Lower Limb Venous Thrombosis
Is there anything new?

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Content

• Aims in DVT Management
• Investigation of Deep Vein Thrombosis
  – Is there anything new?
  – Guidelines, New technologies
• Acute Management
  – Anticoagulation
  – Thrombolysis/Pharmacomechanical thrombectomy
• Ongoing Management
  – Duration of Anticoagulation
  – Compression Hosiery
• Patient Centred Care: Safe Patient Systems
What are our aims in DVT care?

• Reduce morbidity associated with the disease and its’ investigations
  – Patient Centred Care
  – Accurate Diagnosis
  – Avoid/ reduce immediate complications
    • Extension of DVT/ PE
    • Complications of treatment
  – Symptomatic Benefit
    • Rapid clot resolution
  – Prevent long term complications
    • Recurrent events
    • Post thrombotic syndrome/ CTEPH
Venous Thromboembolism

- Incidence 1-2 per 1000 per year
  - Increases with age: >1:100 in over 80s
- Approximately 2/3 will present with DVT
  - Pulmonary embolism in >50% of those with DVT
- Mortality DVT 1-2%
- Post thrombotic syndrome
  - 50% discolouration, swelling, discomfort
  - 25% pain, ulceration
- Mortality PE 10-25%
  - CTEPH 2-8%
Accurate Diagnosis

• Avoid unnecessary treatment
  – Expose patients to risk of anticoagulation

• Avoid treatment omission
  – Risk of extension DVT, embolisation
  – Higher risk of adverse outcomes?
American Society of Hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism

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Background: Modern diagnostic strategies are associated with improved outcomes for patients with venous thromboembolism (VTE). These guidelines are intended to support clinicians and other health care providers in their decisions about the use of anticoagulants for the management of VTE. These guidelines assume the clinician has already made a diagnosis of venous thromboembolism associated with a major bleeding event and the patient is at high risk of recurrence.

Objectives: The evidence-based guidelines of the American Society of Hematology (ASH) are intended to support patients, clinicians, and other health care professionals in their decisions about the use of anticoagulants in the management of VTE. These guidelines assume the clinician has already made a diagnosis of venous thromboembolism associated with a major bleeding event and the patient is at high risk of recurrence.

Methods: ASH formed a multidisciplinary guideline panel to minimize potential bias from conflicts of interest. The McMaster University GRADE Centre supported the guidelines development process, including updating or performing systematic evidence reviews. The panel prioritized clinical questions and outcomes according to their importance for clinicians and patients. The Guidance of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess evidence and make recommendations, which were subject to public comment.

Results: The panel agreed on 25 recommendations and 2 good practice statements to optimize management of patients receiving anticoagulants.

Guideline recommendations: Is there anything new?

• Use a validated clinical decision rule (eg Wells) with ddimer testing.
  – Ddimer no utility in post surgery or in pregnancy

• Lower limb ultrasound- either to above knee or full leg if available
  – In intermediate/high risk patients who had negative proximal US, repeat in one week

• In ? recurrent VTE- ddimer still useful- compare US with previous scans
## Wells score for investigation DVT

<table>
<thead>
<tr>
<th>Wells score or criteria</th>
<th>Score (points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>Active cancer (treatment within last six months or palliative)</strong></td>
<td>1</td>
</tr>
<tr>
<td>2. Calf swelling $&gt; 3$ cm compared to other calf (measured 10 cm below tibial tuberosity)</td>
<td>1</td>
</tr>
<tr>
<td>3. <strong>Collateral superficial veins (non-varicose)</strong></td>
<td>1</td>
</tr>
<tr>
<td>4. <strong>Pitting oedema (confined to symptomatic leg)</strong></td>
<td>1</td>
</tr>
<tr>
<td>5. <strong>Swelling of entire leg</strong></td>
<td>1</td>
</tr>
<tr>
<td>6. <strong>Localized pain along distribution of deep venous system</strong></td>
<td>1</td>
</tr>
<tr>
<td>7. <strong>Paralysis, paresis, or recent cast immobilization of lower extremities</strong></td>
<td>1</td>
</tr>
<tr>
<td>8. <strong>Recently bedridden $&gt; 3$ days, or major surgery requiring regional or general anesthetic in past four weeks</strong></td>
<td>1</td>
</tr>
<tr>
<td>9. <strong>Alternative diagnosis at least as likely</strong></td>
<td>subtract 2</td>
</tr>
</tbody>
</table>

**Interpretation:** For dichotomised evaluation (likely v unlikely)

- **Score of 2 or higher**
  - Deep vein thrombosis is likely.
  - Consider imaging the leg veins.

- **Score of less than 2**
  - Deep vein thrombosis is unlikely.
  - Consider blood test such as D-dimer test to further rule out deep vein thrombosis.
NICE Guidelines

Diagnosis of deep vein thrombosis (DVT)

Patient with suspected DVT

Two-level DVT Wells score

'Likely'

Is a proximal ultrasound scan available within 4 hours?

Yes

Was the proximal ultrasound scan positive?

Yes

D-dimer test + LMWH** or UFH** + proximal ultrasound scan within 24 hours***

No

D-dimer test

Was the D-dimer test positive?

Yes

Repeat proximal ultrasound scan 6–8 days later

Diagnose DVT and start treatment

No

Was the repeat proximal ultrasound scan positive?

Yes

Diagnose DVT and start treatment

No

Take into consideration alternative diagnoses. Advise the patient it is not likely they have DVT.

'Unlikely'

D-dimer test

Was the D-dimer test positive?

Yes

LMWH** or UFH** + proximal ultrasound scan within 24 hours***

No

Was the proximal ultrasound scan positive?

Yes

Diagnose DVT and start treatment

No

Take into consideration alternative diagnoses. Advise the patient it is not likely they have DVT.
Is there anything new in diagnosis?

ThinkSono

Blood and Transplant

Automatic-DVT diagnostic software for the detection of Deep Venous Thrombosis.

PROUD TO MAKE A DIFFERENCE
SHEFFIELD TEACHING HOSPITALS NHS FOUNDATION TRUST
Acute Management

• Avoid/Reduce immediate complications
  – Extension of DVT and PE
  – Complications of treatment

• Anticoagulation
  – LMWH
  – Direct Oral Anticoagulants
  – Warfarin

• Removal of acute thrombosis
  – Thrombolysis/ pharmacomechanical thrombectomy
# Anticoagulants for VTE

<table>
<thead>
<tr>
<th>Injectable therapies</th>
<th>Vitamin K Antagonists</th>
<th>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>[Lepirudin/Bivalirudin]</td>
<td></td>
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</tr>
</tbody>
</table>
ASH Guideline Recommendations

• For patients with high BMI who are receiving LMWH- dose as per actual body weight
• For patients taking medication that inhibits or induces CYP p450 or P-glycoprotein- avoid DOACs
• For patients receiving treatment for VTE- recommends specialist care rather than GP (usual healthcare provider)
Contraindications to DOACs

- Renal failure
  - Avoid if creatinine clearance <30mL/min, care if <15mL/min
- Liver failure
  - Childs B/C
- Pregnancy
  - If planning a pregnancy consider refer to joint haem/obs clinic for consultation before conception. Switch to LMWH ASAP once pregnant.
- Breastfeeding
- Care in individuals at high body weight....?
  - Emerging data more reassuring
- Malignancy
  - If AF on a DOAC continue unless interactions with chemotherapy
  - VTE- particularly if GI luminal tumour
- Mechanical heart valves
  - OK if tissue valve
  - NOT if mechanical heart valve
## Acute VTE Treatment and DOACs

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Initial treatment</th>
<th>Maintenance</th>
<th>Secondary Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>• 15mg bd 21 days</td>
<td>• 20mg od for at least 3 months</td>
<td>• 10mg od</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 15mg od if high bleeding risk</td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>• 10mg bd 5 days</td>
<td>• 5mg bd for 6 months</td>
<td>• 2.5mg bd</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>• Parenteral anticoagulant for 5 days</td>
<td>• 150mg bd for at least 3 months</td>
<td>• 150mg bd</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Consider 110mg dose if gastritis, oesophagitis, GI reflux, high bleeding risk</td>
<td>• 110mg bd if &gt;80yrs, Consider 110mg dose if gastritis, oesophagitis, GI reflux, high bleeding risk</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>• Parenteral anticoagulant for 5 days</td>
<td>• 60mg od for at least 3 months</td>
<td>• 60mg od for at least 3 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 30mg od if:</td>
<td>• 30mg od if:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Moderate/ severe renal impairment, Weight &lt;60kg</td>
<td>• Moderate/ severe renal impairment, Weight &lt;60kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Drug interactions- ciclosporin, dronaderone, ketoconazole, erythromycin</td>
<td>• Drug interactions- ciclosporin, dronaderone, ketoconazole, erythromycin</td>
</tr>
</tbody>
</table>
Liverpool HIV drug interaction checker

<table>
<thead>
<tr>
<th>HIV Drugs</th>
<th>Co-medications</th>
<th>Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Apixaban</td>
<td>No Interaction Expected</td>
</tr>
<tr>
<td>Abacavir</td>
<td>Apixaban</td>
<td>Abacavir</td>
</tr>
<tr>
<td>Atazanavir alone</td>
<td>Apixaban</td>
<td>Apixaban</td>
</tr>
</tbody>
</table>
Clinical Case- Thrombolysis/ Thrombectomy

• Ms SK, 34yrs old
• Recently returned from New York
  – Family history of VTE
• 2 day history pain left lower leg with increasing swelling
• On examination entire leg swollen and dusky discolouration- pulses present, acutely painful
• Wells: DVT likely
  – Ddimers 8762
• Iliofemoral clot on Doppler US scan
• Treatment dose LMWH (dalteparin 18,000iu), leg elevation
• Should she be offered thrombectomy/ thrombolysis?
DVT and PTS

• Anticoagulation
  – Stops PE but not PTS
    • 10–15% recanalisation
      – Most in first 10 days (up to 90 days)
      – Valve dysfunction

• Thrombolysis- early reduction of clot burden
  – Improved QoL
  – Reduces PTS
    • Incidence and severity
Iliofemoral DVTs confer the highest risk of PTS

Iliofemoral DVTs confer the highest anatomic risk for developing the post-thrombotic syndrome

<table>
<thead>
<tr>
<th></th>
<th>Mean Change in Villalta Score over 2 Years (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Popliteal</td>
<td>$-0.11 \ (\ -1.08 \ to \ +0.87)$</td>
<td>0.83</td>
</tr>
<tr>
<td>Superficial femoral</td>
<td>$+0.79 \ (\ -0.13 \ to \ +1.71)$</td>
<td>0.091</td>
</tr>
<tr>
<td>Common femoral or iliac</td>
<td>$+2.23 \ (\ +1.29 \ to \ +3.16)$</td>
<td>$&lt;0.001$</td>
</tr>
</tbody>
</table>

American College of Chest Physicians

• Catheter-directed lysis
  – For acute symptoms and PTS
  – If:
    • Expertise and resources available
    • Iliofemoral DVT
    • Symptoms <14 days
    • Good functional status
    • Life expectancy >1 year
    • Low risk of bleeding

• 2016

Catheter-Directed Thrombolysis for Acute DVT of the Leg
16. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over CDT (Grade 2C).

Remarks: Patients who are most likely to benefit from CDT (see text), who attach a high value to prevention of postthrombotic syndrome (PTS), and a lower value to the initial complexity, cost, and risk of bleeding with CDT, are likely to choose CDT over anticoagulation alone.

Cochrane Review Conclusion

• Thrombolysis increases the patency of veins and reduces the incidence of PTS following proximal DVT by a third…. Strict eligibility criteria appears to improve safety in recent studies…. In those that are treated there is a small increased risk of bleeding… the results across studies were consistent and we have reasonable confidence in these results

Watson et al, Thrombolysis for acute DVT, Cochrane Review, 2016
Catheter-directed lysis: works for very fresh venous thrombosis

- Catheter embedded into clot
  - Low-dose infusion
  - Catheter repositioning
- Average treatment time 40 hours
  - Monitored bed
  - Repeated trips to angiography suite
  - Patient discomfort and confined to bed
  - Repeat blood tests
    - Clotting/fibrinogen
- Risk of systemic effects of lysis
Alternative Methodologies

• If longer clot time
  – >2 or 3 days
  – <10 days

• Mechanical and pharmacomechanical
  – AngioJet®
  – Trellis™
  – Ekos
Clinical case continued

• Offered thrombolysis - accepted
• Pharmaco-mechanical clot clearance day after presentation
• Discharged day +2 on LMWH
• Saw Thrombosis CNS 3 days later - swelling much improved, switched to DOAC
• Leg ‘back to normal’ at 3 weeks
• At 6 months, DOAC dose reduced (secondary prevention dose)
• No symptoms PTS
• 692 patients with proximal DVT assigned to anticoagulation alone, or anticoagulation plus pharmacomechanical thrombolysis
• No difference in PTS (47% PMT, 48% control)
• More bleeding with PTS (1.7% vs 0.3%)
• Moderate-severe PTS in 18% PMT vs 24% controls
• PTS severity scores lower for PMT group cw controls
Prevent Long Term Complications

- Duration of Anticoagulation
- Compression Hosiery
VTE: Aims of anticoagulant therapy

Venous thromboembolic event

Decision point

Acute
1. Heparin/LMWH or fondaparinux together with a VKA (e.g. warfarin) until an INR of 2.0–3.0 achieved
2. Rivaroxaban
3. Apixaban
4. LMWH/ Dabigatran
5. LMWH/ Edoxaban

Continue
1. VKA (e.g. warfarin) INR 2.0–3.0
2. Rivaroxaban
3. Dabigatran
4. Apixaban
5. LMWH
6. Fondaparinux
7. Edoxaban

How long?
3–6 months or lifelong?

Duration of anticoagulation: risk of recurrence

• Recurrence
  – Unprovoked: >9%/year
  – Mildly provoked: 3–9%/year
  – Provoked: <3%/year

• Risk of recurrence highest in the first year after an initial event
  – Risk diminishes over time
  – Risk at 8 years: 46% in unprovoked thrombosis

Risk factors associated with VTE recurrence

- Idiopathic presentation\(^1,^2\)
- Presentation of primary DVT\(^1\)
- Increasing age\(^1\)
- Proximal DVT\(^2\)
- Cancer\(^2\)
- Residual thrombus mass\(^3\)
- Male gender\(^4\)
- High Risk Thrombophilia\(^1\)

Apixaban for Extended Treatment of Venous Thromboembolism

Giancarlo Agnelli, M.D., Harry R. Buller, M.D., Ph.D., Alexander Cohen, M.D.,

A Symptomatic Recurrent VTE or VTE-Related Death

B Major or Clinically Relevant Nonmajor Bleeding

Agnelli G et al, NEJM, 2013
Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism

J. J. Weitz, A. W. A. Lensing, M. H. Prins, R. Bauersachs, J. Bayer-Westendorf,
Duration of Anticoagulation for VTE

• 3 months anticoagulation for all (unless high bleeding risk...)
• Significant provoking factor (surgery, pregnancy, etc)- stop at 3 months
• Minor provoking factor- consider continuing if ongoing RF- case-by-case basis
• Unprovoked- continue unless considered at high bleeding risk
  – DOACs at licensed dose for secondary prevention
  – Rivaroxaban 10mg od or Apixaban 2.5mg bd
Antiphospholipid Syndrome: what anticoagulant to use?

- Triple positive APL patients
- Warfarin target INR 2.5 vs Rivaroxaban 20mg od
- Study terminated prematurely
- Riva arm- 7 arterial thrombotic events- 3 bleeding events
- Warfarin arm- 2 bleeding events

Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial

Susan R Kahn, Stan Shapiro, Philip S Wells, Marc A Rodger, Michael J Kovacs, David R Anderson, Vicky Tagalakis, Adriele H Houweling, Thierry Ducruet, Christina Holcroft, Mira Johri, Susan Solymoss, Marie-José Miron, Erik Yeo, Reginald Smith, Sam Schulman, Jeannine Kassis, Clive Keary, Isabelle Chagnon, Tuyeny Wong, Christine Demers, Rajendar Hanmiah, Scott Kaatz, Rita Selby, Suman Rathbun, Sylvie Desmarais, Lucie Opatrny, Thomas L Ortel, Jeffrey S Ginsberg, for the SOX trial investigators

- 410 patient randomised to receive Elastic Compression Stockings (ECS)
  - PTS in 14.2
- 396 patients randomised to receive Placebo ECS
  - PTS in 12.7
- ECS did not reduce PTS
OCTAVIA study

• One vs Two years of ECS for prevention PTS
• 518 patients- compliant with ECS for 1 year with no symptoms PTS
• Randomised to stop or continue ECS
• Stop ECS group- 19.9% developed PTS
• Continue ECS group- 13% developed PTS
• Conclusion: Stopping ECS was non-inferior to continuing ECS in this population

Mol et al, BMJ 2016
Patient Centred Care: Safe Patient Systems

All VTE diagnosed in ED or as in-patients
Physicians, thrombosis and “DVT” nurses, pharmacist

All VTE
Thrombosis nurse specialist

MDT meeting
Consultant haematologist / thrombosis nurse

Malignancy suspected
2 weeks O.P.A
with consultant haematologist

Unprovoked DVT
4 weeks O.P.A
with consultant haematologist

Provoked DVT
Nurse-led pathway

All PE
3 months
with consultant in haematology / respiratory

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