Treatment of Thromboembolic Disease

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Each year over **25,000-32,000** people in England die from VTE contracted in hospital.

More than combined total of deaths from breast cancer, AIDS and traffic accidents and more than 25 times the number deaths from MRSA.

Many of these deaths are **PREVENTABLE**.

Safe, efficacious and cost effective method of preventing VTE – not as widely administered as should be.
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VIRCHOW’S TRIAD (1856)

- BLOOD FLOW
- BLOOD COAGUABILITY
- VESSEL WALL DAMAGE

- Basic pathogenesis of thrombosis still relies on this basic premise
Deep vein thrombosis

Incidence approximately 1 per 1000 individuals per year (60 000 per year in UK).

Only 20% of patients investigated for DVT on clinical suspicion have DVT on objective testing.

240 000 cases of suspected DVT per year in UK.

1-2% incidence of fatal PE if undiagnosed.
Deep venous thrombosis (DVT)
Clinical manifestations of VTE

- Deep Vein thrombosis (DVT) symptomatic or asymptomatic
- Pulmonary embolism

PE mortality 30% if untreated and 2% if treated

Incidence of VTE is underestimated due to a low autopsy rate and difficult clinical diagnosis\(^1\)

DVT (asymptomatic and symptomatic) is a surrogate marker of PE

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Incidence of Venous thrombosis (DVT & PE) by age and sex

Rates are shown per 100,000 per year

Men = filled bars
Women = open bars

Incidence of VTE

- VTE is common in hospitalised patients
- 10% of hospital death attributed to PE
- In 2005, VTE was registered as an underlying cause of death in more than 6500 patients
- PE incidence: 5% following high-risk surgery and 1% in acutely ill medical patients
VTE incidence

- 1 in 5 medical patients develop VTE if no prophylaxis

- Around 1 in 4 of all VTE (hospital and community) occur in medical patients in hospital

- VTE incidence increasing:
  - Older population (live longer)
  - Obesity
  - Morbidity status
  - Extensive surgeries
VTE complications

- Recurrence
- Post-thrombotic syndrome
- Chronic thromboembolic pulmonary hypertension
Long term complications of VTE

Long-term outcomes after a first DVT

<table>
<thead>
<tr>
<th>Cumulative incidence</th>
<th>Recurrent DVT</th>
<th>Post-thrombotic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 years</td>
<td>17%</td>
<td>25%</td>
</tr>
<tr>
<td>5 years</td>
<td>24%</td>
<td>30%</td>
</tr>
<tr>
<td>8 years</td>
<td>30%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Post-thrombotic syndrome (PTS) is common even when the DVT has been treated and may result in leg ulcer.
Kaplan–Meier Estimates of the Likelihood of Recurrent VTE according to Sex

Post-thrombotic syndrome
VTE complications

Bergan et al NEJM 355 488-498
VTE Risk Factors (NICE 2010)

Patient-related

- Active cancer or cancer treatment
- Age > 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI > 30 kg/m2)
- One or more significant medical comorbidities (e.g.: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
- Personal history or first-degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis
- Pregnancy or < 6 weeks post-partum
Hereditary thrombophilia

- A genetically determined disorder of haemostasis which increases the probability of venous thromboembolism (VTE)
Family Mi

Fig. 1. Pedigree of family Mi.
Thrombophilia screen

- **Single gene defects**
- Antithrombin
- Protein C
- Protein S
- V Leiden
- Prothrombin G20210A

- **Acquired thrombophilia**
- aPL aCL + LA
Diagnosis of Acute VTE

• Clinical Suspicion (use an accepted scoring system - ie Wells)

• Radiology
  – venogram, US Duplex scan
  – CXR, V/Q Scan, CTPA

• Haemostasis
  – D-dimer (negative exclusion)
  – markers of excess thrombin generation
4. Venogram showing deep vein thrombosis

Some risk factors for venous thrombosis and pulmonary embolism may readily be prevented. A classic example of this is the use of anticoagulant therapy after orthopaedic surgery.
**Clinical Indication:** Persisting thrombosis, chronic scarring or incompetence

- Iliac veins: Not examined
- SFJ: Significant reflux (K2 junctions)
- Thigh LSV: Significant reflux
- Calf LSV: Significant reflux
- Ant LSV: Moderate reflux
- Hunter's Perforator: Normal
- Gia: Normal
- SPJ: Absent
- SSV: Normal
- Boyd's Perforator: Normal
- Cockett's Perforator: Normal
- Gastroc. Perforator: Normal
- CFV: Normal
- SFV: Normal
- Pop V: Normal
- Gastroc V: Normal
- PTVs: Normal
- Pero V: Normal

**Limb Venous Duplex Examination**

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11. Diagnosis of pulmonary embolism (perfusion and ventilation scans)

In another 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.
D-dimer

- Reflects \textit{in vivo} fibrin turn over
- Raised in deep vein thrombosis
- Also raised in disseminated intravascular coagulation (DIC), malignancy, liver disease, post-op, sepsis, pre-eclampsia, trauma, etc.
- **Sensitive** but **non-specific** marker for DVT and consequently unsuitable for in-patients
- Use as a negative exclusion for acute DVT
Clinical Probability

Low

D-dimer

Neg

Exclude

Pos

Ultrasound

US Neg & PTP high

D-dimer

Neg

Pos

Repeat Ultrasound in 1/52

Pos

Treat

Neg

D-dimer

High

Treat

Exclude US Neg & PTP high

D-dimer

Neg

Repeat Ultrasound in 1/52

Pos

Treat
CS-2000i

CS-5100
Unfractionated Heparin

- Wide molecular size range (5-40,000 daltons)
- Binds to cells & plasma proteins
- Usually intravenous, needs to be monitored
- Rarely used now for treatment of VTE

Low Molecular Weight Heparin

- Less non-specific binding; not cleared by RE system
- Improved bioavailability
- T/2 4-12 hours. Usually once or twice daily, sc.
- Laboratory monitoring not required
Warfarin 2014

- cheap; widely available for 50+ years
- narrow therapeutic window
- numerous food/drug interactions
- high morbidity rates; mainly bleeding, teratogenic
- clinical use widely recognised, numerous guidelines etc
- monitoring and reversal reasonably defined
- different methods of service delivery
- documentation for patient, clinic and lab extremely variable
- NOAC now licensed and widely prescribed
PT/INR monitoring

- about 1 - 1.25 million of UK population currently take Warfarin
- annual increase in 2000’s of over 10% per year
- the therapeutic window (INR 2.0 - 4.5) is relatively narrow
- the traditional hospital based AC clinic has become seriously overloaded
- there are now several models of long term anticoagulant care
- medico-legal actions frequently related to bleeding/thrombotic complications
VTE prevention became a National Priority

- NICE 2007 clinical guidelines 46
- September 2007 – 2009 *risk assess all patients on admission* by end of 2009
- January 2010 NICE clinical guideline 92 were issued to update and replace NICE 2007
- On 2 March 2010 Department of Health (DOH) issued National Risk Assessment Tool for VTE, based on NICE 2010
Mechanical Prophylaxis

1. Anti-embolism stockings (thigh or knee length)
2. Foot impulse device (FID)
3. Intermittent pneumatic compression (IPC) device (thigh or knee length)
Foot Pumps

- Promote venous return

- Difficult to use outside hospital

- Reduce the incidence of DVT from 40% to 5% in orthopaedic surgery but NO effect on PE rate

- IPC reduces DVT to 5%, 1% PE
VTE incidence by type of surgery without T-P

- Gynaecology
- Urological
- Vascular
- General
- Hip Fracture
- Orthopaedic Elective Hip
- Orthopaedic Mixed
- Orthopaedic Elective Knee

Symptomatic PE  DVT

NICE 2010
VTE is the most common complication post THR despite the use of prophylaxis

Despite currently available prevention methods, a significant risk of VTE still persists\(^1\)

<table>
<thead>
<tr>
<th>Complication</th>
<th>In - hospital (%)</th>
<th>Re-admission (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(most frequent causes of complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>after THR &gt;1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VTE</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Dislocation</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Wound complications</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Peri-operative fracture</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

VTE was the cause of one third of re-admissions

\(^1\)Gregg PJ, Devlin HB. National Total Hip Replacement Outcome Study 2000. www.rcseng.ac.uk
VTE is the main medical complication of THR\textsuperscript{1}

An occurrence of a VTE may increase inpatient stay, cause re-admissions and cost the NHS time and money.

\textit{Fatal PE - 30\% occur 3 weeks after surgery}\textsuperscript{2}

Elective Hip/Knee Replacement surgeries OFFER combined VTE prophylaxis

- Start mechanical prophylaxis **on admission**
- Start pharmacological VTE prophylaxis **after surgery** with any of the following:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran etexilale</td>
<td>1-4 hours after</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>6 hours after</td>
</tr>
<tr>
<td>LMWH</td>
<td>6–12 hours</td>
</tr>
<tr>
<td>UFH if renal failure</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>6-10 hours after</td>
</tr>
</tbody>
</table>

- Continue pharmacological prophylaxis for **28-35 days** after hip surgery and **10-14 days** after knee surgery
On discharge home (if applicable)

Offer patients and/or their families or carers verbal and written information on:

- signs and symptoms of DVT and PE
- importance of using VTE prophylaxis correctly
- correct duration of VTE prophylaxis at home and its importance
- adverse events of VTE prophylaxis-related signs and symptoms

- importance of seeking medical help and who to contact if develop:
  - any problems using the VTE prophylaxis
  - suspected DVT or PE
  - another adverse event
Conclusion

• VTE is **COMMON** and **PREVENTABLE**

• All hospitalised patient should be risked assessed using the NRAT

• Administration of VTE prophylaxis will depend on the trade off between clinical benefit and harms

• The main end points should be the reduction of fatal PE & major bleeding events
Warfarin’s narrow therapeutic window


Requires dose adjustment and regular monitoring

Intracranial bleed

Therapeutic range

Odds ratio

International normalized ratio (INR)

Warfarin's narrow therapeutic window
Clinical utility of new agents

- One tablet, once daily
- Does not require injection or routine coagulation monitoring
- Rapid anticoagulant effects (within 2–4 hours)
- High oral bioavailability: 80 - 100%
- Low potential for drug–drug or food–drug interactions
- Fixed dose in adult patients regardless of age, gender and extreme body weight
New Anticoagulants have single targets


AT, antithrombin.
### New oral anticoagulants – pharmacology

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran(^{1-3})</th>
<th>Rivaroxaban(^{4,5})</th>
<th>Apixaban(^{6,7})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of action</td>
<td>Factor II</td>
<td>Factor X</td>
<td>Factor X</td>
</tr>
<tr>
<td>Half life</td>
<td>12-14 hrs</td>
<td>5-9 hrs (young)</td>
<td>12 hrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11-13 hrs (elderly)</td>
<td></td>
</tr>
<tr>
<td>Tmax (hrs)</td>
<td>2 (6)</td>
<td>2-4</td>
<td>1-3</td>
</tr>
<tr>
<td>Excretion</td>
<td>85% Renal</td>
<td>1/3 Renal</td>
<td>1/4 Renal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2/3 Hepatic</td>
<td>3/4 Non Renal</td>
</tr>
</tbody>
</table>

Which patients are **NOT** suitable for NOAC?

- Non-adherence
- INR range outside of 2.0 to 3.0
- Indications not covered by licence
  - e.g. prosthetic heart valve requiring anticoagulation
- Renal failure
  - CrCL < 30mL/min dabigatran
  - CrCL < 15mL/min rivaroxaban or apixaban
- Certain drug interactions
- Extremes of body weight
  - <45kg or >120kg – discuss with haematologist
- Exclusions as per SPC
Patients at potentially higher risk with NOAC

- Elderly; caution if > 75 years
- Renal impairment
  - RELY (dabigatran) and ROCKET-AF (rivaroxaban) excluded patients with CrCL < 30mL/min;
  - ARISTOTLE (apixaban) excluded CrCL <25mL/min
- Extremes of body weight
- GI bleeding – increased risk with both rivaroxaban and dabigatran
- Concurrent antiplatelet agents
- Myocardial infarction
Conclusion

• Patients have increased expectations about convenience, promptness and accountability of any treatment they receive

• If things go wrong patients have the right to know why.

• For any error, admission of fault early is best course of action with internal risk management assessment