Deep Vein Thrombosis:

Prevention in Acutely Ill Hospitalized Medical Adults

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Disclosure of Financial Relationships

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Has no relationships with any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.
Learning Objectives

• Review the general aspects and epidemiology of deep vein thrombosis in the hospital setting.

• Emphasize the importance of adequate and effective DVT prevention methods in acutely ill hospitalized medical adults.

• Encourage the use of evidence–based practical guidelines on venous thromboprophylaxis from admission to discharge medical practices.
General View - Statistics

VTE

{ Deep Venous Thrombosis
  Pulmonary Embolism

250,000 hospitalizations per year in USA.

- 200,000 new cases annually.
- 20% sudden death due to acute pulmonary embolism.
- 30% VTE syndromes die within 30 days.
- 30% risk for recurrent VTE over 10 years.
- Direct costs of VTE $3 to $4 billion annually.

Annual Incidence of VTE is $+ 0.1\%$. 

RATE $0.01\%$ (early adulthood) to $1\%$ ($> 60$ year old).

* More than half of these events involve Deep Venous Thrombosis (DVT).
Venous Thromboembolism

**FACTS**

- 25% of all cases of VTE are associated with hospitalization.

- 50-75% of VTE cases in hospitalized patients occur in those on the medical service.

- PE is associated with 5-10% of deaths in hospitalized patients.
VTE is a Disease of Hospitalized and Recently Hospitalized Patients

Heit et al. Mayo Clin Proc 2001;76:1102
Venous Thromboembolism
Pathogenesis

**VIRCHOW’S TRIAD:**

1. Alterations in normal blood flow *(stasis)*

2. Endothelial damage *(vessel wall)*

3. Changes in the constitution of blood *(hypercoagulability)*
Virchow’s Triad

Hypercoagulable State
- Malignancy
- Pregnancy and peri-partum period
- Oestrogen therapy
- Trauma or surgery of lower extremity, hip, abdomen or pelvis
- Inflammatory bowel disease
- Nephrotic syndrome
- Sepsis
- Thrombophilia

Vascular Wall Injury
- Trauma or surgery
- Venepuncture
- Chemical irritation
- Heart valve disease or replacement
- Atherosclerosis
- Indwelling catheters

Circulatory Stasis
- Atrial fibrillation
- Left ventricular dysfunction
- Immobility or paralysis
- Venous insufficiency or varicose veins
- Venous obstruction from tumour, obesity or pregnancy
“All institutions should have a program in place that allows for the evaluation of a patient’s risk of developing VTE. If patients are found to be at risk of VTE, appropriate prophylaxis should be implemented (Grade 1A).”

*Chest.* February 2012;141(2)(Suppl):e419S-e494S
CLINICAL SUSPICIOUS OF VTE DISEASE
PROBABILITY

– Wells Criteria Score

Clinical signs and symptoms of DVT.
Pulmonary embolism is #1 diagnosis, or equally likely.
Heart rate > 100 BPM.
Immobilization at least 3 days, or surgery in the previous 4 weeks
Previous, objectively diagnosed with PE or DVT.
Hemoptysis.
Malignancy with treatment within 6 months, or palliative.

http://www.mdcalc.com/wells-criteria-for-pulmonary-embolism-pe/

QUESTION # 1
What is the estimated annual numbers of US acute-care hospital patients at risk for venous thromboembolism?

1. 25%
2. 32%
3. 50%
4. 73%
5. 80%
What is the estimated annual numbers of US acute-care hospital patients at risk for venous thromboembolism?

1. 25%
2. 32%
3. 50%
4. 73%
5. 80%
It is estimated that over half of hospitalized medical patients are at risk for venous thromboembolism (VTE, ie, deep vein thrombosis [DVT] and/or pulmonary embolism [PE]).

QUESTION # 2
One of the following is not considered a high risk factor for venous thromboembolic disease VTE:

1. Intensive Care Unit Patients.
2. Oncological Patients
3. Heart Failure
4. Chronic Corticosteroid Use
5. Pregnancy
One of the following is **not** considered a high risk factor for venous thromboembolic disease VTE:

1. Intensive Care Unit Patients.
2. Oncological Patients
3. Heart Failure
4. Chronic Corticosteroid Use
5. Pregnancy
### VENOUS THROMBOEMBOLIC DISEASE
#### RISK FACTORS

<table>
<thead>
<tr>
<th>Stasis</th>
<th>Hypercoagulability</th>
<th>Endothelial Damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 40</td>
<td>Cancer</td>
<td>Surgery</td>
</tr>
<tr>
<td>Immobility</td>
<td>High estrogen states</td>
<td>Prior VTE</td>
</tr>
<tr>
<td>CHF</td>
<td>Inflammatory Bowel</td>
<td>Central lines</td>
</tr>
<tr>
<td>Stroke</td>
<td>Nephrotic Syndrome</td>
<td>Trauma</td>
</tr>
<tr>
<td>Paralysis</td>
<td>Sepsis</td>
<td></td>
</tr>
<tr>
<td>Spinal Cord injury</td>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Hyperviscosity</td>
<td>Pregnancy</td>
<td></td>
</tr>
<tr>
<td>Polycythemia</td>
<td>Thrombophilia</td>
<td></td>
</tr>
<tr>
<td>Severe COPD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anesthesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicose Veins</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VENOUS THROMBOEMBOLIC DISEASE
RISK FACTORS

Stasis
Age > 40
Immobility
CHF
Stroke
Paralysis
Spinal Cord injury
Hyperviscosity
Polycythemia
Severe COPD
Anesthesia
Obesity
Varicose Veins

Hypercoagulability
Cancer
High estrogen states
Inflammatory conditions
Nephrotic Syndrome
Smoking
Pregnancy

Endothelial Damage
Surgery
Prior VTE
Central lines
Trauma

Most hospitalized patients have at least one risk factor for VTE

QUESTION # 3
Clinical Scenario

• 63 yo Hispanic man with the past medical history of CHF, hypertension, diabetes, CKD Stage 1 and a diabetic ulcer of the left leg, is directly admitted to HIM service with an acute lower extremity cellulitis and severe pain.

• Physical exam: Pulse 100 BP 105/65 RR 24 Inspiratory crackles in the lower lung fields, wheezing, bilateral pedal edema and LLE ulcer. Rest unremarkable.

• Laboratory data: Cr 1.3 eGFR 49. Rest within normal ranges.

• After you reviewed the EMR and preliminary clinical assessment you decided to order venous thromboprophylaxis.
What would be the most appropriate regimen?

1. Low Dose Unfractioned Heparin
2. Low Molecular Weight Heparin
3. Fondaparinux
4. Any of the above
5. Only 2 and 3 options are correct.
For acutely ill hospitalized medical patients at increased risk of thrombosis, we recommend anticoagulant thromboprophylaxis with low-molecular-weight heparin [LMWH], low-dose unfractionated heparin (LDUH) bid, LDUH tid, or fondaparinux (Grade 1B).

*Chest. February 2012;141(2)(Suppl):e278S-e325S*
QUESTION # 4
Clinical Scenario

The previous patient was dismissed from the hospital by the HIM team after 4 days of medical treatment and excellent clinical progress.

No major complications and no surgical interventions required.

You are updating the dismissal summary note and doing a medication reconciliation process prior to send him home.
What would you include in your final plan?

1. Warfarin 2.5 mg PO daily for a total of 10–14 days.

2. Enoxaparin 20 mg subcutaneously daily for 10–14 days.

3. Low dose unfractioned heparin 5,000 units daily for 10–14 days.

4. Rivaroxaban 5 mg PO daily for 10–14 days.

5. None of the above.
What would you include in your final plan?

1. Warfarin 2.5 mg PO daily for a total of 10–14 days.
2. Enoxaparin 20 mg subcutaneously daily for 10–14 days.
3. Low dose unfractioned heparin 5,000 units daily for 10–14 days.
4. Rivaroxaban 5 mg PO daily for 10–14 days.
5. None of the above.
In acutely ill hospitalized medical patients who receive an initial course of thromboprophylaxis, we suggest against extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay (Grade 2B).
QUESTION # 5
Clinical Scenario

- A 28 yo Caucasian woman admitted under Hospital Medicine team care with an acute exacerbation of recurrent, refractory migraine headaches. Past medical history is remarkable for recreational drug use.


- Toxic screen in ED was negative. Rest of the laboratory data was within normal ranges.
What would you use for venous thrombotic disease prophylaxis on this case?

1. Intermittent Pneumatic Device (IPD).
2. Gradient Compression Stockings (GCS).
3. Enoxaparin 30 mg subcutaneously daily.
4. Unfractioned heparin 5.000 units subcutaneously BID.
5. None of the above.
What would you use for venous thrombotic disease prophylaxis on this case?

1. Intermittent Pneumatic Device (IPD).

2. Gradient Compression Stockings (GCS).

3. Enoxaparin 30 mg subcutaneously daily.

4. Unfractioned heparin 5,000 units subcutaneously BID.

5. None of the above.
For acutely ill hospitalized medical patients at low risk of thrombosis, we recommend against the use of pharmacologic prophylaxis or mechanical prophylaxis (Grade 1B).
Rationale for DVT prophylaxis

- DVT/PE remains as complications associated with acute ill medical patients and prolonged hospital stays

- Effective regimens available to reduce risk and prevent events/deaths.
Risk assessment

- **Patient Risk**
  - Low
  - Intermediate
  - High

- **Procedure risk**
  - Low
  - Intermediate
  - High

- **Scoring systems**
  - Caprini Score
  - Rogers Score
### Rogers Risk Score

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Risk Score Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation type other than endocrine</td>
<td></td>
</tr>
<tr>
<td>Respiratory and hernia</td>
<td>9</td>
</tr>
<tr>
<td>Thoracoabdominal aneurysm, embolectomy/thrombectomy, venous reconstruction, and endovascular repair</td>
<td>7</td>
</tr>
<tr>
<td>Aneurysm</td>
<td>4</td>
</tr>
<tr>
<td>Mouth, palate</td>
<td>4</td>
</tr>
<tr>
<td>Stomach, intestines</td>
<td>4</td>
</tr>
<tr>
<td>Integument</td>
<td>3</td>
</tr>
<tr>
<td>Hernia</td>
<td>2</td>
</tr>
<tr>
<td>ASA physical status classification</td>
<td></td>
</tr>
<tr>
<td>3, 4, or 5</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Female sex</td>
<td>1</td>
</tr>
<tr>
<td>Work RVU</td>
<td></td>
</tr>
<tr>
<td>&gt; 17</td>
<td>3</td>
</tr>
<tr>
<td>10-17</td>
<td>2</td>
</tr>
<tr>
<td>Two points for each of these conditions</td>
<td>2</td>
</tr>
<tr>
<td>Disseminated cancer</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy for malignancy within 30 d of operation</td>
<td></td>
</tr>
<tr>
<td>Preoperative serum sodium &gt; 145 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Transfusion &gt; 4 units packed RBCs in 72 h before operation</td>
<td></td>
</tr>
<tr>
<td>Ventilator dependant</td>
<td></td>
</tr>
<tr>
<td>One point for each of the conditions</td>
<td>1</td>
</tr>
<tr>
<td>Wound class (clean/contaminated)</td>
<td></td>
</tr>
<tr>
<td>Preoperative hematocrit level ≤ 38%</td>
<td></td>
</tr>
<tr>
<td>Preoperative bilirubin level &gt; 1.0 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td></td>
</tr>
<tr>
<td>Albumin level ≤ 3.5 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Emergency</td>
<td></td>
</tr>
<tr>
<td>Zero points for each of these conditions</td>
<td>0</td>
</tr>
<tr>
<td>ASA physical status class 1</td>
<td></td>
</tr>
<tr>
<td>Work RVU &lt; 10</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td></td>
</tr>
</tbody>
</table>

**Low** < 7  
**Moderate** 7-10  
**High** > 10  

*ACCP antithrombotic guidelines, 9th edition. CHEST 2012; 141(2)(Suppl):e2425*
## Caprini Risk Score

<table>
<thead>
<tr>
<th>1 Point</th>
<th>2 Points</th>
<th>3 Points</th>
<th>5 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 41-60 y</td>
<td>Age 61-74 y</td>
<td>Age ≥ 75 y</td>
<td>Stroke (≤ 1 mo)</td>
</tr>
<tr>
<td>Minor surgery</td>
<td>Arthroscopic surgery</td>
<td>History of VTE</td>
<td>Elective arthroplasty</td>
</tr>
<tr>
<td>BMI &gt; 25 kg/m²</td>
<td>Major open surgery (&gt; 45 min)</td>
<td>Family history of VTE</td>
<td>Hip, pelvis, or leg fracture</td>
</tr>
<tr>
<td>Swollen legs</td>
<td>Laparoscopic surgery (&gt; 45 min)</td>
<td>Factor V Leiden</td>
<td>Acute spinal cord injury (≤ 1 mo)</td>
</tr>
<tr>
<td>Varicose veins</td>
<td>Malignancy</td>
<td>Prothrombin 20210A</td>
<td></td>
</tr>
<tr>
<td>Pregnancy or postpartum</td>
<td>Confined to bed (≤ 72 h)</td>
<td>Lupus anticoagulant</td>
<td></td>
</tr>
<tr>
<td>History of unexplained or recurrent</td>
<td>Immobilizing plaster cast</td>
<td>Anticardiolipin antibodies</td>
<td></td>
</tr>
<tr>
<td>spontaneous abortion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral contraceptives or hormone</td>
<td>Central venous access</td>
<td>Elevated serum homocysteine</td>
<td></td>
</tr>
<tr>
<td>replacement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis (≤ 1 mo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious lung disease, including</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pneumonia (≤ 1 mo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal pulmonary function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure (≤ 1 mo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of inflammatory bowel disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical patient at bed rest</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Low 1-2   Moderate 3-4   High >5

DVT Prophylaxis – Low risk

• Non pharmacological intervention
  – Early ambulation

• Mechanical prophylaxis while non-ambulatory
  – Sequential compression devices
  – Elastic stockings

• Low dose aspirin??
DVT Prophylaxis – Moderate Risk
Medical and Non Orthopedic surgery

• Low Dose UFH
  – 5,000 units bid or tid
• LMWH
  – Enoxaparin 40mg once daily
  – Dalteparin 5000u daily
• Mechanical
  – Sequential Compression Devices
  – Elastic Stockings
DVT Prophylaxis – High Risk Orthopedic procedures

- Enoxaparin 30mg bid
- Dalteparin 5000 u daily
- Fondaparinux 2.5mg daily
- Adjusted Vitamin K antagonist
  - Warfarin – adjust INR 2-3
- New anticoagulant agents
  - Apixaban 2.5mg bid
  - Rivaroxaban 10mg daily
  - Dabigatran 150mg daily
# Oral Anticoagulant Pharmacology

## Table 1. Comparative Properties of Warfarin, Dabigatran, Rivaroxaban, and Apixaban

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Vitamin K epoxide reductase</td>
<td>Factor II (free and clot-bound thrombin)</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td>Prodrug</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>&gt;95</td>
<td>6.5</td>
<td>&gt;80</td>
<td>50</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic, mainly via CYP2C9, CYP1A2, CYP3A4, CYP2C8, CYP2C18, and CYP2C19</td>
<td>Hepatic</td>
<td>Hepatic, mainly via CYP3A4, CYP3A5, and CYP2J2</td>
<td>Hepatic, mainly via CYP3A4 with minor contributions from CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP2J2</td>
</tr>
<tr>
<td>Plasma protein binding (%)</td>
<td>97</td>
<td>34-35</td>
<td>~92-95 (primarily albumin)</td>
<td>87</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>40</td>
<td>14-17</td>
<td>5-9</td>
<td>9-13 (elderly)</td>
</tr>
<tr>
<td>Elimination</td>
<td>92% renal</td>
<td>80% renal</td>
<td>66% renal</td>
<td>27% renal</td>
</tr>
<tr>
<td>Monitoring</td>
<td>INR adjusted</td>
<td>Not needed</td>
<td>Not needed</td>
<td>Not needed</td>
</tr>
<tr>
<td>Peak effect (h)</td>
<td>72-96</td>
<td>2</td>
<td>2-4</td>
<td>3-4</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>CYP2C9, CYP1A2, and CYP3A4</td>
<td>P-gp inducers/inhibitors</td>
<td>CYP3A4 and P-gp inducers/inhibitors</td>
<td>CYP3A4 and P-gp inducers/inhibitors</td>
</tr>
<tr>
<td>Antidote</td>
<td>Vitamin K</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Reversal via hemodialysis</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*CYP = cytochrome; INR = international normalized ratio; P-gp = P-glycoprotein.*
# Anticoagulant Agents

## Clearance

<table>
<thead>
<tr>
<th>Agent</th>
<th>Excretion</th>
<th>Half life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated Heparin</td>
<td>Renal</td>
<td>1.5 h</td>
</tr>
<tr>
<td>Enoxaparin (Lovenox)</td>
<td>Renal</td>
<td>4-7 h</td>
</tr>
<tr>
<td>Dalteparin (Fragmin)</td>
<td>Renal</td>
<td>3-5 h</td>
</tr>
<tr>
<td>Fondaparinux (Arixtra)</td>
<td>Renal</td>
<td>17-21h</td>
</tr>
<tr>
<td>Dabigatran (Pradaxa)</td>
<td>Renal</td>
<td>12-17h</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto)</td>
<td>Renal, biliary</td>
<td>5-9 h, 11-13 elderly</td>
</tr>
<tr>
<td>Apixaban (Eliquis)</td>
<td>Renal, biliary</td>
<td>12 h</td>
</tr>
<tr>
<td>Edoxaban (Savaysa)</td>
<td>Renal</td>
<td>10-14 h</td>
</tr>
</tbody>
</table>
## Interruption of Therapy with NOAC

<table>
<thead>
<tr>
<th>Agent</th>
<th>GFR &gt; 50</th>
<th>GFR 30-49</th>
<th>GFR 15-29</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard bleeding risk</td>
<td>High bleeding risk</td>
<td>Standard bleeding risk</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>1 day</td>
<td>2-3 days</td>
<td>3 days</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>1 day</td>
<td>2 days</td>
<td>2 days</td>
</tr>
<tr>
<td>Apixaban</td>
<td>1 day</td>
<td>2 days</td>
<td>2 days</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>1 days</td>
<td>2 days</td>
<td>3 days</td>
</tr>
</tbody>
</table>

Agent can be initiated 48 to 72 hours after surgery/procedure hemostasis achieved.
“I like to generalize and state that virtually every patient with an anticipated hospital stay of 48 hours or more warrants prophylactic measures against VTE. I conceptualize prophylaxis as immunization against DVT and PE.

One cannot predict with certainty which patient will develop thrombosis. Therefore the philosophy that I adopt is universal protection, analogous to the procedures adopted universally for vaccination, hand washing and disposing of sharp needles.”
Venous thromboembolism is a very important source of hospital acquired cost, mortality and morbidity.

Thromboprophylaxis is much easier and less expensive than diagnosis and treatment.

Thromboprophylaxis needs to be continued as a preventive initiative in our practice that can improve patient safety in health care settings.

Thromboprophylaxis seen as an universal protection “immunizes” hospitalized patients at risk against DVT and PE.

Thromboprophylaxis is effective, safe and cost-effective, but underutilized in many institutions.
“The best interest of the patient is the only interest to be considered....”

-Dr. William J. Mayo