How I Treat ......

Distal DVT with New Anticoagulant Drugs

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SEALS, PO WH
What is distal DVT?

- Sapheno-femoral junction
- Ext Iliac V
- Femoral V
- Popliteal V
- Long Saphenous V
- Post Tibial V
- Peroneal V
- Ant. Tibial V
- Dorsal Venous Arch
Major Clinical Questions

1. Does isolated calf DVT need anticoagulant therapy?
2. Are distal DVT all the same?
3. Which anticoagulant - NOAC?
4. What duration?
Does distal DVT need anticoagulation?

Why treat VTE

1. Prevent fatal PE
2. Prevent non-fatal PE
3. Prevent proximal propagation
4. Prevent symptomatic recurrent VTE
5. Prevent post-thrombotic syndrome
6. Relief of symptoms
Distal DVT ~ 50% of leg DVT

Distal DVT - outcomes are not exactly known

1. Fatal PE - very uncommon
   <= 1% if no AC versus 1-2% major Hx on AC

2. Non-fatal PE - Lagerstedt et al 1985 suggested a role in high risk patients

3. Proximal propagation in leg - maybe 10% with no AC (0-44% in heterogeneous studies) versus ~2% with AC

4. Symptomatic recurrence - uncommon
   Symptomatic pts with negative proximal CUS or symptomatic pts with negative complete CUS have similar 3m rates of VTE ~ 0.4-0.6%

5. Post-thrombotic syndrome - uncommon

6. No studies on symptom relief
Does distal DVT need anticoagulation?

Role of anticoagulation not proven

Options

1. No initial anticoagulant therapy with repeat scan 1-2 wks and AC for those who propagate to proximal veins

2. Short term AC 2-6 weeks

3. Longer term AC for 3 months

Guidelines

BCSH recommend minimum 6 weeks AC

CHEST ACCP recommend 3 months AC

In practice most patients receive anticoagulant therapy
Are distal DVT all the same?

NO

Risks of adverse outcomes (propagation into proximal veins, non-fatal and fatal PE) higher in patients with permanent risk factors (e.g. active cancer)

Risks of recurrent VTE after AC therapy higher also in patients with permanent risk factors

Implications for practice (and recommendations):

- Temporary risk factors - short duration AC and symptom directed therapy
- Ongoing/permanent risk factors - at least 6-12 wks and maybe longer
Which Anticoagulant for distal DVT?

Intrinsic Activation
- Surface contact
  - Factor XII
  - Vitamin K Antagonists: Inhibit factors II, VII, IX, and X

Extrinsic Activation
- Vessel Injury
  - Factor VII

Factor XII
- Factor IXa
- Factor X
- Factor VIII

Factor Xa Inhibitors
- Rivaroxaban, Apixaban

Factor Xa
- Antithrombin
- LMWH / UFH
- Pentasaccharide

Prothrombin
- Thrombin
- Anti-thrombins
  - Dabigatran etexilate

Fibrinogen
- Fibrin
Novel Oral Anticoagulant Drugs
### 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>Registered Formulation</td>
<td>10, 15, 20 mg tablets</td>
<td>2.5 &amp; 5mg tablets</td>
<td>75, 110 &amp; 150mg capsules</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>&gt;80%</td>
<td>50%</td>
<td>6%</td>
</tr>
<tr>
<td>Pro-drug</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Target</td>
<td>Activated Factor X</td>
<td>Activated Factor X</td>
<td>Thrombin (IIa)</td>
</tr>
<tr>
<td>In vitro Coagulation</td>
<td>Variable prolongations of PT &gt; APTT (at peak drug levels)</td>
<td>No ↑ SBT or effect on platelet aggregation</td>
<td>Several actions of IIa are inhibited at least in vitro</td>
</tr>
<tr>
<td>Other actions</td>
<td>Nil known</td>
<td>Nil known</td>
<td></td>
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</tbody>
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### Oral Direct Anticoagulants (2)

<table>
<thead>
<tr>
<th>Generic</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Dabigatran Etexilate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapidly acting</strong></td>
<td>Onset action at ~ 30 mins with time to Tmax 2.5-4 hrs with Rv, 0.5-2hrs with DE</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Half-life</strong></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><strong>Schedule</strong></td>
<td>15 mg twice daily 3 wks, then 20mg once daily (15mg if renal impairment or risks of bleeding)</td>
<td>10 mg twice daily for 1 week, then 5mg twice daily (2.5 mg twice daily if risks of bleeding)</td>
<td>Initial parenteral AC for minimum 5 days then 150mg twice daily (110 if renal impairment)</td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>66% Renal</td>
<td>25% Renal</td>
<td>80% Renal</td>
</tr>
<tr>
<td><strong>Hepatic metabolism</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Drug Interactions</strong></td>
<td>Potent CYP3A4 &amp; P-glycoprotein inhibitors/inducers</td>
<td></td>
<td>PPI ↓absorption</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PGI 2-fold ↑AUC</td>
</tr>
<tr>
<td><strong>Antidote</strong></td>
<td>No</td>
<td>No</td>
<td>Yes (Idarucizumab)</td>
</tr>
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Pre-treatment requirements for AC

Has to be symptomatic (and no other alternative diagnosis)

Has to be objectively proven DVT

No symptoms of PE

No contraindications to anticoagulation

Baseline pathology FBC, EUC, LFTs, coagulation studies (APTT, PT, Fibrinogen)

Measure weight and calculate GFR

Check medications (avoid aspirin and NSAIDS, certain medications contraindicated)
### Who is not suitable for NOAC?

<table>
<thead>
<tr>
<th>Special Populations</th>
<th>Other Considerations</th>
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<tbody>
<tr>
<td>Pregnancy</td>
<td>High risk bleeding</td>
</tr>
<tr>
<td>Cancer-associated thrombosis ( &amp; secondary prevention)</td>
<td>Bleeding disorder</td>
</tr>
<tr>
<td>Prosthetic Heart Valves</td>
<td>Severe renal impairment</td>
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<tr>
<td>Paediatrics</td>
<td>Liver disease/ Failure</td>
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<tr>
<td>Untested populations</td>
<td>Certain medications ( anti-fungals, anti-retroviral protease inhibitors, anticonvulsants, macrolide antibiotics)</td>
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<tr>
<td>? Catheter-related</td>
<td>Expected poor compliance</td>
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<td>? HIT</td>
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Distal DVT ~50% of all DVT in Australia

Generally recommend anticoagulation for effective relief of symptoms if no contraindications to therapy

Duration of treatment varies according to clinical context (temporary 2-6 wks versus 6-12 wks if ongoing-permanent factors for propagation & recurrence)

NOACs are drugs of choice for the majority of patients