Management of **major bleeding complications** in patient on treatment with **direct oral anticoagulants** in an emergency department

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The laboratory
Management of major bleeding complications in patients on treatment with direct oral anticoagulants in an emergency department

Emergency Department of the Poliambulanza Foundation, Brescia

35 major bleeding events - 2 urgent procedures (January-November 2017)

ISTH criteria

<table>
<thead>
<tr>
<th>Major bleeding</th>
<th>Life-threatening bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in haemoglobin of ≥ 2 g/dL, or</td>
<td>Fatal bleeding, or</td>
</tr>
<tr>
<td>Transfusion of ≥ 2 units of packed RBCs, or</td>
<td>Symptomatic intracranial bleeding, or</td>
</tr>
<tr>
<td>Bleeding into a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal)</td>
<td>Bleeding with decrease of haemoglobin of ≥ 5 g/dL, or</td>
</tr>
<tr>
<td></td>
<td>Bleeding requiring inotropic support, or</td>
</tr>
<tr>
<td></td>
<td>Bleeding requiring surgery, or</td>
</tr>
<tr>
<td></td>
<td>Transfusion of ≥ 4 units of packed RBCs</td>
</tr>
</tbody>
</table>

5 Dabigatran (1 procedure)
7 Apixaban
1 Rivaroxaban
24 AVK (1 procedure)

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- 35 major bleeding events
  - 10 gastro-intestinal bleeding (4 dabigatran: 1 upper, 3 lower: 6 AVK)
  - Intestinal infarction in AVK (procedure)
  - 17 cerebral hemorrhages
  - Upper mesenteric artery
  - Left epigastric artery
  - Esophageal aortic fistula
  - Hemoperitoneum in pelvis fracture
  - Hemopericardium
  - Urosepsis in dabigatran (procedure)
  - Hepatic hematoma
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1: The relative risk of major GI bleeding in the non-valvular atrial fibrillation population: take home points.

1. Adjusted-dose warfarin increases the risk of major GI bleeding approximately three-fold compared with placebo.
2. The addition of aspirin or other anti-platelet agents to warfarin increases the risk of major GI bleeding approximately two-fold (compared with warfarin alone).
3. Compared with warfarin, rivaroxaban and dabigatran (at the 150 mg twice daily dose) increase the risk of major GI bleeding approximately 1.5 fold.
4. Compared with warfarin, apixaban does not significantly alter the risk of major GI bleeding.
5. Compared with warfarin, dabigatran 110 mg twice daily does not significantly alter the risk of major GI bleeding.
6. Concurrent use of anti-platelet agents increases the risk of major GI bleeding associated with rivaroxaban and of major extra-cranial bleeding (presumably including major GI bleeding) associated with dabigatran. Data related to impact of anti-platelet agents on apixaban-related major GI bleeding are not yet available.
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8 Direct FXa inhibitors → PT - APTT were normal

PCCs

5 Dabigatran → PT- APTT were prolonged

Idarucizumab
DOAC anticoagulant activity **should be measured**...

- **Bleeding or thromboembolic events**
  - Before surgery or invasive procedures
  - Thrombolytic therapy in stroke

**Testing could be useful in**...

- Renal, liver disease
- Interaction with other drugs
- Extreme body weight
  - Adherence to the therapy
  - Undercoagulation or overcoagulation is suspected

**2% DOAC → ischaemic stroke**

*References*

- Thromb Haemost 2011; 106: 868-76
- Blood 2013; 121: 4032-5
Management of major bleeding complications in patient on treatment with direct oral anticoagulants in an emergency department

- Appropriate administration in immediate reversal of anticoagulation

**Idarucizumab for Dabigatran Reversal**

Charles V. Pollack Jr., M.D., Paul A. Kelly, Ph.D., John Eikelboom, M.B., B.S., Stephan Giudic, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Mino V. Husman, M.D., Ph.D., Elaine M. Hylek, M.D., Peter W. Kampchmer, M.D., Ph.D., Jorg Kreuzer, M.D., Jerold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Karr, M.D., and Jeffrey I. Weitz, M.D.

**REVERSE-AD: Trial Design**

- Group A (n = 298) Patients taking dabigatran with uncontrolled bleeding
  - 5 g idarucizumab (2 × 2.5 g IV)
  - 0-15 min
  - 90 days follow-up
  - Hospital arrival
  - Pre-1st vial
  - Pre-2nd vial
  - 1 h 2 h 4 h 12 h 24 h 30 d
  - Blood samples

- Group B (n = 196) Patients taking dabigatran requiring emergency surgery

**Primary endpoint:** Maximum reversal within 4 h based on dTT, ECT

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<table>
<thead>
<tr>
<th></th>
<th>Group A (N=51)</th>
<th>Group B (N=39)</th>
<th>Total (N=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated dilute thrombin time at baseline — no. (%)</td>
<td>40 (78)</td>
<td>28 (72)</td>
<td>68 (76)</td>
</tr>
<tr>
<td>Elevated ecarin clotting time at baseline — no. (%)</td>
<td>47 (92)</td>
<td>34 (87)</td>
<td>81 (90)</td>
</tr>
<tr>
<td>Type of bleeding — no. (%)§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial</td>
<td>18 (35)</td>
<td></td>
<td>18 (20)</td>
</tr>
<tr>
<td>Trauma-related</td>
<td>9 (18)</td>
<td>9 (10)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>20 (39)</td>
<td>20 (22)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>11 (22)</td>
<td>11 (12)</td>
<td></td>
</tr>
</tbody>
</table>

11 normal dTT → 64%
40 elevated dTT → 28%

25% Dabigatran concentrations were relatively low before administration of Idarucizumab
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6 patients 12 hours after Idarucizumab
16 patients 24 hours after Idarucizumab

↑ [ dabigatran ]

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### Global Tests

- **Intrinsic Pathway**
  - Surface contact (collagen, platelets)
  - Prekallikrein
- **Extrinsic Pathway**
  - Platelet surface
  - XI → Xlla

### Specific Tests

<table>
<thead>
<tr>
<th>Drug</th>
<th>PT</th>
<th>APTT</th>
<th>TT</th>
<th>dTT</th>
<th>Ecarin</th>
<th>Anti-FXa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>(^a)No</td>
<td>(^b)No</td>
<td>(^c)Yes</td>
<td>Yes</td>
<td>(^d)Yes</td>
<td>No</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>(^e)No</td>
<td>(^f)No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Apixaban</td>
<td>(^g)No</td>
<td>(^h)No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>(^i)No</td>
<td>(^j)No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

PT: prothrombin time; APTT: activated partial thromboplastin time; TT: thrombin time; dTT: dilute thrombin time; anti-FXa: anti-factor Xa activity.

- \(^a\) Poorly responsive to increasing drug concentration and reagent-dependent.
- \(^b\) Responsive to increasing drug concentration and reagent-dependent.
- \(^c\) Strongly responsive even to low levels of the drug. If normal, it may be used to rule out significant circulating drug levels.
- \(^d\) Clotting or chromogenic.
- \(^e\) Moderately responsive to increasing drug concentration, but reagent-dependent.
- \(^f\) Poorly responsive to increasing drug concentration and reagent-dependent.

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**Monitoring ≠ Measuring**
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Table 2 Parameters of coagulation and interlaboratory variability as observed by participants when measuring common freeze-dried plasmas without (plasma A) or with direct oral anticoagulants (DOACs) (dabigatran, plasma E; rivaroxaban, plasma D; or apixaban, plasma C (Survey II)).

<table>
<thead>
<tr>
<th></th>
<th>PT ratio</th>
<th>APTT ratio</th>
<th>TT ratio</th>
<th>Concentration (ng mL⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>A</td>
<td>E</td>
<td>A</td>
<td>E</td>
</tr>
<tr>
<td>No. of participants</td>
<td>233</td>
<td>232</td>
<td>221</td>
<td>219</td>
</tr>
<tr>
<td>Mean*</td>
<td>1.00</td>
<td>1.23</td>
<td>0.99</td>
<td>1.85</td>
</tr>
<tr>
<td>CV*</td>
<td>4.0</td>
<td>3.9</td>
<td>6.2</td>
<td>5.8</td>
</tr>
<tr>
<td>%T</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>A</td>
<td>D</td>
<td>A</td>
<td>D</td>
</tr>
<tr>
<td>No. of participants</td>
<td>233</td>
<td>233</td>
<td>221</td>
<td>221</td>
</tr>
<tr>
<td>Mean*</td>
<td>1.00</td>
<td>1.17</td>
<td>0.99</td>
<td>1.16</td>
</tr>
<tr>
<td>CV*</td>
<td>4.0</td>
<td>6.2</td>
<td>6.2</td>
<td>8.3</td>
</tr>
<tr>
<td>%T</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>A</td>
<td>C</td>
<td>A</td>
<td>C</td>
</tr>
<tr>
<td>No. of participants</td>
<td>233</td>
<td>233</td>
<td>221</td>
<td>221</td>
</tr>
<tr>
<td>Mean*</td>
<td>1.00</td>
<td>1.07</td>
<td>0.99</td>
<td>1.08</td>
</tr>
<tr>
<td>CV*</td>
<td>4.0</td>
<td>4.6</td>
<td>6.2</td>
<td>7.4</td>
</tr>
<tr>
<td>%T</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
...the use of PT or APTT in clinical practice to evaluate DOAC anticoagulant activity could case dangerous misinterpretations!

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Grazie per l'attenzione