Emergency Warfarin Associated Life Threatening Bleeds

Goals.

1) Discuss indications for treatment with Vitamin warfarin
2) Review Coagulation cascade and warfarin mechanism of action
3) Review warfarin reversal options.
4) Analyze efficacy for various warfarin reversal options.

Outline.

1) Warfarin: Indications & Epidemiology
   a. Thromboembolic prevention in:
      i. Atrial Fibrillation / Flutter
      ii. Mechanical / prosthetic heart valves
      iii. Deep Venous Thromosis / Pulmonary Embolism
   b. Warfarin is the most common anticoagulant used world wide.
   c. 2-3 million pts w/ chronic anticoagulation
   d. Use is increasing in many countries.

2) Complications
   a. Life Threatening Complications - 1 to 3% per year
   b. 26,000 to 210,000 episodes of major bleeding per year
   c. Intracranial Bleeding (greatest M&M), GI bleeding with Hemodynamic Instability, or Bleeding requiring over 2 units PRBC transfusion.
   d. Mortality is highest with intracranial Bleeding

3) Risk Factors for Bleeding on Warfarin.
   a. Various Scoring Systems (see attached)
      i. HAS-BLED
      ii. HEMORR(2)HAGES
      iii. Outpatient Bleeding Risk Index

4) Mechanism of Action
   a. Warfarin limits hepatic production of active Vitamin K dependent clotting factors
   b. Activation of clotting factors (II, VII, IX, & X) occurs via Carboxylation, which is inhibited by warfarin.
   c. Coagulation Cascade Attached

5) Causes Supratherapeutic INR
   a. Drug Interactions
   b. Dietary Alterations
   c. Inappropriate Dosing
   d. Systemic Diseases
      i. ex – liver disease, heart failure, hyperthyroidism

6) Vitamin K
   a. Leads to prolonged normalization of INR.
   b. Prevents rebound coagulopathy.
   c. Oral vitamin K can be used to treat non-life threatening bleeding or elevated INR.
   d. IV vitamin K replaces clotting factors faster than Oral Vitamin K
   e. In life threatening bleeding a dose of Vitamin K 10mg should be given IV
f. Anaphylaxis associated with diluents of older preparations, but recommendations remain to give as a slow push

7) Options for Rapid Reversal of INR in Warfarin Related Bleeding
a. FFP
   i. Advantages
      1. Prepared from Whole Blood
      2. Contain all Coagulation Factors and Plasma Proteins
      3. Concentration Diluted by Citrate
      4. Thawed Plasma (TP) stored at 1-6C for 5 days
   ii. Disadvantages
      1. Requires Blood Typing & Cross Matching
      2. Delivery Delayed by Thawing
      3. Risk of Transfusion Related Lung Injury
      4. Risk of Heart Failure
      5. Risks of Viral Infection & Anaphylaxis
b. Recombinant Activated Factor VII
   i. Advantages
      1. Transfected of Human Gene to Cultured Hamster Cells
      2. FDA Approved For
      3. Promoting Hemostasis in Hemophiliacs
      4. Several Off-Label in Non-Hemophilia Bleeding
   ii. Disadvantages
      1. Short Half-Life (2hrs)
      2. Increased Risk of Thromboembolism
      3. Cost
      4. Few Studies
      5. No Outcome Benefit (Morbidity, Mortality) in Warfarin Associated Hemorrhage
c. Prothrombin Complex Concentrate
   i. 3 Factor (II, IX, X) vs 4 Factor (II, VII, IX, X) Forms
   ii. More Rapid Reversal Than FFP
   iii. Produced by Ion-exchange chromatography from large plasma pools
   iv. Clotting factor concentration 25 x FFP
   v. Undergo viral inactivation (solvent detergent treatment or nanofiltration
   vi. Evidence for benefits over FFP
      1. Faster INR Reversal
      2. Lower volumes Required with less Heart Failure
      3. Decreased Bleed Expansion in ICH
      4. Less PRBC Transfusion Requirements
   vii. Until Recently, 4 Factor PCC’s not available in the United States.
   viii. 4 Factor PCC’s may be superior to 3 Factor PCC’s
      1. Likely because of low Factor VII levels in 3 Factor PCC’s.
      2. For many years, a combination of 3 Factor PCC and recombinant Factor VIIa were used to mimic a 4 factor PCC
ix. 4 Factor PCC’s recently shown to be non-inferior to plasma in controlling bleeding in warfarin associated hemorrhage & superior in reversing INR by randomized controlled trial.

x. 4 Factor PCC (KCentra) now available in the United States

xi. American College of Chest Physician Guidelines now recommend the use of 4 factor PCC’s for warfarin associated life threatening bleeding.

xii. Henry Ford Anticoagulation Reversal Guidelines are currently under review.

xiii. Dosing of 4-Factor PCC & FFP

<table>
<thead>
<tr>
<th>Baseline INR</th>
<th>4F-PCC dose (IU of factor IX per kg body weight)*</th>
<th>Plasma dose (mL per kg body weight)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-&lt;4</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>4-6</td>
<td>35</td>
<td>12</td>
</tr>
<tr>
<td>&gt;6</td>
<td>50</td>
<td>15</td>
</tr>
</tbody>
</table>

*Dose calculation based on 100 kg body weight for patients weighing >100 kg. Maximum dose ≤5000 IU of factor IX (4F-PCC) or ≤1500 mL (plasma)

4F-PCC, four-factor prothrombin complex concentrate; INR, International Normalized Ratio
The HAS-BLED Score


<table>
<thead>
<tr>
<th>Letter</th>
<th>Clinical Characteristic</th>
<th>Definition</th>
<th>Points Awarded</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension</td>
<td>Uncontrolled; &gt;160mmHg systolic</td>
<td>1</td>
</tr>
</tbody>
</table>
| A      | Abnormal renal and/or liver function (1 point each) | Renal: chronic dialysis, renal transplant, or Scr> 2  
Liver: chronic hepatic disease or laboratory evidence | 1 or 2          |
| S      | Stroke                  | Prior history of stroke | 1              |
| B      | Bleeding                | Bleeding history, anemia, or predisposition to bleeding | 1              |
| L      | Labile INRs             | Therapeutic time-in-range < 60% | 1              |
| E      | Elderly                 | Age > 65 | 1              |
| D      | Drugs and/or alcohol    | Drugs: concurrent antiplatelet agents or NSAIDS  
Alcohol: 8 or more drinks per week | 1 or 2          |

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>Incidence of Major Bleeding in Euro Heart Survey Patients (%/pt-yr)</th>
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<tbody>
<tr>
<td>0</td>
<td>1.13</td>
</tr>
<tr>
<td>1</td>
<td>1.02</td>
</tr>
<tr>
<td>2</td>
<td>1.88</td>
</tr>
<tr>
<td>3</td>
<td>3.74</td>
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<tr>
<td>4</td>
<td>8.7</td>
</tr>
<tr>
<td>5</td>
<td>12.5</td>
</tr>
<tr>
<td>6</td>
<td>0 bleeds/2 patients</td>
</tr>
<tr>
<td>7</td>
<td>0 patients</td>
</tr>
<tr>
<td>8</td>
<td>0 patients</td>
</tr>
<tr>
<td>9</td>
<td>0 patients</td>
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</table>

Other risk scores:


Current Henry Ford Hospital Reversal Guidelines for Warfarin Associated Life Threatening Bleeding.


Key Pharmacologic Points
- Reversal of warfarin with more than just vitamin K should only be initiated in the setting of serious or life-threatening bleeding or if an urgent procedure is necessary.
- INR target of reversal depends on the clinical situation.
- INR can correct without intervention in approximately 2 - 5 days for MOST patients.
- Vitamin K (both intravenous and oral) will decrease INR within 24 - 36 hours.
  - Vitamin K should not be given subcutaneously or intramuscularly.
- Blood factors (Profilin or Factor VIIa) will decrease INR in 15 to 30 minutes.

Recommendations by Clinical Scenario

Life Threatening Bleeding – Intracranial Hemorrhage (including Traumatic Brain Injury)

<table>
<thead>
<tr>
<th>INR at Presentation</th>
<th>Factor VIIa Dose</th>
<th>Profilin Dose</th>
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<tbody>
<tr>
<td>1.7 - 3.0</td>
<td>10 mcg/kg IV</td>
<td>20 units/kg</td>
</tr>
<tr>
<td>&gt;3.0</td>
<td>20 mcg/kg IV</td>
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Table 1A. Blood Factor Dosing Recommendations

Life Threatening Bleeding – Trauma (excluding Traumatic Brain Injury)

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SERIOUS Bleeding

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</tr>
</thead>
<tbody>
<tr>
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<tr>
<td>&gt;3.0</td>
<td>20 mcg/kg IV</td>
<td>20 units/kg</td>
</tr>
</tbody>
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1 Round doses to the nearest viable sizes available whenever possible.  1 See Appendix A for conversion of FFP to units.