GI bleeding on anticoagulants

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Overview

• Available anticoagulants in the UK
• DOACs
  • Indications
  • Bleeding risk
• Factors to consider in management of GI bleeding on DOACs
  • Which drug
  • Patient characteristic
  • Renal function
• DOACs and the coagulation screen
• Management of GI bleeding in patients on DOACs
  • General measures
  • Specific reversal agents: idarucizumab & Andexanet alpha
  • Role of prothrombin complex concentrate
• Restarting anticoagulation after a GI bleed
### Available Anticoagulant Drugs in the UK

<table>
<thead>
<tr>
<th>Injectable therapies</th>
<th>Vitamin K Antagonists</th>
<th>Direct Oral Anticoagulants (DOACs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH</td>
<td>Warfarin</td>
<td>Dabigatran</td>
</tr>
<tr>
<td>LMWH</td>
<td>Sinthrome (Acenocoumarol)</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>(Phenindione)</td>
<td>Apixaban</td>
</tr>
<tr>
<td>Argatroban</td>
<td></td>
<td>Edoxaban</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Licensed DOAC indications in the UK**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (IIa inhibitor)</th>
<th>Rivaroxaban (Xa inhibitor)</th>
<th>Apixaban (Xa inhibitor)</th>
<th>Edoxaban (Xa inhibitor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthopaedic thromboprophylaxis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>General thromboprophylaxis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NVAF</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>DVT</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>PE</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Prophylaxis atherothrombotic events after ACS (+aspirin or aspirin and clopidogrel)</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Bleeding on DOACs**
**Data from RCT and post marketing studies¹**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Major bleeding</th>
<th>ICH</th>
<th>GI bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran –</strong></td>
<td><strong>RR 0.93 (0.81 – 1.07)</strong></td>
<td><strong>RR 0.40 (0.27-0.60)</strong></td>
<td><strong>RR 1.50 (1.19-1.89)</strong></td>
</tr>
<tr>
<td>Rely</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post marketing</td>
<td><strong>HR 0.66 – 0.97</strong></td>
<td><strong>HR 0.08 – 0.49</strong></td>
<td><strong>HR 0.97 – 1.28</strong></td>
</tr>
<tr>
<td><strong>Rivaroxaban –</strong></td>
<td><strong>HR 1.04 (0.90-1.20)</strong></td>
<td><strong>HR 0.67 (0.47-0.93)</strong></td>
<td><strong>RR 1.46 P &lt; .001</strong></td>
</tr>
<tr>
<td>Pocket AF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post marketing</td>
<td><strong>IR 2.86 – 2.89</strong></td>
<td><strong>IR 0.22</strong></td>
<td><strong>IR 2.53</strong></td>
</tr>
<tr>
<td>(non comparative)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Apixaban –</strong></td>
<td><strong>HR 0.69 (0.60-0.80)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aristotle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post marketing</td>
<td><strong>HR 0.75 (0.63-0.88)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- In general post marketing studies support findings from RCT.
- Majority major bleeding events are GI but have low mortality.
- ICH rare but high mortality.

Villines & Peacock The American Journal of Medicine (2016) 129, S41-S46
DOACs for VTE in malignancy
Select-D and Hokusai trials: meta-analysis

- Recurrent VTE at 6 months
- Major bleeding at 6 months
- CRNMB at 6 months
- Overall mortality at 6 months

Bleeding particularly in GI or urologic malignancy

1. Li et al in press https://doi.org/10.1016/j.thromres.2018.02.144
Management of bleeding DOACs

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (IIa inhibitor)</th>
<th>Rivaroxaban (Xa inhibitor)</th>
<th>Apixaban (Xa inhibitor)</th>
<th>Edoxaban (Xa inhibitor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Licensed for</td>
<td>SPAF Treatment and 2nd prevention of VTE</td>
<td>SPAF Treatment and 2nd prevention of VTE</td>
<td>SPAF Treatment and 2nd prevention of VTE</td>
<td>SPAF Treatment and 2nd prevention of VTE</td>
</tr>
<tr>
<td>Protein binding</td>
<td>35% high</td>
<td>high</td>
<td>high</td>
<td>High</td>
</tr>
<tr>
<td>Peak effect, h</td>
<td>0.5–2</td>
<td>2–4</td>
<td>3–4</td>
<td>1–2</td>
</tr>
<tr>
<td>Excretion</td>
<td>Renal</td>
<td>Renal/hepatic</td>
<td>Renal/hepatic</td>
<td>Renal/hepatic</td>
</tr>
<tr>
<td>T_{1/2}, h</td>
<td>11–14 (27 h CrCl &lt;30 ml/min)</td>
<td>5–13</td>
<td>~12</td>
<td>10–14</td>
</tr>
</tbody>
</table>

- **Patient characteristics**
- **Which drug is the patient taking?**
- **When was the last dose?**
- **FBC, renal function, coagulation screen.**

Heidbuchel *et al*, *Europace* doi:10.1093/europace/euv309
Mortality in upper GI bleeding – Rockall score

Table 1  The Rockall risk scoring system for upper-gastrointestinal haemorrhage

<table>
<thead>
<tr>
<th>Component</th>
<th>Score</th>
<th>Score</th>
<th>Score</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Age (years)</td>
<td>&lt; 60</td>
<td>60–79</td>
<td>≥ 80</td>
<td></td>
</tr>
<tr>
<td>Pulse rate (beat/min)</td>
<td>&lt; 100</td>
<td>≥ 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>≥ 100</td>
<td>≥ 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbidity</td>
<td>None</td>
<td>None</td>
<td>IHD, cardiac failure, any other major comorbidity</td>
<td>Renal failure, liver failure or disseminated malignancy</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Mallory–Weiss lesions or no lesion, no SRH</td>
<td>All other diagnoses</td>
<td>Malignant lesions of the upper-gastrointestinal tract</td>
<td>Any other signs</td>
</tr>
<tr>
<td>Stigmata of recent haemorrhage</td>
<td>No stigmata or dark spot in ulcer base</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IHD, ischaemic heart disease; SBP, systolic blood pressure; SRH, stigmata of recent haemorrhage.

Rockall et al Gut 1996; 38: 316-321
Prevalence of renal dysfunction in patients with AF

Panel A: age stratified eGFR, LM equation

Prevalence of AF in the Swedish population

Friberg Journal of Internal Medicine, 2013, 274; 461–468
Approximate $T_{1/2}$ by renal function

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 80</td>
<td>14</td>
<td>8</td>
<td>7 - 8</td>
<td>8 – 9</td>
</tr>
<tr>
<td>50 - 79</td>
<td>17</td>
<td>9</td>
<td>7 - 8</td>
<td>8 – 9</td>
</tr>
<tr>
<td>30 - 49</td>
<td>19</td>
<td>9</td>
<td>17 - 18</td>
<td>9 – 10</td>
</tr>
<tr>
<td>15 - 29</td>
<td>28</td>
<td>10</td>
<td>17 - 18</td>
<td>17</td>
</tr>
<tr>
<td>&lt; 15</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Adapted from Burnett et al J Thromb Thrombolysis 2016 41:206–232

### Dabigatran
- Estimate normalization of plasma levels:
  - Normal renal function: 12–24 h
  - CrCl 50–80 mL/min: 24–36 h
  - CrCl 30–50 mL/min: 36–48 h
  - CrCl <30 mL/min: ≥48 h

### Anti Xa agents
- Normalization of plasma levels: 12–24 h

Adapted from Steffel et al, ESC Guideline, EHJ 2018
Can routine coagulation testing be used to determine the presence/degree of anticoagulation with DOACs?
Expected levels in DOAC steady state plasma concentrations

Table 9  Plasma levels and coagulation assays in patients treated with non-vitamin K antagonist oral anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran$^{229,230}$</th>
<th>Apixaban$^{231}$, SmPc</th>
<th>Edoxaban$^{184,232}$</th>
<th>Rivaroxaban$^{131,186}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>↑</td>
<td>(↑)</td>
<td>↑(↑)</td>
<td>↑↑ (↑)</td>
</tr>
<tr>
<td>aPTT</td>
<td>↑↑(↑)</td>
<td>(↑)</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>ACT</td>
<td>↑(↑)</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>TT</td>
<td>↑↑↑↑↑</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Expected impact of NOACs on routine coagulation tests

Steffel et al, ESC Guideline, EHJ 2018
Normal APTT in dabigatran or normal PT in anti Xa agents does not always exclude the presence of therapeutic drug levels. 
Do not use for apixaban.
Normal TT excludes dabigatran but too sensitive.
Use specific assays if possible.
# Management of bleeding on DOACs

<table>
<thead>
<tr>
<th></th>
<th>General measures</th>
<th>Specific reversal agent</th>
<th>Charcoal after ingestion</th>
<th>Haemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong></td>
<td>Yes</td>
<td>Idarucizumab</td>
<td>Yes within 2 h</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>Yes</td>
<td>No in Europe Yes in USA: Andexanet alpha</td>
<td>Yes, can be considered</td>
<td>No</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td>Yes</td>
<td>Andexanet alpha</td>
<td>Yes within 2 – 6 hours</td>
<td>No</td>
</tr>
<tr>
<td><strong>Edoxaban</strong></td>
<td>Yes</td>
<td></td>
<td>Yes, can be considered</td>
<td>No</td>
</tr>
</tbody>
</table>
Dabigatran reversal with iv Idarucizumab (Praxbind®)

Healthy volunteers


Emergency surgery

Pollack CV et al. NEJM 2015; 373:511-520
**Praxbind® Administration**

**Praxbind®** is the specific reversal agent for Pradaxa®

- **Praxbind®** should be used when rapid reversal of the anticoagulation effects of Pradaxa® is required:
  - For emergency surgery/urgent procedures
  - In life-threatening or uncontrolled bleeding

**The dose is 5 g**

- Two 50-mL vials of ready-to-use solution equal 1 dose of Praxbind® (2 x 2.5 g).

**Infuse intravenously**

- Give the complete 5-g dose as 2 consecutive intravenous infusions over 5 to 10 minutes each.

**Inject intravenously**

- Give the complete 5-g dose in 2 separate bolus injections as quickly as possible.

**A pre-existing intravenous line that has been fully flushed may be used for administration of Praxbind®.**

- The line must be flushed with sodium chloride injection prior to and at the end of administration.

**Praxbind® provides immediate, complete, and sustained reversal of Pradaxa®**

- Pradaxa® can be re-started after 24 hours.

**Praxbind®:**

- Is specifically designed as a reversal agent for Pradaxa® and will not reverse the effects of other anticoagulants
- May be used with standard supportive measures that are considered appropriate

**Preparation and administration considerations**

- **Solution is clear to slightly opalescent, colourless to slightly yellow**

- **Do not mix or coadminister with other medications**

- **Once Praxbind® has been removed from the vial, administration should begin promptly or within 1 hour**

- **Do not freeze**
Andexanet alpha

Annexa-A trial


Annexa-4 trial, interim analysis

<table>
<thead>
<tr>
<th>Number of Major Bleeds Adjudicated</th>
<th>Number of Patients who Achieved Excellent or Good Hemostasis</th>
<th>Percent of Patients who Achieved Excellent or Good Hemostasis</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>132</td>
<td>109</td>
<td>83%</td>
<td>76% - 89%</td>
</tr>
</tbody>
</table>

Adapted from ACC, slide presentation 12/03/2018. Accessed 06/10/2018
http://www.cronline.org/presentation-detail/interim-report-on-annexa-4-study-andexanet-reversa
Andexanet alpha – Annexa-4 trial, interim analysis

- Thrombotic events occurred within 3 days of andexanet in 6 (2.6%) patients and by 30 days in 24 (11%)
- Anticoagulation re-started in 129 patients (57%) by 30 days
- Therapeutic anticoagulation was re-started in only 9 patients before a thrombotic event occurred
- 27 deaths occurred by 30 days (12%), of which 11 were cardiovascular

Adapted from ACC, slide presentation 12/03/2018. Accessed 06/10/2018
http://www.crtonline.org/presentation-detail/interim-report-on-annexa-4-study-andexanet-reversa

FDA approved dosing, EMA awaited.

<table>
<thead>
<tr>
<th>Dose*</th>
<th>Initial IV Bolus</th>
<th>Follow-On IV Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Dose</td>
<td>400 mg at a target rate of 30 mg/min</td>
<td>4 mg/min for up to 120 minutes</td>
</tr>
<tr>
<td>High Dose</td>
<td>800 mg at a target rate of 30 mg/min</td>
<td>8 mg/min for up to 120 minutes</td>
</tr>
</tbody>
</table>

Accessed 06/10/2018
## Rivaroxaban reversal with PCC/aPCC

<table>
<thead>
<tr>
<th>Reference</th>
<th>Reversal agent</th>
<th>Model</th>
<th>Lab test</th>
<th>Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perzborn 2013</td>
<td>PCC</td>
<td>Rat mesenteric bleeding</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Zhou 2013</td>
<td>PCC</td>
<td>Mouse ICH</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Godier 2012</td>
<td>PCC</td>
<td>Rabbit hepatosplenic bleeding</td>
<td>✓</td>
<td>✗</td>
</tr>
<tr>
<td>Eerenberg 2012</td>
<td>PCC</td>
<td>Human volunteers</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Dinkelaar 2013</td>
<td>PCC</td>
<td>Human in vitro</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Marlu 2012</td>
<td>PCC</td>
<td>Human ex vivo</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Marlu 2012</td>
<td>aPCC</td>
<td>Human ex vivo</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Perzborn 2013</td>
<td>aPCC</td>
<td>Rat mesenteric bleeding</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Perzborn 2013</td>
<td>aPCC</td>
<td>Baboon mesenteric bleeding</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Recommended PCC (Beriplex/Octaplex) dose 50 units/kg (Steffel et al, ESC Guideline, EHJ 2018)
Management of Bleeding

**Bleeding while using a NOAC**

- Inquire about last NOAC intake
- Blood sample to determine creatinine (clearance), hemoglobin etc.
- Rapid coagulation assessment, incl. plasma drug levels (if available)

**Mild bleeding**
- Delay or discontinue next dose
- Reconsider concomitant medication
- Reconsider choice of NOAC, dosing (see chapters 2, 5, and 15)

**Non life-threatening major bleeding**

Supportive measures:
- Mechanical compression
- Endoscopic haemostasis if gastro-intestinal bleed
- Surgical haemostasis
- Fluid replacement
- RBC substitution if needed
- Platelet substitution (if platelet count ≤ 60 x 10⁹/L)
- Consider adjuvant tranexamic acid
- Maintain adequate diuresis

For dabigatran:
- Consider idarucizumab / hemodialysis (if idarucizumab is not available)

**Life-threatening bleeding**

- For dabigatran-treated patients: Idarucizumab 5g i.v.
- For FXa inhibitor-treated patients: Andexanet alpha (pending approval and availability)

Otherwise, consider:
- PCC (e.g. Beriplex®, CoFact®) 50 U/kg; ± 25 U/kg if indicated
- aPCC (Feiba®) 50 U/kg; max 200 U/kg/day

Steffel et al, ESC Guideline, EHJ 2018
Anticoagulation after a GI bleed?

Patient post major gastrointestinal bleeding

Continuing / Restarting NOAC? Consider factors favouring withholding (✓) vs. (re-) starting anticoagulation

✓ Unidentifiable site of bleeding
✓ Multiple angiodysplasias in the GI tract
✓ No reversible / treatable cause?
✓ Bleeding during treatment interruption
✓ Chronic alcohol abuse
✓ Need for dual antiplatelet therapy after PCI
✓ Older age

Net assessment in favour of withholding anticoagulation according to a multidisciplinary decision

Yes

Consider no anticoagulation vs. LAA occlusion

No

(Re-) initiate (N)OAC as early as feasible (after 4-7 days)
If >75 years old, consider NOAC other than dabigatran, rivaroxaban, or higher-dose edoxaban as the first choice

Steffel et al, ESC Guideline, EHJ 2018
Conclusion

• DOACs are increasingly used in AF and VTE
• Major/life-threatening bleeding similar or less than with warfarin.
  – ICH significantly less than with warfarin
  – GI bleeding slightly more than with warfarin (rivaroxaban, dabigatran, edoxaban)
• Patient characteristics, drug and renal function important in assessing the risk/severity of a bleed.
• Routine coagulation testing on of limited use.
• Use general measures for all bleeds
  – Idarucizumab for dabigatran reversal
  – PCC probably effective for bleeding with anti Xa agents
  – Andexanet alpha for rivaroxaban and apixaban reversal awaited
• Individual approach to re-starting anticoagulation after GI bleed
DOACs for VTE in malignancy
Select-D\textsuperscript{1} and Hokusai\textsuperscript{2} trials

- Select-D recurrence at 6 months 11% vs 4%, HR 0.43; 95% CI, 0.19 to 0.99
- Hokusai recurrence at 12 months 11.3% vs 7.9%, HR 0.71 95% CI, 0.48 to 1.06;

DOACs for VTE in malignancy
Select-D\(^1\) and Hokusai\(^2\) trials

- Dalteparin vs rivaroxaban bleeding at 6 months 4% vs 6% HR, 1.83; 95% CI, 0.68 to 4.96
- Dalteparin vs edoxaban bleeding at 12 months 4% vs 6.9% HR 1.77; 95% CI, 1.03 to 3.04

Bleeding particularly in GI or urologic malignancy

The PT and anticoagulant intensity of Anti Xa agents

- **Rivaroxaban & Edoxaban**: PT more sensitive than APTT
  - Dependent on reagent used. Normal result does not exclude therapeutic levels.

- **Apixaban**: PT more sensitive than APTT.
  - Dependent on reagents but normal results are frequently found despite therapeutic levels.

Adapted from Samama et al Thromb Haemost 2010; 103: 815–825
• 15 – 35% of patients >100 ng/ml had normal APTT depending on reagent
• Normal thrombin time excludes the presence of dabigatran but too sensitive