Blood and Guts

Reversal of anticoagulation in GI Bleeding

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Healthy situation

Haemostatic seesaw in a happy balance
Clinical Thrombosis

- Atrial Fibrillation
- Deep Vein Thrombosis
- Pulmonary Embolus
- Cerebral Sinus Thrombosis
- Mesenteric Vein Thrombosis
- Arterial Embolus or Thrombosis
- Metallic Heart Valves
- Ventricular Assist Devices
- Antiphospholipid syndrome
Anticoagulation Therapy

- Atrial Fibrillation
- Deep Vein Thrombosis
- Pulmonary Embolus
- Cerebral Sinus Thrombosis
- Mesenteric Vein Thrombosis
- Arterial Embolus or Thrombosis
- Metallic Heart Valves
- Ventricular Assist Devices
- Antiphospholipid syndrome

ANTICOAGULANT DRUG

Clotting

Bleeding
Successful Anticoagulation

- Atrial Fibrillation
- Deep Vein Thrombosis
- Pulmonary Embolus
- Cerebral Sinus Thrombosis
- Mesenteric Vein Thrombosis
- Arterial Embolus or Thrombosis
- Metallic Heart Valves
- Ventricular Assist Devices
- Antiphospholipid syndrome

ANTICOAGULANT DRUG

Clotting

Bleeding
Unsuccessful Anticoagulation

Atrial Fibrillation
Deep Vein Thrombosis
Pulmonary Embolus
Cerebral Sinus Thrombosis
Mesenteric Vein Thrombosis
Arterial Embolus or Thrombosis
Metallic Heart Valves
Ventricular Assist Devices
Antiphospholipid syndrome

ANTICOAGULANT DRUG

Clotting

Bleeding
Steady increase in numbers of patients receiving anticoagulation

≈1-2% of the UK population anti-coagulated

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>AF</td>
<td>70%</td>
</tr>
<tr>
<td>VTE</td>
<td>25%</td>
</tr>
<tr>
<td>Other</td>
<td>5%</td>
</tr>
</tbody>
</table>
Anticoagulants / Anti-platelets

Unfractionated Heparin

Low Molecular Weight Heparin

Warfarin

Other Vit K antagonists

Anti-Platelet Agents

Aspirin
Clopidogrel
Others

Xa Inhibitors

Rivaroxaban
Apixaban
Edoxaban

Thrombin Inhibitors

Hirudin
Dabigatran
Anticoagulation 2017

Which is best? Side-effect profile
GI bleeding

Who decides? Clinical Trials
Real world experience
Clinician Bias
Patient choice
Anticoagulation 2017

Bleeding still a common clinical scenario

GI Bleeding probably commonest type of bleeding
50 YEAR OLD MAN

1999  Mechanical aortic valve replacement with aortic stent requiring anticoagulation

Ischaemic bowel post op; resection; ileostomy; reversed

2009  GI bleeding – melaena; capsule ? Bleeding near bowel anastomosis
On going iron deficiency anaemia ?on going slow bleeding

INR – target 3-4
50 YEAR OLD MAN

1999  Mechanical aortic valve replacement with aortic stent requiring anticoagulation

   Ischaemic bowel post op; resection; ileostomy; reversed

2009  GI bleeding – melaena; capsule ? Bleeding near bowel anastomosis

   On going iron deficiency anaemia ?on going slow bleeding

   INR – target 3-4

?Options
“The use of dabigatran in patients with mechanical heart valves was associated with increased rates of thromboembolic and bleeding complications, as compared with warfarin, thus showing no benefit and an excess risk”.
Home INR monitoring
COAGUCHECK HOME MONITORING – WARFARIN ADJUSTMENT SCHEDULE

Name:
DOB:
Hospital Number:
Reason for warfarin therapy: Aortic Valve Replacement / Stent
GI Bleeding (near bowel anastomosis)
Consider vitamin K at lower INR than Standard protocol

Regular warfarin dose: 6 mg daily
INR Target Range: 2-2.5 (aiming for 2.5)

INR
> 4 Phone for advice
3.0-4.0 Omit 1 dose; Re-test following day; if still > 3 phone for advice
2.5-3.0 Reduce to 5mg daily. Re-test in 2 days
2-2.5 Continue 6mg daily. Test in 1 week.
<2 Phone for advice (any of the numbers listed below)
THE NATURAL ORDER

CARDIOLOGIST – CAUSES GI BLEEDING

GASTROENTEROLOGIST
STOPS GI BLEEDING

HAEMATOLOGIST
TRYS TO BE HELPFUL
A Haematological Bias

Therapeutic monitoring is a good thing
A Haematological Bias

Therapeutic monitoring is a good thing

Unless you are a bog standard patient with bog standard risk
80 year old woman

Haematemesis

13 day hospital admission

Anaemia – iron deficient – on admission

OGD - severe oesophagitis – 3\textsuperscript{rd} day of admission

Proximal L DVT (ileo-femoral) – 3\textsuperscript{rd} day of admission
80 year old woman

Haematemesis

13 day hospital admission

Anaemia – iron deficient – on admission

OGD - severe oesophagitis – 3\textsuperscript{rd} day of admission

Proximal L DVT (ileo-femoral) – 3\textsuperscript{rd} day of admission

….decided to use rivaroxaban “to avoid the need for monitoring”

15mg bd

“GP to reduce the dose to 20mg od in 3 weeks (12/4) and complete a 6 month course”
Readmitted with a brisk GI bleed
Initially shocked
Responded to resuscitation

<table>
<thead>
<tr>
<th></th>
<th>7/4</th>
<th>8/4</th>
<th>9/4</th>
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<tbody>
<tr>
<td>PT</td>
<td>31</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>APTT</td>
<td>42</td>
<td>37</td>
<td>30</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>3.2</td>
<td>4.2</td>
<td>3.8</td>
</tr>
</tbody>
</table>

V unstable for 48 hours
High dependency
7 units blood
### Anticoagulants / Anti-platelets

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated Heparin</td>
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<tr>
<td>Low Molecular Weight Heparin</td>
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</tr>
<tr>
<td><strong>Warfarin</strong></td>
<td>Other Vit K antagonists</td>
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<tr>
<td>Anti-Platelet Agents</td>
<td>Aspirin</td>
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<tr>
<td></td>
<td>Clopidogrel</td>
</tr>
<tr>
<td></td>
<td>Others</td>
</tr>
<tr>
<td><strong>Xa Inhibitors</strong></td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td></td>
<td>Apixaban</td>
</tr>
<tr>
<td></td>
<td>Edoxaban</td>
</tr>
<tr>
<td><strong>Thrombin Inhibitors</strong></td>
<td>Hirudin</td>
</tr>
<tr>
<td></td>
<td>Dabigatran</td>
</tr>
</tbody>
</table>
Reversal of over-warfarinisation

Options

- Omit warfarin
- Vitamin K - oral or SC or IV
- Coagulation factor replacement

BALANCE IMMEDIATE BLEEDING RISK AGAINST THROMBOTIC COMPLICATIONS

- indication for warfarin
- seriousness of bleeding
- speed of reversal required
- completeness of reversal required
<table>
<thead>
<tr>
<th>Type</th>
<th>Time</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid</td>
<td>10 mins</td>
<td>PCC</td>
</tr>
<tr>
<td>Fast (Partial)</td>
<td>1-2 hrs</td>
<td>FFP</td>
</tr>
<tr>
<td>Prompt</td>
<td>4-6 hrs</td>
<td>IV vitamin K</td>
</tr>
<tr>
<td>Slow</td>
<td>24 hrs</td>
<td>Oral vitamin K</td>
</tr>
<tr>
<td>Ultra-slow</td>
<td>2-4 days</td>
<td>Omit warfarin (No vitamin K)</td>
</tr>
</tbody>
</table>
Emergency reversal of oral anticoagulation: FFP vs PCC

British Guidelines On Warfarin reversal


• All hospitals managing patients on warfarin should stock a Prothrombin Complex Concentrate

• In emergency reversal use 25-50u/kg PCC and 5mg iv vitamin K

• rFVIIa is not recommended

• FFP produces suboptimal correction and should only be used if PCC is not available
Bleeding

Life/Limb/Sight Threatening
Contact Haematologist
- Intracranial (CT or MRI)
- Intraocular (NOT conjunctival)
- Spontaneous muscle bleed with compartment syndrome
- Pericardial
- Active bleeding from any orifice plus either BP ≤ 90 mmHg systolic, oliguria or 2 g fall in haemoglobin

Significant bleeding
- No haemodynamic compromise
  - 2 mg Vitamin K IV
  - Check INR & APTT at 4-6 hours or sooner if clinical deterioration

- Haemodynamic compromise
  - Vitamin K 5 mg IV
  - Prothrombin complex concentrate IV (Beriplex P) 30 units/kg
  - Check INR & APTT immediately
  - Inadequate correction
    - Repeat INR & APTT in 4-6 hours

Minor
- Vitamin K 2 mg PO
- Check INR at 24 hours or sooner if clinical deterioration

INR >8
- Vitamin K 1 mg PO
- Check INR & APTT at 4-6 hours or sooner if clinical deterioration

INR 4.5-7.9
- Remember to document any reason for high INR
- Omit or reduce dose or Vitamin K 1 mg PO if considered "High Risk" of bleeding

NO BLEEDING

Contact Haematologist

NB All bleeding in a patient on warfarin should be taken seriously. Bleeding may occur when the INR is therapeutic. If the INR is sub-therapeutic e.g. <1.5 bleeding may be due to factors other than warfarin and reversal may not be appropriate. If in doubt discuss with haematologist.

Intracranial (CT or MRI)
- Urgent reversal with Beriplex (see below), without waiting for CT scan. NB ensure CT scan is reported and acted on immediately.

Intraocular (NOT conjunctival)
- Urgent reversal with Beriplex (see below), without waiting for CT scan. NB ensure CT scan is reported and acted on immediately.

Spontaneous muscle bleed with compartment syndrome
- Urgent reversal with Beriplex (see below), without waiting for CT scan. NB ensure CT scan is reported and acted on immediately.

Pericardial
- Urgent reversal with Beriplex (see below), without waiting for CT scan. NB ensure CT scan is reported and acted on immediately.

Active bleeding from any orifice plus either BP ≤ 90 mmHg systolic, oliguria or 2 g fall in haemoglobin
- Urgent reversal with Beriplex (see below), without waiting for CT scan. NB ensure CT scan is reported and acted on immediately.

Oral vitamin K is safe and adequate treatment for the majority of patients. There may be some clinical circumstances when 1-2 mg IV vitamin K should be considered e.g. gross over-anticoagulation or unsteady patients

Vitamin K IV may rarely cause anaphylaxis. Give by slow IV bolus

Prothrombin complex concentrate (PCC) may induce a prothrombotic state. Use with caution in patients with DIC or decompensated liver disease

In serious but non-life-threatening bleeding (e.g. GI bleeding or epistaxis without haemodynamic compromise) prompt reversal with IV vitamin K is indicated

The use of FFP for warfarin reversal is no longer recommended
NORTHERN REGION HAEMATOLOGISTS GROUP
GUIDE TO WARFARIN REVERSAL

BLEEDING

Life / Limb / Sight Threatening

CONTACT HAEMATOLOGIST
• Intracranial (CT or MRI)
• Retroperitoneal (CT or MRI)
• Intra-ocular (NOT conjunctival)
• Spontaneous muscle bleed with compartment syndrome
• Pericardial
• Active bleeding from any orifice plus either BP \(\leq\) 90 mmHg systolic, oliguria or 2 g fall in haemoglobin

Vitamin K 5 mg IV and Prothrombin complex concentrate IV (Beriplex P) 30 units/kg

Check INR & APTT Immediately

Adequate correction

Inadequate correction

Repeat INR & APTT in 4-6 hours

Significant bleeding without haemodynamic compromise

2 mg Vitamin K IV

Check INR & APTT at 4-6 hours or sooner if clinical deterioration

Consider other factors contributing to prolonged coagulation tests eg DIC, Congenital coagulation factor deficiency, Liver disease, Inadequate replacement. Seek haematological advice
GUIDE TO WARFARIN REVERSAL

BLEEDING

Life / Limb /Sight Threatening

CONTACT HAEMATOLOGIST

- Intracranial (CT or MRI)
- Retroperitoneal (CT or MRI)
- Intra-ocular (NOT conjunctival)
- Spontaneous muscle bleed with compartment syndrome
- Pericardial
- Active bleeding from any orifice plus either BP \( \leq 90 \text{ mmHg systolic} \), oliguria or 2 g fall in haemoglobin

2mg Vitamin K IV

Check INR & APTT

at 4-6 hours or sooner if clinical deterioration

Vitamin K 5 mg IV and Prothrombin complex concentrate IV (Beriplex P) 30 units/kg

Check INR & APTT Immediately

Adequate correction

Inadequate correction

Repeat INR & APTT in 4-6 hours

Consider other factors contributing to prolonged coagulation tests eg DIC, Congenital coagulation factor deficiency, Liver disease, Inadequate replacement. Seek haematological advice

Significant bleeding without haemodynamic compromise

GI BLEEDING

CONTACT HAEMATOLOGIST

- Intracranial (CT or MRI)
- Significant bleeding

2mg Vitamin K IV

Check INR & APTT

at 4-6 hours or sooner if clinical deterioration
GI BLEEDING

Active GI bleeding plus either BP ≤ 90 mmHg systolic, oliguria or 2 g fall in haemoglobin

Vitamin K 5 mg IV and Prothrombin complex concentrate IV (Beriplex P) 30 units/kg

Check INR & APTT Immediately

Adequate correction

Inadequate correction

Repeat INR & APTT in 4-6 hours

Consider other factors contributing to prolonged coagulation tests eg DIC, Congenital coagulation factor deficiency, Liver disease, Inadequate replacement.

Seek haematological advice

Bigger dose of vitamin K
Smaller dose of PCC

Significant bleeding without haemodynamic compromise

2mg Vitamin K IV

Check INR & APTT at 4-6 hours or sooner if clinical deterioration

Pragmatic interpretation of the protocol
Key Question to Ask

In a patient with “stable” warfarin-associated GI bleeding

Give Vitamin K promptly

What are the consequences for the patient if less “stable” over the next 4 hours

If bad – give PCC
Massively over-anticoagulated
30 units/kg may not be enough
GIVE THE VITAMIN K ASAP IN GI BLEEDING!!
**Initiation**

- **Prothrombin (II)** → **Thrombin Ila**

**Endothelial surface**

- **TF** → **VIIa-TF**

**DOACs** (Direct Oral Anticoagulants)

- **Xa inhibitors**
  - Rivaroxaban
  - Apixaban
  - Edoxaban

**Thrombin Inhibitor**

- Dabigatran
GI bleeding on DOACs

- Establish which drug the patient is taking
- Establish when the last dose was taken
- PT/APTT/TT may be helpful in Xa inhibitors and dabigatran
- Specific drug levels if available
- Wait 1 – 2 half lives if possible
- General supportive measures
- IV Tranexamic Acid
- Activated charcoal (if recent ingestion)
- Do not use non specific haemostatic agents prophylactically as effectiveness unproven & thrombotic risk – consider if life/limb threatening bleeding
Management of bleeding on DOACs: specific reversal agents

- Dabigatran
  - Idarucizumab: Humanised monoclonal antibody fragment
Dabigatran reversal with iv Idarucizumab in healthy volunteers

Dabigatran reversal with Idarucizumab
Clinical endpoints

- Interim analysis of first 90 patients of 300 patient study
- Recruiting in 400 centres in 38 countries
- Group A: Major bleeding, Group B: Emergency surgery
- All got 5g of Idarucizumab over 15 min (2x 2.5g doses)

- Group A: Cessation of bleeding in 11.4 hours
- Group B: Normal haemostasis in 92%

- One thrombosis within 72hrs and four other after this time

- Pollack CV et al. NEJM 2015; 373:511-520
Idarucizumab was 100% effective in reversing
the anticoagulant effect of dabigatran

503 patients

Group A  Uncontrolled Bleeding  301
Group B  Required Urgent Surgery  201
## Indications for Dabigatran Reversal (Group A)

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>%</th>
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<tbody>
<tr>
<td>GI Bleeding</td>
<td>137</td>
<td>45.5</td>
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<tr>
<td>Intracranial</td>
<td>98</td>
<td>32.6</td>
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<tr>
<td>Trauma-related</td>
<td>78</td>
<td>25.9</td>
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<tr>
<td>Other</td>
<td>52</td>
<td>17.3</td>
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<tr>
<td>IM/Retroperitoneal</td>
<td>19</td>
<td>6.3</td>
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<tr>
<td>Pericardial</td>
<td>7</td>
<td>2.3</td>
</tr>
<tr>
<td>Intraarticular</td>
<td>5</td>
<td>1.7</td>
</tr>
<tr>
<td>Intraocular</td>
<td>1</td>
<td>0.3</td>
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<tr>
<td>Unknown</td>
<td>4</td>
<td>1.3</td>
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</table>

Pollack et al NEJM 2017 Volume 377(5):431-441
Patients Who Received More Than One Dose of Idarucizumab.

Table 3. Patients Who Received More Than One Dose of Idarucizumab.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Previous Dose of Dabigatran (mg twice daily)</th>
<th>Index Event</th>
<th>Baseline Level of Unbound Dabigatran (ng/ml)</th>
<th>Creatinine Clearance (ml/min)</th>
<th>Approximate Time to Additional Dose (hr)</th>
<th>Reason for Additional Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>60</td>
<td>Male</td>
<td>110</td>
<td>Gastrointestinal bleeding</td>
<td>955</td>
<td>25.7</td>
<td>48 hr</td>
<td>Recurrent bleeding</td>
</tr>
<tr>
<td>2</td>
<td>79</td>
<td>Male</td>
<td>110</td>
<td>Gastrointestinal bleeding</td>
<td>325</td>
<td>43.4</td>
<td>36 hr</td>
<td>Recurrent bleeding</td>
</tr>
<tr>
<td>3</td>
<td>76</td>
<td>Male</td>
<td>110</td>
<td>Hematuria</td>
<td>1360</td>
<td>15.2</td>
<td>24 hr</td>
<td>Recurrent bleeding</td>
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<tr>
<td>4</td>
<td>73</td>
<td>Male</td>
<td>110</td>
<td>Gastrointestinal bleeding</td>
<td>329</td>
<td>29.0</td>
<td>24 hr</td>
<td>Recurrent bleeding</td>
</tr>
<tr>
<td><strong>Group B</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>85</td>
<td>Female</td>
<td>75</td>
<td>Intestinal occlusion</td>
<td>51</td>
<td>31.2</td>
<td>5 days</td>
<td>New procedure</td>
</tr>
<tr>
<td>6</td>
<td>73</td>
<td>Female</td>
<td>150</td>
<td>Ischemic large bowel</td>
<td>1630</td>
<td>34.0</td>
<td>12 hr</td>
<td>Postoperative bleeding</td>
</tr>
<tr>
<td>7</td>
<td>82</td>
<td>Female</td>
<td>110</td>
<td>Catheter placement for dialysis</td>
<td>271</td>
<td>8.0</td>
<td>6 days</td>
<td>Postoperative bleeding</td>
</tr>
<tr>
<td>8</td>
<td>70</td>
<td>Male</td>
<td>110</td>
<td>Catheter placement for dialysis</td>
<td>240</td>
<td>18.6</td>
<td>3 days (dose 2); 8 days (dose 3)</td>
<td>Postoperative bleeding and new procedure</td>
</tr>
</tbody>
</table>

\textsuperscript{a} One patient who received two doses in error is not included in the table.
# Guide to the Management of Bleeding and Urgent Surgery in Patients Taking Dabigatran (a Direct Thrombin Inhibitor)

## Major Bleed

**Dabigatran**

- Consider time since last oral dose + dosing regimen, concomitant medications
- Measure FBC, U+E, eGFR, PT/aPTT/fibrinogen, thrombin time (TT)
- Dabigatran assay* if TT is abnormal

- Consider oral activated charcoal (<2 hours since ingestion)
- Local haemostatic measures (mechanical compression, surgical/endoscopic/radiological intervention)
- Blood product replacement therapy and optimisation of pH and body temperature as per major haemorrhage protocol
- Tranexamic acid (1g IV)
- If reversal is necessary, administer Idarucizumab (Praxbind®)**

## Limb / Life-threatening Bleed

**Administer Idarucizumab (Praxbind®)**

(Dialysis is an alternative means of removing dabigatran from the circulation if Idarucizumab is not available)

**Measurement of dabigatran level** may be appropriate, particularly if there is concern about impaired renal function as dabigatran is 80% renally excreted. **This is not necessary if the thrombin time is normal as the thrombin time is very sensitive to dabigatran.**

- Dabigatran assay: test available in the RVI laboratory

A level of 200-400 ng/mL at 2-4 hours post-dose reflects therapeutic anticoagulation. A level of 50-150 ng/mL is considered a trough level. A level of <30 ng/mL should reflect negligible anticoagulant effect

Please discuss with a haematologist prior to requesting measurement of drug levels

**A standard dose of 5g IV idarucizumab is administered. This is given as two boluses of 2.5g not more than 15 minutes apart. It is obtained from the RVI EAU antidote cupboard or RVI/FRH emergency drug cupboard.**

Please discuss with a haematologist prior to using Idarucizumab (Praxbind®)

Send a coagulation sample 15 mins after administration and continue to monitor any other factors that are contributing to bleeding
GUIDE TO THE MANAGEMENT OF BLEEDING AND URGENT SURGERY IN PATIENTS TAKING A FACTOR Xa ANTAGONIST

Major bleed

FXa inhibitor (rivaroxaban, apixaban, edoxaban, betrixaban)

Consider time since last oral dose + dosing regimen, concomitant medications

Measure FBC, U+E, eGFR, PT/aPTT/fibrinogen

Drug-specific assay*

- Consider oral activated charcoal (<2 hours since ingestion)
- Local haemostatic measures (mechanical compression, surgical/endoscopic/radiological intervention)
- Blood product replacement therapy and optimisation of pH and body temperature as per major haemorrhage protocol
- Tranexamic acid (1g IV)

Limb / Life-threatening bleed

Consider: Prothrombin complex concentrate (PCC)

Activated PCC (FEIBA)  rFVIIa (NovoSeven)**

No specific reversal agent exists for this class of anticoagulant. Treatment is largely supportive while waiting for the drug to be cleared

*Measurement of drug level may be appropriate, particularly if there is concern about impaired renal function as the FXa inhibitors are 25-35% renally excreted

- FXa inhibitor assay: test available in the RVI laboratory

A level of 200-400 ng/mL at 2-4 hours post-dose reflects therapeutic anticoagulation. A level of 50-150 ng/mL is considered a trough level. A level of <30 ng/mL should reflect negligible anticoagulant effect

Please discuss with a haematologist prior to requesting measurement of drug levels

**There is no published evidence to support the use of haemostatic agents (PCC/aPCC/rFVIIa) in the setting of haemorrhage or urgent surgery in patients taking a factor Xa antagonist

Please discuss with a haematologist prior to use
Recombinant FX expressed in CHO cells with 3 changes
1. Deletion of the GLA domain
2. Deletion of the activation peptide
3. Mutation (S419A) in catalytic domain

More antidotes are coming ..........

**Andexanet alfa**

Antidote for Factor Xa Inhibitors

**Properties**

- An engineered version of human FXa, lacking the direct catalytic activity of the native protein
- Acts as a Factor Xa decoy. Binds with high-affinity, blocking inhibition of FXa
Andexanet Reverses Apixaban and Rivaroxaban in Healthy Volunteers

Siegal D et al NEJM 2015
Andexanet Alfa for Acute Major Bleeding Associated With Factor Xa Inhibitors

Connolly et al NEJM, 2016

67 patients with acute bleeding

20 were found subsequently to have very little anti-Xa inhibition on board (<75 ng/ml)

49% GI Bleeding

Rivaroxaban / Apixaban

Andexanet bolus then 2 hour infusion; dose depended on time since most recent dose of Xa inhibitor
Andexanet Alfa for Acute Major Bleeding Associated With Factor Xa Inhibitors

Connolly et al NEJM, 2016

Effective Haemostasis in 79%

Thrombotic events in 18%
Aripazine - Universal DOAC antidote

- PER977 (Aripazine) from Perosphere Inc
- Synthetic small molecule (512Da)
- Binds all DOACs plus UFH and LMWH
- Action: Binding by charge-charge interaction (non-covalent) preventing the anticoagulant from binding to target
PER977 reverses ~100x overdose of dabigatran etexilate (15mg p.o.) in a rat tail transection model.
Aripazine reverses Apixaban effect

Ansell JE et al. NEJM 2014
DOACS AND THEIR REVERSAL AGENTS – THE FUTURE
Summary

• GI bleeding in anticoagulated patients remains challenging
• For warfarin the antidotes are vitamin K and PCC
• Current DOAC bleeding management is with supportive care, waiting for effect to wear off
• Idarucizimab is licensed and available for Dabigatran reversal
• Andexanet not yet licensed but likely to be available within 1-2 years
• Aripazine may be a universal antidote for Thrombin and Xa inhibitors

• When/If to re-start anticoagulation?
When/If to re-start anticoagulation after GI Bleeding

Most studies have shown an net benefit of restarting anticoagulation

Overcome reluctance to re-start

Individualise decision – type and intensity of anticoagulation