Reversing novel anticoagulants to divert catastrophe

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Novel anticoagulants?

- **Dabigatran (Pradaxa)**
  - Stroke and systemic embolism prevention in non-valvular atrial fibrillation
  - Acute treatment and reduction in risk of recurrence of DVT and PE

- **Rivaroxaban (Xarelto)**
  - Stroke and systemic embolism prevention in non-valvular atrial fibrillation
  - Prophylaxis of DVT and PE in patients undergoing: hip replacement surgery or knee replacement surgery
  - Acute treatment and reduction in risk of recurrence of DVT and PE

- **Apixaban (Eliquis)**
  - Stroke and systemic embolism prevention in non-valvular atrial fibrillation
  - Acute treatment and reduction in risk of recurrence of DVT and PE
A-fib? Not warfarin?

  - Randomized, non-inferiority trial; 18,113 pts; 2 year follow-up
  - Dabigatran vs. Warfarin
    - Stroke or systemic embolism: 1.11% vs. 1.69% per year (p<0.001)
    - Major bleeding: 3.11% vs. 3.36% per year (p=0.31)
    - Hemorrhagic stroke: 0.10% vs. 0.38% per year (p<0.001)
    - All cause mortality: 3.64% vs. 4.13% per year (p=0.051)
Bad press...was RE-LY study flawed?

- NEJM 04/2013: Dabigatran and postmarket reports of bleeding
  - Review of insurance-claim and administrative data from the FDA Mini-Sentinal database from Oct 2010 through Dec 2011
  - Have a-fib? Dabigatran vs. Warfarin
    - GI Hemorrhage 16 (n=10,599) vs. 160 (n=43,541)
    - Intracranial Hemorrhage 8 (n=10,578) vs. 109 (n=43,594)
  - Significantly limited, but supports RE-LY findings...

- NEJM 09/2014: Data internally reviewed by Boehringer Ingelheim and correspondence published with minimal change
DVT: hold the warfarin too?

- **NEJM 10/2009: Dabigatran in acute DVT (RE-COVER)**
  - Double-blinded, randomized non-inferiority trial; 2564 patients, 6 month follow-up
  - Dabigatran vs. Warfarin
    - Recurrent DVT or death due to DVT: 2.4% vs. 2.1%
    - Major bleeding: 1.6% vs. 1.9%
    - **Non-major bleeding: 5.6% vs. 8.8% (p=0.002)**

- **NEJM 02/2013: Dabigatran in recurrent DVT (RE-MEDY)**
  - Double-blinded, randomized non-inferiority trial; 2866 patients, 3-36 month follow-up
  - Prior >3 month treatment w/ any warfarin or study anticoagulant
  - Dabigatran vs. Warfarin
    - Recurrent DVT or death due to DVT: 1.8% vs. 1.3% (p=0.01)
    - Major bleeding: 0.09% vs. 1.8% (p=0.06)
    - **Any bleeding event 19.4% vs. 26.2% (p<0.001)**
What about Rivaroxaban?

- NEJM 09/2011: Rivaroxaban in non-valvular a-fib (ROCKET)
  - Double-blinded, randomized non-inferiority trial; 14,264 patients; variable follow-up
  - Rivaroxaban vs. Warfarin
    - Stroke or systemic embolism: 1.7% vs. 2.2% per year (p<0.001)
    - Major bleeding: 3.6% vs. 3.4% per year (p=0.58)
    - Hemorrhagic stroke 0.5% vs. 0.7% per year (p=0.02)
- NEJM 12/2010: Rivaroxaban for acute DVT (EINSTEIN)
  - Double-blinded, randomized non-inferiority trial; 3449 patients; 3,6,12 month follow-up
  - Rivaroxaban vs. Warfarin
    - Recurrent VTE or death due to VTE: 2.1% vs. 3.0% (p<0.001)
    - Major bleeding: 0.8% vs. 1.2% (p=0.21)
- NEJM 04/2012: Rivaroxaban for acute PE (EINSTEIN-PE)
  - Double-blinded, randomized non-inferiority trial; 4832 patients; 3,6,12 month follow-up
  - Rivaroxaban vs. Warfarin
    - Recurrent VTE or death due to PE: 2.1% vs. 1.8% (p=0.003)
    - Major bleeding: 1.1% vs. 2.2% (p=0.003)
What about Apixaban?

- **NEJM 09/2011: Apixaban in non-valvular a-fib (ARISTOTLE)**
  - Double-blinded, randomized non-inferiority trial; 18,201 patients; 1.8 year follow-up
  - Apixaban vs. Wafarin
    - Stroke or systemic embolism: 1.27% vs. 1.60% per year (p<0.001)
    - **Major bleeding: 2.13% vs. 3.09% per year (p<0.001)**
    - Hemorrhagic stroke 0.24% vs. 0.47% per year (p<0.001)
    - Mortality from any cause: 3.52% vs. 3.94% (p=0.047)

- **NEJM 08/2013: Apixiban for acute DVT (AMPLIFY)**
  - Double-blinded, randomized non-inferiority trial; 5395 patients, 6 month follow-up
  - Apixiban vs. Warfarin
    - Recurrent VTE or death due to VTE: 2.3% vs. 2.7% (p<0.001)
    - **Major bleeding: 0.6% vs. 1.8% (p<0.001)**
More safety information

- JAMA 09/2014: Clinical and safety outcomes with treatment of VTE
  - Meta-analysis of 45 trials, 14,989 patients
  - Adverse bleeding compared with Warfarin
    - Rivaroxaban HR 0.55; 95% CI, 0.35-0.89
    - Apixaban HR 0.31; 95% CI, 0.15-0.62
  - Major bleeding compared with Warfarin over 3 months
    - Rivaroxaban 0.49% (95% CI, 0.29%-0.85%)
    - Apixaban 0.28% (95% CI, 0.14%-0.50%)
    - Warfarin 0.89% (95% CI, 0.66-1.16%)
More bad press?

- Boehringer Ingelheim settled $650 million in May 2014 for cases associated with adverse bleeding...
## Pharmacokinetics

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Mechanism of Action</th>
<th>Time to peak concentration (h)</th>
<th>Half-life (h)</th>
<th>Renal excretion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Direct inhibition of thrombin</td>
<td>1-3</td>
<td>Adults, single dose 7-9&lt;br&gt;Adults, multiple doses 7-17</td>
<td>80-85%</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Direct inhibition of factor Xa</td>
<td>2-4</td>
<td>Adults, single dose 7-17&lt;br&gt;Elderly, single dose 12-13&lt;br&gt;Adults, multiple doses 12-13</td>
<td>66%</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Direct inhibition of factor Xa</td>
<td>1-3</td>
<td>Adults, single dose 8-14</td>
<td>25%</td>
</tr>
</tbody>
</table>
Obligatory coagulation cascade
## Monitoring

<table>
<thead>
<tr>
<th>Novel Anticoagulant</th>
<th>Prothrombin time (PT)</th>
<th>International normalized ratio (INR)</th>
<th>Activated partial thromboplastin time (aPTT)</th>
<th>Thrombin time (TT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Increased or normal</td>
<td>No change</td>
<td>Increased or normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Increased or normal</td>
<td>No change</td>
<td>Increased or normal</td>
<td>No change</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Increased or normal</td>
<td>No change</td>
<td>Increased or normal</td>
<td>No change</td>
</tr>
</tbody>
</table>
# Procoagulant Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Coagulation Factors</th>
<th>Misc. Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh Frozen Plasma (FFP)</td>
<td>II, V, VII, IX, X, XI</td>
<td>Frozen, requiring thaw ABO Crossmatch Larger volume, 1U = 200-250ml</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>Fibrinogen, VIII, XIII and von Willebrand factor</td>
<td>Frozen, requiring thaw</td>
</tr>
<tr>
<td>Prothrombin Complex Concentrate (PCC)</td>
<td>PCC-3: II, IX, X PCC-4: II, VII, IX, X (Kcentra)</td>
<td>Can produce thrombotic complications (DVT, PE, MI, DIC)</td>
</tr>
<tr>
<td></td>
<td>aPCC, II, aVII, IX, X (FIEBA)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>US Versions of PCC-4 include some protein C &amp; S</td>
<td></td>
</tr>
<tr>
<td>Recombinant activated factor VII (rFVIIa)</td>
<td>VII</td>
<td></td>
</tr>
</tbody>
</table>
Evidence to support PCC

- Circulation 09/2011: Reversal of Rivaroxaban and Dabigatran by 4-PCC
  - Randomized, placebo-controlled, crossover study in 12 healthy subjects
  - Rivaroxaban
    - PT after Rivaroxaban, 12.3 vs. 15.8 seconds (p<0.001)
    - PT after 4-PCC, 15.8 vs. 12.8 seconds (p<0.001)
    - PT after normal saline, 15.8 vs. 16.2 seconds (p=.4)
    - Also reversal of ETP
  - Dabigatran
    - aPTT after Dabigatran, 33.6 vs. 59.4 (p<0.001)
    - aPTT after 4-PCC, 59.4 vs. 70.3 (p=0.21)
    - aPTT after saline, 59.4 vs. 57.9 (p=0.64)
    - Also no reversal of ETP lag time, TT, ECT
Evidence to support PCC

- Thrombosis and Haemostasis 01/2012: Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban
- Randomized, ex vivo, crossover study in 10 healthy subjects
- Evaluated, in vitro, use of 4-PCC, a-4PCC and rVIIa on ETP, LT, TTP
  - Dabigatran
    - aPTT prolonged by 1.47x (p<0.001)
    - 4-PCC and a-4PCC had a dose-dependent reversal, while rVIIa was inert
  - Rivaroxaban
    - PT prolonged by 1.37x (p<0.001)
    - 4-PCC and a-4PCC had a dose-dependent reversal, while rVIIa was inert
Coagulation cascade again...
Cost of aPCC

- FIEBA (and Kcentra) have average wholesale price of $2.17/U
- FIEBA dosing is recommended at 25 U/kg
  - 70 kg person requires 1,750 U @ $3,797
  - 100 kg person requires 2,500 U @ $5,425
Thrombotic complications

- DVT
- PE
- DIC
- MI

- All have been reported at different rates
- Range between 1/20,000 to 1/400,000.
Case Reports...

- 69 y/o male on dabigatran w/ non-traumatic subdural and elevated PTT, reversed with FIEBA and discharged in good condition.
- 86 y/o male on rivaroxaban w/ iliac artery aneurysm and extensive retroperitoneal hemorrhage and elevated PT, reversed with FIEBA and discharged in good condition (on rivaroxaban).
- 85 y/o female on dabigatran w/ GCS 9 and extensive hemorrhagic stroke, had mental status improvement after FIEBA. Ultimately suffered a ischemic stroke 6 days after discharge, transitioned to hospice and died on day 16.
- 80 y/o male on dabigatran in septic shock & renal failure 2/2 to cholecystitis w/ uncomplicated biliary drain placement after FIEBA.
- 67 y/o male on dabigatran w/ myocardial perforation 2/2 to invasive cardiac procedure 3L tamponade, only stopped after FIEBA administered.
## Reversal Options

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Charcoal (2h)</th>
<th>Hemodialysis</th>
<th>FFP</th>
<th>Activated factor VIIa</th>
<th>PCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Unlikely</td>
<td>Unclear, Possibly?</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Unlikely</td>
<td>Maybe, Possibly?</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Unlikely</td>
<td>Maybe, Possibly?</td>
</tr>
</tbody>
</table>
Future studies...

- Humanized monoclonal antibody against dabigatran
  - Currently Phase III trial, May 2014 – July 2017, goal 250 patients
- Recombinant, plasma-derived factor Xa antidotes
  - Currently multiple phase II and III trials in process and development
Questions?
References

References Continued


