Management of Venous Thromboembolism for Patients With Hematologic Malignancies

Rowena N. Schwartz, PharmD, BCOP
University of Cincinnati
Learning Objectives

1. Describe the various factors associated with elevated VTE risk in cancer patients
2. Discuss indications and contraindications for cancer-associated VTE prophylaxis and therapy
3. Review available anticoagulation treatment modalities and devices
4. Monitor and assess patient response to anticoagulation treatment
5. Comment on the effective use of emergency antidotes and reversal agents

VTE = venous thromboembolism.
Financial Disclosure

Dr. Schwartz has nothing to disclose.
Definitions for Today’s Discussion

- Venous thromboembolism (VTE)
  - Deep vein thrombosis (DVT)
  - Pulmonary embolism (PE)

- Management of VTE
  - Acute phase: first 5–10 days
  - Short term: 3–6 months
  - Long term: beyond 3–6 months

- Hemostasis: The complex process of maintaining the integrity of the circulatory system following damage to blood vessels
  - Hemostatic clots: localized to the vessel wall
  - Thrombotic clots: impairment of blood flow
Overview of Hemostasis

**Activators**
- Von Willebrand Factor
- Collagen
- Tissue Factor
- Tissue Factor
- Factor VIIa
- Factor VIIIa
- Factor IXa
- Factor Va
- Factor Xa
- Factor XIIIa
- Tissue plasminogen activator

**Inhibitors**
- Antithrombin
- Heparin
- Thrombomodulin
- Protein C
- Protein S
- Tissue factor pathway inhibitor
- Plasminogen activator inhibitor-1

**Vessel wall injury**

**Platelet adhesion and aggregation**

**Coagulation cascade activated**

**Thrombin**

**Fibrin formation**

**Stabilized fibrin clot**

**Fibrinolysis and clot degradation**
Natural Anticoagulants

• Protein C → Destroys factor V and factor VIII
• Protein S → Cofactor to protein C, free and bound
• TFPI
• Prostacyclin (PGI2) → inhibits platelet aggregation
• Antithrombin III → neutralizes thrombin
  • Binds to natural heparin found on surface of normal endothelial cells
  • Inhibits Factor Xa, IXa, and TF bound with VIIa
• tPA→ Converts plasminogen to plasmin, which acts on fibrinogen or fibrin to form FDP (or D dimers)

TFPI = tissue factor pathway inhibitor; tPA = tissue plasminogen activator.
Coagulation Cascade

Intrinsic Pathway
- XII
- XI
- IX
- Prothrombin (II)

Extrinsic Pathway
- VII
- Tissue Factor

Common Pathway
- Thrombin (IIa)
- Fibrinogen (I)
- Fibrin
- Cross Linked Fibrin Clot
Nomenclature

- Heparin
  - UFH: Unfractionated heparin
  - LMWH: Low molecular weight heparin

- Oral Anticoagulants
  - NOACs: Novel/new oral anticoagulants
  - DOACs: Direct oral anticoagulants
  - TSOACs: Target-specific oral anticoagulant

Thrombosis in Cancer: Etiology

Virchow’s Triad

Circulatory Stasis
Endothelial Injury
Hypercoagulable State

Active Cancer and Thrombosis

FT = tissue factor; IL = interleukin; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor

## Relative VTE Risk for Cancer

<table>
<thead>
<tr>
<th>Origin</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck</td>
<td>0.29</td>
<td>0.20–0.40</td>
</tr>
<tr>
<td>Breast</td>
<td>0.44</td>
<td>0.40–0.48</td>
</tr>
<tr>
<td>Prostate</td>
<td>0.98</td>
<td>0.93–1.04</td>
</tr>
<tr>
<td>Lung</td>
<td>1.13</td>
<td>1.07–1.19</td>
</tr>
<tr>
<td>Colon</td>
<td>1.36</td>
<td>1.29–1.44</td>
</tr>
<tr>
<td>Stomach</td>
<td>1.49</td>
<td>1.33–1.68</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1.80</td>
<td>1.65–1.96</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2.05</td>
<td>1.87–2.24</td>
</tr>
<tr>
<td>Leukemia</td>
<td>2.18</td>
<td>2.01–2.37</td>
</tr>
<tr>
<td>Brain</td>
<td>2.37</td>
<td>2.04–2.74</td>
</tr>
<tr>
<td>Uterus</td>
<td>3.34</td>
<td>2.97–3.87</td>
</tr>
</tbody>
</table>

CI = confidence interval; RR = relative risk.
Relative VTE Risk for Cancer

<table>
<thead>
<tr>
<th>Origin</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck</td>
<td>0.29</td>
<td>0.20–0.40</td>
</tr>
<tr>
<td>Breast</td>
<td>0.44</td>
<td>0.40–0.48</td>
</tr>
<tr>
<td>Prostate</td>
<td>0.98</td>
<td>0.93–1.04</td>
</tr>
<tr>
<td>Lung</td>
<td>1.13</td>
<td>1.07–1.19</td>
</tr>
<tr>
<td>Colon</td>
<td>1.36</td>
<td>1.29–1.44</td>
</tr>
<tr>
<td>Stomach</td>
<td>1.49</td>
<td>1.33–1.68</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1.80</td>
<td>1.65–1.96</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2.05</td>
<td>1.87–2.24</td>
</tr>
<tr>
<td>Leukemia</td>
<td>2.18</td>
<td>2.01–2.37</td>
</tr>
<tr>
<td>Brain</td>
<td>2.37</td>
<td>2.04–2.74</td>
</tr>
<tr>
<td>Uterus</td>
<td>3.34</td>
<td>2.97–3.87</td>
</tr>
</tbody>
</table>

Risk for VTE

- Age
- History
- Vascular Stasis
- Hypercoagulable States
- Medications
# Potential Risk Factors in the Individual with Cancer

## Patient-Related
- Age
- Obesity
- History of VTE
- Hypercoagulable conditions
- Comorbidities

## Cancer-Related
- Malignancy
- Extrinsic vascular compression due to cancer and/or lymphadenopathy
- Pathology of disease (e.g., adenocarcinoma)
- Extent of disease (e.g., metastatic cancer)

## Treatment-Related
- Surgery
- Chemotherapy
- Endocrine therapy
- Antiangiogenesis agents
- CVAD
- Medications for symptoms (e.g., ESA)

CVAD = central venous access devices; ESA = erythropoiesis-stimulating agent.
Predictive Model for Chemotherapy-Associated VTE

<table>
<thead>
<tr>
<th>Total Score</th>
<th>Risk Category</th>
<th>Risk of Symptomatic VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>0.8%–3%</td>
</tr>
<tr>
<td>1 or 2</td>
<td>Intermediate</td>
<td>1.8%–8.4%</td>
</tr>
<tr>
<td>≥3</td>
<td>High</td>
<td>7.1%–41%</td>
</tr>
</tbody>
</table>

# Predictive Model for Chemotherapy-Associated VTE

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Site of primary cancer</strong></td>
<td></td>
</tr>
<tr>
<td>• Very high risk (stomach, pancreas)</td>
<td>2</td>
</tr>
<tr>
<td>• High risk (lung, lymphoma, gyn, bladder, testicular)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Pre-chemotherapy platelet</strong> &gt;350 x 10⁹/ L</td>
<td>1</td>
</tr>
<tr>
<td><strong>Hemoglobin &lt;10 g/dL or ESA use</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Pre-chemotherapy leukocyte count</strong> &gt;11x 10⁹/ L</td>
<td>1</td>
</tr>
<tr>
<td><strong>BMI ≥35 kg/m²</strong></td>
<td>1</td>
</tr>
</tbody>
</table>

BMI = body mass index.
Clinical Issues and Thrombosis

Prevention
- Identification of populations and patients at high risk
- Determine strategy(s) for prevention

Diagnosis
- Recognition of signs and symptoms
- Evaluation of patient and treatment factors
- Diagnosis of thrombosis

Management
- Acute management
- Chronic management
- Prevention
DVT

• **Symptoms**
  • Swelling, pain, warmth, or erythema of unilateral extremity
  • Heaviness in extremity
  • Unexplained persistent calf cramping
  • Swelling in face, neck, or supraclavicular space
  • Catheter dysfunction (if catheter is present)

• **Signs**
  • Dilation of superficial veins and a palpable cord
  • Homan’s sign

• **Diagnostic studies**
  • Duplex venous ultrasonography
  • Contrast-enhanced CT (indirect CT venography)
  • MRI
  • Standard venography
  • Serum D-dimer (note: elevated in malignancy)

CT = computed tomography; MRI = magnetic resonance imaging.
Superficial Vein Thrombosis

- Diagnosis primarily on basis of clinical symptoms
  - Tenderness
  - Erythema
  - Indurated cord associated with superficial vein
- Negative ultrasound for DVT
Clinical Presentation of PE

• Symptoms
  • Cough
  • Chest pain and/or tightness
  • Back pain
  • Shortness of breath
  • Dyspnea on exertion
  • Palpitations
  • Hemoptyisis
  • Dizziness
  • Syncope

• Signs
  • Tachypnea
  • Tachycardia
  • Diaphoresis
  • Distention of neck veins
  • Cyanosis
  • Hypotension
  • Radiographic evidence of DVT
PE

• CTA
• VQ lung scan
• Pulmonary angiography

CTA = computed tomography angiography; VQ = ventilation/perfusion.
Assessment of Risk for VTE

• Assessment tools for VTE
  • Role of D-dimer testing
  • Role of probability assessment
    • Wells model
    • Geneva model
  • Clinical decision support tools
    • PERC

PERC = Pulmonary Embolism Rule Out Criteria
## Wells Criteria: Clinical DVT Model

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis, or recent plaster cast immobilization of lower extremity</td>
<td>1</td>
</tr>
<tr>
<td>Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks requiring general or regional anesthesia</td>
<td>1</td>
</tr>
<tr>
<td>Localized tenderness along the distribution of the deep venous system</td>
<td>1</td>
</tr>
<tr>
<td>Entire leg swollen</td>
<td>1</td>
</tr>
<tr>
<td>Calf swelling at least 3 cm larger than the asymptomatic side</td>
<td>1</td>
</tr>
<tr>
<td>Pitting edema confined to the symptomatic 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>Alternative diagnosis at least as likely as DVT</td>
<td>-2</td>
</tr>
</tbody>
</table>

Score of 1 or 2 points indicates moderate risk of DVT; score of 3 or higher indicates a high risk of DVT.

**Wells Criteria: Clinical PE Model**

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer</td>
<td>1</td>
</tr>
<tr>
<td>Surgery or bedridden for 3 days or more during the past 4 weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>History of DVT or PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1</td>
</tr>
<tr>
<td>Heart rate &gt;100 beats/minute</td>
<td>1.5</td>
</tr>
<tr>
<td>PE judged to be the most likely diagnosis</td>
<td>3</td>
</tr>
<tr>
<td>Clinical signs and symptoms compatible with deep venous thrombosis</td>
<td>3</td>
</tr>
</tbody>
</table>

Score of 2–6 points indicates an intermediate probability of PE  
Score > 6 indicates a high probability of PE

Assessment of Risk for VTE (in Cancer?)

- Assessment tools for VTE
  - Role of D-dimer testing
  - Role of probability assessment:
    - Wells model
    - Geneva model
  - Clinical decision support tools
    - PERC

“…in various clinically important subgroups, such as patients with cancer, the validity of the Wells rule is questioned…”
# Predictive Model for Chemotherapy-Associated VTE

<table>
<thead>
<tr>
<th>Total Score</th>
<th>Risk Category</th>
<th>Risk of Symptomatic VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>0.8%–3%</td>
</tr>
<tr>
<td>1 or 2</td>
<td>Intermediate</td>
<td>1.8%–8.4%</td>
</tr>
<tr>
<td>≥3</td>
<td>High</td>
<td>7.1%–41%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of primary cancer</td>
<td></td>
</tr>
<tr>
<td>• Very high risk (stomach, pancreas)</td>
<td>2</td>
</tr>
<tr>
<td>• High risk (lung, lymphoma, gyn, bladder, testicular)</td>
<td>1</td>
</tr>
<tr>
<td>Pre-chemotherapy platelet &gt;350 x 10^9/ L</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin &lt;10 g/dL or ESA use</td>
<td>1</td>
</tr>
<tr>
<td>Pre-chemotherapy leukocyte count &gt;11 x 10^9/ L</td>
<td>1</td>
</tr>
<tr>
<td>BMI ≥35 kg/m²</td>
<td>1</td>
</tr>
</tbody>
</table>

Management Options for Venous Thromboembolism
Physical Barriers: Filter
Target: Coagulation Cascade

Intrinsic Pathway

XII → XIIa
XI → Xla
IX → IXa
X → Xa

Extrinsic Pathway

VIIa → VII

Common Pathway

Prothrombin (II) → Thrombin (IIa) → Fibrinogen (I) → Fibrin (Ia) → Cross Linked Fibrin Clot

Damaged Surface → Vascular injury → Tissue Factor → Trauma
Target: Development of Factors

Reduced Vitamin K

Oxidized Vitamin K

Image courtesy of Open Source Clinical Toxicology Curriculum. http://curriculum.toxicology.wikispaces.net/2.2.7.5.1+Anticoagulant
Pharmacotherapy Options for Treatment of VTE

<table>
<thead>
<tr>
<th>Heparin</th>
<th>Factor Xa Inhibitors</th>
<th>Vitamin K Antagonist</th>
<th>Direct Thrombin Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH</td>
<td>Apixaban (po)</td>
<td>Warfarin (po)</td>
<td>Dabigatran (po)</td>
</tr>
<tr>
<td>LMWH</td>
<td>Edoxaban (po)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fondaparinux (sc)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dalteparin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enoxaparin</td>
<td></td>
<td>Bivalent:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hirudin (IV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Bivalirudin (IV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Desirudin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Lepirudin</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban (po)</td>
<td></td>
<td>Univalent:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Argatroban (IV)</td>
</tr>
</tbody>
</table>

IV = intravenously; po = orally; sc = subcutaneous.
Heparin

- **UFH**
  - Highly sulfated mucopolysaccharide
  - UFH has a mean molecular weight 15,000 kDa (range from 3,000–30,000)

- **LMWH**
  - Derived from UFH by chemical or enzymatic depolymerization
    - About one-third of the size of UFH
    - Prepared using different methods of depolymerization and therefore differ (not interchangeable on a unit-to-unit basis)
Coagulation Cascade

Intrinsic Pathway

XI

XIIa

XII

Xla

IXa

IX

Xa

X

Prothrombin (II)

Common Pathway

Extrinsic Pathway

VIIa

VII

Thrombin (IIa)

VIIIa

Fibrinogen (I)

Fibrin

Cross Linked Fibrin Clot

Cross Linked Fibrin Clot

Damaged Surface

Vascular injury

Tissue Factor

Trauma

2016 JADPRO Live - APSHO
UFH

• Administration
  • Subcutaneously
    • VTE prophylaxis (low dose)
    • VTE treatment (rare)
  • Intravenous infusion for VTE treatment (dose determined by aPTT)

• Dosing
  • Initial dosing for VTE is weight based
    • Heparin 80 units/kg bolus followed by 18 units/kg per hour
  • Dose adjustment to target aPTT
    • Target aPTT of 2–2.5x control

aPTT = activated partial thromboplastin times.
UFH (cont)

- Adverse effects
  - Bleeding
  - HIT
    - Type I: Not antibody mediated
    - Type II: Antibody mediated (0.1%–0.2%)
  - Osteoporosis (UFH 20K units for >6 months)
  - Skin reactions → necrosis (rare)

HIT = heparin-induced thrombocytopenia.
Heparin-Induced Thrombocytopenia

- Characterized
  - ↓ platelet count of > 50% from baseline prior to heparin
  - Hypercoaguability
  - Heparin-dependent platelet activating IgG antibodies

- Onset
  - Onset 5 – 10 days after start of heparin
  - Delayed onset HIT: after cessation of heparin
  - Autoimmune HIT: absence of heparin

- Assessment
  - Platelet count
  - Platelet factor 4-heparin antibody test

- Treatment
  - Discontinuation of all heparin
  - Initiation of alternative anticoagulation (avoid warfarin with acute HIT)

Bleeding With UFH

- Discontinue heparin
  - Heparin serum half-life is ≈ 60–90 minutes
- Transfusion
- Supportive care
- Reversal of anticoagulant effect: Protamine sulfate
  - Dosing is determined by the timing and dose of heparin
  - Maximal tolerated dose of protamine is 50 mg
  - aPTT should be used to assess effects of neutralization
  - Adverse effects are common: hypotension, bradycardia

Role of UFH in Management of VTE in Patients With Hematology Malignancy?

• High bleeding risk ← Short half-life
• Weight
  • BMI >40 kg/m^2
  • <50 kg
• Renal dysfunction
  • Renal dysfunction (CrCl <30 mL/min)
  • Unstable renal function

CrCl = creatinine clearance.
Heparin

• **UFH**
  - Highly sulfated mucopolysaccharide
  - UFH has a mean molecular weight 15,000 kDa (range from 3,000–30,000)

• **LMWH**
  - Derived from UFH by chemical or enzymatic depolymerization
    - About one-third of the size of UFH
    - Prepared using different methods of depolymerization and therefore differ (not interchangeable on a unit-to-unit basis)
LMWH

- **MOA**
  - Pentasaccharide sequence of heparin binds to antithrombin (AT) increasing interaction of antithrombin and Factor Xa
  - Less inhibitory activity against thrombin (Factor IIa) compared with UFH

- **Pharmacokinetics**
  - Peak anti-Factor Xa activity ≈ 3–4-hour post-sc dose
  - Half-life is 3–6 hours after sc dosing
  - >90% bioavailability after sc dosing
  - Clearance is not dependent on dose
  - **Elimination is predominantly renal**

CrCl = creatinine clearance.
## LMWH (cont)

<table>
<thead>
<tr>
<th>Product</th>
<th>Thromboprophylaxis*</th>
<th>VTE Treatment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalteparin</td>
<td>5000 units sc daily</td>
<td>200 units/kg sc daily</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>40 mg sc daily</td>
<td>1 mg/kg sc Q12H</td>
</tr>
</tbody>
</table>

* Modifications may be required dependent on patient specific factors.

LMWH (cont)

• Monitoring
  • LMWH has minimal effect on aPTT
  • Factor Xa activity is used in select situations (e.g., pregnancy, obesity, renal dysfunction, children)

• Reversal of anticoagulation
  • Partially reversed with protamine (approximately 60%)

• Adverse effects
  • Bleeding
  • HIT
  • Osteoporosis
  • Injection site reactions

LMWH: Interpretation of Anti-Xa Levels
Target Ranges for Treatment VTE

<table>
<thead>
<tr>
<th>LMWH</th>
<th>Frequency of Administration</th>
<th>Target Range (4 hr post dose) Anti-Xa units/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>Twice-daily dosing</td>
<td>0.6–1.0</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>Once-daily dosing</td>
<td>&gt;1.0</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>Once-daily dosing</td>
<td>1.05</td>
</tr>
</tbody>
</table>

LMWH: Clinical Considerations

- Role in patients with renal insufficiency \((Cl_{cr} < 30 \text{ mL/min})\)
- Obese (BMI > 30)
- Weight <50 kg
- Elderly >70 years
- Neutralizing LMWH → incomplete anti-Xa neutralization of LMWH by protamine

- Out-of-pocket cost for patients
- Self-administration of sc injections
- Tolerance to LMWH
- Social support
# Pharmacotherapy Options for Treatment of VTE

<table>
<thead>
<tr>
<th>Heparin</th>
<th>Factor Xa Inhibitors</th>
<th>Vitamin K antagonist</th>
<th>Direct Thrombin Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH</td>
<td>Apixaban (po) Edoxaban (po) Fondaparinux (sc)</td>
<td>Warfarin (po)</td>
<td>Dabigatran (po)</td>
</tr>
<tr>
<td>LMWH</td>
<td></td>
<td></td>
<td>Bivalent:</td>
</tr>
<tr>
<td>• Dalteparin</td>
<td></td>
<td></td>
<td>• Hirudin (IV)</td>
</tr>
<tr>
<td>• Enoxaparin</td>
<td></td>
<td></td>
<td>• Bivalirudin (IV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Desirudin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Lepirudin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Univalent:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Argatroban (IV)</td>
</tr>
</tbody>
</table>
Target: Factor Xa
Factor Xa Inhibitors

<table>
<thead>
<tr>
<th>Agent</th>
<th>VTE Treatment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fondaparinux</td>
<td>&lt;50 kg: 5 mg sc daily</td>
</tr>
<tr>
<td></td>
<td>50–100 kg: 7.5 mg sc daily</td>
</tr>
<tr>
<td></td>
<td>&gt;100 kg: 10 mg sc daily</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>15 mg po twice daily for 21 days,</td>
</tr>
<tr>
<td></td>
<td>followed by 20 mg po once daily</td>
</tr>
<tr>
<td>Apixaban</td>
<td>10 mg po twice daily for 7 days,</td>
</tr>
<tr>
<td></td>
<td>5 mg po twice daily</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>60 mg po daily</td>
</tr>
</tbody>
</table>

* The doses listed are per package labeling, and do not reflect dose modifications required for select situations such as organ dysfunction, extreme body weights, or drug interactions.
Fondaparinux

• Synthetic analog of the pentasaccharide sequence found within heparin chains

• Mechanism
  • Inhibitor of Factor Xa
  • No effect on thrombin

• Pharmacokinetics
  • 100% bioavailability (sc administration)
  • Peak levels occur 2–3-hour post-sc administration
  • Renal elimination
  • Half-life is ≈ 17–21 hours (normal renal function)

## Heparin and Heparin Derivatives

<table>
<thead>
<tr>
<th>Feature</th>
<th>Heparin (UFH)</th>
<th>LMWH</th>
<th>Fondaparinux</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source</td>
<td>Biological</td>
<td>Biological</td>
<td>Synthetic</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>15,000 Da</td>
<td>5,000 Da</td>
<td>1,500 Da</td>
</tr>
<tr>
<td>Target</td>
<td>XIIa, IXa, Xla, Xa, Ilα</td>
<td>Xa &gt; Ilα</td>
<td>Xa</td>
</tr>
<tr>
<td>Bioavailability (sc)</td>
<td>30%</td>
<td>90%</td>
<td>100%</td>
</tr>
<tr>
<td>Half-life</td>
<td>1 hour</td>
<td>4 hours</td>
<td>17 hours</td>
</tr>
<tr>
<td>Monitoring test</td>
<td>aPTT, anti-Factor Xa</td>
<td>Anti-Factor Xa</td>
<td>Anti-Factor Xa</td>
</tr>
<tr>
<td>Renal excretion</td>
<td>No</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Antidote</td>
<td>Protamine</td>
<td>Protamine</td>
<td>None</td>
</tr>
<tr>
<td>Incidence of HIT</td>
<td>&lt;5%</td>
<td>&lt;1%</td>
<td>Unreported</td>
</tr>
</tbody>
</table>

Fondaparinux

- Approved for DVT, PE prophylaxis, and treatment
- May be used in patients with history of HIT
- Treatment dosing is weight-based, per package labeling:

<table>
<thead>
<tr>
<th>Patient Weight</th>
<th>Dose Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 kg</td>
<td>5 mg sc daily</td>
</tr>
<tr>
<td>50–100 kg</td>
<td>7.5 mg sc daily</td>
</tr>
<tr>
<td>&gt;100 kg</td>
<td>10 mg sc daily</td>
</tr>
</tbody>
</table>

- Dose for postsurgical prophylaxis and also for bridge therapy is 2.5 mg sc once daily.

Fondaparinux (cont)

• Disadvantages
  • Long half-life (advantage in some situations)
  • Role in patients with renal insufficiency (CrCl <30 mL/min)
  • No proven method for neutralizing LMWH

• Clinical considerations
  • Out-of-pocket costs
  • Willingness to self-administer sc injection
  • Intolerance to LMWH
  • Adherence
  • Support at home
DOAC: Factor Xa

• Competitive, selective potent direct Factor Xa inhibitors
• Reversible binding to the active site of free-floating Factor Xa and Factor Xa within the clot
• Current products
  • Rivaroxaban
  • Apixaban
  • Edoxaban
### Oral Anticoagulants: Target Factor Xa

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Xa</td>
<td>Xa</td>
<td>Xa</td>
</tr>
<tr>
<td><strong>Prodrug</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>80%</td>
<td>50%</td>
<td>62%</td>
</tr>
<tr>
<td><strong>Peak effect</strong></td>
<td>2-4 hours</td>
<td>1-3 hours</td>
<td>1-2 hours</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>5-9 hours</td>
<td>9-14 hours</td>
<td>10-14 hours</td>
</tr>
<tr>
<td><strong>Renal elimination</strong></td>
<td>33%</td>
<td>25%</td>
<td>35%–50%</td>
</tr>
<tr>
<td><strong>Protein binding</strong></td>
<td>90%</td>
<td>87%</td>
<td>55%</td>
</tr>
<tr>
<td><strong>Dialyzable</strong></td>
<td>No</td>
<td>No</td>
<td>Possible</td>
</tr>
<tr>
<td><strong>P'kinetic interactions</strong></td>
<td>Cyp 3A4, P-gp</td>
<td>Cyp 3A4, P-gp</td>
<td>P-gp</td>
</tr>
<tr>
<td><strong>Antidote</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td>PT, Anti-Xa</td>
<td>Anti-Xa</td>
<td>Anti-Xa</td>
</tr>
</tbody>
</table>

## Factor Xa Inhibitors

### Advantages
- Specificity
- No requirement for routine blood monitoring for dose adjustment
- Lack of cross-reactivity with HIT antibody
- Drug interactions (< warfarin)
- “Long” half-life

### Disadvantages
- Dosing in renal insufficiency
- Dosing in obesity
- Reversal agent available
- “Long” half-life
- Patients with cancer were underrepresented in phase III trials
# Pharmacotherapy Options for Treatment of VTE

<table>
<thead>
<tr>
<th>Heparin</th>
<th>Factor Xa Inhibitors</th>
<th>Vitamin K antagonist</th>
<th>Direct Thrombin Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH</td>
<td>Apixaban (po)</td>
<td>Warfarin (po)</td>
<td>Dabigatran (po)</td>
</tr>
<tr>
<td>LMWH</td>
<td>Edoxaban (po)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fondaparinux (sc)</td>
<td></td>
<td>Bivalent:</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban (po)</td>
<td></td>
<td>• Hirudin (IV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Bivalirudin (IV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Desirudin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Lepirudin</td>
</tr>
<tr>
<td>Dalteparin</td>
<td></td>
<td></td>
<td>Univalent:</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td></td>
<td></td>
<td>• Argatroban (IV)</td>
</tr>
</tbody>
</table>
Target: Thrombin
## Direct Thrombin Inhibitors

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lepirudin¹</td>
<td>0.1 mg/kg/hour IV infusion</td>
<td>Renal</td>
</tr>
<tr>
<td>Argatroban²</td>
<td>2 μg/kg/minute IV infusion</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Bivalirudin³</td>
<td>0.15–0.2 mg/kg/hour IV infusion</td>
<td>Renal</td>
</tr>
<tr>
<td>Desirudin⁴</td>
<td>15 mg sc Q12H for prophylaxis</td>
<td>Renal</td>
</tr>
<tr>
<td>Dabigatran⁵</td>
<td>150 mg po twice daily</td>
<td>Renal</td>
</tr>
</tbody>
</table>

Direct Thrombin Inhibitors (cont)

• Dabigatran etexilate (prodrug) $\rightarrow$ Dabigatran (active drug)
• Competitive inhibitor that reversibly binds to both clot and free thrombin
• Inhibition of thrombin-induced platelet aggregation
DOAC: Direct Thrombin Inhibitor Dabigatran

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodrug</td>
<td>Yes</td>
</tr>
<tr>
<td>Absorption</td>
<td>Requires acidic environment</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>6.5% (pH dependent)</td>
</tr>
<tr>
<td>Time to peak effect</td>
<td>1.5–3 hours</td>
</tr>
<tr>
<td>Half-life</td>
<td>12–17 hours</td>
</tr>
<tr>
<td>Dosing frequency</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Conjugated</td>
</tr>
<tr>
<td>Elimination</td>
<td>Renal (80%)</td>
</tr>
<tr>
<td></td>
<td>Biliary (20%)</td>
</tr>
</tbody>
</table>

## Oral Anticoagulants: Target Factor Xa

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>IIa</td>
<td>Xa</td>
<td>Xa</td>
<td>Xa</td>
</tr>
<tr>
<td><strong>Prodrug</strong></td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>6.5% (pH dependent)</td>
<td>80%</td>
<td>50%</td>
<td>62%</td>
</tr>
<tr>
<td><strong>Peak Effect</strong></td>
<td>1.5–3 hours</td>
<td>2–4 hours</td>
<td>1–3 hours</td>
<td>1–2 hours</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>12–17 hours</td>
<td>5–9 hours</td>
<td>9–14 hours</td>
<td>10–14 hours</td>
</tr>
<tr>
<td><strong>Renal elimination</strong></td>
<td>80%</td>
<td>33%</td>
<td>25%</td>
<td>35-50%</td>
</tr>
<tr>
<td><strong>Protein binding</strong></td>
<td>35%</td>
<td>90%</td>
<td>87%</td>
<td>55%</td>
</tr>
<tr>
<td><strong>Dialyzable</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Possible</td>
</tr>
<tr>
<td><strong>P'kinetic interactions</strong></td>
<td>P-gp</td>
<td>Cyp 3A4, P-gp</td>
<td>Cyp 3A4, P-gp</td>
<td>P-gp</td>
</tr>
<tr>
<td><strong>Antidote</strong></td>
<td>Idarucizumab</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td>aPTT, TT, ECT</td>
<td>PT, Anti-Xa</td>
<td>Anti-Xa</td>
<td>Anti-Xa</td>
</tr>
</tbody>
</table>

## DOAC: Coagulation Assays

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>PT/INR</th>
<th>TT</th>
<th>ECT</th>
<th>aPTT</th>
<th>HEPTEST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>-</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>↑</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>↑</td>
</tr>
<tr>
<td>Apixaban</td>
<td>↑</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>↑</td>
</tr>
</tbody>
</table>

ECT = ecarin clotting time; INR = international normalized ratio; PT = prothrombin time; TT = thrombin time.

Old Oral Anticoagulant
Target: Vitamin K
Target: Vitamin K–Dependent Factors
Vitamin K Antagonists

• Mechanism of action
  • Inhibition of vitamin K epoxide/reductase
  • Interferes with cyclic conversion of vitamin K and vitamin K epoxide
  • Impairs carboxylation of vitamin K–dependent clotting factors
  • Inhibits carboxylation of regulatory anticoagulation proteins C, S, and Z

• Examples of vitamin K antagonists (VKA)
  • Warfarin
  • Acenocoumarol
Warfarin: Mechanism of Action

Image courtesy of Open Source Clinical Toxicology Curriculum. http://curriculum.toxicology.wikispaces.net/2.2.7.5.1+Anticoagulant
# Warfarin: Mechanism of Action

<table>
<thead>
<tr>
<th>Protein</th>
<th>Half-life (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coagulation factor</strong></td>
<td></td>
</tr>
<tr>
<td>Factor II</td>
<td>42–72</td>
</tr>
<tr>
<td>Factor VII</td>
<td>4–6</td>
</tr>
<tr>
<td>Factor IX</td>
<td>21–30</td>
</tr>
<tr>
<td>Factor X</td>
<td>27–48</td>
</tr>
<tr>
<td><strong>Regulatory anticoagulant proteins</strong></td>
<td></td>
</tr>
<tr>
<td>Protein C</td>
<td>8</td>
</tr>
<tr>
<td>Protein S</td>
<td>60</td>
</tr>
<tr>
<td>Protein Z</td>
<td>40–45</td>
</tr>
</tbody>
</table>

Overview of Hemostasis

**Activators**
- Von Willebrand Factor
- Collagen
- Tissue Factor
- Tissue Factor
- Factor VIIa
- Factor VIIIa
- Factor IXa
- Factor Va
- Factor Xa
- Factor XIIIa
- Tissue plasminogen activator

**Inhibitors**
- Antithrombin
- Heparin
- Thrombomodulin
- Protein C
- Protein S
- Tissue factor pathway inhibitor
- Plasminogen activator inhibitor-1

**Vessel wall Injury**

**Platelet adhesion and aggregation**

**Coagulation cascade activated**

**Thrombin**

**Fibrin formation**

**Stabilized fibrin clot**

**Fibrinolysis and clot degradation**
Warfarin Is a Racemic Mixture

R-warfarin

S-warfarin

Vitamin K epoxide reductase

Inhibition vitamin K dependent clotting factors
Warfarin: Initiating Therapy

- Routine use of pharmacogenetic testing is not recommended
- Initially administered concomitantly with UFH, LMWH, or fondaparinux for at least 5 days and INR of 2 or more is achieved
- Vitamin K antagonists should not be initiated prior to heparin therapy
- Dose of initiation is determined by patient specific factors
- Frequency of monitoring INR during titration of dose is determined by patient-specific factors
Warfarin: Initiating Therapy (cont)

• Baseline INR should be obtained prior to beginning warfarin
• Identify patients at risk for an increased baseline INR
  • Patients with lupus like anticoagulant
  • Malnourished
  • Chronic diarrhea
  • Liver disease
Warfarin: Maintenance Dose

- Response to warfarin fluctuates over time
- Strategies required to determine changes in warfarin dose during treatment include:
  - INR monitoring
  - Changes in bleeding risk
  - Changes in factors that influence warfarin effect
- It is essential to establish a partnership in providing care
  - Health care team
  - Patient
  - Caregivers
Warfarin: Factors That May Affect INR

- Diarrhea
- Nausea (decrease po intake)
- Vomiting
- Diet (nutritional supplements)
  - Cranberry
  - Grapefruit juice
- Alcohol
  - Chronic
  - Acute
- Thyroid function
- Liver function
- Medication change
- Diet changes
- Nonadherence
- Activity
Warfarin: Drug Interactions

- Proposed mechanism
  - Impact on clotting factor synthesis
  - Impact on clotting factor catabolism
  - Impact on metabolism of warfarin
  - Absorption of warfarin and vitamin K
  - Production of vitamin K by gut flora
  - Additive anticoagulation effects

Warfarin

• Pharmacodynamic effect
  • Caution when combining warfarin with drugs that may increase bleeding.
    • Aspirin → Decrease platelet function
    • Clopidogrel → Decrease platelet function
    • Nonsteroidal anti-inflammatory agents → Gastrointestinal irritation
    • Drugs that decrease platelet number (e.g., cytotoxic chemotherapy)
Warfarin (cont)

• Pharmacodynamic effect
  • As warfarin targets vitamin K–dependent clotting factors, the amount of vitamin K in diet impacts effect
    • Diet plays a significant role in drug efficacy
    • Patients do NOT have to avoid vitamin K rich foods
      • Consistency is essential
      • Communication in changes are also important
  • Examples of food high in vitamin K
    • Leafy green vegetables
    • Liver
    • Green tea
Warfarin: Monitoring of Therapy

• The INR target range is determined based on patient factors and indications

• A common target INR range used in patients being treated for VTE is 2.0–3.0
  • INR below 1.5 is not protective
  • INR 3.0–4.0 is not dangerous in most cases, but is higher than necessary

• Management strategy of patients with INR above target range are based on:
  • INR (absolute level and evolution)
  • Bleeding and/or risk for bleeding
  • Access to monitoring

Management Consideration for Individuals With Hematologic Malignancies with VTE
# Contraindication to Anticoagulation Therapy

## Absolute
- Recent CNS bleed, or intracranial or spinal lesion at high risk for bleed
- Active bleeding (major): More than 2 units transfused in 24 hours

## Relative
- Chronic, clinically significant measurable bleeding >48 hours
- Thrombocytopenia (platelets <50 K/µL)
- Severe platelet dysfunction
- Recent major operation at high risk of bleeding
- Underlying hemorrhagic coagulopathy
- High risk for falls (head trauma)
- Neural anesthesia/lumbar puncture
- Interventional spine and pain procedures

CNS = central nervous system.

Minimizing the Risk of VTE: Prophylaxis

- At-risk populations to consider prophylaxis
  - Hospitalized patients
    - Adult medical and surgical patients
    - Diagnosis of cancer (clinical suspicion of cancer)
  - Ambulatory cancer patients
    - Surgical oncology patients: high-risk abdominal or pelvic cancer surgery patients
    - Myeloma receiving thalidomide, lenalidomide, or pomalidomide

Therapy of VTE

• Evidence-based guidelines
  • VTE: Chest guidelines

• Guidance documents

NCCN = National Comprehensive Cancer Center.
Pharmacologic Treatment of VTE in a Patient With Cancer

• Immediate treatment with one of the following for a minimum of 5–7 days
  • LMWH
  • UFH
  • Fondaparinux

• Chronic therapy is required
  • LMWH
  • Warfarin (requires initial treatment with parenteral anticoagulant)
Therapeutic Anticoagulation for VTE in Cancer

- Acute management
  - LMWH
  - Fondaparinux
  - UFH
    - IV load, then continuous infusion with dose adjusted to target aPTT
    - SC

DOACs are not recommended at this time

Therapeutic Anticoagulation for VTE

- Acute management
  - LMWH
  - Factor Xa inhibitors
    - Fondaparinux
    - Rivaroxaban
    - Apixaban
    - Edoxaban (+ parenteral anticoagulation)
  - UFH
  - Dabigatran (+ parenteral anticoagulation)

Therapeutic Anticoagulation for VTE in Cancer

- Chronic management
  - LMWH as monotherapy
  - Warfarin (target INR 2-3)

DOACs are not recommended at this time

CLOT Trial

- Multicenter, open-label, randomized study (N = 676)

Cancer patients with proximal DVT, PE, or both*

<table>
<thead>
<tr>
<th>Initial</th>
<th>Long-term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalteparin</td>
<td>—</td>
</tr>
<tr>
<td>—</td>
<td>Dalteparin</td>
</tr>
</tbody>
</table>

*Objectively documented

OAC = oral anticoagulant.
CLOT: Study Treatments

<table>
<thead>
<tr>
<th></th>
<th>Initial treatment (5–7 days)</th>
<th>Long-term therapy (6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OAC</td>
<td>Dalteparin 200 U/kg sc once daily</td>
<td>Warfarin or acenocoumarol (target INR 2.5)</td>
</tr>
<tr>
<td>LMWH</td>
<td>Dalteparin 200 U/kg sc once daily</td>
<td>Month 1: Dalteparin 200 U/kg Month 2–6: 75%–80% of full dose</td>
</tr>
</tbody>
</table>

### CLOT: Primary Endpoint
Recurrent VTE

<table>
<thead>
<tr>
<th></th>
<th>Dalteparin (n = 336)</th>
<th>OAC (n = 336)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total VTE</td>
<td>27</td>
<td>53</td>
</tr>
<tr>
<td>DVT</td>
<td>14</td>
<td>37</td>
</tr>
<tr>
<td>Nonfatal PE</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Fatal PE</td>
<td>5</td>
<td>7</td>
</tr>
</tbody>
</table>

### Time in Target INR Range: OAC Group in CLOT Trial

<table>
<thead>
<tr>
<th>INR</th>
<th>Mean Proportion of Total Treatment Time&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Mean Proportion of Total Treatment Time&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3.0</td>
<td>24%</td>
<td>24%</td>
</tr>
<tr>
<td>2.0–3.0</td>
<td>46%</td>
<td>50%</td>
</tr>
<tr>
<td>&lt;2.0</td>
<td>30%</td>
<td>25%</td>
</tr>
<tr>
<td>Mean INR (SD)</td>
<td>2.5 (0.74)</td>
<td></td>
</tr>
</tbody>
</table>

SD = standard deviation.

Bleeding Events in CLOT Trial

<table>
<thead>
<tr>
<th></th>
<th>Dalteparin (n = 338)</th>
<th>OAC (n = 335)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleed</td>
<td>19 (5.6%)</td>
<td>12 (3.6%)</td>
<td>.27</td>
</tr>
<tr>
<td>Any bleed</td>
<td>46 (13.6%)</td>
<td>62 (18.5%)</td>
<td>.09</td>
</tr>
</tbody>
</table>

CLOT Summary

• Efficacy
  • Dalteparin reduced recurrence of VTE by 52% compared with OAC ($P = .002$)
  • Dalteparin was effective in preventing recurrent DVT/PE over the 6-month study period

• Bleeding
  • Dalteparin was associated with a lower 6-month incidence of any bleeding compared with OAC
  • Major bleeding with dalteparin was similar to OAC

Therapeutic Anticoagulation for VTE in Cancer

• Chronic management
  • LMWH as monotherapy
  • Warfarin (target INR 2–3)

DOACs are not recommended at this time

Therapeutic Anticoagulation for VTE in Cancer

• Duration of chronic management
  • Minimum of 3 months
  • Noncatheter-associated DVT or PE → Indefinite anticoagulation while cancer is active, under treatment, or if risk factors for recurrence persists
  • Catheter-associated thrombosis → Continue anticoagulation as long as catheter is in place

• Providers should continue to discuss with patients the risks/benefits of anticoagulation to determine the appropriate duration of therapy

Therapeutic Anticoagulation for VTE

- Chronic management
  - LMWH as monotherapy
  - Warfarin (target INR 2–3)
  - DOAC

Guidelines vs. Clinical Practice

• Retrospective analysis of MarketScan database for adult patients with newly diagnosed cancer

• Findings
  • Warfarin most utilized anticoagulant for outpatient treatment VTE
  • Initiation with LMWH → Oral anticoagulant
  • Increased use of DOACs

When to Consider No Active Treatment

- Patient refusal
- No therapeutic advantage
- No palliative benefit
- Unreasonable burden of anticoagulation treatment

When to Consider Filter* Placement

- Absolute contraindication to therapeutic anticoagulation
- Failure of anticoagulation
- Patient nonadherent with prescribed anticoagulation
- Baseline cardiac or pulmonary dysfunction severe enough to make any new or recurrent PE life threatening
- Patient with documented multiple PE and chronic pulmonary hypertension

*Retrievable filters are strongly preferred.
Complications of IVC Filters

- Access site thrombosis
- DVT
- Filter migration/embolization
- Filter misplacement (outside target zone)
- Filter strut fracture
- Guidewire entrapment
- IVC thrombosis
- IVC penetration
- PE
- Inability to remove retrievable filter

IVC = inferior vena cava.
What Is the Role of Thrombolytic Agents for VTE?

• Thrombolytic agents may reduce PTS by promoting clot lysis and reduce venous outflow obstruction and venous valvular damage.

• Higher rates of complete clot lysis compared with conventional anticoagulation for catheter-directed thrombolysis.

• Patients that may benefit from thrombolytic therapy if eligible:
  • Iliofemoral DVT
  • Symptom duration of <14 days
  • Good functional status
  • Life expectancy of ≥1 year
  • Low bleeding risk

Contraindications to Thrombolysis

**Absolute**
- History of hemorrhagic stroke
- Intracranial tumor
- Ischemic stroke (3 months)
- History of major trauma, surgery, or head injury (3 weeks)
- Low platelet (<100K)
- Active bleeding
- Bleeding diathesis

**Relative**
- Age >75 years
- Pregnancy
- First week postpartum
- Noncompressible puncture site
- Traumatic resuscitation
- Refractory hypertension
- Advanced liver disease
- Infective endocarditis
- Recent gastrointestinal bleed (3 months)
- Life expectancy ≤1 year

Options for an Individual Who Has an Extension of VTE During Therapy?

- Anticoagulation “failure” is defined as an extension of DVT or a new VTE while on therapeutic anticoagulation therapy

- Treatment decision(s) depend on:
  - Site of extension (e.g., new PE on anticoagulation)
  - Potential for HIT
  - Assessment of anticoagulation therapy
    - Patient adherence
    - Agent
    - Dose
    - Regimen
Options for an Individual Who Has a Recurrence of VTE Despite Anticoagulation Therapy?

- Anticoagulation “failure” is defined as an extension of DVT or a new VTE while on therapeutic anticoagulation therapy.
- Patients with potent situational risk factor for thrombosis are at low risk for recurrence, while patients suffering unprovoked events are high risk for recurrence.

Options for an Individual Who Has a Recurrence of VTE Despite Anticoagulation Therapy?

Ottawa Prediction Rule for Recurrent VTE in Cancer

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>+1</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>+1</td>
</tr>
<tr>
<td>Prior VTE</td>
<td>+1</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>-1</td>
</tr>
<tr>
<td>Low stage (TNM stage I)</td>
<td>-2</td>
</tr>
</tbody>
</table>

Low risk < 0 points; Intermediate risk = 0 points; High risk ≥ 1 point

Options for an Individual Who Has a Recurrence of VTE Despite Anticoagulation Therapy?

Strategies for optimizing care

• Assess adherence to therapy
• Identify clinical additions associated with anticoagulation failure:
  • Cancer
  • Antiphospholipid syndrome
  • HIT
  • Vascular compression syndromes
• Consider
  • Warfarin → Increase goal of INR
  • LMWH → Assess Factor Xa and/or escalated dose
  • Alternative agents

What Is the Best Strategy for Reversing Anticoagulation?

• Reversal recommendations for specific agents are provided in the NCCN Guidelines to facilitate care in the event of a life-threatening bleed or emergent surgery.

• Familiarize yourself with availability of these products and the mechanism to order for patient care.
# Reversal of Anticoagulation

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Antidote</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>Protamine</td>
</tr>
<tr>
<td>LMWH</td>
<td>Protamine</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Phytonadione (Vitamin K1)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Idarucizumab</td>
</tr>
</tbody>
</table>

How Do You Manage a Patient Who Has a Planned Procedure?

• Consider the risk of bleeding for the procedure
• Consider the risk of thrombosis in the individual patient
• Recommendation for management outlined in the NCCN Guidelines
• Procedures may include:
  • Surgery
  • Bone marrow biopsy
  • Dental procedures
  • Lumbar puncture
Discussion