UPDATE ON DIRECT ORAL ANTICOAGULANTS: CHOOSING THERAPY, BLEED RISK, AND NEW REVERSAL OPTIONS
UPDATE ON MANAGEMENT OF UPPER GI BLEED

BRIANNA ALEXANDER, PHARMD, BCPS
SEP'T 27, 2016
DISCLOSURE

Neither I nor my spouse/partner have financial/professional relationships with the manufacturer(s) of commercial product(s) and/or the provider(s) of any commercial service(s) discussed in this CME activity.
OBJECTIVES

• Identify the new direct oral anticoagulants (DOACs) and the ideal patient for each of the DOACs based on drug and patient characteristics

• Evaluate data investigating bleeding risk with each of the DOACs compared to warfarin

• Discuss available and future reversal agents for DOACs
ANTICOAGULANTS

• Widely used class of medications for atrial fibrillation (afib) and venous thromboembolism (VTE)

• Afib is most common cardiac arrhythmia and the prevalence is about 1% worldwide
  • Anticoagulants critical for stroke prevention
  • Annual 3-6% risk of thromboembolic complications

• VTE incidence among people of European ancestry ranges from 104 to 183 per 100,000 person years
  • Foundation of therapy

Stroke 1990;21:4-13
TIMELINE OF ANTICOAGULANT APPROVAL

- Warfarin approved in 1954
ANTICOAGULANT MECHANISM

INDICATIONS

Non-valvular atrial fibrillation

Venous thromboembolism
  • Deep vein thrombosis
  • Pulmonary embolism

VTE prophylaxis post-operatively*
  • Hip replacement surgery
  • Knee replacement surgery

*not edoxaban
Anticoagulants recommended
- Non-valvular afib with prior stroke or TIA
- CHADS\(_2\) VASc score of 2 or greater
- Consider in CHADS\(_2\) VASc score of 1

Class I recommendation
- Warfarin (Level of evidence: A)
- Dabigatran (Level of evidence: B)
- Rivaroxaban (Level of evidence: B)
- Apixaban (Level of evidence: B)
2016 VTE CHEST GUIDELINES

For VTE and no cancer diagnosis

- Dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist therapy (Grade 2B recommendation)
- Vitamin K antagonist therapy over low molecular weight heparin therapy (Grade 2C recommendation)

For VTE in cancer patients

- Low molecular weight heparin therapy over vitamin K antagonist, dabigatran, rivaroxaban, apixaban, or edoxaban (Grade 2C recommendation)
DABIGATRAN (PRADAXA®)

- Pharmacokinetics
  - T ½: 12-17 hrs
  - Renal elimination (80% unchanged drug)
- Drug interactions: p-GP inhibitors/inducers
- Administration/storage
  - Do not crush or chew
  - Must be stored in original bottle

<table>
<thead>
<tr>
<th>CrCl</th>
<th>Afib Dose</th>
<th>VTE Treatment Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;30 ml/min</td>
<td>150 mg BID</td>
<td>LMWH/UFH x 5-10 days then 150 mg BID</td>
</tr>
<tr>
<td>15-30 ml/min</td>
<td>75 mg BID</td>
<td>No rec</td>
</tr>
<tr>
<td>&lt;15 or HD</td>
<td>No rec</td>
<td>No rec</td>
</tr>
</tbody>
</table>

UFH-unfractionated heparin
LMWH-low molecular weight heparin

RIVAROXABAN (XARELTO®)

- Pharmacokinetics
  - T ½: 5-9 hours
  - Metabolized by CYP3A4 and CYP2J2
  - Renal elimination (36% unchanged drug)

- Drug interactions: dual p-GP inducers/inhibitors and CYP3A4 inducers/inhibitors

- Administration
  - Take with evening meal
  - May crush and mix with water or applesauce
  - Do not give via feeding tubes placed distal to the stomach

### CrCl | Afib Dose
---|---
>50 ml/min | 20 mg daily
15-50 ml/min | 15 mg daily
<15 ml/min | Avoid

### CrCl | VTE Treatment Dosing
---|---
>30 ml/min | 15 mg BID x 21 days then 20 mg daily
<30 ml/min | Avoid

APIXABAN (ELIQUIS®)

- Pharmacokinetics
  - T ½: 8-15 hours
  - Metabolized via CYP3A4
  - Renal elimination (27% unchanged drug)
- Drug interactions: dual p-GP inducers/inhibitors and CYP3A4 inducers/inhibitors
- May crush and mix with 60 ml of D5W to be given via NG tube
- Dosing
  - Afib: 5 mg BID
    - 2.5 mg BID (if >2 of the following: SCr > 1.5 mg/dl, age > 80 years, or weight < 60 kg)
    - Not recommended CrCl < 15 ml/min
  - VTE: 10 mg BID x 7 days then 5 mg BID (Don’t use CrCl <25 ml/min)

**EDOXABAN (SAVAYSA®)**

- **Pharmacokinetics**
  - $T\frac{1}{2}$: 10-14 hours
  - Renal elimination (35% unchanged drug)
- **Drug interactions:** p-GP inhibitors/inducers
- **No recommendations for crushing**

<table>
<thead>
<tr>
<th>CrCl</th>
<th>Afib Dosing</th>
<th>VTE Treatment Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;95 ml/min</td>
<td><strong>Do not use</strong></td>
<td>LMWH/UFH x 5-10 days then 60 mg daily</td>
</tr>
<tr>
<td>51-95 ml/min</td>
<td>60 mg daily</td>
<td>60 mg daily</td>
</tr>
<tr>
<td>15-50 ml/min</td>
<td>30 mg daily</td>
<td>30 mg daily</td>
</tr>
<tr>
<td>&lt;15 ml/min</td>
<td>Not rec</td>
<td>Not rec</td>
</tr>
<tr>
<td></td>
<td>Weight $\leq$60 kg or P-gp inhibitor: 30 mg daily</td>
<td></td>
</tr>
</tbody>
</table>

## COST COMPARISON

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>75 mg &amp; 150 mg (60)</td>
<td>$419.89</td>
</tr>
<tr>
<td>Apixaban</td>
<td>2.5 mg &amp; 5 mg (60)</td>
<td>$431.90</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>VTE starter pack:</td>
<td>$733.61</td>
</tr>
<tr>
<td></td>
<td>15 mg &amp; 20 mg (30)</td>
<td>$431.53</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>30 mg &amp; 60 mg (50)</td>
<td>$582.60</td>
</tr>
</tbody>
</table>

Lexi Comp Online, Lexi-Drugs; Sept 2016
HOLDING FOR A PROCEDURE

• Dabigatran
  • Hold 24 to 48 hrs prior to major surgery or invasive procedure
    • Hold 3-5 days if CrCL <50 ml/min
  • Consider longer times for patients getting major surgery, spinal puncture or epidural placements

• Rivaroxaban
  • Hold at least 24 hrs prior to surgery
HOLDING FOR A PROCEDURE

• Apixaban
  • Hold at least 48 hrs prior to surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding
  • Hold at least 24 hrs prior to surgery or invasive procedures with low risk of bleeding or where the bleeding would be non-critical and easily controlled

• Edoxaban
  • Hold at least 24 hrs prior to surgery or invasive procedures
### DOAC vs WARFARIN IN AFIB

<table>
<thead>
<tr>
<th></th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
<th>ENGAGE-AF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DOAC</strong></td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
<td>Edoxaban</td>
</tr>
<tr>
<td><strong>Mean CHADS₂ score</strong></td>
<td>2.1</td>
<td>3.5</td>
<td>2.1</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>TTR of warfarin (%)</strong></td>
<td>64</td>
<td>55</td>
<td>62.2</td>
<td>68.4</td>
</tr>
<tr>
<td><strong>Stroke or systemic embolism, HR (CI)</strong></td>
<td>0.66 (0.53-0.82)</td>
<td>0.88 (0.75-1.03)</td>
<td>0.79 (0.66-0.95)</td>
<td>0.79 (0.63-0.99)</td>
</tr>
<tr>
<td><strong>Major bleeding, HR (CI)</strong></td>
<td>0.93 (0.81-1.07)</td>
<td>1.04 (0.9-1.2)</td>
<td>0.69 (0.6-0.8)</td>
<td>0.8 (0.71-0.91)</td>
</tr>
</tbody>
</table>

Granger CB., et al. NEJM 2011;365:981-92  
Giugliano RP., et al. NEJM 2011;369:2093-104  

TTR: time in therapeutic range
## DOAC vs WARFARIN IN VTE

<table>
<thead>
<tr>
<th></th>
<th>RECOVER 1 and 2 (n=5107)</th>
<th>EINSTEIN (n=8282)</th>
<th>AMPLIFY (n=5395)</th>
<th>HOKUSAI-VTE (n=8240)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DOAC</strong></td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
<td>Edoxaban</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>Parenteral anticoagulation (LMWH, UFH, fondaparinux) bridge to warfarin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Duration (months)</strong></td>
<td>6</td>
<td>3,6,or 12</td>
<td>6</td>
<td>3,6,or 12</td>
</tr>
<tr>
<td><strong>Recurrent VTE, HR (CI)</strong></td>
<td>1.09 (0.76-1.57)</td>
<td>0.89 (0.66-1.19)</td>
<td>0.84 (0.60-1.18)</td>
<td>0.89 (0.7-1.13)</td>
</tr>
<tr>
<td><strong>Major bleeding, % ICH,n</strong></td>
<td>1.4% (Dabi) vs 2 % ICH: n=2 (Dabi) vs 5</td>
<td>1.0% (Riva) vs 1.7% ICH: n=5 (Riva) vs 13</td>
<td>0.6% (Apix) vs 1.8% ICH: n=3 (Apix) vs 6</td>
<td>1.4% (Edox) vs 1.6% ICH: n=6 (Edox) vs 18</td>
</tr>
</tbody>
</table>

45 yo female is admitted to hospital with leg swelling and pain in her left leg. She has a CrCl of 100 ml/min and weighs 80 kg. An ultrasound confirmed a new DVT. When presented with treatment options she mentions she is afraid of shots and wants something once daily. What would be the best treatment for her?

A. Edoxaban  
B. Apixaban  
C. Dabigatran  
D. Rivaroxaban
Medical team calls you and requests help with dosing apixaban. The patient is a 90 yo female with new diagnosis of atrial fibrillation. She weighs 50 kg and all her labs on admission are normal. What dosing recommendation would you make?

A. 5 mg BID  
B. 10 mg BID for 7 days then 5 mg BID  
C. 2.5 mg BID  
D. 10 mg BID for 21 days then 5 mg BID
SELECTING THE BEST AGENT
RENAL IMPAIRMENT

• More dose adjustment recommendations in afib

• Severe renal impairment should avoid all DOAC
  • VTE trials excluded patients with CrCl <25-30 ml/min
    • Except edoxaban (excluded CrCl <15 ml/min)
    • Afib trials excluded patients with CrCl <15 ml/min

• Hemodialysis dosing data
  • Small (n=8) PK/PD study of apixaban single dose
  • 5 mg Q12h (listed in package insert)
  • No clinical data in this patient population yet

• Drug of choice: apixaban
  • Smallest percentage cleared renally
  • Better bleeding outcomes in patients with reduced clearance
  • Consider dose modifications for DVT patients (caution in PE)

LIVER IMPAIRMENT

- Apixaban not recommended in severe impairment
- Rivaroxaban and edoxaban not recommended in mod-severe impairment
- **Drug of choice**: dabigatran
EXTREMES OF WEIGHT

Obesity (>120 kg)
- Less apixaban exposure
- Rivaroxaban exposure not affected by weight
- Dabigatran trough concentrations lower

Underweight (<50 kg)
- More apixaban exposure
  - Adjustment with other risk factors (↑ Scr, ↑ age)
- Rivaroxaban exposure not affected by weight

- Meta-analysis showed no difference in clinical or safety outcomes with extremes of weight
- Few patients with body weight > 150 kg included

Drug of choice: consider rivaroxaban in obese and apixaban/edoxaban for underweight

DRUG INTERACTIONS

• Fewer in number as compared to warfarin however cannot monitor the effect

• All DOACs interact with Pgp transporter proteins

• Rivaroxaban and apixaban have cytochrome p450

• No drug of choice
  • Choose based on patient specific medication list
  • There are dosing recommendations for some drug interactions
NON-COMPLIANCE

• Increase rate of events seen in afib trials if abruptly stopped
• Missing a dose of any DOAC can pose short-term risk of VTE recurrence
  • Short half-lives
• Missing a dose of warfarin may not cause INR to fall subtherapeutic
• Rivaroxaban and edoxaban are once daily (after loading periods)

• Drugs of choice: rivaroxaban and edoxaban

AFFORDABILITY

- Cash price is cost prohibitive
- Co-pays with insurance can be unaffordable for some patients
  - Medicare patients are usually affected the most
- Co-pay cards with $0 co-pays or lower co-pays are available
  - Can’t be used with government insurance or cash payers
- Patient assistance programs available
  - Mainly for uninsured patients
  - Some Medicare patients are eligible
  - www.needymeds.org
ELDERLY PATIENTS

• Underuse of anticoagulants in elderly patients, specifically in afib population
  • Perceived increased bleeding risk, falls risk, and polypharmacy
• Patients > 75 yrs well represented in the afib trials
  • Although extensive exclusion criteria
• Dose adjustment for apixaban in afib patients
  • With additional risk factors (↑ Scr, ↓ weight)
• Lower rates of bleeding with apixaban and edoxaban

• **Drug of choice:** apixaban

DOAC IN ELDERLY PATIENTS

**Study Design**
- PubMed, Cochrane, EMBASE, Web of Science, CINAHL
- Through March 2013

**Patients**
- 10 randomized trials with 25,031 patients
- Rivaroxaban, dabigatran, apixaban compared to conventional therapy and reported data in elderly patients ≥ 75 years

**Endpoints**
- Safety outcome was major or clinically relevant bleeding
- Efficacy outcome was VTE or VTE-related death and stroke or systemic embolism

STUDIES INCLUDED

- Drugs evaluated
  - 5 evaluated rivaroxaban
  - 3 evaluated apixaban
  - 2 evaluated dabigatran
- Indications evaluated
  - 2 evaluated VTE or PE
  - 3 evaluated extended treatment of VTE
  - 4 evaluated afib
  - 1 evaluated thromboprophylaxis in medically ill patients
Patients aged more than 75 years: Major or clinically relevant bleeding

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NOAC Events</th>
<th>NOAC Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.1 Rivaroxaban</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EINSTEIN PE, 2012</td>
<td>58</td>
<td>440</td>
<td>67</td>
<td>401</td>
<td>13.9%</td>
<td>0.76 [0.52, 1.11]</td>
<td></td>
</tr>
<tr>
<td>EINSTEIN, 2010</td>
<td>19</td>
<td>215</td>
<td>20</td>
<td>223</td>
<td>10.2%</td>
<td>0.98 [0.51, 1.90]</td>
<td></td>
</tr>
<tr>
<td>EINSTEIN-Extension, 2010</td>
<td>7</td>
<td>88</td>
<td>3</td>
<td>98</td>
<td>4.4%</td>
<td>2.74 [0.69, 10.93]</td>
<td></td>
</tr>
<tr>
<td>MAGELLAN, 2013</td>
<td>75</td>
<td>1,530</td>
<td>29</td>
<td>1,548</td>
<td>13.1%</td>
<td>2.70 [1.75, 4.17]</td>
<td></td>
</tr>
<tr>
<td>ROCKET-AF, 2011</td>
<td>82</td>
<td>3,073</td>
<td>124</td>
<td>3,077</td>
<td>15.0%</td>
<td>0.65 [0.49, 0.87]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>5,346</td>
<td>5,347</td>
<td>5,67%</td>
<td></td>
<td></td>
<td>1.18 [0.64, 2.19]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>241</td>
<td>243</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.39; Chi² = 32.62, df = 4 (P &lt; 0.00001); I² = 88%</td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 0.52 (P = 0.60)</td>
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</tbody>
</table>

| **1.2 Apixaban**           |             |            |                |               |        |                                |                                |
| ARISTOTLE, 2011            | 151         | 2,542      | 224            | 2,393         | 15.8%  | 0.61 [0.49, 0.76]              |                                |
| AVERROES, 2011             | 26          | 909        | 24             | 983           | 11.5%  | 1.18 [0.67, 2.06]              |                                |
| **Subtotal (95% CI)**      | 3,451       | 3,376      | 27.2%          |                |        | 0.80 [0.43, 1.51]              |                                |
| **Total events**           | 177         | 248        |                |               |        |                                |                                |
| Heterogeneity: Tau² = 0.17; Chi² = 4.54, df = 1 (P = 0.03); I² = 78% |
| Test for overall effect: Z = 0.68 (P = 0.50) |

| **1.3 Dabigatran**         |             |            |                |               |        |                                |                                |
| RE-LY, 2009                | 450         | 4,828      | 206            | 2,360         | 16.1%  | 1.07 [0.90, 1.28]              |                                |
| **Subtotal (95% CI)**      | 4,828       | 2,360      | 16.1%          |                |        | 1.07 [0.90, 1.28]              |                                |
| **Total events**           | 450         | 206        |                |               |        |                                |                                |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 0.82 (P = 0.41) |

| **Total (95% CI)**         | 13,625      | 11,083     | 100.0%         |                |        | 1.02 [0.73, 1.43]              |                                |
| **Total events**           | 868         | 697        |                |               |        |                                |                                |
| Heterogeneity: Tau² = 0.17; Chi² = 50.25, df = 7 (P < 0.00001); I² = 86% |
| Test for overall effect: Z = 0.13 (P = 0.89) |
| Test for subgroup differences: Chi² = 0.87, df = 2 (P = 0.65), I² = 0% |

CONCLUSION

• DOACs did not lead to greater bleeding than conventional therapy in elderly population
• DOACs are significantly more effective than conventional therapy in elderly population
• Use caution in elderly patients with other comorbidities such as renal impairment and low body weight
• Individual case-by-case approach should be used rather than a generalization for all elderly patients

HIGH BLEED RISK

- Dabigatran and rivaroxaban had similar major bleed risk compared to warfarin while other agents showed less risk
- Each agent had less incidence of intracranial hemorrhage
- GI bleed risk increased with DOACs for afib (except apixaban) but decreased risk in VTE patients
- Reversal agent approved for dabigatran

**Drugs of choice:** apixaban and edoxaban
- Best safety profiles
- Warfarin if needing reversal agent available

META-ANALYSIS OF BLEEDING COMPLICATIONS

Design
- Electronic searches in MEDLINE, EMBASE, Cochrane
- Two reviewer study selection and extraction

Subjects
- 12 studies with 102,607 patients
- Rivaroxaban, apixaban, dabigatran, edoxaban
- VTE and Afib

Outcomes
- Primary outcome: major bleeding
- Secondary outcomes: GI bleeding, fatal bleeding, intracranial bleeding, and nonmajor bleeding

BASELINE PATIENT CHARACTERISTICS

• Indication
  • 5 Afib trials
  • 7 VTE trials

• Duration of treatment
  • Afib trials: 1.6-2 years
  • VTE: 3-12 months

• Mean/median age range
  • Afib trials: 70-73 years old
  • VTE trials: 54-57 years old

• Time in therapeutic range
  • 55-65%

MAJOR BLEEDING EVENTS

# MAJOR GI BLEEDING

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>TSOACs Events</th>
<th>TSOACs Total</th>
<th>VKAs Events</th>
<th>VKAs Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-MEDY, 2013</td>
<td>5</td>
<td>1430</td>
<td>8</td>
<td>1426</td>
<td>3.6%</td>
<td>0.62 [0.20, 1.90]</td>
</tr>
<tr>
<td>RE-COVER, 2009</td>
<td>9</td>
<td>1274</td>
<td>5</td>
<td>1265</td>
<td>3.7%</td>
<td>1.79 [0.60, 5.32]</td>
</tr>
<tr>
<td>RE-COVER II, 2014</td>
<td>6</td>
<td>1279</td>
<td>10</td>
<td>1289</td>
<td>4.2%</td>
<td>0.60 [0.22, 1.66]</td>
</tr>
<tr>
<td>J-ROCKET AF, 2012</td>
<td>6</td>
<td>639</td>
<td>12</td>
<td>639</td>
<td>4.5%</td>
<td>0.50 [0.19, 1.32]</td>
</tr>
<tr>
<td>AMPLIFY, 2013</td>
<td>7</td>
<td>2676</td>
<td>18</td>
<td>2689</td>
<td>5.3%</td>
<td>0.39 [0.16, 0.93]</td>
</tr>
<tr>
<td>EINSTEIN-DVT,PE 2010/2012</td>
<td>15</td>
<td>4151</td>
<td>26</td>
<td>4131</td>
<td>8.1%</td>
<td>0.57 [0.30, 1.08]</td>
</tr>
<tr>
<td>ARISTOTLE, 2011</td>
<td>105</td>
<td>9088</td>
<td>119</td>
<td>9052</td>
<td>16.3%</td>
<td>0.88 [0.68, 1.14]</td>
</tr>
<tr>
<td>ROCKET AF, 2011</td>
<td>224</td>
<td>7111</td>
<td>154</td>
<td>7125</td>
<td>17.7%</td>
<td>1.46 [1.19, 1.78]</td>
</tr>
<tr>
<td>RE-LY, 2009</td>
<td>385</td>
<td>12091</td>
<td>148</td>
<td>6022</td>
<td>18.1%</td>
<td>1.30 [1.07, 1.56]</td>
</tr>
<tr>
<td>ENGAGE-AF-TIMI-48, 2013</td>
<td>361</td>
<td>14014</td>
<td>190</td>
<td>7012</td>
<td>18.4%</td>
<td>0.95 [0.80, 1.13]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>53753</strong></td>
<td><strong>40650</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td><strong>0.94 [0.75, 1.19]</strong></td>
</tr>
</tbody>
</table>

Total events: 1123 for TSOACs, 690 for VKAs.

Heterogeneity: Tau² = 0.07; Chi² = 30.97, df = 9 (P = 0.0003); I² = 71%

Test for overall effect: Z = 0.50 (P = 0.62)

DISCUSSION

Strengths

• Large sample size allowed for detectable differences in uncommon outcomes
• Only warfarin as comparator
• Included both VTE and afib

Limitations

• Large heterogeneity due to different populations, drugs, and duration of therapy
• Couldn’t look at anti-platelet use, renal disease, or elderly as subgroups
• 3 studies not blinded

CONCLUSIONS

- Significant reductions in all bleeding outcomes
- No difference in overall GI bleeding
- Sub-group analysis
  - Rivaroxaban did not show significant reductions in major and nonmajor bleeding
    - Higher CHADS₂ scores and lower TTR in ROCKET-AF
  - GI bleeding was lower in VTE trials but no difference in afib trials

REVERSAL AGENTS
IDARUCIZUMAB

- Brand name: Praxbind®
- Monoclonal antibody for reversal of dabigatran
- Approved October 2015
- Price: $4200 for two 2.5 mg vials

IDARUCIZUMAB

- Dose: 5 grams delivered as two 2.5 g/50 ml vials given consecutively as boluses (no more than 15 min apart)
  - No renal or hepatic dose adjustments

- If removed from vial use within 1 hour

- Onset: Effects observed within minutes
- Duration: usually up to 24 hours
- Half-life: 47 minutes
## IDARUCIZUMAB FOR DABIGATRAN REVERSAL

| Design                                                                 | Group A: overt, uncontrollable or life-threatening bleeding
|                                                                      | Group B: reversal for surgery
| Primary: maximum percentage reversal of anticoagulant effect         |
| Secondary: normal clotting times and reduction in unbound dabigatran, extent of bleeding |

PATIENT CHARACTERISTICS

- More than 90% on dabigatran for afib
- Median age was 76.5 years
- Median CrCl was 58 ml/min
- Type of bleed in Group A
  - Intracranial bleeding: 18 patients
  - GI bleeding: 20 patients
  - Trauma: 9 patients
  - Other causes: 11 patients
- Median time since last dose was 15.4 hours

RESULTS

- Median maximum reversal was 100% in both groups.
- After one vial of drug the concentration of unbound dabigatran was < 20 ng/ml in all but one patient.
- Median time to cessation of bleeding was 11.4 hours in group A.
- All but 3 patients in group B underwent surgery with normal intraoperative hemostasis.
- 10 deaths due to vascular causes with 5 fatal bleeding events overall.
- 5 thrombotic events occurred.

CONCLUSIONS

• Anticoagulant effect rapidly and completely reversed in 88-98% of patients with elevated clotting times at baseline
• Only one patient had a thrombotic event within 72 hours after idarucizumab
• No dabigatran levels done before enrollment
  • Likely to mirror clinical practice where readily available levels are not accessible
• No control group

ANDEXANET ALFA

• Recombinant modified human factor Xa decoy protein
• Reverses anticoagulation activity for both direct and indirect Factor Xa inhibitors
• Currently being reviewed by FDA under an Accelerated Approval pathway
  - FDA requested more info in Aug 2016

ANDEXANET ALFA FOR REVERSAL OF FACTOR XA INHIBITOR ACTIVITY

Design

- Two parallel, randomized, double-blind, placebo-controlled trials
- Two clinical sites in the US

Outcomes

- Primary: % change in anti-factor Xa activity after administration
- Secondary: proportion with 80% or greater reduction, change in unbound inhibitor concentration, change in thrombin generation

PATIENT SELECTION

145 healthy volunteers
50-75 yo

ANNEXA-A
(Apixaban)

Placebo
Andexanet
Part 1: Bolus
Part 2: Bolus + Infusion

ANNEXA-R
(Rivaroxaban)

Placebo
Andexanet
Part 1: Bolus
Part 2: Bolus + Infusion

DOSING INFORMATION

ANNEXA-A

• Apixaban 5 mg PO Q12h for 3.5 days
• Bolus given 3 hrs after last dose on day 4
• Part 1: **400** mg IV bolus (30 mg/min)
• Part 2: **400** mg IV bolus + IV CI of **4** mg/min for 120 minutes

ANNEXA-R

• Rivaroxaban 20 mg PO daily for 4 days
• Bolus given 4 hrs after last dose on day 4
• Part 1: **800** mg IV bolus (30 mg/min)
• Part 2: **800** mg IV bolus + IV CI **8** mg/min for 120 minutes

ANTI-FACTOR XA ACTIVITY
APIXABAN

A Apixaban Study, Andexanet Bolus

C Apixaban Study, Andexanet Bolus plus Infusion

ANTI-FACTOR XA ACTIVITY
RIVAROXABAN

B Rivaroxaban Study, Andexanet Bolus

D Rivaroxaban Study, Andexanet Bolus plus Infusion

RESULTS

• Thrombin generation was rapidly restored within 2 to 5 minutes and to a greater extent than placebo.

• Mean concentration of unbound apixaban and rivaroxaban was reduced more than placebo within 2 to 5 minutes.

• No thrombotic events.

• One patient had allergic reaction with hives that resolved after diphenhydramine.

CONCLUSION

• Andexanet rapidly reversed apixaban and rivaroxaban-induced changes in anti-factor Xa activity and thrombin generation
• The effect was quick and sustained with continuous infusion followed by quick offset of action
  • Provides flexibility when urgent reversal is needed

• Limitations: healthy volunteers, no clinical efficacy outcomes (ie cessation of bleeding)
• More studies needed in patients with clinical bleeding and during procedures

WHO SHOULD SWITCH TO DOAC?

- Variable diet/poor nutrition
- Alcohol abuse
- Trouble with constantly changing warfarin regimens
  - Dementia
- Difficult to manage drug interactions
- Monitoring issues
  - Labile INR
  - Noncompliant with INR visits
  - Trouble scheduling INR visits (frequent traveler)

TRANSITIONING TO DOAC

• Dabigatran
  • Stop warfarin and start dabigatran when INR < 2
  • Stop LMWH and start dabigatran 0-2 hours before next scheduled dose
  • Stop heparin and start dabigatran simultaneously

• Rivaroxaban
  • Stop warfarin and start rivaroxaban when INR < 3
  • Stop LMWH and start rivaroxaban 0-2 hours before next scheduled dose
  • Stop heparin and start rivaroxaban simultaneously

Pradaxa®[package insert]. 2010
Xarelto®[package insert]. 2011
TRANSITIONING TO DOAC

- **Apixaban**
  - Stop warfarin and start apixaban when INR <2
  - Stop LMWH and start apixaban at next scheduled dose

- **Edoxaban**
  - Stop warfarin and start edoxaban when INR ≤2.5
  - Stop LMWH and start edoxaban at next scheduled dose
  - Stop heparin drip and start edoxaban in 4 hours
WHO SHOULD STAY ON WARFARIN?

- Cant afford DOAC
- Patients with valvular afib
  - Mechanical valves
  - Moderate to severe mitral stenosis
- Patients needing dual antiplatelet therapy
- Stabile on warfarin for years
- Poor renal function
- History of GI bleed

SAMeTT\textsubscript{2}R\textsubscript{2} SCORE

- Assist clinicians in deciding which patients are likely to achieve high-quality anticoagulation if treated with warfarin
- Factors include: sex, age, medical history, interacting drugs, tobacco use, race
- Scores >2 are associated with an increased risk of bleeding, mortality and adverse cardiovascular events while on warfarin and correlates with more labile INRs
- Scores ≤2 likely to benefit from warfarin
- Scores >2 likely to benefit from DOAC

TRANSITIONING OFF DOAC

- **Dabigatran**
  - CrCl ≥50 ml/min, start warfarin 3 days before stopping
  - CrCl 30-50 ml/min, start warfarin 2 days before stopping
  - CrCl 15-30 ml/min, start warfarin 1 day before stopping
  - CrCl ≥ 30 ml/min start LMWH 12 hrs after last dose and start 24 hrs after last dose if CrCl <30 ml/min

- **Rivaroxaban**
  - Since rivaroxaban can affect INR stop rivaroxaban and start LMWH and warfarin at next scheduled dose
    - Stop LMWH when INR >2
TRANSITIONING OFF DOAC

- **Apixaban**
  - Since apixaban can affect INR stop apixaban and start LMWH and warfarin at next scheduled dose
    - Stop LMWH when INR >2

- **Edoxaban**
  - If taking 60 mg reduce to 30 mg and if taking 30 mg reduce to 15 mg → begin warfarin concomitantly → stop edoxaban when INR >2 (measure weekly just prior to edoxaban dose)
  - Stop edoxaban and start LMWH at next scheduled dose
    - If bridging start warfarin and stop LMWH when INR >2
35 yo male is admitted to the hospital with AKI and SOB. CT scan shows a new PE. Her SCr rises to 6 mg/dl, K 6.0 mg/dl, and is altered. Nephrology recommends starting dialysis and states they need to treat her PE. They are concerned she won't be compliant with her INR checks. What regimen would you recommend for her given this information?

A. Rivaroxaban 15 mg BID then 20 mg daily
B. Heparin drip bridge to warfarin
C. Apixaban 5 mg BID
D. Edoxaban 30 mg daily
65 yo female is admitted to hospital with atrial fibrillation. She has a history of HTN, COPD, and GI bleed. She has heard bad things about warfarin and wants to try a new agent. Which agent would be the best given her history and data available?

A. Apixaban
B. Dabigatran
C. Talk her into warfarin
D. Rivaroxaban
75 yo male admitted to ED for intracranial hemorrhage. You are reviewing his medication list and see a prescription for dabigatran 150 mg BID for afib. What would you suggest to reverse the anticoagulation effect of dabigatran?

A. Vitamin K  
B. Andexanet alfa  
C. Idarucizumab  
D. Nothing is approved to reverse dabigatran
SUMMARY

- DOACs provides a great alternative to warfarin with better safety profiles and similar efficacy

- Selection of agent should be patient-specific based on their characteristics, comorbidities, and personal preferences

- Approval of new reversal agents will allow for better reassurance to use these new agents
OBJECTIVES

• Describe current guideline recommendations for the treatment of upper GI bleed

• Evaluate new data comparing different dosing regimens of proton pump inhibitors in upper GI bleed
UPPER GI BLEED

- Defined as bleeding from a source proximal to the ligament of Treitz
  - Variceal and non-variceal
- Incidence ranges from 48 to 160 cases per 100,000 adult years
  - Twice as common in men than women
  - Increases with age
- Results in 400,000 hospital admissions per year
- In-hospital mortality is 13% and rebleeding occurs in 15% of cases

PATHOPHYSIOLOGY

- Peptic ulcer disease
  - Accounts for more than 60% of all bleeding episodes
  - *H. pylori* and NSAIDs are leading causes

- Stress-related mucosal damage
  - Most common cause of bleeding in critically ill
  - Mechanical ventilation and coagulopathy are major risk factors

- Mallory-Weiss tear
MEDICATION INDUCED ULCERS

• NSAIDs
  • Mostly asymptomatic and do not lead to bleeding
  • Elderly patients with continued use are at highest risk
  • Long-term use (>1 week), prior bleed history, history of H. pylori are additional risk factors

• Aspirin
  • Doses of 75-300 mg have been shown to have 2- to 3-fold increased risk of bleeding

• Anticoagulants
• High-dose corticosteroids
• Serotonin reuptake inhibitors
  • In combination with NSAIDs

PRESENTATION

- Abdominal pain

- Hematemesis
  - Coffee ground emesis

- Melena
  - Black tarry stools

- Hematochezia
  - Suggests rapid and significant blood loss

TREATMENT

Blood products
• Target Hgb >7 g/dL and correct INR

Fluid resuscitation

Endoscopic management

Acid suppression therapy

H. pylori treatment

Laine L et al., Am J Gastroenterol 2012;107:345-60
ENDOSCOPIC THERAPY

• Method of choice to control active bleeding
• Early intervention within 24 hrs can reduce rate of rebleeding, mortality, and surgery

• Types of interventions
  • Clips
  • Plasma coagulation
  • Epinephrine or sclerosants
  • Band ligation
  • Laser therapy

Laine L et al., Am J Gastroenterol 2012;107:345-60
H. PYLORI TREATMENT

- Amoxicillin 1000 mg BID + Clarithromycin 500 mg BID + PPI BID

- Metronidazole 500 mg BID + Clarithromycin 500 mg BID + PPI BID (PCN allergic patients)

- Bismuth subsalicylate 525 mg QID + Metronidazole 250 mg QID + Tetracycline 500 mg QID + PPI BID

- Duration: 10-14 days

GASTRIC ACID SUPPRESSION

- Intragastric pH of 6 or higher:
  - Promotes platelet aggregation
  - Promotes clot formation
  - Inhibits fibrinolysis

- Proton pump inhibitors (PPIs) have extensive literature showing a significant reduction in risk of bleeding
  - Traditional studies used continuous infusion (CI) as it was thought this was the best way to obtain goal pH

PROTON PUMP INHIBITORS
AVAILABLE IV PPIS

- Pantoprazole (Protonix)*
  - 80 mg bolus followed by 8 mg/hr infusion
- Omeprazole (Prilosec)*
  - 80 mg bolus followed by 8 mg/hr infusion
- Lansoprazole (Prevacid)
  - 60 mg bolus followed by 6 mg/hr infusion
- Esomeprazole (Nexium)
  - 80 mg bolus followed by 8 mg/hr infusion

- Used interchangeably; usually one on hospital formulary

*most commonly studied
IV PPI VS PLACEBO OR H2 BLOCKER

**Study Design**
- MEDLINE and Cochrane Center
- Through 2008
- 12 trials included

**Patients**
- Randomized controlled trials of endoscopically treated high risk ulcers
- PPI therapy vs control (placebo or H2 blocker)

**Endpoints**
- Primary-persistent and recurrent clinical manifestations of bleeding
- Secondary-surgery, urgent intervention, mortality

# RESULTS

<table>
<thead>
<tr>
<th>Comparison</th>
<th>End point</th>
<th>Number of comparisons</th>
<th>RR (95% CI)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous PPI: bolus plus continuous infusion v placebo</td>
<td>Further bleeding</td>
<td>4⁶⁸,74,81,118,119</td>
<td>0.40 (0.28–0.59)</td>
<td>12 (10–18)</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
<td>3⁷⁴,81,118,119</td>
<td>0.43 (0.24–0.76)</td>
<td>28 (21–67)</td>
</tr>
<tr>
<td></td>
<td>Urgent intervention</td>
<td>3⁶⁸,74,81</td>
<td>0.31 (0.18–0.53)</td>
<td>8 (7–12)</td>
</tr>
<tr>
<td></td>
<td>Mortality</td>
<td>4⁶⁸,74,81,118,119</td>
<td>0.41 (0.20–0.84)</td>
<td>45 (33–167)</td>
</tr>
<tr>
<td>Intravenous PPI: bolus plus continuous infusion v H2RA</td>
<td>Further bleeding</td>
<td>3⁷⁰,75,117</td>
<td>0.63 (0.37–1.08)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
<td>2⁷⁵,117</td>
<td>1.11 (0.49–2.49)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Urgent intervention</td>
<td>2⁷⁵,117</td>
<td>0.37 (0.04–3.36)²</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Mortality</td>
<td>3⁷⁰,75,117</td>
<td>0.62 (0.20–1.96)</td>
<td>—</td>
</tr>
<tr>
<td>PPI: oral or intermittent intravenous bolus v placebo</td>
<td>Further bleeding</td>
<td>5⁴⁹,68,69,73,80</td>
<td>0.53 (0.35–0.78)</td>
<td>10 (7–21)</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
<td>4⁴⁹,69,73,80</td>
<td>0.62 (0.25–1.53)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Urgent intervention</td>
<td>2⁶⁸,80</td>
<td>0.43 (0.12–1.62)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Mortality</td>
<td>5⁴⁹,68,69,73,80</td>
<td>0.61 (0.18–2.04)</td>
<td>—</td>
</tr>
</tbody>
</table>

CONCLUSIONS

- Even after successful endoscopic therapy, PPI therapy does seem beneficial.

- Data appears strongest for infusion therapy.

- Few trials comparing intermittent vs infusion showed no suggestion of a difference but stronger data warranted before intermittent therapy recommended as first line therapy.

INTERMITTENT VS CI

Study Design
- BioMedCentral, MEDLINE, EMBASE, COCHRANE, and CINHAHL
- 7 studies included

Patients
- Randomized trials of endoscopically treated ulcers
- Received intermittent or CI PPI

Endpoints
- Primary-recurrent ulcer bleeding within 30 days
- Secondary-surgery, mortality

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Analysis</th>
<th>High-Dose PPI</th>
<th>Non-High-Dose PPI</th>
<th>Rebleeding, No. (%)</th>
<th>Surgical Intervention, No. (%)</th>
<th>Mortality, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td>High-Dose PPI</td>
<td>Non-High-Dose PPI</td>
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<tr>
<td>Udd et al,27</td>
<td>142</td>
<td>PP</td>
<td>Omeprazole (IV 80-mg bolus and IF 8 mg/h for 3 d)</td>
<td>Omeprazole (IV 20 mg/d for 3 d)</td>
<td>8/69 (11.6)</td>
<td>6/73 (8.2)</td>
<td>5/69 (7.2)</td>
</tr>
<tr>
<td>2001</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Cheng et al,22</td>
<td>105</td>
<td>ITT</td>
<td>Omeprazole (IV 80-mg bolus and IF 200 mg/d for 3 d)</td>
<td>Omeprazole (IV 80-mg bolus and IF 80 mg/d for 3 d)</td>
<td>21/52 (40.4)</td>
<td>23/53 (43.4)</td>
<td>Unavailable</td>
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<td>2005</td>
<td></td>
<td></td>
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<tr>
<td>Yilmaz et al,26</td>
<td>211</td>
<td>ITT</td>
<td>Omeprazole (IV 80-mg bolus and IF 8 mg/h for 3 d)</td>
<td>Omeprazole (oral 40 mg every 12 h for 3 d)</td>
<td>7/112 (6.2)</td>
<td>5/99 (5.1)</td>
<td>3/112 (2.7)</td>
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<td>2006</td>
<td></td>
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<tr>
<td>Bajaj et al,28</td>
<td>25</td>
<td>ITT</td>
<td>Pantoprazole (IV 80-mg bolus and IF 8 mg/h for 3 d)</td>
<td>Pantoprazole (oral 80 mg every 12 h for 3 d)</td>
<td>2/13 (15.4)</td>
<td>0/12</td>
<td>1/13 (7.7)</td>
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<td>2007</td>
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<tr>
<td>Hung et al,23</td>
<td>103</td>
<td>PP</td>
<td>Pantoprazole (IV 80-mg bolus and IF 8 mg/h for 3 d)</td>
<td>Pantoprazole (IV 80-mg bolus and IF 40 mg every 12 h for 3 d)</td>
<td>2/54 (3.7)</td>
<td>2/49 (4.1)</td>
<td>0/54</td>
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<tr>
<td>2007</td>
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<td></td>
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<tr>
<td>Andriulli et al,24</td>
<td>474</td>
<td>PP</td>
<td>Omeprazole or pantoprazole (IV 80-mg bolus and IF 8 mg/h for 3 d)</td>
<td>Omeprazole or pantoprazole (IV 80-mg bolus and IF 40 mg/d for 3 d)</td>
<td>28/238 (11.8)</td>
<td>19/236 (8.1)</td>
<td>3/238 (1.3)</td>
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<td>2008</td>
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<td></td>
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<tr>
<td>Yüksel et al,25</td>
<td>97</td>
<td>PP</td>
<td>Pantoprazole (IV 80-mg bolus and IF 8 mg/h for 3 d)</td>
<td>Pantoprazole (IV 40 mg/d for 3 d)</td>
<td>4/48 (8.3)</td>
<td>3/49 (6.1)</td>
<td>2/48 (4.2)</td>
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<tr>
<td>2008</td>
<td></td>
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</tr>
</tbody>
</table>
**REBLEEDING**

<table>
<thead>
<tr>
<th>Source</th>
<th>High-Dose PPI</th>
<th>Non-High-Dose PPI</th>
<th>Weight, %</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Udd et al, 2001</td>
<td>8</td>
<td>69</td>
<td>11.3</td>
<td>1.46 (0.48-4.46)</td>
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<tr>
<td>Cheng et al, 2005</td>
<td>21</td>
<td>52</td>
<td>29.7</td>
<td>0.88 (0.41-1.92)</td>
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<tr>
<td>Yilmaz et al, 2006</td>
<td>7</td>
<td>112</td>
<td>10.9</td>
<td>1.25 (0.38-4.08)</td>
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<tr>
<td>Bajaj et al, 2007</td>
<td>2</td>
<td>13</td>
<td>0.9</td>
<td>5.43 (0.24-125.59)</td>
</tr>
<tr>
<td>Hung et al, 2007</td>
<td>2</td>
<td>54</td>
<td>4.4</td>
<td>0.90 (0.12-6.67)</td>
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<tr>
<td>Andriulli et al, 2008</td>
<td>28</td>
<td>238</td>
<td>36.8</td>
<td>1.52 (0.83-2.81)</td>
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<tr>
<td>Yüksel et al, 2008</td>
<td>4</td>
<td>48</td>
<td>6.0</td>
<td>1.39 (0.29-6.59)</td>
</tr>
</tbody>
</table>

**Total**

<table>
<thead>
<tr>
<th>High-Dose PPI</th>
<th>Non-High-Dose PPI</th>
<th>Weight, %</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>72</td>
<td>58</td>
<td>100.0</td>
<td>1.30 (0.88-1.91)</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 2.19, P = .90, I^2 = 0\%.$
Test for overall effect: $z = 1.33, P = .18$
MORTALITY

CONCLUSION

- Continuous infusion PPIs are not superior to intermittent dosing in reducing rates of rebleeding, surgical intervention, or mortality
  - Two studies had Asian populations which are thought to be more sensitive to the effects of PPIs
  - Some of the studies enrolled patients with lesser severity of bleeding peptic ulcers
  - Small populations that were underpowered

- This analysis provides insufficient evidence to recommend one dosing regimen over the other

H2 blocker antagonist not recommended

Post-endoscopy therapy

- IV bolus followed by continuous infusion PPI should be used in patients with high risk stigmata

Oral daily dose PPI on discharge

Pre-endoscopic IV PPI (80 mg/hr followed by 8 mg/hr)
- To decrease higher risk stigmata of hemorrhage
- To decrease those who receive endoscopic therapy
- For those who can’t get endoscopy or will be delayed

Post-endoscopic IV PPI bolus and continuous infusion
- Ulcer with active bleeding
- Non-bleeding visible vessel
- Adherent clot
- Continue for 72 hours

Post-endoscopic oral PPI (once daily)
- Ulcers with flat pigmented spots or clean bases

INTERMITTENT VS CI

Study Design
- MEDLINE, EMBASE, Cochrane Center, Abstracts
- Through December 2013
- Non-inferiority study

Patients
- Randomized trials of endoscopically treated high-risk bleeding ulcers
- Received IV/oral intermittent or IV CI PPI

Endpoints
- Primary-rebleeding within 7 days
- Secondary- urgent intervention, mortality, blood transfusion, length of stay

HYPOTHESIS

Intermittent use of PPIs is noninferior to bolus plus continuous infusion of PPIs

- Non-inferiority margin was predefined as an absolute risk difference of 3%

Table 1. Characteristics of Studies Included in the Meta-analysis

<table>
<thead>
<tr>
<th>Source</th>
<th>PPI</th>
<th>Dose, Route, and Frequency of Intermittent PPI</th>
<th>Cumulative Dose of Intermittent PPI, mg</th>
<th>Type of Study</th>
<th>Stigmata of Recent Hemorrhage</th>
<th>Endoscopic Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andriulli et al, 16</td>
<td>Omeprazole(n = 330); pantoprazole (n = 144)</td>
<td>40 mg/d IV</td>
<td>120</td>
<td>Superiority</td>
<td>Spurting, 50; oozing, 155; NBVV, 166; clot, 103</td>
<td>Epinephrine; epinephrine with bipolar/argon plasma coagulation; epinephrine with clips</td>
</tr>
<tr>
<td>Chan et al, 15</td>
<td>Omeprazole</td>
<td>40 mg/d IV</td>
<td>120</td>
<td>Equivalence</td>
<td>Spurting, 8; oozing, 46; NBVV, 39; clot, 29</td>
<td>Epinephrine with heater probe; epinephrine with clips</td>
</tr>
<tr>
<td>Chen et al, 16</td>
<td>Omeprazole</td>
<td>40 mg/d IV</td>
<td>120</td>
<td>Superiority</td>
<td>Spurting, 12; oozing, 71; NBVV, 117; clot, 0</td>
<td>Epinephrine with heater probe</td>
</tr>
<tr>
<td>Choi et al, 17</td>
<td>Pantoprazole</td>
<td>40 mg/d IV</td>
<td>120</td>
<td>Superiority for pH difference</td>
<td>Spurting, 5; oozing, N5; NBVV, N5; clot, N5</td>
<td>Epinephrine with argon plasma coagulation with or without clips</td>
</tr>
<tr>
<td>Hsu et al, 18</td>
<td>Pantoprazole</td>
<td>Bolus: 80 mg IV once, then 40 mg IV every 6 h</td>
<td>560</td>
<td>Superiority</td>
<td>Spurting, 12; oozing, 40; NBVV, 52; clot, 16</td>
<td>Epinephrine with bipolar; bipolar</td>
</tr>
<tr>
<td>Hung et al, 19</td>
<td>Pantoprazole</td>
<td>Bolus: 80 mg IV once, then 40 mg IV every 12 h</td>
<td>320</td>
<td>Superiority of PPI Infusion to no treatment</td>
<td>Spurting, 12; oozing, 52; NBVV, 26; clot, 13</td>
<td>Epinephrine with heater probe</td>
</tr>
<tr>
<td>Jang et al, 24</td>
<td>Pantoprazole</td>
<td>40 mg PO every 12 h</td>
<td>400</td>
<td>Uncertain</td>
<td>Spurting, 7; oozing, 4; NBVV, 13; clot, 0</td>
<td>Epinephrine with argon plasma coagulation; clips</td>
</tr>
<tr>
<td>Javid et al, 20</td>
<td>Omeprazole (n = 36); pantoprazole (n = 35); rabeprazole (n = 35)</td>
<td>Bolus: 80 mg PO once, then 40 mg PO every 12 h; bolus: 80 mg PO once, then 80 mg PO every 12 h; bolus: 80 mg PO once, then 40 mg PO every 12 h</td>
<td>320, 520, 320</td>
<td>Noninferiority for pH difference</td>
<td>Spurting, 17; oozing, 20; NBVV, 53; clot, 0</td>
<td>Epinephrine with heater probe</td>
</tr>
<tr>
<td>Kim et al, 21</td>
<td>Rabeprazole</td>
<td>20 mg PO every 12 h</td>
<td>120</td>
<td>Noninferiority</td>
<td>Spurting, 10; oozing, 29; NBVV, 44; clot, 23</td>
<td>Epinephrine; epinephrine with monopolar; epinephrine with clips; epinephrine with monopolar and clips</td>
</tr>
<tr>
<td>Sung et al, 25</td>
<td>Esomeprazole</td>
<td>40 mg PO every 12 h</td>
<td>240</td>
<td>Superiority</td>
<td>Spurting, 5; oozing, N5; NBVV, N5; clot, N5</td>
<td>N5</td>
</tr>
<tr>
<td>Ucbilak et al, 26</td>
<td>Pantoprazole</td>
<td>Bolus: 80 mg IV once, then 40 mg IV every 12 h</td>
<td>320</td>
<td>Uncertain</td>
<td>Spurting, 5; oozing, N5; NBVV, N5; clot, N5</td>
<td>Epinephrine with sclerotherapy</td>
</tr>
<tr>
<td>Yamada et al, 22</td>
<td>Pantoprazole</td>
<td>Bolus: 80 mg IV once, then 40 mg IV every 12 h</td>
<td>240</td>
<td>Superiority</td>
<td>Spurting, 13; oozing, 3; NBVV, 6; clot, 5</td>
<td>Epinephrine with bipolar; epinephrine with clips</td>
</tr>
<tr>
<td>Yüksel et al, 23</td>
<td>Pantoprazole</td>
<td>40 mg IV every 12 h</td>
<td>240</td>
<td>Uncertain</td>
<td>Spurting, 7; oozing, 60; NBVV, 30; clot, 0</td>
<td>Epinephrine with heater probe</td>
</tr>
</tbody>
</table>

Abbreviations: IV, Intravenous; NBVV, nonbleeding visible vessel; N5, not stated; PO, orally; PPI, proton pump inhibitor.
## RESULTS

### Table 2. Meta-analysis of Intermittent PPI vs Bolus With Continuous-Infusion PPI<sup>a</sup>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Studies</th>
<th>No. of Patients</th>
<th>Risk Ratio</th>
<th>Absolute Risk Difference, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 7 d</td>
<td>10&lt;sup&gt;14,16,17,20-26&lt;/sup&gt;</td>
<td>1346</td>
<td>0.72 (0.97)</td>
<td>-2.64 (-0.28)</td>
</tr>
<tr>
<td>Within 30 d</td>
<td>13&lt;sup&gt;14-26&lt;/sup&gt;</td>
<td>1691</td>
<td>0.89 (1.17)</td>
<td>-0.97 (1.49)</td>
</tr>
<tr>
<td>Within 3 d</td>
<td>9&lt;sup&gt;14,16,17,20-24,26&lt;/sup&gt;</td>
<td>1146</td>
<td>0.73 (1.02)</td>
<td>-2.36 (0.17)</td>
</tr>
<tr>
<td>Mortality</td>
<td>11&lt;sup&gt;14-16,18-24,26&lt;/sup&gt;</td>
<td>1453</td>
<td>0.64 (1.21)</td>
<td>-0.74 (0.43)</td>
</tr>
<tr>
<td>Surgery/RI</td>
<td>12&lt;sup&gt;14-24,26&lt;/sup&gt;</td>
<td>1491</td>
<td>0.87 (1.49)</td>
<td>-0.30 (1.12)</td>
</tr>
<tr>
<td>Urgent interventions</td>
<td>9&lt;sup&gt;14-20,22,23&lt;/sup&gt;</td>
<td>1283</td>
<td>0.95 (1.27)</td>
<td>-0.45 (2.43)</td>
</tr>
<tr>
<td>Length of hospital stay, d</td>
<td>8&lt;sup&gt;14-16,18,21-23,26&lt;/sup&gt;</td>
<td>1204</td>
<td>-0.26 (0.09)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Blood transfusion, U</td>
<td>9&lt;sup&gt;14-16,18,21-24,26&lt;/sup&gt;</td>
<td>1242</td>
<td>-0.22 (-0.02)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> For each outcome, more than one study was included. Risk ratios were calculated as the ratio of the number of events in the intermittent PPI group to the number of events in the bolus PPI group. Significance levels for the absolute risk differences are based on the 95% confidence interval (CI). Significant differences are indicated by <sup>b</sup>.
STUDY CONCLUSIONS

• Intermittent PPI is noninferior to currently recommended continuous infusion
• An appropriate intermittent regimen can not be determined due to various regimens used in the studies
• Given ease of use and lower cost and resource utilization, intermittent therapy should be regimen of choice post endoscopy
• Recommend guidelines incorporate this new information

2015 EUROPEAN SOCIETY GUIDELINES

- Post-endoscopy (IV bolus + continuous infusion)
  - Receive endoscopic hemostasis
  - Adherent clot
  - Give for 72 hours
  - Strong recommendation

- Post-endoscopy (IV intermittent twice daily)
  - Receive endoscopic hemostasis
  - Adherent clot
  - Consider for 72 hours
  - Weak recommendation

RESTARTING NSAIDS

• If NSAID induced ulcer, the need for NSAID should be carefully assessed

• NSAIDs should not be resumed if possible

• If NSAID must be resumed a Cox-2 selective NSAID at lowest effective dose with a daily PPI is suggested (strong recommendation)
RESTARTING ANTIPLATELETS

• If low dose aspirin-associated bleeding ulcer, the need for aspirin should be assessed
• Primary prevention (conditional recommendation)
  • Not recommended to resume
• Secondary prevention (conditional recommendation)
  • Restart as soon as possible once bleeding ceases, ideally within 1-3 days but at least by 7 days
  • Give daily PPI
• Dual antiplatelet therapy (strong recommendation)
  • Restart aspirin and assess need for clopidogrel
  • Give daily PPI

Laine L et al., Am J Gastroenterol 2012;107:345-60
RESTARTING ANTICOAGULANTS

- No recommendations in the 2012 American College of Gastroenterology guidelines or 2010 International Consensus guidelines
- 2016 European Society Guidelines
  - Restart warfarin in patients with indication for long-term anticoagulation
  - Restarting warfarin between 7-15 days after bleed appears safe and effective in preventing clots
  - Restarting warfarin prior to 7 days may be considered for patients at high thrombotic risk
  - No recommendation for DOAC (use caution)
## Study Design
- Retrospective cohort study
- Henry Ford Medical Center 2005-2010

## Patients
- 1329 patients included
- Nonvalvular afib with GIB and stopped warfarin > 2 days

## Endpoints
- Recurrent major GIB within 90 days
- Thromboembolism within 1 year
- Mortality

*GIB-gastrointestinal bleed

PATIENT CHARACTERISTICS

- Mean age: 75 years
- Men: 55.7%
- Median CHADS$_2$ score: 3
- Median HAS-BLED score: 3
- Less likely to be started on warfarin ($p < 0.05$)
  - Upper and lower GIB
  - Diabetics
  - Renal disease
  - Coronary artery disease
  - History of falls

RESULTS

• Restarting warfarin associated with decreased mortality (HR 0.67, p<0.0001)
  • Restarting > 30 days had increasing mortality

• Restarting warfarin not associated with statistically significant increase in recurrent GI bleed (HR 1.18, p- 0.47)

• Restarting warfarin associated with decreased thromboembolism (HR 0.71, p-0.01)

### TIMING OF WARFARIN REINITIATION

<table>
<thead>
<tr>
<th></th>
<th>&lt; 7 days (n=62)</th>
<th>7-15 days (n=51)</th>
<th>15-21 days (n=58)</th>
<th>21-30 days (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE HR (p value)</td>
<td>0.76 (0.47)</td>
<td>0.48 (0.09)</td>
<td>0.60 (0.14)</td>
<td>1.00 (&gt;0.99)</td>
</tr>
<tr>
<td>GI bleed HR (p value)</td>
<td>3.27 (0.002)</td>
<td>1.03 (0.93)</td>
<td>1.42 (0.37)</td>
<td>1.5 (0.42)</td>
</tr>
</tbody>
</table>

CONCLUSION

- Resuming anticoagulation demonstrated lower risk of VTE and mortality
- No differences in GI bleed when restarting warfarin >1 week versus > 30 days
- Some bias present in that those at highest risk for GI bleed were likely not restarted on warfarin
- Restarting warfarin between 7-15 days is reasonable

You are rounding on medical team who has just admitted a patient with a GI bleed overnight. The patient was started on PPI drip and is coming back from endoscopy where the bleeding was stopped. The team asks if it's ok to switch to IV BID dosing of the PPI. Which statement below is accurate?

A. Don’t switch; the data for PPI drip demonstrated superiority in comparison to intermittent dosing
B. Stay on the drip to save money and resources
C. Switch to BID dosing since it demonstrated noninferiority compared to drip
D. None of the above
True or False. All current guidelines on upper GI non-variceal bleeding have recommended continuous infusion over intermittent dosing.

A. True
B. False
SUMMARY

• Proton pump inhibitors are mainstay of therapy for GI bleed
  • Consider using IV intermittent dosing in lieu of continuous infusion as it has shown to be non-inferior
• Evaluate drug therapy post GI bleed and eliminate unnecessary or inappropriate high-risk drugs
• Assess individual patient for optimal timing of restarting antiplatelets or anticoagulants
  • Aspirin: 1-7 days
  • Warfarin: 7-15 days
UPDATE ON DIRECT ORAL ANTICOAGULANTS: CHOOSING THERAPY, BLEED RISK, AND NEW REVERSAL OPTIONS

UPDATE ON MANAGEMENT OF UPPER GI BLEED

BRIANNA ALEXANDER, PHARMD, BCPS
SEPT 27, 2016