=2 (DM/HTN) on rivaroxaban for stroke prevention presents with melena, BP 120/80, HR 90, HCT 30 (baseline 40). PT 18. How do you manage his anticoagulation?
- 1. hold rivaroxaban and transfuse PRBC IV fluids as needed
- 2. hold rivaroxaban and administer PCC
- 3. hold rivaroxaban and transfuse FFP

Take Home Points-Bleeding on Anticoagulation

- Warfarin-life threatening bleeding PCC + IV vit K preferred. Non life threatening FFP + IV Vit K
- DOAC-no antidote. No data to support use of products. Have protocol in place for how to approach these cases. Agent specific antidotes in development
Case 5

58 yo male presents to ED with chest pain and shortness of breath. CT reveals bilateral PE. Vital signs are stable. Medical history unremarkable other than obesity (Ht=68”, wt=155 kg). Which of the following do you recommend for initial PE treatment?

a. Enoxaparin 150mg twice daily + warfarin
b. IV heparin + warfarin
c. Rivaroxaban 15 mg BID x21 days then 20 mg daily
d. Any of the above

LMWH Labeling in Obesity

- Tinzaparin
  Weight-based dosing is appropriate in heavy/obese patients

- 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
Obesity Summary

- Observations when dosing LMWH based on total body weight (TBW) in obesity:
  - Anti-Xa activity is not significantly increased
  - TBW predicts anti-Xa activity better than lean body weight
  - No increase in bleeding
- Consider twice daily dosing for LMWH
- Few studies evaluated TBW > 150kg or BMI > 50kg/m²

DOACs and Obesity

- The RE-LY trial noted a 20% ↓ in trough if wt >100 kg; however, dose adjustments have not been recommended
- Studies with rivaroxaban have a small #s with a BMI >28 kg/m² or wt> 100 kg; however, subgroup analyses have shown dose modifications are not needed
- One study found 10-mg dose of apixaban 20% ↓ in peak if weight >120 kg. authors concluded this was not clinically significant and no dose alteration is needed
- Decrease dose recommend for low weight-apixaban/Edoxaban

Buehler et al Formulary watch 2013
DOACs and Obesity

- Very little data for patients > 150 kg
- No reliable way to measure anticoagulant effect

Case 5

58 yo male presents to ED with chest pain and shortness of breath. CT reveals bilateral PE. Vitals signs are stable. Medical history unremarkable other than obesity (Ht=68”, wt=155kg). Which of the following do you recommend for initial PE treatment?

a. Enoxaparin 150mg twice daily + warfarin
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c. Rivaroxaban 15 mg BID x21 days then 20 mg daily
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WORKSHOP

- When to restart anticoagulation after ICH/retroperitoneal bleed
- IVC filters
- Thrombophilia work up
- Transitioning between anticoagulants and other pearls
- Management of patient with recurrent VTE despite therapeutic anticoagulation
- Calf vein thrombosis, superficial vein thrombosis, PICC line thrombosis and more
• QUESTIONS?