Rapid Reversal of Anticoagulation for Intracerebral Hemorrhage

Fred V. Plapp & Sharon Rice
Saint Luke’s Regional Laboratories
Kansas City, MO
Two Types of Stroke

Ischemic stroke: A clot blocks blood flow to an area of the brain.

Hemorrhagic stroke: Bleeding occurs inside or around brain tissue.
Intracranial Hemorrhage Facts

• 15% of all strokes
• 3 major types
  – SDH, SAH & ICH
• 15-30 cases per 100,000
  – African American & Asian
  – Risk doubles every 10 years after age 35
• 20,000 deaths per year
• 30 day mortality is 44%
Spontaneous ICH Etiology

- Hypertension
- Cerebral amyloid angiopathy
- Arteriovenous malformation
- Aneurysmal rupture
- Hemorrhagic transformation ischemic infarct
- Cerebral venous thrombosis
- Intracranial neoplasm
- Vasculitis & Moyamoya
- Sympathomimetic drug abuse
- Bleeding disorders
  - Liver, thrombolytics, anticoagulants
Warfarin

- 3 million patients prescribed warfarin
  - Atrial fibrillation, hypercoagulable states, stroke
- Narrow therapeutic window
  - INR 2.0-3.0 or 2.5-3.5
  - Patients outside window 30% of time
- Major side effect is bleeding
  - Black Box warning regarding bleeding risk
  - 15-20% of patients per year
  - 1-3% life-threatening and fatal
  - 2% suffer ICH with 44-68% mortality at 30 days
    - Warfarin accounts for 20% of all ICH
Warfarin ICH

• Associated with
  – Increased initial hematoma volume
  – Increased risk of hematoma expansion
  – Increased likelihood of IVH
  – Worse outcomes
    • Permanent disability
    • Death
Warfarin Mechanism

Warfarin decreases Factor II, VII, IX & X activity
Warfarin Effect on Coagulation Pathway

Warfarin prolongs PT first & then PTT
Peak effect occurs 36–72 hours after initiation

FII = 2-5 d

FVII = 4-7 h

FX = 32-48 h

FIX = 20-24 h

Tested by PT
Extrinsic pathway
Factor VIIa, tissue factor

Intrinsic pathway
Factors VIIIa, IXa, XIa
calcium, phospholipid

Tested by PT and aPTT

Prothrombinase complex
Factors Va, X, calcium, phospholipid

Tested by thrombin time

Prothrombin
Thrombin

Factor XIII
Factor XIIIa
Soluble fibrin
Fibrinogen

Insoluble fibrin
### INR & Coagulation Factor Levels

<table>
<thead>
<tr>
<th>INR</th>
<th>FII</th>
<th>FVII</th>
<th>FIX</th>
<th>FX</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>60</td>
<td>100</td>
<td>120</td>
<td>90</td>
</tr>
<tr>
<td>2.0</td>
<td>40</td>
<td>40</td>
<td>60</td>
<td>20</td>
</tr>
<tr>
<td>2.5</td>
<td>25</td>
<td>35</td>
<td>40</td>
<td>15</td>
</tr>
<tr>
<td>2.8</td>
<td>20</td>
<td>25</td>
<td>35</td>
<td>15</td>
</tr>
<tr>
<td>Normal</td>
<td>50-150</td>
<td>50-150</td>
<td>50-150</td>
<td>50-150</td>
</tr>
<tr>
<td>MHC</td>
<td>20-40</td>
<td>10-20</td>
<td>25-50</td>
<td>10-25</td>
</tr>
</tbody>
</table>

Equilibrium levels of II, IX & X are 15-40% of normal at one week when INR is between 2.0 and 3.0.
Oral Direct Factor Xa Inhibitors

- **Rivaroxaban** (Xarelto®)
  - Peak effect at 2-4 hours after dosing
  - Circulating half life is 11-13 hours
  - PT, INR, aPTT increased, but not reliable to assess degree of AC

- **Apixiban** (Eliquis®)
  - Peak effect at 1-2 hours after dosing
  - Circulating half life is 8-15 hours
  - PT, INR, aPTT not significantly increased

- **Indications**
  - Reduce risk stroke and thromboembolism in NV-AF
  - Treat DVT and PE
  - DVT prophylaxis
# Direct Fxa Inhibitor Bleeding Risk

<table>
<thead>
<tr>
<th>Event</th>
<th>Rivaroxaban</th>
<th>Apixiban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>3.6% per year</td>
<td>3.6% per year</td>
<td>3.4% per year</td>
</tr>
<tr>
<td>ICH</td>
<td>0.5% per year</td>
<td>0.3% per year</td>
<td>0.7% per year</td>
</tr>
<tr>
<td>GI bleed</td>
<td>3.2% per year</td>
<td>0.8% per year</td>
<td>0.9-2.2% per year</td>
</tr>
</tbody>
</table>

ROCKET study, NEJM 2009;361:1139
ARISTOTLE study, NEJM 2011;365:981
Direct Fxa Inhibitor Mechanism
Emergent Reversal of Fxa Inhibitors

• Challenges
  – Difficult to assess level of anticoagulation
  – No specific antidote
  – No standard procedure to reverse effect

• Recommendations
  – Discontinue the drug
  – Supportive care
  – Nonactivated 3 or 4 factor PCC
    • Excess Fxa neutralizes drug effect
Warfarin Reversal Strategies

• Vitamin K replacement
• Plasma infusion
• 3-Factor Prothrombin Complex Concentrate
  – Alone or with rFVIIa (NovoSeven)
• 4-Factor Prothrombin Complex Concentrate
Vitamin K

- Vitamin K is only specific antidote to warfarin
- Sustained reversal of warfarin effect
- IV administration begins correct INR within 4h
  - Too slow to prevent hematoma expansion
  - Cannot be used alone
- Vitamin K should be given with PCC or plasma
  - Factor VII has short half life of 7 hours
  - Factor IX has a large volume of distribution
Plasma Products

- 175 – 250 mL per bag
- Thaw time
- ABO compatible
- Each bag ↑ level of any coagulation factor by 2-3%
- 15 mL/Kg → 10% increase
- Usual adult dose is 2-4 bags per transfusion
- Long infusion time
- Short term effect
- Risk of TACO
## INR Correction w/ Plasma

<table>
<thead>
<tr>
<th>Pre-transfusion INR</th>
<th>INR correction per Unit of Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 – 1.5</td>
<td>0 – 0.1</td>
</tr>
<tr>
<td>1.6 – 1.8</td>
<td>0 – 0.3</td>
</tr>
<tr>
<td>1.9 – 2.6</td>
<td>0.1 – 0.5</td>
</tr>
<tr>
<td>2.7 – 4.9</td>
<td>0.3 – 1.1</td>
</tr>
<tr>
<td>5.0 – 9.9</td>
<td>0.8 – 2.5</td>
</tr>
<tr>
<td>10.0 – 14.0</td>
<td>4.0 – 6.0</td>
</tr>
<tr>
<td>14.1 – 20.0</td>
<td>5.8 – 8.4</td>
</tr>
</tbody>
</table>

INR of plasma is 1.2 – 1.3
3 Factor Prothrombin Complex Concentrate

• Profilnine SD Factor IX Complex (Grifols)
• FDA licensed for Rx of hemophilia B
• Contains Factors II, IX & X
  – Trace amount of Factor VII
• Labeled with FIX potency in IU
  – SLHS stocks vials with ~1000 IU of FIX
• Can supplement 1 mg NovoSeven (rFVIIa)
  – FDA licensed for Rx of Hemophilia A/B inhibitors
4-Factor Prothrombin Complex Concentrate

• Kcentra in U.S. & Beriplex in Europe & Canada
  – CLS Behring
• 4 factor complex concentrate
  – Factors II, VII, IX, X, Protein C & S
    • Lower risk of thrombosis?
• Dosing based on Factor IX
• FDA approval on April 29, 2013
  – urgent reversal of warfarin in adults
  – Acute major bleeding or urgent invasive procedure
Plasma vs PCC

Plasma
- ABO compatibility
- Thaw time
- Large volume (500-1000)
- Low specific activity
- IV drip – 30 to 60 minutes
- Less expensive
  - ~$60/bag

PCC
- Blood type not necessary
- Reconstitution time
- Small volume (80-120 mL)
- High specific activity
- IV push – 3 minutes
- More expensive
  - $1.27 to $1.39 per U
ICH Treatment Recommendations
2012 ACCP & 2010 AHA/ASA

• Stop all anticoagulant & antiplatelet Rx
• Confirm Dx with noncontrast head CT
• 10 mg Vitamin K by slow IV infusion
• Infuse rapid reversal reagent
  – 4-factor PCC or
  – 3-factor PCC supplemented with plasma or
  – Plasma
3F-PCC ICH order set
April 1, 2013

Discontinue antithrombotic & antiplatelet medications
If warfarin, give 10 mg Vitamin K IV in 50 mL D5W over 1h
Give PCC per orders below:

<table>
<thead>
<tr>
<th>INR</th>
<th>&lt;70 kg</th>
<th>70-100 kg</th>
<th>&gt;100 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 – 3.0</td>
<td>2000 U PCC</td>
<td>3000 U PCC</td>
<td>4000 U PCC</td>
</tr>
<tr>
<td>&gt;3.0</td>
<td>3000 U PCC</td>
<td>4000 U PCC</td>
<td>5000 U PCC</td>
</tr>
</tbody>
</table>

1 mg vial of rFVIIa if on warfarin & INR>1.4
Check PT/INR at 30 minutes post-infusion
Consider repeat dose if INR remains >1.4
If patient taking apixaban or rivaroxaban use INR>3.0 dose
3F-PCC + rFVIIa Experience

• 33 patients treated from Apr 1 – Oct 31, 2013
• 32 taking warfarin & 1 rivaroxaban
• Very effective correction of INR
  – Average post-INR was 0.8
  – Post-INR often ≤0.7
• 2 patients had thrombosis
  – 1 had history of APLA syndrome
  – 1 with history of severe CAD & PAD
• Inpatient mortality was 21% (7/34)
INR Correction with PCC + rFVIIa
Combination Protocol Concerns

- Off label use of both products
- Confusion in ordering, issuing & reconstituting 2 different products
- Over-correction of INR
- Expense
- Reimbursement
Kcentra

- 4 factor Prothrombin Complex Concentrate
- FDA approved Apr 2013 for urgent reversal of acquired coagulation deficiency in adults with major bleeding or needing invasive procedure
Kcentra Reconstitution & Infusion

- Stock 500 & 1000 U vials
- Reconstitute with 20 or 40 mL sterile water
- Administer each vial over 3 minutes IV push
- Use separate infusion line
- Check INR/Protime within 30 minutes
4F-PCC ICH Order Set
Nov 6, 2013

Discontinue antithrombotic & antiplatelet medications
If warfarin, give 10 mg Vitamin K IV in 50 mL D5W over 1h
Give PCC per orders below:

<table>
<thead>
<tr>
<th>INR</th>
<th>&lt;79 Kg</th>
<th>≥80 Kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤3.9</td>
<td>2000 IU</td>
<td>2500 IU</td>
</tr>
<tr>
<td>≥4.0</td>
<td>3000 IU</td>
<td>3500 IU</td>
</tr>
</tbody>
</table>

Check PT/INR at 30 minutes post-infusion
Consider repeat dose if INR remains >1.4
If patient on rivaroxaban or apixiban use INR ≥4.0 dose
Kcentra Contraindications

• Known anaphylactic or severe systemic reactions to albumin, factors or heparin
• Disseminated intravascular coagulation
• Heparin induced thrombocytopenia
• Thromboembolic event in past 3 months
Pretreatment INR Values

Apixiban INR 1.1-1.4 & Rivaroxaban INR 1.1 – 1.9
INR Correction with 4F-PCC
4F-PCC Protocol Experience

• 69 cases Nov 6, 2013 through Mar 24, 2015
  – 57 warfarin, 7 rivaroxaban, 5 apixiban
• All warfarin patients corrected to INR <1.5
  – Average post-INR was 1.2
• 3 patients developed DVT (2) or PE (1) during stay
  – >24 hours after 4F-PCC
  – 1 had APLA syndrome
• 15 patients had neurosurgery (14 survived)
• Inpatient mortality was 14% (10/69)
  – 9 on warfarin (9/57 = 16%)
  – 1 on rivaroxaban (1/7 = 14%)
## Outcomes Comparison

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Plasma</th>
<th>3F-PCC + rFVIIa</th>
<th>4F-PCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>%Pt w/ INR &lt;1.5*</td>
<td>24%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Average Post-INR*</td>
<td>1.9</td>
<td>0.8</td>
<td>1.2</td>
</tr>
<tr>
<td>%Pt w/ INR &lt;1.0*</td>
<td>0%</td>
<td>92%</td>
<td>0%</td>
</tr>
<tr>
<td>Ave time to INR &lt;1.5</td>
<td>1229 min</td>
<td>148 min</td>
<td>98 min</td>
</tr>
<tr>
<td>In hospital mortality</td>
<td>32%</td>
<td>19%</td>
<td>14%</td>
</tr>
<tr>
<td>Acquisition cost</td>
<td>$134</td>
<td>$4171</td>
<td>$3600</td>
</tr>
</tbody>
</table>

*Post-INR statistics measured on warfarin patients
Need to measure modified Rankin scale at 90 days and 1 year
Summary

- 4F-PCC rapidly reversed OAC
  - 12x faster than plasma
- Simplified dosing schedule corrected INR to 1.5 or lower regardless of initial value
- Inpatient mortality reduced from 32% to 14%
  - Mortality same for warfarin & rivaroxaban
- Acquisition cost increased 26 fold compared to plasma
- Reimbursement has been adequate
- To do
  - Determine 90d and 1y outcomes (modified Rankin Scale)
  - Determine impact on hematoma expansion
Anticoagulant Reversal, Blood Pressure Levels, and Anticoagulant Resumption in Patients With Anticoagulation-Related Intracerebral Hemorrhage

CONCLUSIONS AND RELEVANCE
Among patients with OAC-associated ICH, reversal of INR <1.3 within 4 hours and systolic BP <160mmHg at 4 hours were associated with lower rates of hematoma enlargement