Unprovoked VTE: to screen or not to screen

VTE Study Day
3rd May 2018
New Diagnosis of VTE

- Provoked
- Unprovoked

Duration of Anticoagulation
Provoked VTE

- Immobility
- Recent surgery / fracture
- Obesity
- Pregnancy / Puerperium
- OCP/ HRT
- Malignancy
  - *Inherited thrombophilia*

  - **Transient**
  - **Persistent**

  - **3/12 Anticoagulation**
  - **Long-term Anticoagulation**

**Dehydration**
- Cancer treatments
- Infection/ Sepsis
- Hyopalbuminaemia / Nephrotic syndrome
- HIT – Heparin Induced Thrombocytopenia
- DIC - Disseminated Intravascular Coagulation
- PNH - Paroxysmal Nocturnal Haemoglobinuria
- MPD – Myeloproliferative Disorders
History/ Clinical context

- Immobility
- Recent surgery / fracture
- Obesity
- Pregnancy / Puerperium
- OCP/ HRT
- Malignancy
- Inherited thrombophilia
- Dehydration
- Infection

Blood / Screening Tests

- Full Blood Count
- Biochemistry
- Coagulation
- NICE (2012)
- Serum Calcium
- Liver Function Tests
- CxR
- Urinalysis

- Occult malignancy
- Inherited thrombophilia
- Hyopalbuminaemia / Nephrotic syndrome
- HIT – Heparin Induced Thrombocytopenia
- DIC – Disseminated intravascular Coagulation
- PNH – Paroxysmal Nocturnal Haemoglobinuria
- MPD – Myeloproliferative Disorders
Cancer in VTE

• 15 – 20% of VTE patients have overt cancer at diagnosis
• ≈ 4% have occult malignancy
• Approx 10% will develop over following 5 - 10 years
  • 1 – 2% annual risk after diagnosis
  • Risk uniform over time
  • > 2-fold higher annual risk in those with unprovoked VTE (0.83 vs 1.76%)

• Risk factors
  • Unprovoked event (HR 1.86)
  • Advancing age (HR 1.32)
Exclusion of Malignancy

• NICE (2012)
  • Offer all patients diagnosed with unprovoked DVT or PE who are not already known to have cancer:

1. Physical examination/ Full history
2. Chest X-ray
3. Blood tests (full blood count, serum calcium and liver function tests)
4. Urinalysis.

• Consider **abdomino-pelvic CT scan** (and a mammogram for women)
  • All patients aged over 40 years with a first unprovoked DVT or PE who do not have signs or symptoms of cancer based on initial investigation
Is extensive screening for malignancy necessary?
SOMIT Study (2004) - Screening for Occult Malignancy in Thrombosis

- 201 patients with idiopathic VTE with no initial signs/ symptoms of malignancy

- Random allocation
  - Extensive screening vs no further testing
  - 2 years follow-up

- Screening group: 14 malignancies (13 during screening, 1 during follow-up)
  - 10/13 detected by CT-AP alone
  - Control group: 10 malignancies during follow-up
  - Relative Risk 9.7 (p<0.001)

- Cancer related mortality:
  - 2.0% (screening) vs 3.9% - Not significant

Is a CT necessary?

• Carrier et al (2015)
  • Multicentre, randomised trial
  • Limited screening vs limited screening + CT
    • CT included virtual colonoscopy, gastroscopy and pancreatography
  • 1 year follow-up
    • Primary end-point: New cancers missed during screening

• 854 patients
  • Mean age: 54 years
  • 33 new diagnoses of cancer during f/u
    • 14 (3.2%) in limited screening – 4 missed (29%)
    • 19 (4.5%) in limited + CT – 5 missed (26%)
  • No difference in time to diagnosis or mortality
Is a CT necessary?

• Hildyard (2016)
  • 16 month audit all patients referred to VTE service
  • 239 patients with confirmed DVT (190 malignancy free)
    • 164 over 40 years of age
      • 139 with unprovoked VTE
  • 62 agreed to CTAP
  • 28 (45%) abnormal scans
  • Only 1 malignancy diagnosed

Is extensive screening for malignancy necessary?

• Addition of CT-Abdo/pelvis
  • Does not increase screening sensitivity
  • No mortality benefit
    • Although, cancer may be detected earlier

• Is this true in an older population?
  • Mean age (Carrier et al) = 54 years
  • Prandoni (2016)
    • 195 patients, mean age 69 years, 2 years follow-up
    • Randomised to limited * screening vs limited + CT-TAP
    • Cancers detected in 10% vs 8%
    • 2 cancers developed in each group during follow-up

What to conclude?

• “Limited” screening may be as effective as extensive
  • Uncertain, even good quality studies limited:
    • Underpowered to detect differences in cancer-related mortality
    • Wide confidence intervals – low numbers of occult cancers detected

• How limited is limited?
  • Variation in protocols between studies
    • Carrier (2015): FBC, Biochemistry, LFTs, CxR, PAP-Smear, Mammography, Prostate exam/PSA
    • Prandoni (2016): Any test at physicians discretion other than CT-TAP
(Who) Should we screen for inherited thrombophilia?
Normal Haemostasis

Clot Production

- TF-VIIa
- IXa + VIIIa
- Xa+Va
- Thrombin

Clot Breakdown

- XIa
- APC + PS
- TFPI
- AT
- TAFI

Fibrin
- Fibrinolys
Clot Production

- Prothrombin gene variant (PG 20210A mutation)
- Antiphospholipid antibodies

Clot Breakdown

- Anti-thrombin deficiency
- Protein C deficiency
- Protein S deficiency
- Factor V Leiden/ APC resistance
- Antiphospholipid antibodies
Who Should be tested?

• BCSH guidelines (2010)
  • Complicated and confusing

• Hardly ever recommended
  • Results will not change management of index case or relatives

• Most patients are tested at the wrong time
When to test

• Can be done anytime:
  • Genotypic tests: FVL, PGV
  • APS antibodies: β-2-glycoprotein, aCL antibodies

• After 3 months & off anticoagulation
  • Protein C, S, Antithrombin, lupus anticoagulant

• Results will never influence initial treatment
  • ie first 3/12 of anticoagulation

• Potential for inappropriate anticoagulant management
Why test for inherited thrombophilias?

- Intensity of anticoagulation
- Duration of anticoagulation
- Predict risk of recurrence
  - Predict risk in asymptomatic relatives
Duration of Anticoagulation

• ACCP (2016) and ESC (2014) consensus guidelines
  
  • Initial anticoagulation should be for 3 months duration
  
  • “Suggest anticoagulants should be continued indefinitely in unprovoked VTE patients with non-high bleeding risk” (GRADE 2B- Weak recommendation)
  
• Risk scores
  
  • DASH, HERDOO2, Vienna
  
  • None identified inherited thrombophilia as a risk
# Predicting risk of recurrence

<table>
<thead>
<tr>
<th>Prevalence in the general population</th>
<th>Antithrombin deficiency</th>
<th>Protein C deficiency</th>
<th>Protein S deficiency</th>
<th>Factor V Leiden</th>
<th>Prothrombin 20210A mutation</th>
<th>Lupus anticoagulant*</th>
<th>Anti-cardiolipin antibodies*</th>
<th>Anti-β2 GPI antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.02%</td>
<td>0.2%</td>
<td>0.03%-0.13%</td>
<td>3.7%</td>
<td>0.7%-4%</td>
<td>1%-8 %</td>
<td>5</td>
<td>3.4</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relative risk for a first venous thrombosis</th>
<th>5-10</th>
<th>4.6-5</th>
<th>1-10</th>
<th>3.5</th>
<th>2.9</th>
<th>3.1</th>
<th>0.7</th>
<th>2.4</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Relative risk for recurrent venous thrombosis</th>
<th>1.9-2.6</th>
<th>1.4-1.8</th>
<th>1.0-1.4</th>
<th>1.4</th>
<th>1.4</th>
<th>2-6</th>
<th>1-6</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Relative risk for arterial thrombosis</th>
<th>No association</th>
<th>No consistent association</th>
<th>No consistent association</th>
<th>1.3</th>
<th>0.9</th>
<th>10</th>
<th>1.5-10</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Relative risk for pregnancy complications</th>
<th>1.3-3.6</th>
<th>1.3-3.6</th>
<th>1.3-3.6</th>
<th>1.0-2.6</th>
<th>0.9-1.3</th>
<th>No consistent data</th>
<th>No consistent data</th>
</tr>
</thead>
</table>

*Note: The numbers represent the relative risk or prevalence compared to a reference value or baseline.
Who (not) to Test – NICE 2015

• Do not offer thrombophilia testing to patients who have had provoked DVT or PE.
• Do not offer thrombophilia testing to patients who are continuing anticoagulation treatment.
• Do not routinely offer thrombophilia testing to first-degree relatives of people with a history of DVT or PE and thrombophilia.

• **Consider** testing for antiphospholipid antibodies in patients who have had unprovoked DVT or PE if it is planned to stop anticoagulation treatment.
• **Consider** testing for hereditary thrombophilia in patients who have had unprovoked DVT or PE and who have a first-degree relative who has had DVT or PE if it is planned to stop anticoagulation treatment.
Appendix I: Obstetric thromboprophylaxis risk assessment and management

Antenatal assessment and management (to be assessed at booking and repeated if admitted)

- **HIGH RISK** Requires antenatal prophylaxis with LMWH
  - Refer to trust-nominated thrombosis in pregnancy expert/team

- **INTERMEDIATE RISK** Consider antenatal prophylaxis with LMWH

- **LOWER RISK** Mobilisation and avoidance of dehydration
  - Four or more risk factors: prophylaxis from first trimester
  - Three risk factors: prophylaxis from 28 weeks

- **LOWEST RISK** Early mobilisation and avoidance of dehydration

**Notes:**
- Any previous VTE except a single event related to major surgery
- Hospital admission
- Single previous VTE related to major surgery
- High-risk thrombophilia + no VTE
- Medical comorbidities e.g. cancer, heart failure, active SLE, IBD or inflammatory polyarthropathy, nephrotic syndrome, type I DM with nephropathy, sickle cell disease, current IVDU
- Any surgical procedure e.g. appendicectomy and OHSS (first trimester only)

- Obesity (BMI ≥ 30 kg/m²)
- Age > 35
- Parity ≥ 3
- Smoker
- Gross varicose veins
- Current pre-eclampsia
- Immobility, e.g. paraplegia, PGP
- Family history of unprovoked or estrogen-provoked VTE in first-degree relative
- Low-risk thrombophilia
- Multiple pregnancy
- IVF/ART

- Transient risk factors: Dehydration/hyperviscosity; current systemic infection; long-distance travel

Postnatal assessment and management (to be assessed on delivery suite)

- **HIGH RISK** At least 6 weeks’ postnatal prophylactic LMWH

- **INTERMEDIATE RISK** At least 10 days’ postnatal prophylactic LMWH
  - NB if persisting or > 3 risk factors consider extending thromboprophylaxis with LMWH

- Age > 35 years
- Obesity (BMI ≥ 30 kg/m²)
- Parity ≥ 3
- Smoker
- Elective caesarean section
- Family history of VTE
- Low-risk thrombophilia
- Gross varicose veins
- Current systemic infection
- Immobility, e.g. paraplegia, PGP, long-distance travel
- Current pre-eclampsia
- Multiple pregnancy
- Preterm delivery in this pregnancy (< 37th weeks)
- Stillbirth in this pregnancy
- Mid-cavity rotational or operative delivery
- Prolonged labour (> 24 hours)
- PPH > 1 litre or blood transfusion

**Notes:**
- Any previous VTE
- Anyone requiring antenatal LMWH
- High-risk thrombophilia
- Low-risk thrombophilia + FHx

**Caesarean section in labour**
- BMI ≥ 40 kg/m²
- Readmission or prolonged admission (≥ 3 days) in the puerperium
- Any surgical procedure in the puerperium except immediate repair of the perineum
- Medical comorbidities e.g. cancer, heart failure, active SLE, IBD or inflammatory polyarthropathy; nephrotic syndrome, type I DM with nephropathy, sickle cell disease, current IVDU

**Antenatal and postnatal prophylactic dose of LMWH**
- Pregnancy group 1: 0 mg
  - 50 mg enoxaparin or 5000 units dalteparin or 5000 units tinzaparin daily
- Pregnancy group 2: 0 mg
  - 50–90 mg enoxaparin or 5000 units dalteparin or 5000 units tinzaparin daily
- Pregnancy group 3: 0 mg
  - 25–120 mg enoxaparin or 10,000 units dalteparin or 5000 units tinzaparin daily
- Pregnancy group 4: 0 mg
  - 120 mg enoxaparin or 60 mg dalteparin or 5000 units tinzaparin daily
  - 120 mg enoxaparin or 60 mg dalteparin or 5000 units tinzaparin daily
Who do we Test?

• Pregnancy
  • Asymptomatic patients with 1st degree relative with VTE and known thrombophilic defect

• Unprovoked VTE
  • Only those wishing to stop after 3/12

• Family history
  • Screen asymptomatic relatives if very strong history
  • Ie Multiple events in multiple 1st degree relatives with known thromphophilic defect