Reversal of direct oral anticoagulants in the patient with GI bleeding

Marc Carrier
Disclosure

• Faculty: Dr. Marc Carrier

• Relationships with commercial interests:
  – Grants/Research Support: Leo Pharma, Bristol-Myers Squibb, Bayer, Octapharma
  – Speakers Bureau/Honoraria: Pfizer, Sanofi, Boehringer Ingelheim, LEO Pharma, Bayer
  – Advisory Board: Pfizer, Sanofi, LEO Pharma
Learning objectives

• Review the rates of major bleeding episodes (including gastro-intestinal (GI) bleeding) in patients on direct anticoagulants (DOACs) or vitamin K antagonist (VKA) trials.

• Review the evidence of the general measures to manage including reversal in patients with life threatening GI bleeding episodes for patients on oral anticoagulation.
Background

- DOACs (dabigatran, rivaroxaban and apixaban) have numerous indications in Canada
  - Primary prevention of venous thromboembolism (VTE) in patients post total hip or knee arthroplasty.
  - Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.
  - Acute treatment and secondary prevention of VTE.

<table>
<thead>
<tr>
<th>Pharmocodynamic Properties of New Oral Anticoagulants</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct factor inhibition</td>
<td>Xa</td>
<td>Ila</td>
<td>Xa</td>
</tr>
<tr>
<td>Peak action ($t_{\text{max}}$)</td>
<td>1-3 hr</td>
<td>1-3 hr</td>
<td>1-3 hr</td>
</tr>
<tr>
<td>Protein binding</td>
<td>84%</td>
<td>35%</td>
<td>92-95%</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>25%</td>
<td>80%</td>
<td>33%</td>
</tr>
</tbody>
</table>
Bleeding episodes in Phase 3 trials

DOAC vs. VKA

Major bleeding
0.72 (0.62-0.85)

Fatal bleeding
0.53 (0.43-0.64)

Intracranial bleeding
0.43 (0.37-0.50)

Clinically relevant non-major bleeding
0.78 (0.68-0.90)

Major GI bleeding
0.94 (0.75-1.19)

Patient Management in the world of oral anticoagulation

MANAGEMENT OF MAJOR BLEEDING EPISODES FOR PATIENTS ON DOAC
KEEP CALM AND STOP BLEEDING
Management of major bleeding episodes

• Identify and stop all oral anticoagulants, parenteral anticoagulants and antiplatelet agents.
• Identify source of bleeding (if not already done)
• Apply local and surgical measures to gain source control (including embolization) as appropriate
Management of major bleeding episodes

• Supportive measures (Volume replacement and blood products as needed) to maintain hemodynamic stability and urine output.

• Confirm timing of last dose of oral anticoagulant. If < 2 to 6 hours consider activated charcoal

• Consider tranaxemetic acid (1 g IV)
Management of major bleeding episodes

• Measure coagulation parameters:
  – DOAC-specific assays if available:
    • Hemoclot® for Dabigatran
    • Chromogenic anti-Xa assays for rivaroxaban and apixaban

*
Management of major bleeding episodes

• Measure coagulation parameters:
  – Standard coagulation parameters may help assessing the intensity of anticoagulation but not the plasma levels
    • Dabigatran:
      – Normal TT: No dabigatran
      – Abnormal TT but normal aPTT: Low [ ] of dabigatran
    • Rivaroxaban:
      – Normal anti-Xa: No rivaroxaban
      – Abnormal anti-Xa but normal PT: Low [ ] of rivaroxaban
    • Apixaban:
      – Normal anti-Xa: No apixaban
Management of major bleeding episodes

- Measure creatinine clearance (and estimate half life)

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>CrCl (mL/min)</th>
<th>Drug half life (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 50</td>
<td>14 (12-18)</td>
</tr>
<tr>
<td></td>
<td>≥ 30 to ≤ 50</td>
<td>18 (13-23)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rivaroxaban or apixaban</th>
<th>CrCl (mL/min)</th>
<th>Drug half life (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 50</td>
<td>8 (7-10)</td>
</tr>
<tr>
<td></td>
<td>≥ 30 to ≤ 50</td>
<td>11 (9-13)</td>
</tr>
</tbody>
</table>
And if the bleeding continues?
Approaches to reverse DOAC effect

• Enhanced clearance of the drug (e.g. Hemodialysis)
  • Dabigatran only

• General hemostatic agents
  – Prothrombin complexes (PCC) (e.g. Octaplex, beriplex)
  – Activated PCC (aPCC) (FEIBA)

– Antidotes
General hemostatic agents (PCC or aPCC)

• Keep in mind:
  
  • Preclinical evidence only (animal studies, healthy volunteers, in vivo, etc.)
  
  • Effect on bleeding outcome may not reflect the effect on standard coagulation parameters
  
  • Potential risk of prothrombotic events (especially with aPCC)
General hemostatic agents (PCC or aPCC)

European Heart Rhythm Association Practical Guide

• PCC: 25 U/Kg: may be repeated once or twice
  • no clinical evidence
• aPCC: 50 U/Kg (max 200 U.kg/day)
  • No strong data about additional benefit over PCC.
  • Can be considered before PCC if available
• Activated FVIIa (90 mcg/kg)
  • No data about additional benefit + expensive

Antidotes

• Rapid effect for DOACs
• Potentially neutralizes drug activity
• Minimal risk of pro-thrombotic effects
• Not yet available and efficacy for control of bleeding still unproven
Idarucizumab

• Dabigatran antidote
  – Humanized antibody fragment (Fab)

  – Restoration of coagulation
    • Structurally similar to thrombin but with a higher affinity for dabigatran (350 times higher)

    • Once idarucizumab binds to dabigatran, it prevents it from binding to thrombin (No more anticoagulant effect)

    • No pro-coagulant or anticoagulant effects

Idarucizumab

- Easy and rapid administration
  - IV administration
  - Immediate onset of action
  - Storage: Refrigerated

- Dose-dependent affect (Phase 1 and 2 studies)

- Low risk of adverse reactions
  - No endogenous targets

- RE-VERSE AD study
  - 5 g IV

RE-VERSE AD study

- A Phase III Case Series Clinical Study of the Reversal of the Anticoagulant Effects of Dabigatran by Intravenous Administration of 5.0g Idarucizumab
  - Group A (Bleeding patients)
  - Group B (Patients who are taking dabigatran who may not be bleeding, but do require an emergency surgery or procedure for a condition other than bleeding)
## Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A</th>
<th>Group B</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>n=51</td>
<td>n=39</td>
<td>N = 90</td>
</tr>
<tr>
<td>Indication for dabigatran stroke prevention in A Fib</td>
<td>47/51</td>
<td>39/39</td>
<td>86/90</td>
</tr>
<tr>
<td>Age median, range (years)</td>
<td>77 (48–93)</td>
<td>76 (56–93)</td>
<td>76.5 (48–93)</td>
</tr>
<tr>
<td>Creatinine clearance median, range (mL/min)</td>
<td>51.5 (15.8–186.8)</td>
<td>60.1 (11.5–171)</td>
<td>57.6 (11.5–186.8)</td>
</tr>
<tr>
<td>Patient-reported time since last dose, median (hours)</td>
<td>15.2</td>
<td>16.6</td>
<td>15.4</td>
</tr>
<tr>
<td>Elevated dTT at baseline</td>
<td>40/51</td>
<td>28/39</td>
<td>68/90</td>
</tr>
<tr>
<td>Elevated ECT at baseline</td>
<td>47/51</td>
<td>34/39</td>
<td>81/90</td>
</tr>
<tr>
<td>Elevated dTT or ECT at baseline</td>
<td>47/51</td>
<td>34/39</td>
<td>81/90</td>
</tr>
</tbody>
</table>

Pollack C et al. NEJM 2015;377:511-520
### Demographics

<table>
<thead>
<tr>
<th>Type of bleeding</th>
<th>Group A (n=51)</th>
<th>Group B (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Other*</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reason for surgery†</th>
<th>Group B (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic dissection</td>
<td>1</td>
</tr>
<tr>
<td>Pericardial tamponade</td>
<td>1</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>1</td>
</tr>
<tr>
<td>Acute mesenteric ischaemia with sepsis</td>
<td>2</td>
</tr>
<tr>
<td>Bone fractures</td>
<td>8</td>
</tr>
<tr>
<td>Acute cholecystitis</td>
<td>5</td>
</tr>
<tr>
<td>Acute renal insufficiency, catheter placement</td>
<td>4</td>
</tr>
<tr>
<td>Acute appendicitis</td>
<td>3</td>
</tr>
<tr>
<td>Joint/wound infection</td>
<td>3</td>
</tr>
<tr>
<td>Abscess (suprapubic, scrotal)</td>
<td>2</td>
</tr>
</tbody>
</table>

Pollack C et al. NEJM 2015;377:511-520
Primary endpoint in group A

Pollack C et al. NEJM 2015;377:511-520
Results

- Median maximum reversal within 4 hours was 100% for both dTT and ECT (95% CI, 100–100).
- Similar results for TT and aPTT

Pollack C et al. NEJM 2015;377:511-520
Clinical outcomes

Group A
51 Patients

Assessable in 38 patients

Median local investigator-determined time to bleeding cessation 11.4 hours*

Group B
39 Patients

Surgery performed in 36 patients

Intraoperative hemostasis:
- 33 normal
- 2 mildly abnormal
- 1 moderately abnormal

Pollack C et al. NEJM 2015;377:511-520
AHA update

• Follow-up analysis (n=494 patients)
  – 285 (60%) - Group A
  – 196 (40%) – Group B
    • 62% - dabigatran 110 mg BID
    • 30% - dabigatran 150 mg BID
  – Median age was 78 years
  – Median time since last dose was 15.3 hours
  – At baseline,
    • dTT was elevated in 77%
AHA update

• Group A patients
  – 97 ICH, 135 GI bleeds, and 87 others

• Group B patients
  – 45 acute abdomen, 30 bone fractures, 20 infections, 11 acute renal failure due to obstruction

• Primary end point
  – Median maximum reversal within 4 hours was 100% for both dTT and ECT (95% CI, 100%-100%)
  – Normalization of dTT within 4 hours
    » Group A - 98.7% (235/238)
    » Group B - 98.6% (131/143)
AHA update

- Clinical endpoints:
  GI bleeding: Median time to bleeding cessation was 3.5 hours
  Non GI non ICH: Median time to bleeding cessation was 4.5 hours

- Thrombotic events
  6.3% (31/494) patients at 90 days

- Mortality rates (30 days)
  Group A - 12.3%
  Group B - 12.4%
Life Threatening Bleeding Protocol for Patients on Direct Oral Anticoagulants (Rivaroxaban, apixaban and dabigatran)

Initial Management

Estimated or actual patient weight: _______ kg

- Discontinue co-medication which may contribute to bleeding, e.g. antithrombotic therapies, low-molecular-weight-heparin, warfarin, non-aspirin anti-inflammatory drugs, etc.

Resuscitation

- Initiate resuscitation measures in a monitored area, as clinically appropriate
- Clinically appropriate local hemostatic measures, as dictated by site of bleeding.
- Where appropriate, consultation for procedural/surgical intervention

Anticoagulant (check the box to indicate which agent patient is reported to be taking currently)

- Apixaban
- Rivaroxaban
- Dabigatran

Estimated Date and time of last dose __________________________

Labor (baseline labs, required for all patients)

- CBC, aPTT, PT/INR, TT, anti-Xa STA1
- Group-Screen, crossmatch 2 units PRBCs
- Creatinine

Drug Specific Levels (if appropriate)

- Patient on Apixaban: Apixaban-calibrated anti-Xa activity assay (anti-Xa levels)
- Patient on Rivaroxaban: Rivaroxaban-calibrated anti-Xa activity assay (anti-Xa levels)

Reversal or Anticoagulant Neutral

Calibrated anti-Xa Level > 30 ng/mL

- Dalteparin: ___________ units (50 units/kg, no maximum amount) IV STA1 (FPCC product as supplied by Transfusion Medicine Laboratory)
  - Repeat rivaroxaban or apixaban-calibrated anti-Xa level 10 minutes after infusion completed (target anti-Xa < 30 ng/mL)

Neutralisation Neutral

Abnormal thrombin time (TT)

- Administer 3 grams of idarucuzumab in 2 doses, as ordered below (supplied by Pharmacy):
  - Idarucuzumab 2.5 grams IV as a 30 mL bolus (1st dose) immediately followed by:
  - Idarucuzumab 2.5 grams IV as a 30 mL bolus (2nd dose)

Adjunctive Therapy

Consider:

- Thrombin: Add 1 gram IV bolus, then 1 gram IV over 6 hours.

Version 1.0 2017-01-31
Initial Management

Estimated or actual patient weight: __________Kg

☐ Discontinue co-medications which may contribute to bleeding, e.g. antiplatelet therapies, low-molecular-weight-heparin, warfarin, non-steroidal anti-inflammatory drugs, etc.

Resuscitation

☒ Initiate resuscitation measures in a monitored area, as clinically appropriate
☐ Clinically appropriate local hemostatic measures, as dictated by site of bleeding,
☐ Where appropriate, consultation for procedural/surgical intervention

Anticoagulant (check the box to indicate which agent patient is reported to be taking currently)
☐ Apixaban
☐ Rivaroxaban
☐ Dabigatran

Estimated Date and time of last dose ________________________________
Labs (baseline labs, required for all patients)
- CBC, aPTT, PT/INR, TT, anti-Xa **STAT**
- Group+Screen, crossmatch 2 units PRBCs
- Creatinine

**Drug Specific Levels (if appropriate)**
Patient on Apixaban:
- Apixaban-calibrated anti-Xa activity assay (anti-Xa levels)
Patient on Rivaroxaban:
- Rivaroxaban-calibrated anti-Xa activity assay (anti-Xa levels)

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**Rebleeding Protocol**

Initial Management
- Estimated or actual patient weight: _____ kg
  - Discontinue medications which may contribute to bleeding, e.g. antiplatelet therapies, low-molecular-weight-heparin, warfarin, non-steroidal anti-inflammatory drugs, etc.
  - Initiate resuscitation measures in a monitored area, as clinically appropriate

Transfusion Medicine Laboratory
- Repeat rivaroxaban or apixaban-calibrated anti-Xa level 10 minutes after infusion completed (target anti-Xa = 30 ng/mL)

**Abnormal Thrombin Time (AT)**
- Administer 3 grams of Idarucizumab in 2 doses, as ordered below (supplied by Pharmacy):
  - Idarucizumab 1.5 grams IV as a 30 mL bolus (1st dose) immediately followed by:
  - Idarucizumab 1.5 grams IV as a 30 mL bolus (2nd dose)

**Adverse Effects**
- Transaminase 1 gram IV bolus, then 1 gram IV over 6 hours.

Version 1.0 2017-01-31
Rivaroxaban or Apixaban Reversal

Calibrated anti-Xa Level ≥ 30 ng/mL

☐ Octaplex ___________ units (50 units/ kg, no maximum amount) IV STAT (PCC product as supplied by Transfusion Medicine Laboratory)

☐ Repeat rivaroxaban or apixaban-calibrated anti-Xa levels 10 minutes after infusion completed (target anti-Xa < 30 ng/mL)
Dabigatran Reversal

Abnormal thrombin time (TT)

☐ Administer 5 grams of Idarucizumab in 2 doses, as ordered below (supplied by Pharmacy):
  • Idarucizumab 2.5 grams IV as a 50 mL bolus (1st dose) immediately followed by:
  • Idarucizumab 2.5 grams IV as a 50 mL bolus (2nd dose)
### Bleed Management

**What type of bleeding does the patient have?**

- Minor bleeding (e.g., subconjunctival hemorrhage, small bruising/abrasions, dental bleeding, anterior epistaxis, hemorrhoidal bleeding)
- Moderate bleeding (e.g., hemodynamically stable gastrointestinal bleeding, uncontrolled posterior epistaxis)
- Severe/Life-threatening bleeding
  - Intracranial hemorrhage
  - Critical site (e.g., retroperitoneal, intra-spinal, intra-ocular, intra-articular)
  - Actual or impending hemodynamic compromise (e.g., massive GI bleed)
  - Clinically overt bleeding with hemoglobin decrease ≥20 g/L or administration of ≥2 units RBCs
New antidote
Bottom line

• Risk of major bleeding on DOAC is comparable (or lower) to risk on warfarin for all indications

• If life threatening bleeding episodes or urgent surgery required for patients on dabigatran, idarucizumab should be considered

• If life threatening bleeding episodes for patients on rivaroxaban or apixaban, general hemostatic agents can be considered (PCC, FEIBA)

• Establish a local protocol for the management of major bleeding for patients on oral anticoagulants (DOACs or VKA)