Management of Bleeding in the Anticoagulated Patient

“Short Snappers” CSIM 2015
Elizabeth Zed, MD, FRCPC
October 17, 2015
Disclosures

- Off label use of PCC and aPCC will be discussed

- My centre participates in research studies with the following companies
  - Bayer Inc
  - Janssen Research & Development, LLC
Objectives

- Review the mechanism of action of commonly used anticoagulants
- Develop a generalized approach to managing the anticoagulated bleeding patient
- Develop strategies to reverse specific anticoagulants, including antidotes when available
Outline

- Review MOA:
  - Warfarin, UFH, LMWH, Direct oral anticoagulants

- Review a framework to approaching the bleeding patient
  - HASHTI

- Reversal of anticoagulants
  - Antidotes
  - Specific approaches to DOAC associated bleeding

- References

- Questions
Contact Factors (HMWK, Prekallikrein)

**INITIATION**
- FXII → FXIIa

**Tissue Factor**
- TF - VIIa complex → VIIa

**PROPAGATION**
- FXI → FXIa
- FIX → FIXa
- FVIII → FVIIIa

**Ca^{2+} + PL**
- FXIa → FXIa
- FVIIIa → FVIIIa
- FX → FXa
- FVa → FVa

**Prothrombin (FII) → Thrombin (FIIa)**

**AMPLIFICATION**
- Prothrombin (FII) → Thrombin (FIIa)

**AMPLIFICATION**
- Fibrinogen → Soluble Fibrin

**Fibrin Clot Formation and Stabilization**
- Soluble Fibrin → FXIIIa

**Insoluble cross-linked fibrin**
- FXIIIa → Insoluble cross-linked fibrin

Bloody Easy 3
MOA: Warfarin

- Oral vitamin K antagonist
  - Decreases production of vitamin K dependent factors by limiting carboxylation

- Vitamin K dependent factors:
  - FII, FVII, FIX, FX, Protein C and Protein S

- Hepatically cleared

- T½ 36-42 hrs

- Monitored by PT- converted to INR
MOA: UFH

- Long chain glycosaminoglycans that bind thrombin and antithrombin, induce a conformational change
  - Activates Antithrombin
  - “Indirect” anticoag inhibits FIIa, Xa, IXa, XIa, XIIa

- Hepatically cleared

- $T^{1/2}$ 60-90 mins

- Monitored by PTT
MOA: LMWH

- Shorter chain glycosaminoglycans bind antithrombin and activates antithrombin
  - Less inhibitory effect on thrombin as does not bind
  - Indirect anticoag: inhibits Xa and IIa

- 80% renally cleared

- T½ 3-6 hrs

- Monitored by anti-Xa activity
**MOA: Dabigatran**

- Oral thrombin inhibitor
- “Direct” anticoag: inhibits IIa
  - Prevents conversion of fibrinogen to fibrin
- Primarily cleared by kidneys
- \( T^{\frac{1}{2}} 12-18 \text{ hrs} \)
- Does not requiring monitoring:
  - Will variably affect PT/PTT/TT
  - Generally a normal thrombin time suggests no dabigatran activity
MOA: Rivaroxaban

- Oral inhibitor of Factor Xa
- “Direct” anticoag
- 66% renal excretion
- $T_{1/2}$ 11-13 hrs
- Monitoring not required
  - Variably effects PTT and PT
MOA: Apixaban

- Oral inhibitor Factor Xa
- “Direct” anticoag
- 25% renally cleared
- T½ 8-15 hrs
- Monitoring not required:
  - Variably effects PTT, PT
Approach to the Anticoagulated Bleeding Patient

- **“HASHTI”**
  - Hold further doses
  - Consider Antidote
  - Supportive treatment
    - Fluid resuscitation
    - Hemodynamic support/monitoring
  - Hemostatic measures: local or surgical
    - Anti-fibrinolytics
  - Transfusion
    - RBC: severe or symptomatic anemia
    - Platelets: if low platelets or on long-acting anti-platelet
  - Investigate source of bleeding

Cushman, Lim and Zakai. ASH 2014.
Antidotes: Warfarin

- **Vitamin K**: 1-10mg IV/PO
  - Takes 6-24 hours to reverse warfarin

- **FP**: 10-30ml/kg
  - Repletes all coag factors but will not fully correct INR
  - Large volumes
  - Short T¹⁄₂ life: repeat dosing at 6 hrs

- **PCC**: 25-50u/kg
  - Rapidly corrects INR in warfarin treated patients
  - Short T¹⁄₂ 6 hrs
  - Give with IV Vitamin K
1. **Reversal of Warfarin (Coumadin®, Jantoven®)**

<table>
<thead>
<tr>
<th>Non-Urgent</th>
<th>Urgent (Not bleeding)</th>
<th>Urgent (Bleeding)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Stop 5 days prior to procedure</td>
<td>• If procedure can be delayed 6-24 hours, vitamin K 5-10 mg PO/IV; otherwise:</td>
<td>• HASHTI</td>
</tr>
<tr>
<td>• Check INR 1-2 days prior</td>
<td>• FFP or PCC prior to procedure. Repeat in 6-12 hours if INR &gt;1.5 and Vitamin K 5-10 mg PO/IV if sustained reversal is desired</td>
<td>• Vitamin K 5-10 mg IV; repeat in 12 hours as needed</td>
</tr>
<tr>
<td>• If INR &gt;1.5 administer vitamin K 1-2 mg PO</td>
<td></td>
<td>• PCC or FFP; repeat every 6 hours as needed</td>
</tr>
</tbody>
</table>
Antidotes: Heparin

- Protamine sulfate: 12.5-50mg IV

3. Protamine Dose for Reversal of Heparin and LMWH

<table>
<thead>
<tr>
<th>Agent*</th>
<th>Half-Life</th>
<th>Protamine Sulfate Dosing for Reversal</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td></td>
<td><strong>Maximum dose is 50 mg</strong></td>
</tr>
<tr>
<td>Heparin</td>
<td>1-2 hours</td>
<td>• 1 mg per 90-100 units heparin given in previous 2-3 hours&lt;br&gt;• e.g., 25-35 mg if 1000-1250 units/hour heparin infusion</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>4.5 hours</td>
<td>• 1 mg per 1 mg Enoxaparin in previous 8 hours</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>2.2 hours</td>
<td>• 1 mg per 100 units Dalteparin in previous 8 hours</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>3.9 hours</td>
<td>• 1 mg per 100 units Tinzaparin in previous 8 hours</td>
</tr>
</tbody>
</table>

Cushman, Lim and Zakai. ASH 2014.
Antidotes: DOACs

- Idarucizumab
- Andexanet Alfa
- PER977
Antidote: DOACs

- **Idarucizumab:** monoclonal antibody fragment
  - Binds dabigatran with affinity 350 times that of thrombin
  - Neutralizes dabigatran activity
  - $T_\frac{1}{2}$ 45 mins
  - Complete reversal of dabigatran activity
Antidotes: DOACs

**REVERSE-AD:**

- Interim results of 90 patients on dabigatran and requiring emergency surgery or uncontrolled bleeding
  - Primary endpoint % reversal based on diluted Thrombin Time or Ecarin clotting time
- 5 g idarucizumab given
  - dTT normalized in 98% and 93% of patients
  - ECT normalized in 89% and 88% of patients
  - Sustained reversal over 12hrs in >90%
- Thrombotic events: 1 early DVT
  - 4 events 7-26 days after

Antidotes: DOACs

- **Andexanet Alfa**
  - Recombinant human FXa variant
  - Target: FXa inhibitors
  - Currently in clinical development
  - IV bolus and infusion with short $\frac{1}{2}$ life

- **PER977**
  - Small synthetic molecule
  - Targets: UFH, LMWH, FXa inhibitors, anti-thrombin
  - Currently in clinical development
Approach to the Anticoagulated Bleeding Patient

**“HASHTI”**
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- Supportive treatment
  - Fluid resuscitation
  - Hemodynamic support/monitoring
- Hemostatic measures: local or surgical
  - Anti-fibrinolytics
- Transfusion
  - RBC: severe or symptomatic anemia
  - Platelets: if low platelets or on long acting anti-platelets
- Investigate source of bleeding

Cushman, Lim and Zakai. ASH 2014.
Specific approaches for DOACs

- Coagulation Factor Replacement
  - PCC: no high quality evidence establishing efficacy and safety of PCC for reversal
  - Appears to normalize PT and endogenous thrombin potential in people on rivaroxaban
    - Similar results were not seen with dabigatran
    - Animal models inconclusive
  - Preferred agent for rivaroxaban and apixaban

Specific Approaches for DOACs

- Activated PCC (FEIBA)
  - Contains FII, VI, IX, X in activated form
  - Low risk of thrombosis
  - Clinical evidence lacking
  - In vitro data suggests that aPCC corrects lab abnormalities caused by DOACs
  - Case report of aPCC use in dabigatran-treated patient
  - Preferred agent for dabigatran

Specific approaches for DOACs

- Recombinant FVIIa
  - Rapidly corrects elevated INR due to warfarin
    - Does not restore hemostasis as only replaces FVIIa
  - Short $T\frac{1}{2}$: dosing q2 hrs
  - No clinical studies
  - Animal models: failed to ameliorate bleeding in animals treated with dabigatran or rivaroxaban
  - Variable effects on lab coagulation abnormalities
  - Higher risk of thrombosis (5-10%)

Cushman, Lim and Zakai. ASH 2014.
Specific Approaches to DOACs

- Hemodialysis
  - Rivaroxaban and apixaban: protein bound, HD not effective
  - Dabigatran:
    - 49-68% of active drug removed by HD
    - Better removal with longer duration of dialysis
<table>
<thead>
<tr>
<th>Agent</th>
<th>Dabigatran</th>
<th>Rivaroxaban or Apixabanb</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Factor Prothrombin Complex Concentrate (PCC; Beriplex, Octaplex)</td>
<td>Possibly beneficial</td>
<td>Probably beneficial</td>
</tr>
<tr>
<td>3-Factor Prothrombin Complex Concentrate</td>
<td>No available evidence</td>
<td>No available evidence</td>
</tr>
<tr>
<td>Activated 4-Factor Prothrombin Complex Concentrate (FEIBA)</td>
<td>Probably beneficial</td>
<td>Probably beneficial</td>
</tr>
<tr>
<td>Recombinant activated Factor VII (Novoseven, Niastase)</td>
<td>Possibly beneficial</td>
<td>Possibly beneficial</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>Probably ineffective</td>
<td>Probably ineffective</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>Probably ineffective</td>
<td>Probably ineffective</td>
</tr>
<tr>
<td>Antifibrinolytic agents (aminocaproic acid - Amicar; tranexamic acid - Cyclokapron)</td>
<td>No available evidence but may be helpful</td>
<td>No available evidence but may be helpful</td>
</tr>
</tbody>
</table>
Figure 1: Suggested Strategy for Management of NOAC-Associated Bleeding

Patient with bleeding on a NOAC

Assess severity of bleeding

Mild bleeding
- Local hemostasis
- Hold 1 or more doses of NOAC if necessary
- Observation

Moderate bleeding
- General Measures
  - Hold NOAC
  - Local hemostasis (compression, surgery)
  - IV fluids → diuresis
  - Transfuse RBCs if needed
  - Oral activated charcoal if overdose <2 hrs before

Severe bleeding
- Time of last dose?
- CBC, INR, aPTT, creatinine
- General Measures PLUS
  - Tranexamic acid (1 G IV followed by 1 G infusion over 8 hours)
  - For apixaban, rivaroxaban: consider 4-factor PCC 50 IU/kg
  - For dabigatran: consider aPCC (FEIBA) 80 IU/kg
  - Consider hemodialysis for dabigatran

**Urgent:**

Hold further doses of dabigatran, rivaroxaban, or apixaban

- Draw baseline coagulation tests*
  - Activated charcoal if recent ingestion:
    - Apixaban: <6 hours
    - Dabigatran: <2 hours
    - Rivaroxaban: <8 hours

**Normal aPTT**—Unlikely dabigatran is contributing to bleeding

**Normal PT**—Unlikely rivaroxaban is contributing to bleeding if last ingestion >24 hours prior

**Prolonged aPTT**—Dabigatran present and may be contributing to bleeding

**Prolonged PT**—Rivaroxaban present and may be contributing to bleeding

**No antidote available**

For bleeding consider:
- PCC
- activated PCC (FEIBA)
- rFVIIa
  - hemodialysis for dabigatran (if patient has renal failure)

**HASHTI**

**Reassess patient** repeat abnormal coagulation tests*

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Cushman, Lim and Zakai. ASH 2014
Approach to the Anticoagulated Bleeding Patient

"HASHTI"

- Hold further doses
- Consider Antidote
  - Vitamin K, PCC, FP, Protamine Sulfate, aPCC, Idarucizumab
- Supportive treatment
  - Fluid resuscitation
  - Hemodynamic support/monitoring
- Hemostatic measures: local or surgical
  - Anti-fibrinolytics
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Resources

Clinical Protocols (and Reversals): Rivaroxaban

Presented by the American Society of Hematology, adapted in part from the American College of Chest Physicians Evidence-Based Clinical Practice Guideline on Antithrombotic and Thrombolytic Therapy (8th Edition).

*This pocket guide is a revision of the 2011 Clinical Practice Guide on Anticoagulant Dosing and Management of Anticoagulant-Associated Bleeding Complications in Adults.

Look for this pocket guide as a downloadable app by searching for “ASH Guides” in the iTunes store or Android market.
References


- Mechanisms in Hematology. www.mechanismssinhematology.com

Questions?