Direct Oral Anticoagulants in clinical practice:
Guidance, Management, Interactions and reversal

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Declaration of interests

• The practice has received funding from: Abbott, Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Dawn, INRStar, Medtronic, Oberoi Consulting, Pfizer, Roche, Sanofi-Aventis, Servier.

• An advisor to: Anticoagulation Europe, Arrhythmia Alliance, Heart Valve Voice, National Stroke Association, Syncope Trust

• A trustee of Thrombosis UK, AF Association
The perfect anticoagulant

- Effective
- Oral
- Fast onset of action
- Short half life
- Predictable pharmacokinetics
- No drug/food interactions
- Fully reversible

- Do the NOACs fulfill these criteria?
## Indications and Dosing

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of VTE post THR/TKR</td>
<td>110mg bd</td>
<td>2.5mg bd</td>
<td></td>
<td>10mg od</td>
</tr>
<tr>
<td>Prevention of CVA in AF</td>
<td>150mg bd</td>
<td>5mg bd</td>
<td>60mg od</td>
<td>20mg od</td>
</tr>
<tr>
<td></td>
<td>(110mg bd)</td>
<td>(2.5mg bd)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of acute VTE</td>
<td>150mg bd</td>
<td>10mg bd for 7/7</td>
<td>60mg od</td>
<td>15mg bd for 3/52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5mg bd</td>
<td></td>
<td>20mg od</td>
</tr>
</tbody>
</table>
## Renal function

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Creatinine clearance (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30-50</td>
</tr>
<tr>
<td>Apixaban</td>
<td>5mg bd</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>150mg bd (110mg bd)</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>60mg</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>15mg od</td>
</tr>
</tbody>
</table>

*AVOID*: Avoid these dosages in patients with the specified creatinine clearance.
What do NOACs interact with?
<table>
<thead>
<tr>
<th>Interaction Type</th>
<th>Outcome</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaco kinetic</td>
<td><strong>Increase</strong> of at least 50% in anticoagulant plasma concentration</td>
<td>Amiodarone, Dronedarone, Ketoconazole, Quinidine, Verapamil</td>
<td>Clarithromycin, Itraconazole, Ketoconazole, Posaconazole, Ritonavir, Voriconazole</td>
<td>Itraconazole, Ketoconazole, Posaconazole, Ritonavir, Voriconazole</td>
</tr>
<tr>
<td>Pharmaco kinetic</td>
<td><strong>Decrease</strong> of at least 50% in anticoagulant plasma concentration</td>
<td>Carbamazepine, Rifampin, St. John’s Wort</td>
<td>Carbamazepine, Phenobarbital, Phenytoin, Rifampin, St. John’s Wort</td>
<td>Carbamazepine, Phenobarbital, Phenytoin, Rifampin, St. John’s wort</td>
</tr>
<tr>
<td>Pharmaco dynamic</td>
<td><strong>Increased</strong> risk of bleeding</td>
<td>ASA, NSAIDs, Platelet aggregation inhibitors, Anticoagulants, Thrombolytics</td>
<td>ASA, NSAIDs, Platelet aggregation inhibitors, Anticoagulants, Thrombolytics</td>
<td>ASA, NSAIDs, Platelet aggregation inhibitors, Anticoagulants, Thrombolytics</td>
</tr>
</tbody>
</table>
How do NOACs affect the coagulation screen?
# Coagulation tests with Anticoagulant Drugs

<table>
<thead>
<tr>
<th>Test</th>
<th>UFH</th>
<th>LMWH</th>
<th>Warfarin</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>-</td>
<td>-</td>
<td>↑↑↑</td>
<td>↑/-</td>
<td>-/↑</td>
<td>-/↑</td>
</tr>
<tr>
<td>APTT</td>
<td>↑↑↑</td>
<td>-/↑</td>
<td>↑</td>
<td>-/↑</td>
<td>-/↑</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Thrombin Time</td>
<td>↑↑↑</td>
<td>↑</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Anti-Xa</td>
<td>↑</td>
<td>↑↑↑</td>
<td>-</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>-</td>
</tr>
<tr>
<td>Haemoclot</td>
<td>↑↑</td>
<td>↑</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>↑↑↑</td>
</tr>
</tbody>
</table>
Switching from one anticoagulant to another
Switching from warfarin to NOAC

- **Apixaban**
  - Wait till INR < 2.0
- **Dabigatran**
  - Wait till INR < 2.0
- **Edoxaban**
  - Wait till INR < 2.5
- **Rivaroxaban**
  - Wait till INR < 3.0 AF
  - Wait till INR < 2.5 DVT, PE
What to do if a dose of a NOAC is missed?

• **Once daily regimens**
  – Take the forgotten dose up to 12hrs after time of usual intake

• **Twice daily regimens**
  – Take the forgotten dose up till 6hrs after time of usual intake
Bleeding

- Local measures
- Stop NOAC temporarily
- Tranexamic acid
- Coagulation screen
- Renal function
- Discuss with haematologist if ongoing issue
Elective minor
(when warfarin would not be stopped)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixababan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor dental work</td>
<td>12 hours post dose</td>
<td>18-24 hours post dose</td>
<td>&gt;24 hours post dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major dental work</td>
<td>24 hours post dose</td>
<td>24 hours post dose</td>
<td>24-48 hours post dose</td>
</tr>
<tr>
<td></td>
<td>Next dose &gt; 4 hours post procedure</td>
<td>Next dose &gt; 4 hours post procedure</td>
<td>Next dose &gt; 4 hours post procedure</td>
</tr>
<tr>
<td>Upper/lower Endoscopy + simple biopsy</td>
<td>24 hours post dose</td>
<td>24 hours post dose</td>
<td>24-48 hours post dose</td>
</tr>
<tr>
<td>Cataract removal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint injection</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NHS GGC Guidance based on SPC Dabigatran, Rivaroxaban, Apixababan
Emergency Surgery and Bleeding
Warfarin

- **Vitamin K**
  - IV 6 hours
  - PO 24 hours

- **Prothrombin complex concentrates (PCCs)**
  - Factors II, VII, IX, X
  - Reversal within 30 minutes

- Can assess INR for effectiveness/safety
NOACs

• No specific reversal agent
• Well-adsorbed to activated charcoal
  – give within two hour of swallowing
• Dialysis
  – Dabigatran – yes
  – Rivaroxaban, apixaban – no
• General principles
  – Check coagulation screen
    • Assess effect
  – Check renal function
    • Assess half life
• Products
  – largely speculation/ based on non-clinical data
  – off-licence use; safety issues (thrombosis)
Vitamin K - no Immediate Effect on INR

- Schematic diagram showing effect of vitamin K on INR
- Vitamin K has a slow onset (>24 hours)\(^1\)
  - Vitamin K supports generation of normal, functioning clotting factors in the liver
  - Effectivity of INR normalization depending on VKA used (different half-lifes; (from 9–11 hours for acenocoumarol, to 90–140 hours for phenprocoumon)\(^1,2\)

Emergencies in Anticoagulated Patients

- Schematic diagram showing PK/PD characteristics of VKA and rivaroxaban
  - Reversal strategies may be required if action of drug is long and needs to be antagonized in emergency situations

PD, pharmacodynamic; PK, pharmacokinetic; \( t_{1/2} \), half-life

Rivaroxaban-Induced Anticoagulation Reversal with PCC

- 20 mg rivaroxaban was administered bid for 2.5 days followed by PCC (Prothrombin Complex Concentrate - Cofact®, 50 U/kg body weight)
- Prolongation of PT was reversed completely by PCC
- ETP was reversed by PCC with an overshoot in effects
- Limitation
  - PT agent used showed low sensitivity to rivaroxaban
  - Prolongation of PT in this study was approximately 4 seconds at maximum

## Specific Reversal Agents for Non-VKA Oral Anticoagulants

<table>
<thead>
<tr>
<th>Company</th>
<th>Compound</th>
<th>Reversal for:</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>**Portola Pharma-</td>
<td>PRT064445/</td>
<td>Factor Xa inhibitor</td>
<td>Yes (antithrombin-mediated Factor Xa inhibition)</td>
</tr>
<tr>
<td>ceuticals</td>
<td>(andexanet alfa)</td>
<td>Factor IIa inhibitor</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LMWH/fondaparinux</td>
<td>No</td>
</tr>
<tr>
<td>**Boehringer Ingelhe</td>
<td>BI 655075 (idarucizumab)</td>
<td>No</td>
<td>Specific for dabigatran</td>
</tr>
<tr>
<td>**Perosphere, Inc.</td>
<td>PER977 (aripazine)</td>
<td>Universal</td>
<td>Universal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LMWH/fondaparinux</td>
<td>Universal</td>
</tr>
</tbody>
</table>
Idarucizumab development process

- Monoclonal mouse antibody developed with high dabigatran binding affinity
- Monoclonal antibody was then humanized and directly expressed as a Fab fragment in mammalian cells
Idarucizumab mode of action

Idarucizumab rapidly binds to dabigatran in the plasma

Idarucizumab alters the equilibrium – dabigatran dissociates from thrombin
Guideline for management of bleeding (and urgent reversal in case of need for emergency surgery) in patients on rivaroxaban

Rivaroxaban is an oral factor Xa inhibitor with a half-life of 7-11 hours and mostly renal 66% excretion. There is no licensed reversal agent for rivaroxaban.

Rivaroxaban-related bleeding
Or requirement for urgent reversal in case of need for emergency surgery

STOP rivaroxaban

- Assess clinical bleeding\(^1,2\) and resuscitate patient as appropriate. May need to act before lab results are back in emergency.
- Check: FBC, G&S, U&E and Clotting screen, PT, APTT, TT, Fibrinogen, d-dimer
- Rivaroxaban prolongs PT – if PT is normal rivaroxaban levels are low.
- Consider rivaroxaban plasma level
- Indicate time of last rivaroxaban dose when requesting test and considering management options.

Mild bleeding

- Delay next dose or discontinue treatment as appropriate.
- With normal renal function level of rivaroxaban reduces rapidly in 24 hours
- Monitor clotting screen and PT

Moderate-Severe bleeding

- Discuss with haematologist on call

Activate massive haemorrhage pathway
- Symptomatic treatment
- Consider tranexamic acid (avoid in DIC)
- Mechanical compression
- Surgical intervention
- Activated charcoal if rivaroxaban ingestion < 2 hours before
- Fluid replacement and haemodynamic support - ensure good diuresis
- Consider Prothrombin complex concentrate (Octaplex) (50 units/Kg), max 3000 units, IV infusion at 10ml/min
- blood product support as indicated
- consider role for interventional vascular radiology

Life-threatening or site critical bleeding

- Discuss with haematologist on call

- Manage as for Moderate-Severe bleeding
- Give Prothrombin complex concentrate (Octaplex) (50 units/Kg), max 3000 units, IV infusion at 10ml/min

Reassess clinically
- Repeat FBC, U&E, Clotting, PT and rivaroxaban level to be monitored

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\(^1\)Moderate to Severe bleeding: - reduction in Hb ≥ 2g/dL, transfusion of ≥ 2 units of red cells or symptomatic bleeding in critical area (i.e. intracardiac, intracranial, intraspinal, intramuscular with compartment syndrome, retroperitoneal, intraarticular or pericardial bleeding).

\(^2\)Life-threatening bleeding: – symptomatic intracranial bleed, reduction in Hb ≥ 5g/dL, transfusion of ≥ 4 units of red cells, hypotension requiring inotropic agents or bleeding requiring surgical intervention.
Practical Considerations
Starting a patient on a NOAC

• Check patient is not taking interacting drugs
• Counsel patient: it is an anticoagulant
  – Head injury, trauma, melaena, significant GI bleed, prolonged epistaxis, large ecchymoses/haematoma
• Compliance- important to take as advised (od Rivaroxaban, bd Apixaban, bd Dabigatran)
• Baseline FBC, renal and liver function
Summary of use of NOACs

• Benefits of novel anticoagulants
  – Non inferior/superior to warfarin
  – More stable anticoagulation (in patients poorly controlled on warfarin)
  – Shorter half life
  – No requirement for anticoagulant monitoring
  – Fewer drug-drug interactions
  – No food-drug interactions
  – Less intracranial bleeding

• But
  – Limited reversal options
  – Increased drug costs compared to warfarin
  – Current lack of familiarity
Bleeding

- Local measures
- Stop NOAC temporarily
- Tranexamic acid
- Coagulation screen
- Renal function
- Discuss with haematologist if ongoing issue
Monitoring of Anticoagulants
Thank you for your attention

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