Reversing Old and New Anticoagulants and Managing Bleeding in the Anticoagulated Patient

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PLATELET INHIBITORS
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• Aspirin
• P2Y12 inhibitors: Clopidogrel, Prasugrel, Ticagrelor, Cangrelor
• IIb/IIIa inhibitors: abciximab, eptifibatide, tirofiban
PLATELET FUNCTION EVALUATION

- Platelet count
- Bleeding time
- Aggregation
- Platelet function assays: Multiplate, VerifyNow
- Experimental
Treating Thienopyridine Treated Patients with Life-threatening Hemorrhage


Non vitamin K Oral Anticoagulants NOACs/DOACs
In clinical trials, DOACs have demonstrated favorable safety and efficacy profiles compared with warfarin.

- **51%** Hemorrhagic stroke
- **52%** Intracranial bleeding
- **19%** Stroke/se
- **10%** All-cause mortality

Meta-analysis of data from RE-LY®, ROCKET-AF, ARISTOTLE, ENGAGE AF-TIMI 48
Assessment of renal function and coagulation tests aid decision-making for all NOACs in emergency situations

**Renal function assessment**
- Estimate time of elimination
- Renal impairment may reduce capacity for elimination of NOAC

**Coagulation tests**
- Determine if OAC is present and may be contributing to bleeding
- Timing and NOAC dose influence coagulation tests

Standard assays can be used to determine anticoagulation status in patients on dabigatran, but not other DOACs

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma peak</strong></td>
<td>2 h after ingestion</td>
<td>2–4 h after ingestion</td>
<td>3-4 h after ingestion</td>
</tr>
<tr>
<td><strong>Plasma trough</strong></td>
<td>12–24 h after ingestion</td>
<td>16–24 h after ingestion</td>
<td>12–24 h after ingestion</td>
</tr>
<tr>
<td>aPTT</td>
<td>✔</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>TT, dTT (quantitative)</td>
<td>✔</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>ECT</td>
<td>✔</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Anti-FXa assays</td>
<td>✗</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>PT</td>
<td>✗</td>
<td>✔</td>
<td>✗</td>
</tr>
<tr>
<td>INR</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
</tbody>
</table>

Time of last DOAC dose should always be considered when interpreting test results

aPTT, activated partial thromboplastin time; dTT, direct thrombin time; ECT, ecarin clotting time; FXa, Factor Xa; INR, international normalized ratio; PT, prothrombin time; TT, thrombin time Adapted from Heidbuchel H et al. Europace 2013;15:625–51; Pradaxa®: EU SPC, 2014; Eliquis®: EU SPC, 2014; Xarelto®: EU SPC, 2014 Siegal & Crowther. Eur H J ePub Dec 7 2012
MANAGING BLEEDING
Reversal Agents
(Antidotes)
Are reversal strategies/antidotes needed?

- The safety of DOACs was without specific reversal strategies.
- Shorter half lives of DOACs compared to warfarin is important.
- But novel drugs create novel paradigms, especially with reversal.

DOAC reversal agents in development

**Idarucizumab**
Target: dabigatran

- Phase I
- Phase II
- Phase III
  - Patients requiring urgent surgery/with major bleeding; started May 2014
  - Approved by EMA/FDA

**Andexanet alfa**
(PRT064445)
Target: FXa inhibitors

- Phase I
- Phase II
- Phase III
  - Patients with major bleeding; under FDA review

**Ciraparantag**
(PER977)
Target: universal?

- Phase I

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Idarucizumab: Fab fragment to dabigatran

- **Restoration of coagulation**
  - Potent binding: affinity ~350 times higher than dabigatran to thrombin
  - No procoagulant effects
  - Short half-life
- **Easy and rapid administration**
  - IV administration, immediate onset
- **Low risk of adverse reactions**
  - No Fc receptor binding
  - No endogenous targets

**Fully humanized antibody fragment (Fab)**

IV = intravenous

Idarucizumab (Praxbind): a specific reversal agent

Study to evaluate reversal of the anticoagulant effects of dabigatran with idarucizumab in:

- **Bleeding patients** – overt bleeding judged by the physician to require a reversal agent
- **Surgical patients** – require an emergency surgery or procedure for a condition other than bleeding

Diluted Thrombin Time Assessment of Dabigatran Reversal

Group A

Group B

Time post-idarucizumab

Median and 25th/75th percentiles

10th/90th percentiles

5th/95th percentiles

RE-VERSE AD

Study of reversal effects of idarucizumab in patients on active dabigatran
Dabigatran Reversal Measured as Unbound Dabigatran and aPTT

Groups A and B

Unbound dabigatran (ng/mL)

Time post-idarucizumab

Groups A and B

aPTT (seconds)

Time post-idarucizumab

Median and 25th/75th percentiles
10th/90th percentiles
5th/95th percentiles

Study of reversal effects of idarucizumab in patients on active dabigatran
### Group A: Site of Index Bleed and Severity (n=301)

<table>
<thead>
<tr>
<th>Type of Bleeding*</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial</td>
<td>98 (32.6)</td>
</tr>
<tr>
<td>Subdural</td>
<td>39</td>
</tr>
<tr>
<td>Subarachnoid</td>
<td>26</td>
</tr>
<tr>
<td>Intracerebral</td>
<td>53</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>137 (45.5)</td>
</tr>
<tr>
<td>Lower</td>
<td>47</td>
</tr>
<tr>
<td>Upper</td>
<td>52</td>
</tr>
<tr>
<td>Unknown</td>
<td>42</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>9 (3.0)</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>10 (3.3)</td>
</tr>
<tr>
<td>Intra-pericardial</td>
<td>7 (2.3)</td>
</tr>
<tr>
<td>Intra-articular</td>
<td>5 (1.7)</td>
</tr>
<tr>
<td>Intraocular</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Other</td>
<td>52 (17.3)</td>
</tr>
<tr>
<td>Not identified</td>
<td>4 (1.3)</td>
</tr>
</tbody>
</table>

**Adjudicated ISTH Bleeding Severity:**

- 88% Major and Life-threatening bleeding

**Other characteristics:**

- 38% Hemodynamic instability
- 20% Surgical intervention required
- 26% Trauma-related

*Bleeding may occur at more than one site.*

GI, gastrointestinal; ICH, intracranial hemorrhage; ISTH, International Society on Thrombosis and Haemostasis
Group B: Indications for Surgery / Procedures (n=202)

Examples:
- Peritoneal infection, bowel obstruction
- Hip & femur fracture, open extremity
- Aneurysm repair, pacemaker implant
- Craniotomy
- Cholecystitis, cholangitis
- Chest trauma
- Acute renal failure
- Hematoma, abscess
- Intentional Overdose

Group B: Peri-procedural Hemostasis (NEJM Jun 11, 2017)

- 197 of 202 (97.5%) patients underwent surgery/procedures
- Median time from administration to procedure was 1.6 hours
- Adequacy of hemostasis during surgery determined locally

Reversal Strategies: PCCs (off label)
Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Stuart J. Connolly, M.D., Truman J. Milling, Jr., M.D., John W. Eikelboom, M.D., C. Michael Gibson, M.D., John T. Curnutte, M.D., Ph.D., Alex Gold, M.D., Michele D. Bronson, Ph.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Peter Verhamme, M.D., Ph.D., Jeannot Schmidt, M.D., Saskia Middeldorp, M.D., Alexander T. Cohen, M.D., Jan Beyer-Westendorf, M.D., Pierre Albaladejo, M.D., Jose Lopez-Sendon, M.D., Shelly Goodman, Ph.D., Janet Leeds, Ph.D., Brian L. Wiens, Ph.D., Deborah M. Siegal, M.D., Elena Zotova, Ph.D., Brandi Meeks, B.Eng., Juliet Nakamya, Ph.D., W. Ting Lim, M.Sc., Mark Crowther, M.D., for the ANNEXA-4 Investigators

N Engl J Med
Volume 375(12):1131-1141
September 22, 2016
## Subgroup Analysis of Hemostatic Efficacy

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Percent Adjudicated as Excellent or Good Hemostasis (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients with efficacy analyses</td>
<td>47</td>
<td>79 (64–89)</td>
</tr>
<tr>
<td>Drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>26</td>
<td>81 (61–93)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>20</td>
<td>75 (51–91)</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24</td>
<td>71 (49–87)</td>
</tr>
<tr>
<td>Female</td>
<td>23</td>
<td>87 (66–97)</td>
</tr>
<tr>
<td>Site of bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>25</td>
<td>84 (64–96)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>20</td>
<td>80 (56–94)</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>7</td>
<td>71 (29–96)</td>
</tr>
<tr>
<td>65–75 yr</td>
<td>9</td>
<td>89 (52–100)</td>
</tr>
<tr>
<td>≥75 yr</td>
<td>31</td>
<td>77 (59–90)</td>
</tr>
<tr>
<td>Andexanet dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>42</td>
<td>76 (61–88)</td>
</tr>
<tr>
<td>High</td>
<td>5</td>
<td>100 (48–100)</td>
</tr>
<tr>
<td>Anti–factor Xa &lt;75 ng/ml or &lt;0.5 IU/ml</td>
<td>17</td>
<td>82 (57–96)</td>
</tr>
</tbody>
</table>

Anti–FXa Activity and % Change from Baseline in Patients Receiving Rivaroxaban and Apixaban

**A Rivaroxaban (N=26)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Median</th>
<th>Percent Change (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>277.0</td>
<td>-89 (-58 to -94)</td>
</tr>
<tr>
<td>End of Bolus</td>
<td>16.8</td>
<td>-86 (-55 to -93)</td>
</tr>
<tr>
<td>End of Infusion</td>
<td>30.6</td>
<td>-39 (-27 to -45)</td>
</tr>
<tr>
<td>4 Hr</td>
<td>177.7</td>
<td>-127.1 (-43 to -57)</td>
</tr>
<tr>
<td>8 Hr</td>
<td>97.9</td>
<td>-64 (-51 to -70)</td>
</tr>
</tbody>
</table>

**B Apixaban (N=20)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Median</th>
<th>Percent Change (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>149.7</td>
<td>-93 (-87 to -94)</td>
</tr>
<tr>
<td>End of Bolus</td>
<td>10.3</td>
<td>-92 (-85 to -94)</td>
</tr>
<tr>
<td>End of Infusion</td>
<td>12.5</td>
<td>-30 (-23 to -46)</td>
</tr>
<tr>
<td>4 Hr</td>
<td>103.0</td>
<td>-107.1 (-19 to -38)</td>
</tr>
<tr>
<td>8 Hr</td>
<td>100.2</td>
<td>-31 (-27 to -41)</td>
</tr>
</tbody>
</table>

Connolly SJ: NEJM 2016;375:1131-1141
Prothrombin Complex Concentrates (PCCs)
Anticoagulant reversal of warfarin by Beriplex®
Human plasma with INR≈5 spiked with PCC or rFVIIa

INR, international normalised ratio; PCC, prothrombin complex concentrate; rFVIIa, recombinant activated factor VII

Reversing DOACs with PCCs: DATA


- Zahir H et al. Edoxaban effects on bleeding following punch biopsy and reversal by a 4-factor PCC. Circulation. 2015 Jan 6;131(1):82-90.

Management of rivaroxaban or apixaban associated major bleeding with PCCs: a cohort study

- Prospective evaluation of MBEs in rivaroxaban or apixaban pts Rx with PCCs from 1/2014 to 10/2016.
- PCCs efficacy assessed with ISTH criteria
- Safety outcomes- TE and mortality within 30 days
- 84 pt Rx with PCCs: ~2000 IU (1500-2000 IU).
- ICH in 59 pts (~70%), GI bleeding in 13 (15.5%).
- PCCs effective in 58 (69.1%): ineffective in 26 (30.9%)
- 16/26 pts had ICH (61.5%).
- 2 pts developed an ischemic stroke, 5-10d after PCC.
- 27 pts (32%) died within 30 d after MBE.
How I use fibrinogen replacement therapy in acquired bleeding

by Jerrold H. Levy, and Lawrence T. Goodnough

Blood
Volume 125(9):1387-1393
February 26, 2015
Clinically Important Bleeding?

Yes

- Consider early tranexamic acid administration:
  - 1 g load
  - 1 g infusion over 8 hours

- Send coagulation tests:
  - Fibrinogen level
  - Platelet count
  - PT/PTT
  - INR
  - ROTEM®/TEG®

- Maintain homeostasis:
  - Normothermia
  - Normocalcemia
  - Normal pH

Fibrinogen level < 1.5-2.0 g/L and/or
FIBTEM A10 < 6-8 mm

Yes

- Fibrinogen concentrates (25-50 mg/kg)
  or
  Cryoprecipitate (8-10 units)

Platelet count < 100,000/mm³

Yes

- Platelet concentrate (8-10 units)

INR > 1.7 and Hypovolemia

Yes

- FFP (20-30 mL/kg)
  or
  PCCs (25-50 units/kg)

Massive transfusion protocol

Yes

Managing Bleeding with DOACs

- Reversal strategies are part of a multimodal strategy in addition to fixing the bleeding lesion.
- Reversal agents will **ONLY** remove the role of the anticoagulant.
- However, critical is to identify and take out the source while minimizing the amount of blood loss.
- Critically ill patients require resuscitation, and measure coags including fibrinogen.

Implementing reversal strategies in clinical practice

- Develop institutional wide protocols for emergencies
- Reversal of anticoagulation ≠ improved clinical outcomes