

Venous Thromboembolism and Travel

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Venous Thromboembolism

- A common, lethal disease
- Affects hospitalized and non-hospitalized patients
- Recurs frequently
- Long-term complications
- Frequently overlooked

Deep Vein Thrombosis

Pulmonary Embolism
Venous Thromboembolism

- Nomenclature
- Epidemiology
- Risk factors
- Diagnosis
- Management
- Prevention
- Long-term complications
- Travel and venous thromboembolism

VTE Nomenclature

- Venous Thromboembolism (VTE)
  - Lower extremity deep vein thrombosis (DVT)
  - Pulmonary embolism (PE)
- Other VTE entities
  - Upper extremity DVT
  - Cerebral venous thrombosis
  - Visceral vein DVT (mesenteric, portal, renal)
  - Superficial venous thrombosis (SVT)
VTE Epidemiology

• Third most common cardiovascular disease after myocardial infarction and stroke
• Affects approximately 1:1,000 US citizens
• Approximately 300,000 US citizens have a fatal PE each year (mortality exceeds that of breast cancer, HIV and motor vehicle accidents combined)
• PE is the most common preventable cause of hospital death (responsible for 10% to 15% of all in-hospital deaths)

Source: 2009 AHA Heart Disease and Stroke Statistics
NEJM 2008; 358: 1037-1052

Burden of Venous Thromboembolism

Death
Pulmonary hypertension
Pulmonary embolism
Post-thrombotic syndrome
Symptomatic Deep Vein Thrombosis
Asymptomatic Deep Vein Thrombosis

Am Journal of Therapeutics 2009; 16: 300-303
VTE Hereditary Risk Factors

**Definite Causes**
- Factor V Leiden mutation
- Prothrombin gene mutation
- Protein C deficiency
- Protein S deficiency
- Antithrombin deficiency
- Hyperhomocysteinemia
- Dysfibrinogenemia

**Probable - Possible Causes**
- Elevated levels of Factors II, VIII, IX and XI
- Factor XIII polymorphisms
- Plasminogen activator inhibitor (PAI-1)
- MTHFR polymorphisms

VTE Acquired Risk Factors

- Advanced age and male gender
- Immobilization
- Surgery or trauma (within 3 months)
- Pregnancy and pueperium
- OCP’s or HRT
- Obesity
- Malignancy
- CVP catheters, PICC lines, pacemakers
- CHF, stroke, systemic illness
- IV drug use, HIV/AIDS
- Antiphospholipid syndrome
- Heparin-induced thrombocytopenia (HIT)
- Extended (air) travel
- Dehydration
- Atherosclerosis, smoking
- Varicose veins
- Chemotherapy: L-asparaginase, Tamoxifen, Bevacizumab, Thalidomide, Lenalidomide
- Hyperviscosity syndromes
  - Waldenstrom’s macroglobulinemia
- Myeloproliferative disorders
- Inflammatory bowel disease
- Nephrotic syndrome, chronic renal disease
- SLE, Behcet’s disease, TAO
Acquired Risk Factors

- Trauma
- Older age
- HRT use
- Cancer
- Recent surgery

Acquired Risk Factors

- Older age
- IVC filters
- Obesity

DOS CME Course 2011
Acquired Risk Factors

- Air travel
- Catheter-related
- Pacemaker wires

Signs and Symptoms of DVT

- Pain
- Edema
- Erythema
- Cyanosis
- Pallor
- Dilated veins (upper or lower extremity)
- Palpable cord (superficial thrombophlebitis)
- May be clinically silent
- Clinical exam, often unreliable
Not all DVT’s are Clinically Apparent

An untreated proximal DVT has an approximate 50% risk for PE

Pain
Edema
Not all DVT’s are Clinically Apparent

- Cyanosis
- Erythema

Associated with:
- CVP, PICC lines, pacemaker wire
- Thoracic outlet syndromes
Clinical Decision Rule - Pre-test Probability - DVT

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer (treatment ongoing or within previous 6 months or palliative treatment)</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis, recent plaster immobilization of lower extremities</td>
<td>1</td>
</tr>
<tr>
<td>Recently bedridden for &gt; 3 days or major surgery within 4 weeks</td>
<td>1</td>
</tr>
<tr>
<td>Local tenderness along the distribution of the deep venous system</td>
<td>1</td>
</tr>
<tr>
<td>Swelling of the entire leg</td>
<td>1</td>
</tr>
<tr>
<td>Calf swelling (more than 3cm &gt; asymptomatic side)</td>
<td>1</td>
</tr>
<tr>
<td>Pitting edema</td>
<td>1</td>
</tr>
<tr>
<td>Collateral superficial veins (non varicose)</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis likely</td>
<td>-2</td>
</tr>
</tbody>
</table>

Clinical probability:
- High: (3 or more points) PPV of 75%
- Moderate: (1 to 2)
- Low: (0 points) NPV of 96%; if d-dimer (-) 99%

Objective Testing for DVT
- D-dimer
- Duplex Ultrasonography
- CT Venography
- MR Venography
- Venography
Diagnosis of DVT - Plasma D-dimers

D-dimer levels are also elevated in:

- Pneumonia
- Sepsis, DIC
- Trauma, surgery
- Malignancy
- Pregnancy
- MI
- Hemorrhage

Sensitive indicator of thrombosis
Very high negative predictor value

Ann Intern Med 2004; 140: 589-602
Blood 2009; 113: 2878-2887

Ultrasound Findings of DVT

- Non-compressibility
- Visualize thrombus
- Venous Distention
- Absence of flow
- Lack of collaterals

A remote or residual DVT identified by U/S also predicts the likelihood of recurrent DVT

Ann Intern Med 2009; 150: 577-585
Key Points in the Diagnosis of DVT

- Clinical exam often unreliable
- Negative D-dimer excludes DVT
- Duplex ultrasound - first objective test
- Anticoagulate once SUSPECT DVT

Pulmonary Embolism – Frequently Overlooked

- As many as 25% of patients present as sudden death
- Most non-sudden deaths are due to failure to diagnose
- Hospital patients are at particularly high risk
- Most common preventable cause of in-hospital deaths
- Many PE’s do not manifest until after discharge

Accounts for 10% - 15% of all in hospital deaths

Major contributing factor in an additional 10%

Source: 2009 AHA Heart Disease and Stroke Statistics
NEJM 2008; 358: 1037-10520
**Clinical Decision Rule - Pre-Test Probability - PE**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)</td>
<td>3.0</td>
</tr>
<tr>
<td>Alternative diagnosis less likely than pulmonary embolism</td>
<td>3.0</td>
</tr>
<tr>
<td>Heart rate &gt; 100/minute</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization (&gt;3d) or surgery in the previous week</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous pulmonary embolism or deep vein thrombosis</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1.0</td>
</tr>
<tr>
<td>Malignancy (receiving treatment or treated in last 6 months or palliative)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Clinical probability of PE unlikely 4 or less points

Clinical probability of PE likely more than 4 points

Semin Thromb and Haemost 2000; 26:643

**Signs and Symptoms of PE**

- Dyspnea
- Tachypnea
- Pleuritic pain
- Leg edema, erythema, tenderness, palpable cord
- Cough/hemoptysis

Consider massive PE in patients with sudden onset of syncope, hypotension, extreme hypoxemia, electromechanical dissociation or cardiac arrest

Am J Med 2007; 120: 871-879

NEJM 2008; 358: 1037-1052
Objective Testing for PE

• D-dimer
• Computed tomography pulmonary angiogram (CTPA)
• Ventilation perfusion scan
• Pulmonary angiography
• 2-D or transesophageal echocardiogram
• Biomarkers (troponin and BNP)
• Duplex ultrasonography

Computed Tomographic Pulmonary Angiography (CTPA)

• Readily available
• Directly visualizes thrombi best in the main, lobar or segmental pulmonary arteries
• Also detects nonthromboembolic pathology (mediastinal and parenchymal structures)

Circulation 2004; 109: 2401-2404
NEJM 2008; 358: 1037-1052
2-D Echocardiography

- Rapid bed-side assessment
- Helpful to risk stratify patients looking for signs of right ventricle strain (indicating a higher in-hospital and long-term mortality)

**Direct Findings:**
- Right-sided intracardiac thrombus
- Pulmonary artery thrombus

**Indirect Findings:**
- RV dilation
- Decreased RV function

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Biomarkers – (Troponins and BNP) in acute PE

- Levels correlate with ECG and echo findings of right ventricular pressure overload
- Are predictors of adverse outcomes: associated with overall mortality, major clinical events, and recurrence

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Am J Med 2006; 119: 1048

Circulation 2007;116:427-433
Venous Duplex for the Diagnosis of PE

ADVANTAGES:
- Perform at bedside
- Noninvasive
- Positive duplex generally adequate for treatment
- Combine with spiral CT to help exclude/include PE

Key Points in the Diagnosis of PE
- Clinical examination often unreliable
- Negative D-dimer excludes PE
- CTPA first objective diagnostic test
- Anticoagulate once you suspect PE
Treatment Options for VTE

- Heparin (IV or SC)
- LMWH (SC) (avoid if creatinine clearance < 30 mL/min)
- Fondaparinux (SC) (avoid if creatinine clearance < 30 mL/min)
- Thrombolytic therapy
- IVC filters
- Pulmonary embolectomy
- Mechanical thrombectomy for DVT
- Warfarin (oral)
- Compression hose (30 to 40 mmHg)

Treat to prevent PE, PTS, CTPH, Recurrent VTE

More Aggressive Therapy: Thrombolytic Therapy for Acute PE

- Confirmed PE
  - Initiate anticoagulation (unless contraindication)

  - Hemodynamically unstable
    - Assess thrombolytic contraindications
      - Contraindicated
        - Consider pulmonary embolectomy
      - No contraindication
        - Thrombolytic therapy
  - Hemodynamically stable
    - Risk stratification
      - Troponin
      - BNP
      - Echocardiogram
      - RV dysfunction
      - Positive biomarkers
      - Severe hypoxemia
      - Significant residual DVT
      - Extensive/saddle PE

Chest 2009; 135: 1321-29
More Aggressive Therapy: Mechanical Thrombectomy for Acute DVT

• Extensive iliofemoral or more proximal DVT with symptoms of pain, swelling and/or cyanosis

Indications for IVC Filters for VTE

Absolute Indications:
• Contraindication to anticoagulation
• Failure of adequate anticoagulation
• Significant complication of anticoagulation
• Pulmonary embolectomy

Relative Indications:
• Massive PE
• Primary prophylaxis
• Free floating thrombi
• Cardiac or pulmonary insufficiency
• Poor compliance
• Ataxia

Routine use of IVC filters for VTE is NOT recommended
Retrievable IVC Filters

Remove Because of:

- Filter migration
- Organ penetration
- Recurrent VTE
- Caval occlusion
- Clot above filter

Arch Surg 2003;138:591
J Vasc Interv Radiol 2006; 17:449-459

Prevention of VTE

- 2/3 of all VTE events related to hospitalization
- Only 1/3 of all hospitalized patients at risk for VTE receive prophylaxis
- **National Quality Forum**: all adult patients should be risk assessed and receive prophylaxis
- **CMS**: VTE is considered a preventable hospital acquired condition (POA)

Arch Intern Med 2002;162:1245-1248
Methods for Prevention of VTE

- Pharmacologic:
  - LMWH (enoxaparin, dalteparin)
  - Heparin
  - Fondaparinux
  - Iprivask
  - Warfarin

- Mechanical:
  - Intermittent pneumatic compression
  - Graduated elastic compression stockings

Long Term - Non-Fatal Complications of VTE

- Recurrent VTE
- Chronic thromboembolic pulmonary hypertension (CTPH)
- Post-thrombotic syndrome

References:
Chest. 2008;133(6)(suppl):381S-453S.
Air Travel and Venous Thromboembolism

Incidence of VTE following air travel is approximately 3.2 per 1,000 person-years (general population reported incidence is 1.0 per 1,000 person-years).

Acute pulmonary embolism incidence ranges from:
- 1.65 per million patients in flights longer than 8 hours
- 4.80 per million patients in flights longer than 12 hours or distances greater than 6200 miles

References:
PloS Med 2007; 4:1508-1514
J Intern Med 2007; 4:615-634
Arch Intern Med 2003; 163:2766-2770
Air Travel and VTE – Additional Risk Factors

• Long distance flights > 8 to 10 hours or multiple flights of at least 4 hours
• More frequent flights of any duration within days or weeks
• Short people <165 CM (5’ 5”) in height
• Tall people >185 CM (6’1”) in height
• Highest risk within the first 2 weeks after the trip, decreases after 8 weeks

Prevention: Long-Distance Air Travelers

• Exercise the legs by flexing and extending the ankles at regular intervals
• Walk about the cabin periodically, 5 minutes for every hour on longer duration flights (> 4 hours)
• Drink adequate amounts of water and fruit juices
• Avoid alcohol and caffeinated beverages (prevent dehydration)
• Do not overeat during the flight
Prevention: Long-Distance Air Travelers

• Request an aisle seat (or business first class) if you are at increased risk

• Do not place baggage underneath the seat in front of you

• Do not sleep in a cramped position, avoid sleep aids

• Avoid wearing constrictive clothing around the waist or legs

Prevention: Long Distance Air Travelers

• No known risk factors for VTE; regardless of the duration of the flight – no additional measures needed

• Increased risk factors - use 15 to 30 mmHg below the knee compression stockings for flights > 8 to 10 hours

• Travelers whose risk seems especially high – administer SC LMWH or Fondaparinux
Pharmacological and Mechanical Methods for Prevention of VTE During Air Travel

<table>
<thead>
<tr>
<th>Pharmacological Methods</th>
<th>Mechanical Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMWH:</td>
<td>* Exercises while traveling</td>
</tr>
<tr>
<td>• Enoxaparin 40 mgs SC prior to departure</td>
<td></td>
</tr>
<tr>
<td>• Dalteparin 5,000 IU SC prior to departure</td>
<td></td>
</tr>
<tr>
<td>Anti-Xa inhibitor:</td>
<td>* Graduated compression stockings of 15 to 30 mmHg (below knee)</td>
</tr>
<tr>
<td>• Fondaparinux 2.5 mg SC prior to departure</td>
<td></td>
</tr>
<tr>
<td>• Rivaroxaban*</td>
<td></td>
</tr>
<tr>
<td>Direct thrombin inhibitor:</td>
<td></td>
</tr>
<tr>
<td>• Dabigatran*</td>
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</tbody>
</table>

*not currently available for prophylaxis in the US

Economy Class Syndrome – Why Not Use Prophylaxis on Everyone?

• WRIGHT Study (WHO Research Into Global Hazards of Travel)
  - Study among employees of International and Multinational organizations
  - Found 1 thrombotic event per 6000 flights among 10,000 employees
  - NNT would be 6,000 to prevent 1 venous thrombotic event
Why Not Use Prophylaxis on Everyone?

- Risk of major hemorrhage with LMWH (0.4%) over 14 day period
- Grade I elastic stockings reported to cause symptomatic superficial vein thrombosis in 3% patients
- Tight stockings may pose risk in patients with limb ischemia

Empiric Treatment in Underdeveloped Countries

1. High pretest probability for VTE
2. No diagnostic methods available
3. SC Heparin or LMWH or Fondaparinux
4. Evacuate
# Empiric Treatment in Underdeveloped Countries

## Heparin: IV or SC
- Heparin IV (80 units/kg bolus followed by 18 units/kg per hour)
- Heparin SC (5,000 unit IV bolus followed by 17,500 units SC every 12 hours) OR
- Heparin SC (333 units/kg SC bolus followed by 250 units/kg SC every 12 hours)

## Low Molecular Weight Heparins: SC
- Enoxaparin (Lovenox®) 1mg/kg q12 hours
- Dalteparin (Fragmin®) 200 IU/kg q 24 hours not to exceed 18,000 IU per day
- Tinzaparin (Innohep®) 175 anti-Xa IU/kg administered q 24 hours

All LMWHs must be adjusted if creatinine clearance is <30 mL/min and contraindicated if on hemodialysis

## Anti-Xa inhibitors: SC
- Fondaparinux (Arixtra®): weight dependent dosing:
  - 5 mg every 24 hours for weights < 50 kg
  - 7.5 mg every 24 hours for weights between 50 to 100 kg
  - 10mg every 24 hours for weights over 100 kg

Anti-Xa inhibitors are contraindicated if the creatinine clearance is < 30 mL/min or patients on hemodialysis

## Warfarin (Coumadin®) administered orally
- Available in doses of 1, 2, 2.5, 3, 4, 5, 6, 7.5 and 10mg

## Graduated compression stockings
- 30 to 40 mmHg to prevent the post-thrombotic condition. Should be given to ALL patients with lower extremity DVT
Estimation of VTE Risk for Travelers

As for all travelers, standard thromboprophylaxis precautions should be strongly recommended for travelers who have the following risk factors for VTE:

• Pregnancy or recent delivery within 6 weeks
• Use of contraceptives or hormone replacement therapy
• Select chemotherapy agents (Tamoxifen)
• Autoimmune disorders
• Congestive heart failure, pneumonia, chronic obstructive lung disease
• Leg varicosities
• Obesity (BMI > 30 kg/m²)
• Tall stature (> 185 cms or 73 inches)
• Short stature (<165 cms or 65 inches)
• Age > 70
• Family history of VTE and/or thrombophilia (hypercoagulable states)

When a patient, who will have air travel of more than 10 hours duration has any of these risk factors, the clinician should consider the addition of LMWH or an anti-Xa inhibitor.

Estimation of VTE Risk for Travelers

Any ONE of the following conditions should prompt consideration for use of LMWH or an anti-Xa inhibitor prior to departure

• Prior provoked VTE with ongoing risks
• Recurrent VTE or unprovoked VTE at any time
• Known thrombophilia (Factor V Leiden, Prothrombin gene mutation G20210A, elevated levels of Factor VIII, deficiency of proteins S, C or antithrombin or the antiphospholipid syndrome)
• Myeloproliferative disorders (essential thrombocytosis or polycythemia vera with HCT > 55)
• Malignancies and on-going chemotherapy treatment
• Flaccid leg paralysis, inability to ambulate, or the presence of a non-removable long leg cast or brace
• Major surgery within the prior 4 to 12 weeks, most notably total hip and knee replacements, hip fracture or recently bedridden for more than 3 consecutive day
• Recent major trauma
Air travel and venous thromboembolism: Minimizing the risk

ABSTRACT

Not those traveling on long flights, the risk of deep venous thrombosis or pulmonary embolism, generally referred to as venous thromboembolism (VTE), is real and dangerous. Therefore, it is imperative to minimize the risk of VTE during travel and how to diagnose and treat it.

KEY POINTS

The risk of VTE is about three times higher in passengers on long distance flights than in the general population, although the absolute risk is still low.

All long distance air passengers should perform stretching and moving of all limbs while en route to prevent VTE, and they should also try hydrated.

For patients at higher risk due to hypercoagulable conditions, prophylaxis with mechanical and chemical measures is safer and more effective than low molecular weight heparin or a factor Xa inhibitor to be taken before the flight, or both.

The evaluation of a patient with suspected VTE should include an estimation of the post-test probability of disease. A negative or highly discordant imaging study, and laboratory markers.

The article focuses on defining VTE and presenting practical information, as well as avoiding complications and deficiencies in presentation, diagnostic, and treat the complications in people with VTE.

WHAT IS VENOUS THROMBOEMBOLISM?

Deep vein thrombosis and pulmonary embolism represent different mechanisms of the same clinical entity, VTE. VTE is a serious, lethal disorder that affects hospitalized and ambulatory patients, frequently recurs.