Management of Anticoagulation in Hip Fracture

Dr Tim Brighton
Consultant Haematologist
Clinical Director Haematology SEALS POWH
Issues in Hip Fracture

- Thromboprophylaxis
- Management of patients taking antithrombotic medication who require hip fracture surgery
Hip Fracture patients are at high risk of thromboembolism.

Some patients with hip fracture are at very high risk due to co-morbidities:
- Active cancer
- Prior history of VTE
- Chronic venous insufficiency/VV
- Obesity
- Other conditions leading to poor post-operative mobility
Thromboprophylaxis is routine in Hip #

- **Optimal agent**
  - LMWH, fondaparinux, DOACs

- **Optimal timing**
  - pre-operative and re-commence 8-12 hours post-operatively

- **Duration**
  - Most guidelines recommend extended TP to 35 days post-operatively

- **Mechanical TP**
  - IPC intra-operatively and whilst immobile

- **Very high risk patients**
  - Need anticoagulant + mechanical TP and consider therapeutic anticoagulation post-operatively
Bridging Therapy

Admission with Hip #

Patient on antithrombotic therapy

Pre-op period  Surgery  Post-op period

Target AC

No AC
Warfarin and acute Surgery

• Identify indication for warfarin and need to peri-operative anticoagulation
• Measure INR
• <1.5 fit for surgery
• >1.5 need reversal prior to surgery
  – Immediate reversal with FFP or prothrombinex
  – Vitamin K 1-2mg if OT 24 hrs
• Need to plan post-operative anticoagulation before surgery
Direct Oral Anticoagulant Drugs (DOACs)
Anticoagulant Drugs – mechanism action

**Intrinsic Activation**
- Surface contact
  - Factor XII

**Extrinsic Activation**
- Vessel Injury
  - Factor VII

**Factor Xa**
- Factor VIII
- Factor IXa

**Factor Xa Inhibitors**
- Rivaroxaban, Apixaban

**Vitamin K Antagonists**
- Inhibit factors II, VII, IX, and X

**Factor Xa**
- Prothrombin
- Thrombin

**Antithrombins**
- Dabigatran etexilate

**Pentasaccharide**
- Antithrombin

**LMWH / UFH**
- Fibrinogen
- Fibrin
## New Oral Direct Anticoagulants (1)

<table>
<thead>
<tr>
<th>Generic</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Dabigatran Etexilate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade</td>
<td>Xarelto®</td>
<td>Eliquis ®</td>
<td>Pradaxa®</td>
</tr>
<tr>
<td>Target</td>
<td>Activated Factor X</td>
<td>Activated Factor X</td>
<td>Thrombin (IIa)</td>
</tr>
<tr>
<td>Prevention VTE</td>
<td>Authority</td>
<td>Authority</td>
<td>Authority</td>
</tr>
<tr>
<td>Arthroplasty</td>
<td>Authority</td>
<td>Authority</td>
<td>Authority</td>
</tr>
<tr>
<td>Stroke Prevention - NVAF + ≥ 1 RF</td>
<td>Streamline authority</td>
<td>Streamline authority</td>
<td>Streamline authority</td>
</tr>
<tr>
<td>Acute DVT/PE</td>
<td>Streamline authority</td>
<td>Streamline authority</td>
<td>TGA indication</td>
</tr>
<tr>
<td>Prevention VTE</td>
<td>Streamline authority</td>
<td>Streamline authority</td>
<td>TGA indication</td>
</tr>
</tbody>
</table>
## Oral Direct Anticoagulants (4)

<table>
<thead>
<tr>
<th>Generic</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Dabigatran Etexilate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapidly acting</td>
<td>Onset action at (\sim) 30 mins with time to (T_{\text{max}}) 2.5-4 hrs with Rv &amp; Ap, 0.5-2hrs with DE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Half-life</td>
<td>5-9 hrs (11-13 hrs elderly)</td>
<td>9-14 hrs</td>
<td>7-9 hrs (12-14 hrs elderly)</td>
</tr>
<tr>
<td>Excretion</td>
<td>33% Renal</td>
<td>25% Renal</td>
<td>80% Renal</td>
</tr>
<tr>
<td>Hepatic metabolism</td>
<td>66% – CYP3A4, 2J2 and CYP-independent</td>
<td>75% - CP3A4/5</td>
<td>No</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>Potent CYP3A4 &amp; P-glycoprotein inhibitors/inducers</td>
<td></td>
<td>PPI ↓ absorption PGI 2-fold ↑ AUC</td>
</tr>
<tr>
<td>Contra-Indications</td>
<td>Severe renal or hepatic disease</td>
<td>Severe renal or hepatic disease</td>
<td>Severe renal or hepatic disease</td>
</tr>
<tr>
<td>Antidote</td>
<td>In development</td>
<td>In development</td>
<td>Idarucizumab</td>
</tr>
</tbody>
</table>
DOACs and Acute Surgery

• Identify indication for DOAC and requirements for peri-operative anticoagulation

• Need to know
  – Dose and schedule, time last dose, weight & serum creatinine (and calculate Cl_{CR})

• Need to measure
  – APTT, TT, and Haemoclot if dabigatran
  – APTT PT and anti-Xa assay for rivaroxaban or apixaban

• Prolongation clotting times (APTT/ PT) are variable with each DOAC and with varying reagents/analysers

• Drug assays take 24 hrs or longer
Dabigatran and Acute Surgery

• Need to know
  – Dose and schedule, time last dose, weight & creatinine (calculate $\text{Cl}_{\text{CR}}$)
• Need to measure
  – APTT, TT, and Haemoclot if dabigatran
• Prolongation PT/APTT variable between reagents
  • TT is very sensitive to dabigatran
  • Abnormal APTT $\sim 25$-$50$ng/ml and PT $\sim 100$ng/ml
  • APPT ratio 1.5 and 2.0 at $\sim 100$ng/ml and $\sim 300$ng/ml respectively
  • INR 2.0 at $\sim 500$ ng/ml
• Normal TT = no drug = surgery can proceed
• AbN TT & Normal APTT = low level drug so surgery can proceed (or delay 24 hours)
• Abn TT & APTT = significant drug level so either
  – Delay surgery pending drug assay
  – Surgery with reversal with Idarucizumab (Praxbind)
## Pre-operative approach to NOACs

spyropoulos ac, douketis jd blood 2012:120(15):2945-2962

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal Function</th>
<th>Low bleeding risk ¶</th>
<th>High bleeding risk §</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 150mg twice daily (t½ ~ 12-17 hrs)</td>
<td>Cl&lt;sub&gt;cr&lt;/sub&gt; ≥50 mls/min</td>
<td>4 doses</td>
<td>6 doses</td>
</tr>
<tr>
<td></td>
<td>Cl&lt;sub&gt;cr&lt;/sub&gt; 30-49 mls/min</td>
<td>6 doses</td>
<td>8-10 doses</td>
</tr>
<tr>
<td>Rivaroxaban 20mg once daily (t½ ~ 5-13 hrs)</td>
<td>Cl&lt;sub&gt;cr&lt;/sub&gt; ≥50 mls/min</td>
<td>1 dose</td>
<td>3 dose</td>
</tr>
<tr>
<td></td>
<td>Cl&lt;sub&gt;cr&lt;/sub&gt; 30-49 mls/min</td>
<td>1 dose</td>
<td>3 doses</td>
</tr>
<tr>
<td>Apixaban 5mg twice daily (t½ ~ 8-15 hrs)</td>
<td>Cl&lt;sub&gt;cr&lt;/sub&gt; ≥50 mls/min</td>
<td>2 doses</td>
<td>4 doses</td>
</tr>
<tr>
<td></td>
<td>Cl&lt;sub&gt;cr&lt;/sub&gt; 30-49 mls/min</td>
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¶ Interval last dose and surgery 2-3 half lives
§ Interval last dose and surgery 4-5 half lives
Figure 1 Time Course of the Dilute Thrombin Time before and after the Administration of Idarucizumab. The analyses included 39 who required urgent surgery or intervention. Idarucizumab was administered in two infusions. Blood samples were obtained at baseline, after the first infusion, at 10 to 30 minutes after the administration of the second infusion, and at 1, 2, 4, 12, and 24 hours.
Rivaroxaban and Acute surgery

- **Need to know**
  - Dose and schedule, time last dose, weight & creatinine (calculate Cl\textsubscript{CR})

- **Need to measure**
  - PT, APTT, and specific a-FXa assays
  - Prolongation PT > APTT
    - PT doubled at ~100ng/ml
    - APTT doubled at ~300ng/ml

- Normal PT & APTT = Low level drug (<50ng/ml) = *most* surgery can proceed
- Abnormal PT & Normal APTT = delay surgery if possible pending drug assay
- Abnormal PT & APTT = higher drug level so delay surgery if possible pending drug assay otherwise expect bleeding
Apixaban and acute surgery

• Need to know
  – Dose and schedule, time last dose, weight & creatinine (calculate Cl\textsubscript{CR})

• Need to measure
  – PT, APTT, and specific a-FXa assays

• Clotting times minimally prolonged even at therapeutic apixaban levels so APTT/PT unhelpful and reliant on specific drug assay.

• Emperic delay in surgery according to expected/measured drug concentration

• No reversal strategy available

• Surgery often can be done with supportive management
Reversal Direct anti-Xa AC in development

Siegel DM et al NEJM 2015;373:2413-2424

D  Rivaroxaban Study, Andexanet Bolus plus Infusion

- Placebo (N=13)
- Andexanet (N=26)

Anti-Factor Xa Activity (ng/ml) vs Hours since Bolus

End of bolus
End of infusion
Thank-you Questions

Timothy.Brighton@health.nsw.gov.au