Importance of VTE and Superficial Thrombosis for Primary and Emergency Care

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GPwSI and Co-Founder Westcliffe Cardiology Service
GP Partner Westcliffe Medical Group
Declaration of interests

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

• Trustee of Thrombosis UK, AF Association
• Three sections
  – Recognition and Diagnosis of DVT
  – Recognition, diagnosis and treatment SVT
  – Recognition and Diagnosis of PE
Deep Vein Thrombosis

• DVT is the formation of a blood clot in a deep vein.
• Usually in the legs; partially or completely obstructs blood flow.
• Annual incidence is about 1 in 1000 people.
• The most serious complication is pulmonary embolism.
• Only about a third of people with a clinical suspicion of DVT have the condition.

Based on the CKS topic DVT (April 2013) and NICE guidance (2012a); Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing.
Deep Vein Thrombosis

• Risk factors include:
  – Previous venous thromboembolism.
  – Cancer (known or undiagnosed).
  – Increasing age.
  – Being overweight or obese.
  – Male sex.
  – Heart failure.
  – Acquired or familial thrombophilia.
  – Chronic low-grade injury to the vascular wall (for example vasculitis, hypoxia from venous stasis, or chemotherapy).

*Based on the CKS topic DVT (April 2013) and NICE guidance (2012a); Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing.*
Deep Vein Thrombosis

- Risk factors that temporarily raise the likelihood of DVT:
  - Immobility, significant trauma, or direct trauma to a vein.
  - Hormone treatment (for example oestrogen-containing contraception or hormone replacement therapy).
  - Pregnancy and the postpartum period.
  - Dehydration.

Based on the CKS topic DVT (April 2013) and NICE guidance (2012a); Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing.
Deep Vein Thrombosis

• **Differential Diagnosis**
  - Physical trauma:
    • Calf muscle tear or strain.
    • Haematoma
    • Sprain or rupture of the Achilles tendon.
    • Fracture.
  - Cardiovascular disorders:
    • Superficial Venous Thrombosis
    • Post-thrombotic syndrome
    • Venous obstruction or insufficiency, or external compression of major veins
    • Arteriovenous fistula and congenital vascular abnormalities
    • Acute limb ischaemia
    • Vasculitis
  - Other conditions including:
    • Ruptured Baker’s cyst
    • Cellulitis (commonly mistaken as DVT)
    • Other causes of oedema:-Dependent oedema, Heart failure, Cirrhosis. Nephrotic syndrome.
    • Lymphatic obstruction.
    • Septic arthritis.
    • Compartment syndrome.

*Based on the CKS topic DVT (April 2013) and NICE guidance (2012a): Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing.*
Deep Vein Thrombosis

• Suspect a DVT if the person has:

  – Signs or *symptoms* of a DVT:
    • Pain and swelling in one leg, although both legs may be affected.
    • Tenderness, changes to skin colour and temperature, and vein distension.
  – A risk factor for DVT
    • previous VTE
    • Immobility

• To exclude an alternative cause:
  – Carry out a physical examination.
  – Review the person's general medical history.

*Based on the CKS topic DVT (April 2013) and NICE guidance (2012a): Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing.*
Deep Vein Thrombosis

Managing a suspected DVT

• Refer immediately if pregnant or given birth within the past 6 weeks.
  – Requires same-day assessment and management as it is not possible to accurately assess the risk of DVT in primary care.

• For everyone else, use the two-level DVT Wells score to assess likelihood of DVT and inform further management.

Based on the CKS topic DVT (April 2013) and NICE guidance (2012a): Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing.
Using the two-level DVT Wells score

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer (treatment ongoing, within the last 6 months, or palliative).</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis, or recent plaster immobilization of the legs</td>
<td>1</td>
</tr>
<tr>
<td>Recently bedridden for 3 days or more, or major surgery within the last 12 weeks requiring general or local anaesthetics</td>
<td>1</td>
</tr>
<tr>
<td>Localized tenderness along the distribution of the deep venous system (such as the back of the calf)</td>
<td>1</td>
</tr>
<tr>
<td>Entire leg is swollen.</td>
<td>1</td>
</tr>
<tr>
<td>Calf swelling by more than 3 cm compared with the asymptomatic leg (measured 10 cm below the tibial tuberosity).</td>
<td>1</td>
</tr>
<tr>
<td>Pitting oedema (greater than on the asymptomatic leg)</td>
<td>1</td>
</tr>
<tr>
<td>Collateral superficial veins (non-varicose).</td>
<td>1</td>
</tr>
<tr>
<td>Previously documented DVT</td>
<td>1</td>
</tr>
<tr>
<td>If an alternative cause is considered more likely than DVT.</td>
<td>-2</td>
</tr>
</tbody>
</table>

Based on the CKS topic DVT (April 2013) and NICE guidance (2012a); Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing.
Deep Vein Thrombosis

Two-level DVT Wells score

- Validated, simple scoring system that takes into account previous DVT.
  - DVT is *likely* if the score is two points or more.
  - DVT is *unlikely* if the score is one point or less.

Based on the CKS topic DVT (April 2013) and NICE guidance (2012a); Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing.
Deep Vein Thrombosis

Other methods of assessment

• Do not use:
  – Individual symptoms and signs on their own.
    • On their own they are poor predictors of the presence or absence of DVT.
  – A positive Homans' sign (pain in the calf or popliteal region on passive, abrupt, forceful dorsiflexion of the ankle with the knee in a flexed position):
    • Is insensitive and nonspecific.
    • Can be painful, and there is a theoretical possibility of dislodging a thrombus.

Based on the CKS topic DVT (April 2013) and NICE guidance (2012a): Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing.
Deep Vein Thrombosis
If DVT likely (≥2 points)

• Refer for a proximal leg vein ultrasound scan to be carried out within 4 hours.
• If a proximal leg vein ultrasound scan cannot be carried out within 4 hours of being requested:
  – Take a blood sample for D-dimer testing.
  – Give an interim 24-hour dose of an anticoagulant
• Ensure a proximal leg vein ultrasound scan is carried out within 24 hours of being requested.

Based on the CKS topic DVT (April 2013) and NICE guidance (2012a): Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing.
Deep Vein Thrombosis

Which anticoagulant?

- **Offer a choice of low molecular weight heparin (LMWH)**
  - Licensed LMWHs for DVT treatment include dalteparin, enoxaparin, and tinzaparin.

- **Offer a choice of Xa Inhibitor**
  - Apixaban and Rivaroxaban
  - Fondaparinux is a synthetic pentasaccharide that inhibits activated factor X but is parenteral

- **Choice of anticoagulant depends on:**
  - Comorbidities
  - Contraindications
  - Cost

- **Local policy may also influence choice.**

*Based on the CKS topic DVT (April 2013) and NICE guidance (2012a); Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing.*
Deep Vein Thrombosis

If DVT unlikely (≤ 1 point)

- Offer D-dimer testing.
- If negative D-dimer test - consider an alternative diagnosis to explain symptoms.
- If positive D-dimer test - refer for a proximal leg vein ultrasound scan to be carried out within 4 hours.
- If a proximal leg vein ultrasound scan cannot be carried out within 4 hours of being requested:
  - Give an interim 24-hour dose anticoagulant
- Ensure a proximal leg vein ultrasound scan is carried out within 24 hours of being requested.

Based on the CKS topic DVT (April 2013) and NICE guidance (2012a): Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing.
Deep Vein Thrombosis
Compressive US

Common Femoral Vein + Artery

Non-Compressed

Compressed
Deep Vein Thrombosis
US Positive for DVT
Compression
Deep Vein Thrombosis

Three point compression

Above knee only
Deep Vein Thrombosis

What about Serial US?

- **No US required if**
  - Low risk and Negative D Dimer

- **One US will do if**
  - Negative US and Negative D Dimer  - <1% DVT
  - Negative US and Low risk  - <1% DVT

- **Two US required if**
  - High risk and Positive D Dimer
## Deep Vein Thrombosis

### Serial US

**Influence of Wells’ score AND Ddimer on need to repeat US**

<table>
<thead>
<tr>
<th>Tack et al. (14)</th>
<th>Clinical score</th>
<th>811 outpatients with suspected DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>Moderate/high</td>
</tr>
<tr>
<td>Number of patients</td>
<td>280</td>
<td>531</td>
</tr>
<tr>
<td></td>
<td>35%</td>
<td>65%</td>
</tr>
<tr>
<td>Prevalence DVT on CUS</td>
<td>30</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td>11%</td>
<td>56%</td>
</tr>
<tr>
<td>Study design:</td>
<td></td>
<td>SimpliRed</td>
</tr>
<tr>
<td>First CUS</td>
<td></td>
<td>neg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pos</td>
</tr>
<tr>
<td></td>
<td></td>
<td>148</td>
</tr>
<tr>
<td>Second CUS</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Post-test prevalence DVT</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2%</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>98%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

High risk, positive D-dimer, initial negative CU, 9.75% had DVT on repeat CU at one week.  Ruis-Gimenez 2004
Superficial Venous Thrombosis
Superficial Venous Thrombosis

Risk factors:
- Varicose veins
- Immobilization
- Trauma
- Surgery
- Pregnancy and post-partum
- Hormonal contraception or replacement therapy
- Increasing age
- Obesity
- History of VTE
- Malignancy
- Autoimmune disease
- Thrombophilia
- IV catheter
Superficial Venous Thrombosis

Clinical Presentation

• Female (55-70% all presentations)
• Varicose Veins
• Traumatic
• Septic and Suppurative
• Migratory
• Short saphenous
• Upper extremity
• Post endovascular vein treatment
Superficial Venous Thrombosis

Consequence

• A prospective study of 844 patients with SVT >5cm
  – 4% symptomatic PE
  – 10% proximal DVT
  – 13% distal DVT

• Without VTE at presentation, despite 90% treated
  – 3.1% developed symptomatic DVT
  – 1.9% had recurrent DVT
  – 3.3% had extension of the DVT in the same location
Superficial Venous Thrombosis

Diagnosis

• Compression USS
Superficial Venous Thrombosis

CALISTO study, guidelines recommend

2.5 mg fondaparinux for 45 days

Comparison of Arixtra in Lower Limb Superficial Vein Thrombosis (CALISTO) Trial

• Randomized, double blind, placebo-controlled trial of 3002 patients with SVT ≥ 5 cm in length
• Treatments for 45 days of either
  - fondaparinux 2.5mg daily (1502 patients)
  or
  - placebo (1500 patients)
• Primary outcome: death, symptomatic PE, symptomatic DVT, or symptomatic extension, symptomatic recurrence
## Superficial Venous Thrombosis Baseline Characteristics

**Table 1. Baseline Characteristics of the Study Patients.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fondaparinux (N = 1502)</th>
<th>Placebo (N = 1500)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>57.1±13.3</td>
<td>56.9±13.6</td>
<td>0.69</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>974 (64.8)</td>
<td>944 (62.9)</td>
<td>0.29</td>
</tr>
<tr>
<td>Body-mass index‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>29.2±5.2</td>
<td>29.0±5.4</td>
<td>0.32</td>
</tr>
<tr>
<td>≥30 — no. (%)</td>
<td>574 (38.2)</td>
<td>536 (35.7)</td>
<td>0.16</td>
</tr>
<tr>
<td>Medical conditions — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicose veins</td>
<td>1331 (88.6)</td>
<td>1329 (88.6)</td>
<td>1.00</td>
</tr>
<tr>
<td>Previous superficial-vein thrombosis</td>
<td>178 (11.9)</td>
<td>178 (11.9)</td>
<td>1.00</td>
</tr>
<tr>
<td>Previous deep-vein thrombosis or pulmonary embolism</td>
<td>105 (7.0)</td>
<td>104 (6.9)</td>
<td>1.00</td>
</tr>
<tr>
<td>Cardiovascular disease‡</td>
<td>71 (4.7)</td>
<td>66 (4.4)</td>
<td>0.73</td>
</tr>
</tbody>
</table>
Superficial Venous Thrombosis

Results

Fondaparinux 2.5mg per day x 45 days

• 5% absolute risk reduction
• 85% reduction of symptomatic thromboembolic complications or death
• Statistically and clinically significant reductions in risk of primary efficacy outcome (death, symptomatic PE, symptomatic DVT, symptomatic extension, or symptomatic recurrence)

Superficial Venous Thrombosis

Results

Placebo

Thrombotic complications occurred more often if

- SVT involved the long saphenous vein (92% patients in control group)
- Extended to within 10 cm from the saphenofemoral junction (9% of patients)
- Involved veins above the knee (46% of patients)
- If VTE (7% of patients) or SVT (12% of patients) had occurred previously.
Superficial Venous Thrombosis

Results

Number need to treat (NNT) to prevent one primary efficacy outcome. **NNT = 20**

Recall primary outcome: death symptomatic PE, symptomatic DVT, symptomatic extension, or symptomatic recurrence

**NNT = 80**, to prevent DVT or PE
A randomized trial of dalteparin compared with ibuprofen for the treatment of superficial thrombophlebitis.

Rathbun SW, Aston CE, Whitsett TL.

Abstract

BACKGROUND: Superficial thrombophlebitis can produce pain and result in a deep vein thrombosis (DVT) if not treated. Conservative therapies including prescription of non-steroidal anti-inflammatory drugs (NSAID) and heat have been standard care. Recently, studies have been published reporting efficacy and safety of low-molecular-weight heparin for the treatment of superficial thrombophlebitis. However, there are few comparative trials to conservative therapy. We studied the effectiveness and safety of treatment with dalteparin compared with ibuprofen in patients with confirmed superficial thrombophlebitis.

METHODS: Consecutive patients were randomized to receive daily dalteparin vs. ibuprofen three times daily for up to 14 days. The primary outcome measure was the incidence of extension of thrombus or new symptomatic venous thromboembolism during the 14-day and 3-month follow-up period. The secondary outcome was a reduction in pain. The outcome measure of safety was the incidence of major and minor bleeding.

RESULTS: Of 302 consecutive patients screened, 72 were enrolled. Four patients receiving ibuprofen compared with no patients receiving dalteparin had thrombus extension at 14 days (P = 0.05), however, there was no difference in thrombus extension at 3 months. Both treatments significantly reduced pain. There were no episodes of major or minor bleeding during the treatment period.

CONCLUSIONS: Dalteparin is superior to the NSAID ibuprofen in preventing extension of superficial thrombophlebitis during the 14-day treatment period with similar relief of pain and no increase in bleeding. However, questions concerning the optimal treatment duration should be explored in future trials.
A randomized double-blind study of low-molecular-weight heparin (parnaparin) for superficial vein thrombosis: STEFLUX (Superficial ThromboEmbolism and Fluxum).


Abstract

BACKGROUND: Optimal doses and duration of low-molecular-weight heparin (LMWH) for the treatment of superficial vein thrombosis (SVT) are still uncertain.

OBJECTIVES: To compare the efficacy and safety of different doses and durations of LMWH parnaparin for symptomatic lower limb SVT.

PATIENTS AND METHODS: Outpatients with at least a 4-cm-long SVT of long or short saphenous veins or their collaterals were randomized to receive parnaparin either 8500 UI once daily (o.d.) for 10 days followed by placebo for 20 days (group A) or 8500 UI o.d. for 10 days followed by 6400 UI once daily (o.d.) for 20 days (group B) or 4250 UI o.d. for 30 days (group C) in a double-blind fashion in 16 clinics. Primary outcome was the composite of symptomatic and asymptomatic deep vein thrombosis (DVT), symptomatic pulmonary embolism (PE) and relapse and/or symptomatic or asymptomatic SVT recurrence in the first 33 days with 60 days follow-up.

RESULTS: Among 664 patients, primary outcome occurred in 33/212 (15.6%), 4/219 (1.8%) and 16/217 (7.3%) subjects in groups A, B and C, respectively (B vs. A: absolute risk reduction [ARR]: 13.7%, 95% confidence intervals [CI]: 8-18.9 P<0.001; B vs. C: ARR: 5.5%; 95% CI: 1.6-9.4 P= 0.011; C vs. A: ARR: 8.2%, 95% CI: 2-14 P = 0.012). During days 0-93, the event rate was higher in group A (22.6%) than either in group B (8.7%; P=0.001) or C (14.3%, P=0.034). No major hemorrhages occurred.

CONCLUSIONS: An intermediate dose of parnaparin for 30 days is superior to either a 30-day prophylactic dose or a 10-day intermediate dose for lower limb SVT treatment.
Superficial Venous Thrombosis

Summary

- LMWH or NSAID effective for reducing pain and extension/VTE but risk stratification model not available
- Goals of treatment met by LMWH but dose and duration of LMWH not clear

**ACCP 2012** recommendation (no change 2017):

- Superficial thrombosis $\geq 5 \text{ cm in length}$ should receive prophylactic dose fondaparinux or LMWH for 45 days (2B).
- **Fondaparinux 2.5 mg** is preferred over LMWH (2C).

- No UK national guidance on treatment of SVT
Pulmonary Embolism
Pulmonary Embolism

- A PE is where one or more emboli are lodged in and obstruct the pulmonary arterial system.
- The annual incidence of PE is around 3–4 per 10,000 people.
- A PE may be:
  - Provoked – associated with a transient risk factor (e.g. significant immobility, surgery).
  - Unprovoked – no identifiable risk factor or a risk factor that is persistent and not easily correctable (e.g. active cancer).

Based on the CKS topic Pulmonary embolism (June 2013), and NICE guidance (2012a): Venous thromboembolic disease: the management of venous thromboembolic diseases and the role of thrombophilia testing.
Pulmonary Embolism

Sources of emboli

- The most common source is deep vein thrombosis (DVT) in the lower limbs (80%).
- Other sources include:
  - Emboli originating in the abdominal or axillary veins, or from the right ventricle.
  - Tumours – mostly prostate and breast cancer.
  - Fat from long bone fractures.
  - Amniotic fluid – pregnant women.
  - Sepsis – e.g. infected indwelling catheters.
  - Foreign bodies (e.g. during IV drug use).
  - Air – admitted during surgery.

Based on the CKS topic Pulmonary embolism (June 2013), and NICE guidance (2012a): Venous thromboembolic disease: the management of venous thromboembolic diseases and the role of thrombophilia testing.
Pulmonary Embolism

• Major risk factors include:
  – Deep vein thrombosis (DVT).
  – Previous DVT or pulmonary embolism.
  – Active cancer.
  – Recent surgery, hospitalization, lower limb trauma, or other immobilization (including long-distance sedentary travel).
  – Pregnancy, in particular 6 weeks postpartum.

Based on the CKS topic Pulmonary embolism (June 2013), and NICE guidance (2012a): Venous thromboembolic disease: the management of venous thromboembolic diseases and the role of thrombophilia testing.
Pulmonary Embolism

- Other risk factors include:
  - Increasing age (older than 60 years of age).
  - Combined oral contraception and hormone replacement therapy.
  - Obesity (body mass index greater than 30 kg/m²).
  - One or more significant medical comorbidities (e.g. heart disease, acute infectious disease, inflammatory conditions).
  - Varicose veins.
  - Superficial venous thrombosis.
  - Known thrombophilias.

Based on the CKS topic Pulmonary embolism (June 2013), and NICE guidance (2012a): Venous thromboembolic disease: the management of venous thromboembolic diseases and the role of thrombophilia testing.
Other conditions that could mimic the symptoms of a PE include:

- Respiratory conditions (e.g. pneumothorax).
- Cardiac conditions (e.g. acute coronary syndrome).
- Musculoskeletal chest pain.
- Gastro-oesophageal reflux disease.
- Pregnancy.
- Any cause for collapse such as vasovagal syncope.

Based on the CKS topic Pulmonary embolism (June 2013), and NICE guidance (2012a): Venous thromboembolic disease: the management of venous thromboembolic diseases and the role of thrombophilia testing.
Complications

• Mortality
  – Untreated, the risk of death from a PE is high (23–87%).
  – When treated with heparin and anticoagulants the risk of death ranges from 2-6%.
  – For a clinically massive PE the risk of death is about 50%.
  – PE is the leading cause of maternal deaths in the UK.

• Chronic thromboembolic pulmonary hypertension (CTEPH)
  – Occurs in 0.5–5% of people with treated PE.

*Based on the CKS topic Pulmonary embolism (June 2013), and NICE guidance (2012a): Venous thromboembolic disease: the management of venous thromboembolic diseases and the role of thrombophilia testing.*
Pulmonary Embolism

• Suspect a PE if the person has:
  • Dyspnoea, tachypnoea, pleuritic chest pain, or features of a DVT.
    • These features are present in 97% of people with PE, but
    • Only 15% of people with a PE have signs of DVT.
  • Other features such as tachycardia, haemoptysis, syncope, hypotension (systolic BP less than 90 mmHg), crepitations, cough or fever.
  • A risk factor for PE (e.g. previous DVT/PE, pregnant).

Based on the CKS topic Pulmonary embolism (June 2013), and NICE guidance (2012a): Venous thromboembolic disease: the management of venous thromboembolic diseases and the role of thrombophilia testing.
Pulmonary Embolism

• To exclude an alternative cause:
  – Carry out a physical examination.
  – Review the person's general medical history.

• ECG or chest X-ray
  – Are of limited value as they are usually normal in someone with a PE.
  – May be done as part of investigations for breathlessness or chest pain when another diagnosis seems more likely.

Based on the CKS topic Pulmonary embolism (June 2013), and NICE guidance (2012a): Venous thromboembolic disease: the management of venous thromboembolic diseases and the role of thrombophilia testing.
Pulmonary Embolism

• **Arrange immediate admission if the person is:**
  – Pregnant or has given birth within the past 6 weeks.
    • It is not possible to accurately assess the risk of PE in primary care.
  – **Severely ill with:**
    • Altered level of consciousness.
    • Systolic BP of less than 90 mm Hg.
    • Heart rate of more than 130 beats per minute.
    • Respiratory rate of more than 25 breaths per minute.
    • Oxygen saturation of less than 91%.
    • Temperature of less than 35°C.

*Based on the CKS topic Pulmonary embolism (June 2013), and NICE guidance (2012a): Venous thromboembolic disease: the management of venous thromboembolic diseases and the role of thrombophilia testing.*
Pulmonary Embolism

Managing a suspected PE

• For all other people use the two-level PE Wells score to assess likelihood of PE and inform further management.

• Using this score a PE is:
  – *Likely* if the score is more than 4 points.
  – *Unlikely* if the score is 4 points or less.
Using the two-level PE Wells score

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer (treatment ongoing, within the last 6 months, or palliative).</td>
<td>1</td>
</tr>
<tr>
<td>Heamoptysis</td>
<td>1</td>
</tr>
<tr>
<td>Recently bedridden for 3 days or more</td>
<td>1.5</td>
</tr>
<tr>
<td>Surgery within the previous 4 weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Heart Rate of greater than 100bpm</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous DVT or PE.</td>
<td>1.5</td>
</tr>
<tr>
<td>There are clinical features of a DVT</td>
<td>3</td>
</tr>
<tr>
<td>If an alternative diagnosis is considered less likely than PE.</td>
<td>3</td>
</tr>
</tbody>
</table>

Based on the CKS topic DVT (April 2013) and NICE guidance (2012a); Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing.
Pulmonary Embolism

If PE likely (>4 points)

• Arrange immediate admission for a computed tomography pulmonary angiogram (CTPA), or
• If there will be a delay in the person receiving a CTPA:
  o Give immediate interim low molecular weight heparin (LMWH) or fondaparinux, or oral Xa inhibitor
  o Arrange hospital admission.

Based on the CKS topic Pulmonary embolism (June 2013), and NICE guidance (2012a): Venous thromboembolic disease: the management of venous thromboembolic diseases and the role of thrombophilia testing.
Pulmonary Embolism

If PE unlikely (4 points or less)

• Arrange a D-dimer test.
• If the D-dimer test is positive:
  o Arrange admission to hospital for an immediate CTPA, *or*
  o If a CTPA cannot be carried out immediately, give LMWH, fondaparinux or oral Xa inhibitor and arrange hospital admission.
• If the D-dimer test is negative, consider an alternative diagnosis.

*Based on the CKS topic Pulmonary embolism (June 2013), and NICE guidance (2012a): Venous thromboembolic disease: the management of venous thromboembolic diseases and the role of thrombophilia testing.*
ECG

- ECG may be normal
- ECG may reveal tachycardia
- Right Heart Strain
  - Deep S wave in lead I
  - Deep Q wave in Lead III
  - Inverted T wave in Lead III
  - Right Bundle Branch Block
Perfusion and ventilation scans

In a patient with pulmonary embolism, a perfusion scan shows that an embolus has stopped the blood flow to part of one lung.

The ventilation scan shows that this area is ventilated normally.
CT Angiogram

• Quickly becoming the test of choice for initial evaluation of a suspected PE.

• CT unlikely to miss any lesion.

• CT has better sensitivity, specificity and can be used directly to screen for PE.

• CT can be used to follow up “non diagnostic V/Q scans.”
Treatment DVT and PE
Why Treat?

• Prevent DVT becoming PE
• Allow fibrinolysis and recanalization.
• Prevent recurrent PE
• Prevent death
• Prevent Re-occurrence
• Prevent Post Thrombotic Syndrome
Pharmacological interventions

• Confirmed PE or proximal DVT – offer low molecular weight heparin (LMWH) or fondaparinux as soon as possible, unless:
  • severe renal impairment
  • increased risk of bleeding
  • haemodynamically unstable

• Confirmed PE or proximal DVT and active cancer: offer LMWH, continue for 6 months
Unfractionated heparin
Low molecular weight heparin
Fixed-dose LMWH was as effective and showed a similar safety profile to UFH (i.v. and aPTT controlled) for VTE treatment.

COLUMBUS: incidence of recurrent VTE at 12 weeks

<table>
<thead>
<tr>
<th></th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMWH/VKA (n=510)</td>
<td>5.3%</td>
</tr>
<tr>
<td>UFH/VKA (n=511)</td>
<td>4.9%</td>
</tr>
</tbody>
</table>

Equivalence criteria met

- Rates of major bleeding: 3.1% LMWH versus 2.3% UFH

LMWH versus UFH: data from a meta-analysis

- In a Cochrane meta-analysis of 23 studies, fixed-dose subcutaneous LMWH was more effective and showed a better safety profile than dose-adjusted UFH for the initial treatment of VTE.

<table>
<thead>
<tr>
<th></th>
<th>LMWH</th>
<th>UFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>3.6%</td>
<td>5.3%</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.1%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>4.3%</td>
<td>5.8%</td>
</tr>
</tbody>
</table>

- OR=0.70 95% CI 0.57–0.85
- OR=0.58 95% CI 0.40–0.83
- OR=0.77 95% CI 0.63–0.93

Erkens PM, Prins MH. Cochrane Database Syst Rev 2010;9:CD001100
Problems with LMWH use

• Subcutaneous injection
• Injection site problems
• Risk of osteoporosis (although less than with UFH)
• A lower risk of HIT compared with UFH
• Risk of accumulation with renal impairment

Oral anticoagulants
Vitamin K antagonists
VKAs: optimization of initial anticoagulation

- Early studies showed that initial treatment with VKA plus heparin (started together) was more effective than VKA alone\(^1\)

Incidence (%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>VKA alone</th>
<th>VKA + heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic extension or recurrence of VTE</td>
<td>20%</td>
<td>6.7%</td>
</tr>
<tr>
<td>Asymptomatic extension of thrombosis</td>
<td>39.6%</td>
<td>8.2%</td>
</tr>
</tbody>
</table>

Duration of VKA therapy

- The optimal treatment duration should be based on the underlying risk factors of VTE recurrence and the benefit–risk of long-term anticoagulant therapy.
VTE recurrence with continued versus shorter VKA treatment

- Meta-analysis of eight studies of 2,994 patients: consistent reduction in VTE recurrence with prolonged versus shorter treatment (OR=0.18; 95% CI 0.13–0.26)

<table>
<thead>
<tr>
<th>Study/sub-group</th>
<th>Favours prolonged treatment</th>
<th>Favours shorter treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levine 1995</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schulman 1995</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schulman 1997</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kearon 1999</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agnelli 2001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pinede 2001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agnelli 2003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kearon 2004</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Peto OR and 95% CIs

Hutten B, Prins M. Cochrane Database Syst Rev 2006;1:CD001367
Incidence of major bleeding with continued versus shorter VKA treatment

- Meta-analysis of four studies (N=808)*: significant increase in major bleeding with prolonged versus shorter VKA treatment (OR=4.87; 95% CI 1.31–18.15)

<table>
<thead>
<tr>
<th>Study/sub-group</th>
<th>Favours prolonged treatment</th>
<th>Favours shorter treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levine 1995</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kearon 1999</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agnelli 2001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Kearon 2004 not presented (no major bleeding events)

Hutten B, Prins M. Cochrane Database Syst Rev 2006;1:CD001367
Outcomes with prolonged VKA therapy

- Prolonged VKA treatment showed consistent reduction in VTE recurrence compared with shorter treatment\(^1\)
- Major bleeding was increased with prolonged VKA therapy versus shorter treatment\(^1\)

Duration of VKA therapy and VTE recurrence

Prolonged therapy is associated with a lower rate of VTE recurrence.

No significant difference in mortality or in the incidence of major bleeding.¹

---

**DURAC 1¹**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>6 weeks (n=443)</th>
<th>6 months (n=454)</th>
<th>OR (95% CI), pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>1 (0.2)</td>
<td>5 (1.1)</td>
<td>0.2 (0.0–1.7), 0.23</td>
</tr>
<tr>
<td>Death</td>
<td>22 (5.0)</td>
<td>17 (3.7)</td>
<td>1.3 (0.7–2.6), 0.46</td>
</tr>
</tbody>
</table>

Duration of VKA therapy and VTE recurrence

- Indefinite VKA therapy after a second episode of VTE was associated with a much lower rate of recurrence – 4 years follow-up
- Trend towards higher rates of major bleeding with indefinite VKA therapy

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>6 months (n=111) n (%)</th>
<th>Indefinite (n=116) n (%)</th>
<th>RR (95% CI), pvalue</th>
<th>ARR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>3 (2.7)</td>
<td>10 (8.6)</td>
<td>0.3 (0.1–1.1), 0.084</td>
<td>-5.9</td>
</tr>
<tr>
<td>Recurrence</td>
<td>23 (20.7)</td>
<td>3 (2.6)</td>
<td>8.0 (2.5–25.9), &lt;0.001</td>
<td>18.1</td>
</tr>
<tr>
<td>Death</td>
<td>16 (14.4)</td>
<td>10 (8.6)</td>
<td>1.7 (0.8–3.5), 0.21</td>
<td>5.8</td>
</tr>
</tbody>
</table>

Side-effects associated with VKA use

• Skin necrosis affects <0.1% of patients receiving VKA therapy\(^1\)
• An increased risk of osteoporosis in elderly patients with atrial fibrillation was noted in men but not in women in a retrospective cohort study\(^2\)
• Reports of alopecia and birth defects have not been supported
  – Surveys of dermatology practices suggest alopecia is uncommon\(^3\)
  – Data collected by institutes collaborating in the European Network of Teratology Information Services (ENTIS) between 1988 and 2004 suggest risk of coumarin embryopathy is very small\(^4\)

What’s so wrong with warfarin?

• **Pros**
  – Huge clinical experience
  – Highly effective
    • VTE treatment and secondary prevention; stroke prevention in AF; thromboembolic complications with artificial valves
  – Predictably reversible (Vit K; PCCs e.g. Beriplex)

• **Cons**
  – Prolonged effect
  – Drug interactions
  – Food interactions including alcohol
  – Pharmacokinetics unpredictable
    • Requires regular INR monitoring
Limitations with VKAs

- Narrow therapeutic window
  - Difficult to keep within therapeutic range\(^1\)
- Variability in dose response\(^1\)
- Slow onset/offset of action\(^2\)
- Frequent INR monitoring/dose-adjustment\(^1\)
- Multiple drug–drug and food–drug interactions\(^1\)
- Increased risk of bleeding – when outside of the therapeutic range/window\(^1\)

Time in therapeutic range (TTR) matters

![Graph showing cumulative survival vs. survival to stroke (days) for different TTR groups. The legend indicates the survival percentages for each TTR group: 71–100%, 61–70%, 51–60%, 41–50%, 31–40%, <30%, and Non warfarin. The graph illustrates the significant impact of TTR on survival.]

Newer Alternatives
Other therapeutic options
## Phase III studies for VTE treatment

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Design</th>
<th>Initial treatment with LMWH/fondaparinux</th>
<th>Treatment duration (months)</th>
<th>Long-term treatment regimen</th>
<th>Active comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EINSTEIN DVT</td>
<td>Open label</td>
<td>No</td>
<td>3, 6 or 12</td>
<td>od</td>
<td>LMWH/VKA</td>
</tr>
<tr>
<td>EINSTEIN PE</td>
<td>Open label</td>
<td>No</td>
<td>3, 6 or 12</td>
<td>od</td>
<td>LMWH/VKA</td>
</tr>
<tr>
<td>EINSTEIN EXT</td>
<td>Double blind</td>
<td>No</td>
<td>6 or 12</td>
<td>od</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Dabigatran</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-COVER</td>
<td>Double blind</td>
<td>Yes*</td>
<td>6</td>
<td>bid</td>
<td>Warfarin</td>
</tr>
<tr>
<td>RE-COVER II</td>
<td>Double blind</td>
<td>Yes</td>
<td>6</td>
<td>bid</td>
<td>Warfarin</td>
</tr>
<tr>
<td>RE-MEDY</td>
<td>Double blind</td>
<td>No</td>
<td>18</td>
<td>bid</td>
<td>Warfarin</td>
</tr>
<tr>
<td>RE-SONATE</td>
<td>Double blind</td>
<td>No</td>
<td>6</td>
<td>bid</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMPLIFY</td>
<td>Double blind</td>
<td>No</td>
<td>6</td>
<td>bid</td>
<td>LMWH/warfarin</td>
</tr>
<tr>
<td>AMPLIFY-EXT</td>
<td>Double blind</td>
<td>No</td>
<td>12</td>
<td>bid</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Edoxaban</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hokusai-VTE</td>
<td>Double blind</td>
<td>Yes</td>
<td>12</td>
<td>od#</td>
<td>Heparin/warfarin</td>
</tr>
</tbody>
</table>

*Median=9 days; *two 30 mg tablets

Apixaban: AMPLIFY

Treatment period of 6 months

Standard therapy
Enoxaparin 1 mg/kg bid until INR ≥2.0, and warfarin adjusted to INR 2.0–3.0 od for 6 months

Apixaban
Enoxaparin placebo 1 mg/kg bid until sham INR ≥2.0, and warfarin placebo dosing to target sham INR 2.0–3.0 od for 6 months

Apixaban placebo 10 mg bid for 7 days, then 5 mg bid for 6 months

Apixaban 10 mg bid for 7 days, then 5 mg bid for 6 months

Symptomatic DVT or PE

Estimated N=4,816

Primary efficacy outcome: VTE recurrence or death during study treatment
Secondary outcome: bleeding during study treatment

Apixaban: AMPLIFY-EXT

• Primary efficacy outcome: VTE recurrence or death during study treatment
• Secondary outcome: bleeding during study treatment

Prevention of VTE recurrence or death in patients who have completed their intended treatment for DVT or PE

Treatment period of 12 months

Apixaban
Apixaban 2.5 mg bid for 12 months
Apixaban 5 mg bid for 12 months

Placebo
Apixaban placebo bid for 12 months

Estimated N=2,430

Day 1

R

Rivaroxaban EINSTEIN phase III: study designs

EINSTEIN DVT\(^1\) and EINSTEIN PE\(^2\) (non-inferiority studies)

- **Confirmed acute symptomatic DVT without symptomatic PE**
  - Rivaroxaban: 15 mg bid
  - Enoxaparin: 1.0 mg/kg bid for at least 5 days, followed by VKA to start ≤48 hours, target INR range 2.0–3.0
  - N=3,449

- **Confirmed acute symptomatic PE with or without symptomatic DVT**
  - Rivaroxaban: 20 mg od
  - Enoxaparin: 1.0 mg/kg bid for at least 5 days, followed by VKA to start ≤48 hours, target INR range 2.0–3.0
  - N=4,845

- **EINSTEIN Extension\(^1\) (superiority study)**
  - Confirmed symptomatic DVT or PE completing 6 or 12 months of rivaroxaban or VKA
  - Rivaroxaban: 20 mg od
  - Placebo
  - N=1,197

---


*EINSTEIN PE is still ongoing*
**Dabigatran: RE-COVER study designs**

- Primary efficacy outcome:¹,² composite of symptomatic recurrent VTE and VTE related death within 6 months
- Principal safety outcome:¹,² bleeding events

---

Dabigatran: RE-MEDY

- Primary efficacy outcome: composite of recurrent symptomatic VTE (DVT and PE) and deaths related to VTE
- Secondary outcome: composite of recurrent symptomatic VTE and all-cause mortality

Treatment period of up to 36 months

Dabigatran
Dabigatran etexilate 150 mg bid plus warfarin placebo as decided by sham INR measurements

Standard care
VKA target INR 2.5 (range 2.0–3.0) plus dabigatran placebo bid

Long-term treatment of symptomatic VTE (after 3–6 months’ anticoagulation)

N=2,867

Edoxaban: Hokusai-VTE study

- Primary efficacy outcome: recurrent symptomatic VTE (DVT, non-fatal and fatal PE) 12 months from randomization
- Primary safety outcome: clinically relevant bleeding (major or non-major clinically relevant bleeding) during treatment

Maximum treatment period of 12 months

Symptomatic DVT and/or PE VTE

Day 1

R

Estimated N=7,500

Edoxaban

LMWH/UFH followed by edoxaban 60 mg od for up to 12 months

Standard care

LMWH/UFH and warfarin (INR 2.0–3.0) for up to 12 months

Thrombolytic therapy

Consider catheter-directed thrombolytic therapy for patients with symptomatic iliofemoral DVT who have:

- symptoms of less than 14 days’ duration and
- good functional status and
- a life expectancy of 1 year or more and
- a low risk of bleeding.
Advice to patients

- Walk regularly after discharge from hospital.
- Elevate the affected leg when sitting.
- Refrain from extended travel, or travel by aeroplane, for at least 2 weeks after starting anticoagulant treatment.

Based on the CKS topic DVT (April 2013) and NICE guidance (2012a); Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing.
Thank you for your attention

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@fatherofhan