Venous Thromboembolism (VTE)

**Patient population:** Outpatient adults with suspected acute deep venous thrombosis (DVT) of the upper and lower extremity, pulmonary embolus (PE), or both (VTE).

**Objectives:** (1) Improve the recognition of VTE and selection of appropriate testing. (2) Improve selection of appropriate therapy. (3) Shorten resolution time for clinical symptoms. (4) Reduce bleeding and other complications. (5) Reduce mortality. (6) Avoid preventable Emergency Department visits and hospital admissions.

**Key Points**

- **Initiate treatment immediately.** Patients without contraindications to anticoagulation should begin treatment at time of diagnosis [IA*]. If PE is clinically likely, initiation of anticoagulation should not await testing; if only DVT is suspected and testing will be prompt, initiation may await testing. Therapeutic levels of anticoagulation should be achieved as quickly as possible. If warfarin is used for anticoagulation, initiate it on treatment day 1 simultaneous to initiation of low molecular weight heparin. Other oral agents may not require bridging treatment with heparin.

**Diagnosis**

- **Deep venous thrombosis (lower extremity DVT)**
  - Clinical likelihood estimation. Symptoms and signs alone are not adequately sensitive or specific for diagnosis or exclusion of DVT but clinical likelihood estimation based on symptoms and signs is a necessary step in the testing strategy [IA].
  - Venous color duplex doppler ultrasound imaging. This imaging is the standard for diagnosis [IA].

- **Pulmonary embolism**
  - D-dimer testing must be interpreted in the context of pretest probability [1C]. D-dimer testing alone is not adequately sensitive or specific to diagnose or exclude PE [IIA]. (See Figure 1.)

- **Diagnostic testing determined by clinical likelihood estimation.** The diagnostic approach differs depending on prior probability (see Figure 1, Tables 5, 6, 7, 8, and Appendix A. Low probability patients with negative D-dimer require no further testing [IA]. Others should generally undergo CT scanning [IA]. High or intermediate probability patients with negative CT or low probability patients with CT positive for sub- or segmental PE require further investigation (see text) [IA].

**Treatment**

- **Heparin**
  - Low molecular weight heparin (LMWH). LMWH is preferred for initial treatment over unfractionated heparin (UFH) or fondaparinux due to better safety and outcomes [IA].
  - Outpatient use of LMWH for DVT. LMWH is appropriate for most patients with DVT to use at home [IIA].
  - Some require initial brief hospital admission and stabilization. Clinically stable patients not at elevated risk due to comorbidities can be managed entirely as outpatients using LMWH.
  - Unfractionated heparin. UFH is no longer first line therapy. If UFH is used, it should be initiated and dosed in a structured manner (see Appendix B) [IIA].
  - Minimum time period. When warfarin is chosen as an oral agent, continue heparin (LMWH or UFH) until either INR is optimally > 2.0 or for at least five days to minimize risk of extension of thrombosis or occurrence/recurrance of embolism [IB].
  - If heparin contraindicated. When heparin is contraindicated (bleeding risk or drug sensitivity), consider a non-heparin anticoagulant agent (e.g., argatroban) [IB]. If anticoagulation is contraindicated, place inferior vena cava filter to prevent pulmonary embolization [IB].

- **Vitamin K antagonist: warfarin.** Patients should begin warfarin on day 1 of heparin, and INRs should optimally be >2.0 before discontinuation of heparin [IA, B]. Start warfarin at the anticipated therapeutic dose [IC].
  - If warfarin contraindicated. Patients who can receive heparin but cannot take warfarin (e.g., during pregnancy) may be anticoagulated with full-dose subcutaneous heparin [IA], preferably LMWH.

- **Direct factor Xa inhibitors: rivaroxaban, apixaban.** For selected patients (see text) begin rivaroxaban or apixaban as immediate monotherapy. See Table 12 [IB].

- **Aggressive therapy.** Patients with “massive” proximal DVT producing severe limb swelling and pain, or patients with “massive” PE producing shock or systemic hypoperfusion, may be candidates for emergent thrombolytic therapy or (in the case of DVT) thrombectomy. Such patients should be discussed with a consultant immediately [IIA].

**Duration of therapy.** Most patients with VTE should be anticoagulated for 3 months [IB].

---

*Strength of recommendation:*

- **I = generally should be performed;** II = may be reasonable to perform; III = generally should not be performed.

*Levels of evidence for the most significant recommendations*

- A = randomized controlled trials; B = controlled trials, no randomization; C = observational studies; D = opinion of expert panel
### Table 1. Glossary of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPTT</td>
<td>Activated Partial Thromboplastin Time</td>
</tr>
<tr>
<td>APS</td>
<td>Antiphospholipid antibody syndrome</td>
</tr>
<tr>
<td>ABGs</td>
<td>Arterial Blood Gases</td>
</tr>
<tr>
<td>BNP</td>
<td>B-type natriuretic peptide</td>
</tr>
<tr>
<td>CVA</td>
<td>Cerebrovascular accident</td>
</tr>
<tr>
<td>CTEPH</td>
<td>Chronic thromboembolic pulmonary hypertension</td>
</tr>
<tr>
<td>CTA</td>
<td>Computed tomography angiography</td>
</tr>
<tr>
<td>CTV</td>
<td>Computed tomographic venography</td>
</tr>
<tr>
<td>COCs</td>
<td>Estrogen-containing combined oral contraceptives</td>
</tr>
<tr>
<td>DVT</td>
<td>Deep venous thrombosis</td>
</tr>
<tr>
<td>GSV</td>
<td>Great saphenous vein</td>
</tr>
<tr>
<td>HIT</td>
<td>Heparin-induced thrombocytopenia</td>
</tr>
<tr>
<td>HRT</td>
<td>Hormone replacement therapy</td>
</tr>
<tr>
<td>LMWH</td>
<td>Low molecular weight heparin</td>
</tr>
<tr>
<td>MRA</td>
<td>Magnetic resonance angiography</td>
</tr>
<tr>
<td>MRV</td>
<td>Magnetic resonance venography</td>
</tr>
<tr>
<td>NPV</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Non-steroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>PE</td>
<td>Pulmonary embolus</td>
</tr>
<tr>
<td>PESI</td>
<td>Pulmonary Embolism Severity Index</td>
</tr>
<tr>
<td>PERC</td>
<td>PE Rule-out Criteria</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>PTS</td>
<td>Post-thrombotic syndrome</td>
</tr>
<tr>
<td>PT</td>
<td>Prothrombin time</td>
</tr>
<tr>
<td>RV</td>
<td>Right ventricle</td>
</tr>
<tr>
<td>VTE</td>
<td>Venous thromboembolism</td>
</tr>
<tr>
<td>V/Q scan</td>
<td>Ventilation/perfusion lung scan</td>
</tr>
<tr>
<td>UFH</td>
<td>Unfractionated heparin</td>
</tr>
</tbody>
</table>

### Table 2. Risk Factors for VTE (DVT and PE)

- Prior history of venous thromboembolism
- Advanced age (>70)
- Presence of a central venous catheter
- Malignancies, most commonly of the lung, pancreas, colorectal, kidney, and prostate
- Surgery (especially orthopedic)
- Trauma
- Pregnancy
- Oral contraceptive containing estrogen
- Hormone replacement therapy with estrogen
- Obesity
- Immobilization
  - Hospitalization
  - Prolonged travel
  - Limb immobilization (casting)
  - Stroke with movement deficit
  - Spinal cord injury; quadriplegia/paraplegia
- Inherited thrombophilias (most common)
  - Factor V Leiden mutation
  - Prothrombin gene mutation
  - Protein S deficiency
  - Protein C deficiency
  - Antithrombin deficiency
- Antiphospholipid antibody syndrome (APS)
- Congestive heart failure
- Myeloproliferative disorders
  - Polycythemia vera
  - Essential thrombocytosis
- Inflammatory bowel disease
- Nephrotic syndrome
- Hyperhomocysteinemia
- Paroxysmal nocturnal hemoglobinuria

Sources: UpToDate 2013, Bauer, Lip (literature review through May 2013)
### Table 3. Wells Criteria for Likelihood Estimation of Lower Extremity Deep Venous Thrombosis

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer (patient receiving treatment for cancer within the previous 6 months or currently receiving palliative treatment)</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis, or recent plaster immobilization of the lower extremities</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 that on the asymptomatic side (measured 10 cm below tibial tuberosity)</td>
<td>1</td>
</tr>
<tr>
<td>Pitting edema confined to the symptomatic leg</td>
<td>1</td>
</tr>
<tr>
<td>Previously documented deep-vein thrombosis</td>
<td></td>
</tr>
<tr>
<td>Collateral non varicose superficial veins</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis at least as likely as deep-vein thrombosis</td>
<td>-2</td>
</tr>
</tbody>
</table>

A score of < 2 is considered low probability for DVT  

### Table 4. Clinical Findings Associated with Pulmonary Embolism

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
<th>Chest X-ray b</th>
<th>Electro-cardiogram c</th>
<th>Arterial Blood Gases (ABGs) d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>Tachypnea</td>
<td>Elevated hemidiaphragm (lung volume loss)</td>
<td>Sinus tachycardia</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>Chest pain (pleuritic)</td>
<td>Tachycardia</td>
<td>Infiltrate</td>
<td>S1Q3T3</td>
<td>Hypocapnia</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>Evidence of lower extremity DVT</td>
<td>Pleural effusion</td>
<td>Rightward QRS axis</td>
<td>Increased A-a gradient</td>
</tr>
<tr>
<td>Syncope</td>
<td>Hypotension</td>
<td>Atelectasis</td>
<td>Transient RBBB</td>
<td></td>
</tr>
<tr>
<td>Apprehension</td>
<td>Fever</td>
<td></td>
<td>T wave inversion, ST segment depression in right precordial leads</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>Crackles</td>
<td></td>
<td>P pulmonale pattern</td>
<td></td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>Loud P2</td>
<td></td>
<td>ST segment elevation in lead III</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gallop rhythm</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Within each category findings are listed in approximate order of positive predictive value (expert opinion).
b Most common finding is normal chest x-ray.
c Changes found in fewer than 10% of cases of PE.
d Cannot use normal ABGs to exclude PE. In one study, for patients with suspected PE and with normal paO2, paCO2, and P (A-a)O2, 38% were found to have PE.
Table 5. Modified Wells’ Criteria for Assessment of Pretest Probability for Pulmonary Embolism*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs and symptoms of DVT (objectively measured calf swelling and pain with palpation in the deep vein region)</td>
<td>3.0</td>
</tr>
<tr>
<td>An alternative diagnosis is less likely than PE</td>
<td>3.0</td>
</tr>
<tr>
<td>Heart rate &gt;100 beats per minute</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization or surgery in the previous four weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1.0</td>
</tr>
<tr>
<td>Malignancy (on treatment, treated in the past six months, or palliative care)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Interpretation of Point Total

<table>
<thead>
<tr>
<th>Score</th>
<th>Mean Probability</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2</td>
<td>3.6</td>
<td>Low</td>
</tr>
<tr>
<td>2-6</td>
<td>20.5</td>
<td>Intermediate</td>
</tr>
<tr>
<td>&gt;6</td>
<td>66.7</td>
<td>High</td>
</tr>
</tbody>
</table>


Table 6. Studies Useful in Diagnosis of Pulmonary Embolism

<table>
<thead>
<tr>
<th>Study</th>
<th>Role in Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commonly used</td>
<td></td>
</tr>
<tr>
<td>Helical CT scanning</td>
<td>Primary imaging study for patients without contraindication with intermediate or high prior probability or positive D-dimer</td>
</tr>
<tr>
<td>Color duplex Doppler ultrasound of lower extremity</td>
<td>Establish diagnosis in high-likelihood patient with symptoms and signs of PE without need for CT, V/Q scan, or angiography</td>
</tr>
<tr>
<td>High-sensitivity D-dimer</td>
<td>Exclude PE in low-prior-probability patients (Wells criteria)</td>
</tr>
<tr>
<td>Other tests</td>
<td></td>
</tr>
<tr>
<td>V/Q Scan</td>
<td>Useful testing modality when CT contraindicated, additional testing needed; option as primary in absence of pulmonary infiltrate</td>
</tr>
</tbody>
</table>

Table 7. Test Characteristics of Multidetector Helical CT Angiography for PE

<table>
<thead>
<tr>
<th>CTA Findings By Prior Probability</th>
<th>Predictive Values, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Prior Probability</strong></td>
<td></td>
</tr>
<tr>
<td>CTA only, PPV</td>
<td>96</td>
</tr>
<tr>
<td>CTA+CTV, PPV</td>
<td>96</td>
</tr>
<tr>
<td>CTA only, NPV</td>
<td>60</td>
</tr>
<tr>
<td>CTA+CTV, NPV</td>
<td>82</td>
</tr>
<tr>
<td><strong>Intermediate Prior Probability</strong></td>
<td></td>
</tr>
<tr>
<td>CTA only, PPV</td>
<td>92</td>
</tr>
<tr>
<td>CTA+CTV, PPV</td>
<td>90</td>
</tr>
<tr>
<td>CTA only, NPV</td>
<td>89</td>
</tr>
<tr>
<td>CTA+CTV, NPV</td>
<td>92</td>
</tr>
<tr>
<td><strong>Low Prior Probability</strong></td>
<td></td>
</tr>
<tr>
<td>CTA only, PPV</td>
<td>58</td>
</tr>
<tr>
<td>CTA+CTV, PPV</td>
<td>57</td>
</tr>
<tr>
<td>CTA+/=CTV, PPV for main/lobar</td>
<td>97</td>
</tr>
<tr>
<td>CTA+/=CTV, PPV for segmental</td>
<td>68</td>
</tr>
<tr>
<td>CTA+/=CTV, PPV for subsegmental</td>
<td>25</td>
</tr>
<tr>
<td>CTA only, NPV</td>
<td>96</td>
</tr>
<tr>
<td>CTA+CTV, NPV</td>
<td>97</td>
</tr>
</tbody>
</table>

Note: negative predictive values (NPV) are shaded in gray. From Stein et al., N Engl J Med 2006;354:2317-27.

Table 8. V/Q Scanning, Pretest Probability for PE*, and Incidence of PE

<table>
<thead>
<tr>
<th>Scan Report</th>
<th>Incidence of PE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall performance</strong></td>
<td></td>
</tr>
<tr>
<td>Normal scan</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Low probability scan</td>
<td>14%</td>
</tr>
<tr>
<td>Intermediate probability scan</td>
<td>30%</td>
</tr>
<tr>
<td>High probability scan</td>
<td>90%</td>
</tr>
<tr>
<td><strong>Low clinical likelihood</strong></td>
<td></td>
</tr>
<tr>
<td>Normal scan</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Low probability scan</td>
<td>4%</td>
</tr>
<tr>
<td>Intermediate probability scan</td>
<td>16%</td>
</tr>
<tr>
<td>High probability scan</td>
<td>80%</td>
</tr>
<tr>
<td><strong>High clinical likelihood</strong></td>
<td></td>
</tr>
<tr>
<td>Normal scan</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Low probability scan</td>
<td>14%</td>
</tr>
<tr>
<td>Intermediate probability scan</td>
<td>66%</td>
</tr>
<tr>
<td>High probability scan from PIOPED data</td>
<td>&gt;90%</td>
</tr>
</tbody>
</table>

* For pretest probability, see Table 5.
Figure 1. Algorithm for the Diagnosis of Pulmonary Embolism

(See Table 4 for clinically suspicious findings, Table 5 for Wells score for PE, and Table 7 and 8 respectively for test characteristics of CT scanning and V/Q scanning)

* Absent contraindication, begin full-dose LMWH immediately pending completion of diagnostic testing
** "Venous study" may be either color duplex Doppler venous ultrasound or CT venography.
***Discordance between prior probability and CTA findings requires further investigation, e.g., a second expert reading of the CTA images, V/Q scanning, pulmonary angiography, or expert consultation.
Table 9. DVT: Indications for Inpatient Admission or Referral to Specialist

**Absolute**
- Massive thrombosis (subjective assessment as no formal criteria for “massive” has been defined)
- Presence of active bleeding/hemorrhage from any source
- High risk of hemorrhage (e.g., patients who are very old, have recently undergone surgery, or have a history of bleeding (e.g. GI bleeding within previous 6 months)
- History of heparin hypersensitivity or heparin-induced thrombocytopenia (for heparin or LMWH administration)
- Underlying liver disorder (INR > 1.5)
- Clinically unstable pulmonary embolus:
  - hypotension (systolic bp <100 mmHg)
  - hypoxemia (arterial blood oxygen saturation <90%)
  - respiratory distress
  - medical co-morbidities
- Extensive DVT with severe pain, swelling, cyanosis (phlegmasia cerulea dolens and phlegmasia alba dolens*)
- Social factors that prevent safe administration (e.g. no phone, unsuitable home environment, lack of social support)

**Relative**
- Platelet count < 100,000
- History of GI bleed within previous 6 months
- Severe hypertension (systolic BP > 220 mm Hg and/or diastolic BP > 120 mm Hg)
- Renal insufficiency (serum creatinine > 2.5 mg dL)
- Morbid obesity (BMI>40)
- Comorbidity that might increase the risk of home treatment (congestive heart failure, COPD, diabetes, cancer, recent myocardial infarction or stroke, altered mental status, age>70, or any other condition increasing risk to the patient treated at home vs. in the hospital)
- Thrombus involving the iliofemoral veins
- Postural or gait instability

* Phlegmasia cerulea dolens (literally: painful blue edema) is an uncommon severe form of deep venous thrombosis resulting from extensive thrombotic occlusion (blockage by a Thrombus) of the major and the collateral veins of an extremity. It is characterized by sudden severe pain, swelling, cyanosis and edema of the affected limb.

Phlegmasia alba dolens: sudden total occlusion of the deep venous system resulting in pain and edema of the leg. It may occur after childbirth or a severe febrile illness.

Table 10. Pulmonary Embolism Severity Index (PESI) to Guide Emergency Department Disposition

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1 point per year</td>
</tr>
<tr>
<td>Male gender</td>
<td>+10 points</td>
</tr>
<tr>
<td>Hypotension (systolic blood pressure &lt;100 mmHg)</td>
<td>+30 points</td>
</tr>
<tr>
<td>Tachycardia (pulse ≥100 beats/minute)</td>
<td>+20 points</td>
</tr>
<tr>
<td>Tachypnea (respiratory rate ≥30 breaths/minute)</td>
<td>+20 points</td>
</tr>
<tr>
<td>Hypoxia (oxygen saturation &lt;90%)</td>
<td>+20 points</td>
</tr>
<tr>
<td>Abnormal temperature (temperature &lt;36°C)</td>
<td>+20 points</td>
</tr>
<tr>
<td>Abnormal mental status</td>
<td>+60 points</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>+10 points</td>
</tr>
<tr>
<td>Malignancy</td>
<td>+30 points</td>
</tr>
<tr>
<td>Heart failure</td>
<td>+10 points</td>
</tr>
</tbody>
</table>

**PESI Score Interpretation**

<table>
<thead>
<tr>
<th>Classification (death risk)</th>
<th>Total point score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I (none) *</td>
<td>65 or less</td>
</tr>
<tr>
<td>Class II (1 percent) *</td>
<td>66-85</td>
</tr>
<tr>
<td>Class III (3.1 percent)</td>
<td>86-105</td>
</tr>
<tr>
<td>Class IV (10.4 percent)</td>
<td>106-125</td>
</tr>
<tr>
<td>Class V (24.4 percent)</td>
<td>Greater than 125</td>
</tr>
</tbody>
</table>

* Classes I and II identify low-risk patients.

### Table 11. Clinical Considerations for Duration of Anticoagulant Therapy

<table>
<thead>
<tr>
<th>Patient Subgroup</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calf-vein thrombosis (symptomatic) with no previous venous thromboembolism and reversible time-limited cause</td>
<td>3 months of anticoagulant therapy</td>
</tr>
<tr>
<td>First event proximal DVT with reversible or time-limited risk factors</td>
<td>3 months of anticoagulant therapy</td>
</tr>
<tr>
<td>Proximal DVT or pulmonary embolism with no previous venous thromboembolism, without reversible or time-limited risk factor</td>
<td>3 months of full-dose anticoagulant therapy; after 3 months, evaluate for risk-benefit of extended therapy. If low to moderate bleeding risk, recommend extended anticoagulation</td>
</tr>
<tr>
<td>VTE in the setting of active cancer</td>
<td>Indefinite anticoagulation over 6 months with LMWH, then continuing use should be reassessed at periodic intervals (e.g., annually)</td>
</tr>
<tr>
<td>Congenital or acquired risk factor present (Thrombophilia) with VTE a</td>
<td>For the most common heterozygous Factor V Leiden and prothrombin gene mutations, 3 months for a first event. For protein C, protein S deficiencies with positive first-degree relatives, consider long-term anticoagulation. For more than one factor, consider long-term anticoagulation. For antithrombin deficiency and antiphospholipid antibody syndrome (APS), long-term anticoagulation. For acquired risk factors, consider more aggressive use of extended anticoagulation until risk factor has resolved.</td>
</tr>
<tr>
<td>Recurrent unprovoked venous thromboembolism</td>
<td>Indefinite anticoagulation if low to moderate bleeding risk; 3 months anticoagulation if high bleeding risk</td>
</tr>
<tr>
<td>Venous thromboembolism during pregnancy</td>
<td>Therapy with adjusted dose LMWH. Total duration of therapy should be a minimum of 3 months and for at least 6 weeks post-partum. When delivery is planned, discontinue the anticoagulation at least 24-36 hours prior to induction of labor or C-section unless the VTE occurs close to delivery date and stopping anticoagulation may be hazardous due to high risk of PE (temporary IVC filter, or use of UFH to facilitate stopping 1 hour prior to anticipated delivery would then be appropriate).</td>
</tr>
<tr>
<td>Upper Extremity DVT</td>
<td>3 months of anticoagulant therapy is recommended when not associated with a catheter. In cases of catheter-associated DVT, therapy should be continued as long as the catheter remains in place.</td>
</tr>
</tbody>
</table>


Note: These general guidelines are based upon clinical trials and expert opinion. Each patient must be managed individually, which may require an alternative treatment plan to that suggested above. Subspecialty consultation (i.e. hematology or pulmonology) for those with risk factors or unprovoked DVT/PE is recommended as prolonged anticoagulation can be a complex decision.

a Thrombophilic risk factors include factor V Leiden; prothrombin gene mutation; hyperhomocysteinemia; congenital deficiencies of protein C, protein S, antithrombin; and antiphospholipid antibodies.
### Table 12. Currently Available Oral Anticoagulation Agents*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Starting Dose / Max Dose</th>
<th>Cost: Generic / Brand</th>
<th>Monitoring</th>
<th>Consideration for concurrent use with UFH/LMWH during Initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin / Coumadin</td>
<td>5mg/10mg</td>
<td>$6 / $53-74</td>
<td>PT/INR prior to initiation and then first test 3 days after. Subsequent monitoring based on guidelines (see Appendix C)</td>
<td>Always for VTE diagnoses. Discontinue concurrent heparin at second therapeutic INR and at least 5 days after initiating warfarin</td>
</tr>
<tr>
<td>Rivaroxaban / Xarelto</td>
<td>Start: 15mg bid for 3 weeks Maint: 20 mg daily</td>
<td>$NA / $287</td>
<td>None available or needed</td>
<td>Not needed</td>
</tr>
<tr>
<td>Apixaban / Eliquis</td>
<td>Start: 10 mg bid x 7 days Maint: 5mg bid</td>
<td>$NA / $286-573</td>
<td>None available or needed</td>
<td>Not needed</td>
</tr>
<tr>
<td>Dabigatran / Pradaxa</td>
<td>Start and Maint: 150 mg bid</td>
<td>$NA / $315</td>
<td>None available or needed</td>
<td>Bridge for at least 5 (and up to 10) days of therapeutic levels of LMWH or UMH</td>
</tr>
</tbody>
</table>

* Consider consultation when evaluating need for bridging with IV or Sub Q anticoagulation

Cost =For brand drugs, Average Wholesale Price minus 10%. AWP from Red Book Online 1/15/14. For generic drugs, Maximum Allowable Cost plus $3 from BCBS of Michigan MAC List, 1/1/14. Prices calculated for 30 day supply unless otherwise noted

---

### Table 13. Indications for IVC Filter Placement

**Contraindications to anticoagulation**
- Fresh surgical wound
- Active GI or other bleeding (not occult blood)
- Recent hemorrhage CVA
- Multiple/major trauma
- Recent neurosurgery
- Inability or unwillingness to comply with oral anticoagulation
- Pregnancy and impending delivery date

**Complications of anticoagulation**
- Major bleeding
- Heparin-induced thrombocytopenia *
- Warfarin-induced skin necrosis

**Failure of anticoagulation**
- Pulmonary embolectomy

*Agatroban is primary treatment; IVC filters may rarely be used in addition.*
Clinical Background

Clinical Problem

Deep venous thrombosis (DVT) and pulmonary embolism (PE) together comprise the spectrum of venous thromboembolic disease (VTE). VTE is one of the most frequent causes of hospitalization for adults and often complicates surgery and childbirth, carries significant risk of death and of long-term sequelae such as postphlebitic syndrome and core pulmonale. Historically, prior to the widespread use of heparin, approximately 12% of all patients with clinically evident DVT died, most often from PE.

Clinical findings alone are not adequate for diagnosis or exclusion. Imaging modalities are important, but their characteristics need to be understood and incorporated into cost-effective diagnostic strategies.

Management of heparinization historically caused extended hospital stays. Since LMWH usage has become standard, complications of anticoagulation have decreased. However, some patients are not able to receive anticoagulants, and some cannot receive any anticoagulation at all, complicating management of their VTE.

Throughout this document DVT of the veins distal to the knee is not distinguished from proximal DVT. Studies of PE rates find that over 30% of distal DVTs embolize (compared to 50% of proximal ones), and symptomatic recurrence rates for untreated distal DVT exceed 30%. The risks posed by distal DVTs are lower than proximal DVT, but not enough lower to alter treatment. The exception is isolated calf DVT with no evidence of progression, for which no treatment is needed.

Rationale for Recommendations

Diagnosis of Venous Thromboembolism

The diagnosis of DVT and PE share some common principles, including developing clinical likelihood estimates and comparing those estimates with probabilities developed independently from laboratory tests or imaging studies. However, the operational details differ appreciably for DVT and PE. Therefore, the diagnosis of DVT and of PE are described separately.

Primary risk factors. Primary risk factors for both DVT and PE are the same, and are summarized in Table 2.

The pathogenesis of both DVT and VTE has historically been based upon Virchow’s triad of:

- limitation of blood flow/stasis
- endothelial injury and
- hypercoaguable state.

Each of these risk factors for the development of VTE can be either hereditary or acquired.

The most common risk factors for the development of VTE include prior VTE, surgery, trauma, hospitalization/immobilization, pregnancy, estrogen-containing combined oral contraceptives (COCs) and other oral estrogen products, cardiovascular catheters, inherited thrombophilia, advanced age and malignancies. The risk for VTE escalates with a combination of these risk factors. In addition, the antiphospholipid antibody syndrome (including anticardiolipin antibodies and lupus anticoagulants) involves acquired immunologic abnormalities that can promote a hypercoaguable state.

Diagnosis of Deep Venous Thrombosis

Clinical recognition of DVT. The clinical diagnosis of DVT is challenging and characterized by uncertainty.

Lower extremity DVT may be suspected in the “clinical situations” in Table 3 (Wells criteria for lower extremity DVT), but is by no means limited to these settings. Typical symptoms and signs include swelling and tenderness of the calf. However, half of significant DVTs are without clinical symptoms or signs, so these may not be relied on for diagnosis.

Similar to lower extremity DVT, upper extremity DVT presents with symptoms of arm discomfort, edema, dilated venous collateral and discoloration. Upper extremity venous thrombosis accounts for 5-10% of all DVT’s, and is seen most frequently in the subclavian vein followed by the axillary and brachial vein. 75% of cases are associated with the presence of intravenous catheters. The main complications include mortality, recurrent thromboembolism and post-thrombotic syndrome. Mortality usually relates to underlying malignancy or other medical problems.

Superficial thrombophlebitis may closely resemble DVT, as may ruptured Baker’s cyst, gastrocnemius-soleus muscle injuries, and other conditions. In addition, these injuries may themselves be considered risk factors for the occurrence of DVT. For example, in a prospective epidemiologic study including 844 patients with symptomatic superficial thrombophlebitis, 210 (25%) had concomitant DVT at the time of diagnosis of superficial thrombophlebitis.

Superficial thrombophlebitis must be differentiated from DVT. Superficial thrombophlebitis is a relatively common problem affecting almost 125,000 patients in the United States annually. Superficial thrombophlebitis may lead to under-appreciated complications of venous thromboembolism including deep venous thrombosis (DVT) and pulmonary embolism (PE).

Presentation. Patients often present with leg pain and a warm, tender, palpable ‘cord’ affecting the involved venous segment may be identified on physical exam with surrounding erythema and soft tissue edema.
• Risk factors. Risk factors are similar to those of DVT. The most prevalent risk is venous varicosities, identified in 2/3 of patients with superficial thrombophlebitis. Up to 70% of patients may have associated superficial venous insufficiency.

• Testing. Duplex ultrasonography, as with DVT, is the diagnostic gold standard.

Treatment of superficial thrombophlebitis is addressed near the end of this guideline in the section on special treatment issues.

The diagnosis of DVT cannot be made or excluded solely on clinical grounds, therefore threshold for testing should be low. Formal criteria such as the Wells Criteria (Table 3), can be used to select low-probability patients after the diagnosis is suspected, but are not used for determining whether to suspect DVT.

**Testing for DVT.** A variety of clinical decision rules have been developed (see Appendix A). None of them are sensitive enough to exclude the diagnosis of DVT by themselves, and all are specific to lower extremity DVT. All of the listed rules in combination with an appropriately sensitive d-dimer can exclude DVT. Evidence is insufficient to recommend one decision rule over another.

Venous color duplex imaging is standard for both upper and lower extremity DVTs, although D-dimer serologic testing may be considered as an alternative in low probability settings where imaging is not readily available. For upper extremity DVT, duplex cannot evaluate certain locations well such as behind the clavicle. For central locations, CT venography or MR venography may be most effective in making a diagnosis.

Venous color duplex Doppler ultrasound imaging. The current standard clinical practice at the University of Michigan for the diagnosis of deep venous thrombosis is whole leg venous color duplex Doppler ultrasound imaging. A meta-analysis of 13 studies comparing CT with ultrasound for proximal DVT found a sensitivity of 71-100% and specificity between 93-100%. In symptomatic patients, sensitivity is approximately 93%; specificity 98%, accuracy 97%, with approximately 30% of studies indeterminate in the calf.

The positive and negative predictive values for gray-scale imaging are inferior to color imaging. Data from the Prospective Investigation of Pulmonary Embolism Diagnosis II (PIOPED II), a multicenter study of 711 patients, were used to compare the clinical value of CT venography (CTV) after multidetector CTA with venous compression ultrasonography for the diagnosis of VTE. There was 95.5% concordance between CTV and ultrasonography for the diagnosis or exclusion of DVT ($\kappa=0.809$). The sensitivity and specificity of combined CTA and CTV were equivalent to combined CTA and ultrasonography. The usefulness of duplex imaging depends to some degree on the pretest probability of the patient for a DVT.

**Low pretest probability.** A formal Bayesian method can avoid Doppler studies in a subset of patients. A validated predictive rule such as the Wells criteria for DVT (Table 3) must be used to calculate a clinical likelihood of DVT, in advance of D-dimer testing. If the patient’s pretest probability is low, a negative high-sensitivity D-dimer test can exclude DVT with a negative predictive value of approximately 99.5% (roughly 0.5% false negatives). Still, roughly one-third of low-probability patients will have positive D-dimers. (Those patients should proceed to Doppler imaging, as D-dimer alone does not establish the diagnosis of DVT.) If pretest probability is not low, additional imaging studies must be done; D-dimer can only exclude DVT for low-probability patients.

D-dimer requires that a high-sensitivity D-dimer assay (such as the advanced turbidimetric method or ELISA) is used. Alternatively, use of color duplex Doppler ultrasound both above and below the knee is also acceptable if D-dimer testing is not readily available.

A single good-quality color duplex Doppler study is sufficient (NPV > 99.5%) to exclude proximal DVT. Repeat scanning is seldom indicated unless the initial study was technically suboptimal. A truly negative study means that all the segments of the leg are negative by ultrasound imaging and clear by Doppler flow, including the external iliac, common femoral, femoral, popliteal, and calf veins (+/- saphenous system).

**Moderate pretest probability.** In a patient with a moderate pretest probability for DVT:

- If duplex ultrasound is positive, the patient should undergo treatment.
- If duplex ultrasound is done only on the proximal veins and is negative, repeat the imaging in one week or add in a D-dimer biomarker test concurrent to the ultrasound.
- If D-dimer is negative, no further testing is necessary.
- If whole leg duplex was done and is negative, no further testing is necessary.

**High pretest probability.** In a patient with a high pretest probability for DVT, the D-dimer is not useful. Even a negative result would need further testing.

- If duplex ultrasound is positive, the patient should undergo treatment.
- If limited duplex ultrasound of only the proximal veins is negative, either:
  - Perform D-dimer – if negative, withhold anticoagulation, if positive, repeat in one week
  - Repeat the limited duplex ultrasound in 3-7 days (3 days if very suspicious, 7 days if less suspicious).
- If whole leg duplex is negative, no further testing is necessary.

During pregnancy, follow the above recommendations, but also remember to assess for iliac vein thrombosis.

**Recurrence of DVT.** Recurrence of DVT is relatively common. The diagnosis of recurrent DVT can be difficult, since the postphlebitic syndrome (pain and edema without recurrent thrombosis) can mimic recurrent DVT. However,
Diagnosis of Pulmonary Embolism

Clinical recognition of PE. No set of bedside diagnostic findings are definitive. Clinicians select patients for testing for PE based on a high index of suspicion and awareness of clinical findings of PE illustrated in Table 4. As is the case with DVT, formal criteria (Table 5) can be applied for identifying low-probability patients after the diagnosis is suspected, but are not used for determining which patients to suspect of PE.

Within each category in Table 4, the clinical features are listed in approximate order of positive predictive value. However, specific test characteristics for each finding are not available.

The clinical detection of PE is not amenable to checklist or rule-based diagnosis. It remains a pattern-recognition task, requiring the skills of an experienced clinician. Clinicians less familiar with PE are encouraged to consult an expert when the question arises. Formal clinical likelihood (prior probability) estimation (see Table 5) should be applied to determine diagnostic strategy after the diagnosis is suspected, but is not used for determining whether to suspect PE.

Testing for PE. The recommended approach to diagnosis of PE continues to evolve with advances in diagnostic tests and in their interpretations.

The cornerstone of diagnostic assessment continues to be the use of clinical stratification rules prior to obtaining ancillary diagnostic tests. As illustrated in Figure 1, assessment begins with prior clinical likelihood estimation for all patients (Table 5). Several clinical assessment rules are available (see Appendix A) that appear to perform similarly in this regard.

- Patients with low clinical likelihood assessment for PE should have D-dimer testing (similar to patients with low clinical likelihood of DVT). Patients with both low clinical likelihood and negative D-dimer require no further investigation.
- Patients with intermediate or high likelihood assessment should undergo image-based assessments without D-dimer

Several recent reports indicate over-utilization of imaging in suspected PE due to failure to properly apply clinical stratification and D-dimer testing. Appropriate diagnostic strategy requires considering both clinical likelihood and the results of D-dimer/imaging.

Table 5 lists several tests that may be relevant for PE diagnosis. In summary, multidetector helical CTA (pulmonary angiography) and CTV (pelvic venography) is the imaging modality employed in most patients. Radionuclide V/Q scanning remains a valuable alternative, particularly for patients without infiltrates or large effusions on radiography in whom CT is contraindicated. A positive lower-extremity color duplex Doppler study in a high clinical likelihood patient can establish the diagnosis without lung imaging. Each of these tests is addressed in more detail below.

Plasma D-Dimer. D-dimer testing is recommended to exclude PE in patients with low clinical prior likelihood (i.e., Wells score < 2; Table 3). As with DVT, for PE D-dimer testing has a role in diagnosis only if prior probability is low. Use of D-dimer testing in PE diagnosis requires that a high-sensitivity D-dimer assay (such as the advanced turbidimetric method) validated at the local institution be used. Patients with both low probability and negative D-dimer require no further investigation as the negative predictive value is 99%.

Other biomarkers. Two other biomarker are not part of routine algorithms: B-type natriuretic peptide (BNP) and troponin.

BNP is released by ventricular myocardial cells in response to wall stretch and volume overload. BNP is a prognostic (not diagnostic) biomarker for PE. BNP levels generally indicate right ventricular strain due to elevated pulmonary vascular resistance in the lungs. If measured early (within 4 hours of admission for PE), elevated BNP levels (>90 pg/mL) demonstrate a sensitivity of 85% and specificity of 75% in predicting PE-related outcomes. Conversely, normal BNP values in the setting of acute PE carry a 97% to 100% negative predictive value for in-hospital death.

When elevated in acute PE, troponins represent myocyte ischemia and microinfarction due to acute cardiac strain of the right ventricle. Approximately 30% to 50% of patients with large PE will have elevations in troponins I and T that are mild and short-lived. They correlate with worse RV function and a high incidence of complications. Normal troponin T levels have a 97% to 100% negative predictive value for in-hospital death.

CT angiography. Multidetector helical CT angiography (CTA) is the primary imaging modality. Alternatives are V/Q scanning, particularly for patients with otherwise normal lungs in whom interpretability of the test is optimal, and a positive lower-extremity color duplex Doppler study in a high probability patient.

Multidetector scanners, such as those in use at the University of Michigan Health System, have significantly improved the sensitivity and specificity as well as the positive and negative predictive value of CTA. Recent outcome studies have found the sensitivity and specificity of CTA to be greater than 95%, and a negative CTA carries a 3-month risk of VTE of 1% to 2%.
CTA establishes the diagnosis of PE if it is positive in an intermediate- or high-probability patient, or in a low-probability patient with findings of a main-stem or lobar embolus. A negative scan excludes the diagnosis of PE in low-probability patients. It may be combined with CT venography, as shown in Table 7.

CT venography of the femoral veins can be accomplished at the time of CTA. Although CTV adds incrementally to the sensitivity and specificity of the exam, venous compression ultrasonography is just as accurate and does not expose the patient to ionizing radiation. Discordance between prior clinical likelihood assessment and CTA findings require further investigation, including checking for technically inadequate studies.

For patients with low clinical likelihood, further investigation is required if either:
- CTA apparently positive for sub- or segmental embolism
- a high or intermediate clinical likelihood, but negative CTA results.

A prudent initial step in these instances is to obtain a second expert reading of the CTA. Subsequent V/Q scanning may be helpful (see below). Pulmonary angiography may be required in some cases, to avoid the risk of missing a PE or of committing a patient to long-term therapy unnecessarily.

**V/Q scan.** A normal V/Q scan effectively excludes PE (see Table 8 and Figure 1). For anything other than normal tests, V/Q scanning returns a probability statement as a result that must be evaluated in conjunction with the clinical likelihood assessment (and Table 8).

V/Q scanning can sometimes assist in further evaluating patients with discordant CTA and clinical likelihood findings, particularly for patients who do not have underlying lung disease that would impair the interpretability of the V/Q images. It may be also be used as the primary imaging study for patients with contraindications to CTA (e.g., renal disease, severe contrast allergy, radiation dose concern). An algorithm describing the use and interpretation of V/Q scans in the diagnosis of PE is presented in Appendix D.

As with CTA (above), if the results of both clinical likelihood assessment and V/Q scan do not agree, additional testing is indicated.

**Venous color duplex Doppler ultrasound.** Since PE and DVT represent the continuum of VTE, an alternative initial test is venous color duplex Doppler ultrasound of the lower extremities. A positive test in the presence of symptoms and signs of PE is sufficient to establish the diagnosis and is sufficient to treat for PE. The converse is not true; a negative lower extremity ultrasound cannot exclude PE.

**Pulmonary angiography.** Outcome studies have found comparable results between angiography and CTA; a negative result with either study confers approximately a 1% VTE rate within 6 months. However, because angiography is invasive, it carries a greater risk of complications and mortality. The mortality from angiography has been estimated at 0.5% while 1% may experience major complications including arrhythmias, hypotension, bleeding, and nephrotoxicity.

We do not recommend pulmonary angiography, except in circumstances such as inadequate V/Q imaging or when catheter-directed thrombolysis is recommended. Currently, pulmonary angiography is used to settle discordant diagnostic tests, or in the setting of pharmacomechanical thrombolysis for massive or sub-massive PE.

In the absence of a higher standard, the specificity and sensitivity of pulmonary angiography cannot be discussed using commonly accepted definitions of these terms. Instead, the accuracy of pulmonary angiography is discussed in terms of inter-observer variability in the reading of pulmonary angiograms obtained in the context of large multicenter trials. Studies demonstrate that the larger the embolus, the better the inter-observer agreement. For segmental and larger emboli, agreement exceeds 95%. For subsegmental emboli, agreement is considerably less.

**Other testing modalities.** In some situations an echocardiogram, arterial blood gas sampling, or pulse oximetry may be helpful as some prognostic clinical prediction rules utilize this information. Phlebography is rarely indicated. It carries appreciable local morbidity, the risk of contrast administration, and is technically inadequate in 7-20% of studies.

**Echocardiogram.** Due to its low sensitivity and specificity, transthoracic or transesophageal echocardiography has limited diagnostic value for PE. For critically ill patients too unstable for transport, echocardiography can suggest the diagnosis of PE by showing dilatation or hypokinesis of the right ventricle (RV). Acute changes in the RV pressure, size, and function are commonly seen, indicating increased RV strain and pulmonary arterial pressures. These changes suggest PE in the absence of alternative diagnoses. Although of limited value in the diagnosis of PE, echocardiography is of great prognostic use in stratifying risk for patients with acute PE. Right ventricular dysfunction or dilatation in acute PE is associated with worse outcomes, including increased mortality.

**Arterial blood gas sampling and pulse oximetry.** Neither pulse oximetry nor arterial blood gas sampling have sufficient sensitivity or specificity to reliably be used in diagnosis of DVT or PE. However, pulse oximetry and arterial blood gas sampling may be helpful in general assessment of patient stability and in the risk stratification of those patients diagnosed with PE or for whom PE is strongly suspected. In the clinical assessment of patients presenting with symptoms of tachypnea and tachycardia, these tests can be used as an adjunctive to help elucidate differential diagnostic possibilities.

**Future developments in testing.** Recently the efficacy of magnetic resonance angiography (MRA), magnetic resonance venography (MRV), and the combination of the two have been studied for the diagnosis of acute PE. At this
Improvements in imaging technology have resulted in conversion of V/Q data collections from planar to tomographic (SPECT) imaging. Further advances include the use of hybrid SPECT/CT imaging to provide attenuation correction and localization in V/Q images. These approaches are gaining increased utilization, but prospective validations are limited. Additional changes in V/Q scanning include the possible simplification of classification from high-intermediate-low probability (PIOPED scheme) to PE present vs. absent (PISAPED scheme). Again, prospective validations are presently limited.

**Treatment of Venous Thromboembolism**

Treatment for VTE may involve:

- **Anticoagulation** – the most common form of treatment for both upper and lower extremity DVT and for PE. Thrombosis of superficial veins or those distal to the brachial vein (such as basilic or cephalic) do not require treatment with anticoagulation
- **Inferior vena cava filter** – placed when anticoagulation is contraindicated or has failed
- **Aggressive clot removal** – emergent thrombolytic therapy or (for DVT) more rarely thrombectomy – performed for “massive” PE or limb-threatening iliofemoral DVT when not contraindicated. It is also appropriate in cases of upper extremity DVT associated with thoracic outlet compression.
- **Secondary prevention and prophylaxis**

For upper extremity DVT associated with a catheter or line, the thrombosis is treated with anticoagulation with catheter removal if the catheter is no longer needed, or anticoagulation leaving the catheter in place if still needed. If the catheter must remain in place for ongoing medical therapy it is recommended that anticoagulation be continued for the duration that the catheter remains in place.

The management approaches are explained below, with a primary focus on anticoagulation.

**Anticoagulation for VTE**

**Anticoagulation treatment setting: outpatient or inpatient.** In general, outpatient treatment has advantages of lower cost and greater comfort for patients while inpatient treatment provides closer monitoring and quicker response to clinical changes. A substantial number of patients with DVT may be safely treated as outpatients. Only a limited number of patients with PE have sufficiently low risk that outpatient treatment can be considered.

**Outpatient or inpatient treatment of DVT.** Numerous clinical studies have demonstrated that most patients with uncomplicated DVT can be safely and effectively treated as outpatients with LMWH if a system is in place to identify complications and manage the transition to warfarin. Patients must be able to clearly understand and effectively adhere to the detailed instructions necessary. Proper patient (or caregiver) education is critical to safe outpatient management, and should be carried out by specifically trained health care staff. Patients who may have difficulty understanding or adhering to therapy, or who have high-risk comorbid conditions, should be hospitalized at least initially.

Most contraindications to outpatient treatment are relative although some should be considered absolute (see Table 9).

LMWH is less costly in overall treatment expense though its acquisition cost is higher. Shorter, or even no, hospital stays account for some of that advantage. However, even in the inpatient setting the costs of IV administration and monitoring make UFH costlier than LMWH.

**Outpatient or inpatient treatment of PE.** A select group of patients diagnosed with pulmonary embolism can be safely treated with anticoagulation as an outpatient. These patients should be hemodynamically stable and normoxic before outpatient treatment is considered. Signs of right ventricular dysfunction by echocardiography or CTA should lead to inpatient therapy, but there is not sufficient evidence to recommend the routine use of echocardiography. The Pulmonary Embolism Severity Index (PESI) (Table 11) performed better than the Geneva prediction rule, identifying Classes I and II patients as low risk. However, low risk scores should not exclude clinical judgment. Contraindications to outpatient management of DVT would also apply to PE patients (see Table 9).

Recent randomized controlled studies have demonstrated safety and efficacy of outpatient PE management. A review article by Wells (Wells, Forgie, Rodger, 2014) suggest an algorithm for acute treatment of PE utilizing either the PESI (table 10) or other validated rules. Outpatient PE management is being applied by risk criteria for patients in many locations in Canada.

Mortality from PE can range from approximately 60% to less than 1% depending on patient characteristics. Biomarkers can help predict outcome but are not definitive: normal BNP being highly predictive of good outcome and elevated troponin being predictive of patients who are at higher risk of adverse outcome.

**Heparin anticoagulation.** Anticoagulation with heparin followed by warfarin reduces the incidence of recurrent thrombosis and pulmonary embolism in patients with lower extremity DVT by more than 55 per 100 patients. It also reduces mortality due to PE from about 25-30% to about 2.5%.

Warfarin alone is inadequate. A study testing an oral-agent-only approach (using acenocoumarol) was terminated early due to an absolute risk excess for asymptomatic pulmonary embolism of 13 per 100 patients. No reduction in incidence of bleeding complications occurred with the acenocoumarol-only strategy.

**Preference for LMWH.** LMWH is at least as effective and safe as UFH, and in practical terms is clearly superior because therapeutic dosing is more rapidly and dependably
achieved. A number of high-quality randomized controlled trials have compared the several preparations of LMWH to UFH in the treatment of DVT. As summarized in AHRQ's evidence report, LMWH for venous thrombosis confers a lower risk of major bleeding complication (absolute risk reduction approximately 2 per 100 patients treated; relative risk 0.6-0.7), a lower risk of recurrent thromboembolic disease (RR 0.7-0.8), and a lower risk of death (RR 0.7-0.8).

UFH may still be elected in the case of renal disease with GFR < 30 ml/min or clinically unstable patients who may require surgery on an unpredictable basis, as LMWH is only partially reversible by protamine. Use of UFH is detailed in Appendix B.

**Dosing of LMWH.** Several LMWHs are currently marketed. Each is dosed differently; some are administered IV or SQ, and some SQ only. The common factor is that doses are fixed in total amount or by body weight, not adjusted by APTT.

The two most commonly used LMWHs are enoxaparin and dalteparin. The package insert for enoxaparin (Lovenox) calls for 1 mg/kg SQ q12hr or 1.5 mg/kg q24hr for VTE. For obese and morbidly obese patients who weigh over 200 kg, consider consultation with a pharmacologist for dosing that potentially exceeds 400 mg daily. Our opinion is that once daily dosing is superior due to improved patient compliance for non-pregnant patients. Twice daily dosing should be used in pregnancy due to increased GFR after 20 weeks, but once daily dosing may still be considered to enhance compliance. Dalteparin is used 120 anti-Xa units/kg SQ q12hr to treat VTE.

**Optimal duration of heparin therapy.** For UFH, a five day course has been shown to be as effective as longer courses of treatment in preventing recurrent thrombosis, provided that warfarin is started early (usually within 24 hours of diagnosis) and therapeutic oral anticoagulation is achieved prior to discontinuing heparin. LMWH has not been specifically tested but is believed to behave similarly.

Certain patients may use LMWH as the sole antithrombotic agent throughout their course. For patients with malignancies and acute DVT, that strategy appears to roughly halve the risk of recurrence without an increase in adverse events and avoids difficult warfarin management resulting from variable food intake. For asymptomatic patients with DVT limited to the calf and no risk factors, serial ultrasound imaging is preferred over anticoagulation. If no extension is noted after 1 week (some studies suggest 2 weeks), anticoagulation can be withheld.

**Monitoring heparin therapy.** LMWH does not normally require monitoring for therapeutic effect, and does not prolong APTT at therapeutic levels as much as does standard UFH. LMWH's effect can be monitored by peak anti-factor Xa activity. Doing so may be useful when using LMWH in pregnancy, for patients with GFR < 30 ml/min, or for those who are morbidly obese.

Heparin-induced thrombocytopenia, or HIT, is an uncommon but serious complication of heparin therapy that can cause arterial and venous thrombosis, and less often bleeding. It is caused by a heparin-dependent platelet antibody that leads to platelet aggregation. The diagnosis should be suspected in:
- a patient who develops thrombosis on heparin
- when platelet count falls to <100,000 or a decline by ≥50% from baseline counts during heparin therapy

While HIT is reported with LMWH, it is less common than with UFH. A modest and clinically unimportant reduction in platelet counts is more common than HIT.

Monitoring of platelet counts should begin on the 4th day of heparin therapy (earlier if the patient has previously been exposed to heparin), and repeated on or about days 7, 10, and 14; development of HIT past that point is very unusual. If the syndrome is suspected, stop heparin at once, change to a different anticoagulant (a direct thrombin inhibitor) and consult with a specialist for testing and treatment options.

**Transition from heparin to vitamin K antagonists (warfarin).** Heparin and warfarin therapy should overlap during the acute management of VTE. Clinical trials suggest that heparin can be discontinued safely once the INR enters the therapeutic range (2.0-3.0) if the patient has received ≥ 5 days of heparin therapy. Some recommend that heparin be continued until the INR has been in the therapeutic range for >2 days, since the antithrombotic effect of warfarin may be delayed relative to its effect on the prothrombin time. However, clinical trials have not tested whether this approach offers greater protection against thrombosis than discontinuation of heparin as soon as the INR is therapeutic.

Patients with malignancy should not be transitioned to warfarin, but instead should continue on LMWH due to superior reduction of risk of recurrent VTE compared to warfarin, and a 3-fold increase in risk of recurrence compared to patients without cancer. The recommended treatment duration is at least 6 months after cure or remission.

**Subsequent warfarin anticoagulation.** Warfarin and other vitamin K antagonists reduce the incidence of recurrence of thrombosis in patients with DVT and pulmonary embolism by 30 or more per 100 patients treated.

**Administration and monitoring of warfarin.** Warfarin should be started early, usually concurrent with the initiation of heparin therapy. The use of loading doses of warfarin is not recommended, as the coagulation factors are not reduced symmetrically and the INR may not accurately reflect warfarin's antithrombotic effect during the initiation phase of therapy.

**Initial warfarin dosing is 5 mg daily, with doses given in the evenings.** Lower or higher initial doses may be appropriate for some patients (see Appendix C). Lower doses should be considered for elderly, debilitated, liver disease, or heart failure patients.
Subsequent dosing depends on the results of PT/INR testing, which should be performed at least twice during the first week of therapy and the first test no later than the 3rd day of warfarin. A target INR of 2.5 (range 2.0-3.0) is effective in preventing thrombus extension or recurrence and is associated with a relatively low risk of bleeding. Utilization of a dedicated anticoagulation team to track INR, manage dose adjustments, and insure proper follow up minimizes adverse events and optimizes maintaining a therapeutic INR for the duration of therapy.

Patients with venous thromboembolism treated with warfarin have a major bleeding risk of 6%/year. This estimate is based on a combined analysis of 7 studies reveals that 19 of 1,283 patients (1.5%) with venous thromboembolism experienced major bleeding during a 3-month course of warfarin with target INR 2.5 (range 2.0-3.0).

Some patients, such as those with VTE along with anti-phospholipid antibodies may require more intense warfarin therapy (i.e. INR range 2.5-3.5 or 3.0-4.0). However, this point is controversial, and recent randomized trials suggest that a target INR range of 2.0-3.0 is as effective as more intense anticoagulation in reducing recurrent thrombotic events in patients with anti-phospholipid antibodies.

Diet and drug interactions with warfarin. Patients taking warfarin should be aware of the effect of both diet and drug interactions on their anticoagulation status. Information on dietary sources of vitamin K that can reduce the effect of warfarin should be provided as part of patient education, as should warning about OTC vitamin supplements. Since the list of medications that interact with warfarin is lengthy, anticoagulated patients should be advised to consult with their physician and/or a pharmacologist before taking any prescription or OTC medications, and be given a written list of potential interactions (such as a package insert or patient education sheet).

Duration of oral anticoagulation. The optimal duration of full-dose oral anticoagulant therapy after DVT or PE depends upon clinical circumstances (see Table 11). The risk of recurrence must be discussed and decided together with the patient.

Natural history studies suggest that after a first DVT the risk of recurrent venous thromboembolism varies from 3 to 10% at 1 year and 10 to 30% at 5 years. These observations are sharply different for patients with and without a provocation (i.e. patients with unprovoked or “idiopathic” VTE have a significantly increased risk, and should be considered as patients with a continuing risk factor). Patients with continuing risk factors for thrombosis, such as active malignancy, immobility, or hypercoagulable states, are at higher risk, while patients who experience thrombosis under transient circumstances (e.g., post-operatively) are at lower risk of recurrence.

In general, patients with a first episode of venous thrombosis should receive 3 months of full-dose warfarin. Risk is low for major bleeding during properly monitored warfarin therapy (particularly in patients with transient risk factors for thrombosis). Comparative clinical trials have shown that six months of full-dose warfarin therapy after a first episode of DVT results in a lower rate of recurrence than 6 weeks of therapy. Studies of very brief (4 weeks) courses have involved small numbers of highly selected patients, not representative of usual clinical practice.

Patients with a second episode of venous thromboembolism have a significantly lower rate of recurrence if they receive full-dose warfarin indefinitely (2.6% risk during 4 years of follow-up) as opposed to 6 months (20.7% risk of recurrence). However, this exposes the patient to a higher risk of bleeding complications. Therefore, duration of therapy must be determined individually taking into consideration risks for bleeding and thromboembolism.

Optimal duration of warfarin therapy in patients with a first episode of venous thrombosis and an irreversible risk factor depends on the risk factor. ACCP/Chest 2012 guidelines call for indefinite anticoagulation in patients with:

- active cancer
- two or more spontaneous thrombosis (or one in patient with anti-phospholipid antibody syndrome (APAS) or anti-thrombin 3 (ATIII) deficiency, any life threatening thrombosis, VTE at unusual site or evidence of more than one genetic defect).

Those guidelines further recommend serious consideration for indefinite anticoagulation in patients with:

- recurrent VTE (balanced with bleeding risk)
- one spontaneous or idiopathic thrombosis if bleeding risk is felt not to be high.

Dosing for long-term warfarin therapy. If long-term anticoagulation is desired, full-dose warfarin should be used. Two trials have addressed extended use of low-intensity (INR 1.5-2) warfarin to prevent recurrent idiopathic VTE. The PREVENT trial of patients with a first episode of VTE found that indefinite use of low-intensity warfarin prevented 4.6 recurrent VTEs per 100 patient-years, a relative risk reduction of 64% compared to placebo. The risk of major hemorrhage did not differ significantly from full dose warfarin. However, the ELIATE trial found that extended conventional-intensity warfarin was more effective than low-intensity warfarin, and low-intensity treatment had no lower incidence of clinically important bleeding episodes than full-dose treatment. Most current guidelines do not endorse low-intensity treatment, but rather risk-stratified full-intensity treatment. To that end, a full discussion with the patient is recommended to formulate a treatment plan.

Assessing risk after discontinuing warfarin. If indefinite therapy is a consideration in patients with spontaneous or idiopathic VTE, decision-making may be aided by D-dimer testing one month after completion of warfarin therapy. An elevated D-dimer suggests ongoing increased risk, indicating resumption of full-dose anticoagulation. In one study of patients with idiopathic or spontaneous VTE, investigators found a low rate (6.2%) of recurrence of VTE when D-dimer is normal 1 month after discontinuation of warfarin, but a 15% rate of recurrence among those with
abnormal D-dimer. Resumption of warfarin among those with abnormal D-dimers reduced recurrence rate to 2.9%. Similar findings have been reported in other studies.

The use of repeat (serial) lower extremity ultrasound has also been proposed as a test for whether to continue anticoagulation beyond the usual timeframe, but is not supported by most guidelines.

**Newer anticoagulants.** Current prevention and treatment of venous thromboembolism (VTE) employs agents which have been in use for many years including unfractionated heparin, low molecular weight heparin (LMWH), and vitamin K antagonists such as warfarin. A number of novel, target-specific, oral anticoagulants are now available or in development to either replace vitamin K antagonists in concert with initial heparin or LMWH, or for use as monotherapy. These agents and their indications are described individually further below.

These agents hold the promise of not requiring monitoring, and exhibiting lower bleeding risk than current agents, with equal or improved efficacy. Problems with these new agents include the inability at the present time to reliably reverse the anticoagulant effects of these drugs, the fact that little data are available on bridging of these agents when other procedures need to be performed, and the fact that they are non-generic.

We recommend these agents only for patients with sensitivity or complications on warfarin, and/or patients with minimal to no bleeding potential. Their usefulness will improve when adequate reversal agents become clinically available.

Caution is advised in assuming that patients who have been non-compliant with INR monitoring while on warfarin will be managed better on a newer agent that does not require monitoring. Patients who are not compliant may also not consistently take their medications. Due to the pharmacologic properties of these newer agents, a missed dose can potentially result in non-therapeutic levels. The resulting higher risk of recurrent VTE is similar to the increase in risk when monitoring does not occur consistently. The impact on recurrence rate of non-adherence is unknown, and cannot be inferred from clinical trials.

**Rivaroxaban (Xarelto®).** Rivaroxaban is FDA approved for VTE prophylaxis in patients undergoing hip or knee replacements, for stroke and systemic embolization prevention in patients with atrial fibrillation, and for VTE treatment. It targets activated factor X (factor Xa).

Rivaroxaban is currently the only FDA approved alternative to warfarin therapy for acute VTE, and is without most of the drug and diet limitations of warfarin, as it has little hepatic metabolism, and is not affected by vitamin K intake. Roughly a quarter to a third of rivaroxaban metabolism is renal, however, and therefore caution should be exercised in patients with abnormal renal function. No dosage change is recommended based on renal function, but it should be avoided completely in patients with GFR < 30 ml/min.

Eight major trials studying VTE and rivaroxaban compared to standard therapy have been published, with rivaroxaban non-inferior in 6 and superior in 2. The Einstein trial evaluated rivaroxaban compared to standard anticoagulation in the treatment of acute DVT. As monotherapy, (i.e. without use of any initial heparin therapy), rivaroxaban was found statistically non-inferior to standard therapy, without increased bleeding risk. Additionally, the Einstein group added a continued treatment group compared to placebo for an additional 6 to 12 months. Patients were considered eligible for this extended therapy study if the potential benefit was thought to counterbalance risk of extended therapy. (It should be noted that the vast majority of patients in both parts of this study had unprovoked, or idiopathic VTE). Extended rivaroxaban showed a significant decrease in recurrent VTE without a significant increase in major bleeding. (It should also be noted that roughly half of the subjects in the extended therapy trial had a diagnosis of PE). In a trial for atrial fibrillation, rivaroxaban showed statistically less intracranial bleeding or fatal bleeding.

**Dabigatran (Pradaxa®).** Dabigatran is FDA approved for VTE treatment or prophylaxis. It targets activated factor II (factor IIa), Dabigatran etexilate is also FDA approved for stroke and systemic embolization prevention in patients with atrial fibrillation.

In trials compared to standard therapy for VTE, out of 6 randomized controlled trials, dabigatran was non-inferior in three, superior in two trials, and inferior in one trial. In the Recover trial which compared dabigatran 150mg to therapeutic anticoagulation with vitamin K antagonists (INR 2-3) in the treatment of DVT for 6 months, after both were given LMWH or unfractionated heparin for an average of 9 days, dabigatran was non-inferior in the 6 month rate of VTE recurrence. Clinically important bleeding was not significantly different when compared to warfarin. In extended duration treatment dabigatran had fewer recurrent VTEs compared to placebo.

**Apixaban (Eliquis®).** Apixaban is currently FDA approved for prevention of complications for atrial fibrillation as well as for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism, in patients who have undergone hip or knee replacement surgery. Like Rivaroxaban, it targets activated factor X (factor Xa).

This agent has been compared to standard therapy in 6 studies involving VTE. It was non-inferior in 2, superior in 3, and a failure in one. In a recent study, Apixaban was given for 7 days of initial treatment for DVT, followed by a lower dose bid vs. standard enoxaparin followed by warfarin for 6 months. Apixaban was non-inferior to standard therapy with less bleeding. Apixaban was also studied as extended treatment of VTE. After a standard duration of treatment, an additional 12 months of apixaban therapy compared to placebo revealed a significant decrease in the rate of VTE without an increase in bleeding. (It should be noted that the vast majority of subjects in the apixaban VTE study had idiopathic, or unprovoked VTE, thus putting them at
increased risk of recurrence, and possibly indicating prolonged or indefinite therapy).

**Edoxaban (Lixiana®).** Edoxaban is not yet FDA approved for any indication. Like apixaban and rivaroxaban it is a factor Xa inhibitor. Edoxaban was recently compared with warfarin in a randomized, double-blind, noninferiority study. In this study, 4921 patients with confirmed DVT and 3319 patients with pulmonary embolism were randomized, after receiving at least day five days of LMWH or unfractionated heparin, to either 60 mg of Edoxaban once daily (or 30 mg once daily in the case of patients with creatinine clearance of 30-50 mL per minute or a body weight less than 60 kg), or standard treatment with warfarin with a target INR of 2 to 3. Edoxaban was non-inferior to weight less than 60 kg), or standard treatment with warfarin

6.2%; HR 0.52; 95% CI 0.28-0.98).

Venous thromboembolism subgroup, there was a lower rate of recurrent

creatinine clearance of 30 -50 mL per minute or a body

3319 patients with pulmonary embolism were randomized,

after receiving at least day five days of LMWH or

unfractionated heparin, to either 60 mg of Edoxaban once
day (or 30 mg once daily in the case of patients with

venous thromboembolism with Edoxaban (3.3% versus

6.2%; HR 0.52; 95% CI 0.28-0.98).

**Argatroban (Acova®).** Argatroban is a parenteral direct thrombin inhibitor that is FDA approved for the treatment or prophylaxis of thrombosis in patients with heparin induced thrombocytopenia (HIT). Argatroban reversibly binds to the thrombin active site, and unlike heparin, does not require the co-factor antithrombin III for antithrombotic activity.

The intravenous route of administration, cost and monitoring requirements limit its use to inpatient settings where it is primarily utilized for the prophylaxis of VTE in patients with active HIT or in treatment of patients with thrombosis associated with HIT. When bridging from argatroban to warfarin, the INR must be above 4 for warfarin to be therapeutic because argatroban falsely elevates INR.

**Fondaparinux (Arixtra®).** Fondaparinux is a synthetic pentasaccharide that binds to antithrombin and inhibits factor Xa. It is FDA approved for prophylaxis of VTE in patients undergoing abdominal surgery, total knee arthroplasty. It is also approved for DVT/PE treatment when administered in conjunction with warfarin.

An important distinguishing feature is that fondaparinux has a low affinity for platelet factor 4 (PF4) and does not cross react with HIT antibodies. Numerous case reports and case series suggest that fondaparinux is safe to treat patients with HIT. The efficacy and safety of the fondaparinux derivatives, idraparinux and idrabiotaparinux, have not yet been established.

Fondaparinux is given once daily as a subcutaneous injection without the need for routine coagulation monitoring. Routine coagulation tests, such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are insensitive at measuring the effects of fondaparinux. If necessary to assess the anticoagulation effect, fondaparinux specific anti-Xa assays can be used, though the therapeutic anti-Xa range has not been established. There is no specific reversal agent for fondaparinux, but in cases of hemorrhage recombinant factor VIIa may be useful.

**Anticoagulation and pregnancy.** The incidence of VTE associated with pregnancy is not precisely known, but it is believed to be substantially greater than in non-pregnant women. Two-thirds of DVTs occur before delivery and are distributed fairly uniformly throughout the pregnancy, but 40-60% of PEs occur in the 4 to 6 weeks after delivery. DVT has a marked (~80%) predilection for the left leg in pregnancy, because of compression effects on the left iliac vein.

VTE in pregnancy appears to be strongly associated with thrombophilies: up to 60% of pregnant women with first VTE episodes may have factor V Leiden, and other thrombophilies are also common. Antithrombin, protein C, and protein S deficiency do not appear strongly associated, but prothrombin gene mutation, hyperhomocysteinemia, and antiphospholipid antibodies do. Pregnant women with a VTE associated with thrombophilia are more likely to have a recurrence in subsequent pregnancies. However, routine prospective screening for thrombophilies in all women is not recommended because thrombophilies in the absence a VTE during a prior pregnancy is not predictive of subsequent VTE risk and thrombophilies do not have a significant role in determining length of anticoagulation in pregnant women.

**Prophylactic anticoagulation in pregnancy.** To reduce VTE risk, women with antithrombin deficiency or prior pregnancy associated VTE should receive prophylactic anticoagulation with LMWH during their entire pregnancy. This prophylactic dosing should be stopped 24 hours prior to anticipated delivery. Women with other thrombophilies but without a history of VTE can be monitored for VTE occurrence but do not require prophylactic LMWH.

Women with a history of recurrent early pregnancy loss (more than 3) or late pregnancy loss should be screened for anti-phospholipid antibodies. Those who test positive should also receive prophylactic LMWH.

**Diagnosing DVT and PE in pregnancy.** When DVT is suspected during pregnancy, standard testing with compression ultrasound is the test of choice as it has similar efficacy to that of testing in non-pregnant patients. However, serum testing with D-dimer level as an adjunct is not as reliable for patients with low pre-test probability compared to non-pregnant patients. D-dimer levels increase normally during pregnancy, thus using the standard threshold values for ‘abnormal’ results in a high false positive rate. One study evaluated a higher threshold based on trimester and found that this modification could be reliable, however standard values have not been established.

When pulmonary embolism is suspected during pregnancy, consideration of radiation exposure levels in determining which test to use is warranted. The American Thoracic Society / Society of Thoracic Radiology Clinical Practice Guideline on suspected pulmonary embolism during pregnancy, which has been endorsed by the American
Anticoagulation facilitation.

Anticoagulation with LMWH in pregnancy. LMWH is safe and effective for both prophylaxis and treatment of VTE during pregnancy and in the post-partum period. It is superior to warfarin due to the potential risk for embryopathy with warfarin and risk of intracranial hemorrhage at the time of delivery. LMWH is preferred over UFH when the patient is able to manage LMWH administration.

Warfarin for VTE should be discontinued in favor of LMWH when pregnancy is planned or discovered. LMWH can be continued throughout pregnancy. Neither UFH nor LMWH cross the placenta. Though heparin anticoagulation could increase the risk of abruptio, it causes neither teratogenicity nor fetal bleeding.

Warfarin does cross the placenta. While it appears safe in the first 6 weeks of gestation, is associated with a significant risk of embryopathy between 6 and 12 weeks, and presents a risk of fetal bleeding (including intracranial hemorrhage) especially at the time of delivery.

In patients with special circumstances (e.g. significant arterial thromboembolism risk), transition to UFH near the time of delivery is recommended. Use of UFH near delivery is helpful as it can be stopped closer to the time of delivery, thus minimizing the duration of time without anticoagulation. If UFH is not deemed a viable option based on the clinical situation, placement of a temporary IVC filter should be considered. Post-partum patients with need of ongoing anticoagulation could re-initiate warfarin after 12 weeks. Warfarin does not cross into breast milk in active form, and may be used during nursing.

Anticoagulation in pulmonary hypertension. Pulmonary hypertension is a known and common sequela of pulmonary embolism. Of patients with an acute PE, 3-4% develop chronic thromboembolic pulmonary hypertension (CTEPH). Patients with suspected CTEPH should receive a full evaluation, including an operability assessment. Once a patient has CTEPH, anticoagulation should be continued life-long due to high risk of VTE recurrence.

Anticoagulation facilitation. Institutional services and home monitoring can improve anticoagulation management.

Anticoagulation management service. A dedicated anticoagulation management service (e.g., http://www.med.umich.edu/i/cvc/anticoag/) can achieve fewer days of sub- or supra-therapeutic INRs than usual clinical management in many cases.

Home INR monitoring. Home INR monitoring devices are available and may be appropriate for some patients. Insurance coverage is problematic.

Inferior Vena Cava Filters

In some situations anticoagulation is either contraindicated or has failed. Vena cava filters are used in these cases to prevent pulmonary emboli. Experts estimate that approximately 50% of patients with untreated proximal DVT sustain pulmonary emboli, 30% of which are fatal. Summaries of case series suggest that 1.9% to 2.4% of patients will have pulmonary embolization after filter placement, far lower than the embolism rate for untreated DVT.

Indications for IVC filters. Indications for placing a filter are summarized in Table 13.

Prophylactic placement of IVC filters is common clinical practice in addition to anticoagulation for patients with poorly-adherent free-floating thrombus (though the only prospective study does not support this indication), and for patients with malignancy at risk of hemorrhage if anticoagulated. Some advocate IVC filters prophylactically for elderly patients with isolated long bone fractures, comatose patients with severe head injury, patients with multiple long bone and pelvic fractures, and spinal cord patients with para- or quadriplegia, because case studies from the surgical literature suggest an approximate 75% absolute risk reduction for PE.

Removable filters. The advent of removable filters allows for retrieval if the risk factor(s) no longer exist. Removal guidelines do not yet exist, so consultation on a case-by-case basis is required. Retrieval filters vary in their recommended windows for percutaneous extraction, depending on the filter model. The commonest reason for failure to retrieve a filter is loss of the patient to medical follow-up, and in clinical series retrieval rates have been reported as low as 20%. A decision to place a retrievable filter should be accompanied by a plan to remove the filter after exposure to the risks of VTE has declined to baseline or anticoagulation can resume.

Complications of filters. The use of IVC filters may result in the following complications:

- DVT at insertion site
- Change in filter position (tilting, migration)
- Perforation of inferior vena cava
- Fracture of filter elements and distal migration
- IVC thrombosis
- Local trauma to skin, vessels, nerves at insertion site
- Entanglement of central venous catheters is possible with supra-renal IVC placement. Patients with such placements require a warning placed in their medical records.

More Aggressive Initial Treatment

Patients who present with DVT that could potentially result in significant long-term pain and swelling, or limb loss due to ischemia, or who are clinically unstable due to PE (hypotensive, tachycardia, hypoxia, tachypnea) may benefit from initial treatment beyond simple anticoagulation.
Patients in this situation are best managed in the inpatient setting. Options for management include cathater directed thrombolysis (with or without a mechanical device), thrombectomy, and systemic thrombolysis. These options should be carefully considered with expert consultation.

**Catheter Directed Pharmacomechanical Thrombolysis for DVT**

Patients with acute iliofemoral venous thrombosis are at high risk of the post-thrombotic syndrome, a chronic condition consisting of pain, swelling, itching, feelings of heaviness, and skin changes in the affected limb. These patients may benefit from catheter-directed pharmacomechanical thrombolysis, which includes various techniques of safely eliminating the occlusive clot and restoring lumen patency and valve function. Treatment should be delivered within 2 weeks of symptom onset, and typically requires 2-3 days of inpatient therapy. As this field is rapidly evolving, prospective candidates for this therapy should be discussed with vascular surgery or interventional radiology.

**Systemic thrombolysis.** For acute PE, in controlled trials, systemic thrombolysis has been shown to improve hemodynamics, imaging, and echocardiography faster than heparin alone. However mortality is not improved. The significant risk of systemic bleeding must be balanced against the relatively uncertain benefit of systemic thrombolytics. The risk of dying from PE is estimated at 70% if associated with cardiopulmonary arrest and 30% if associated with hypotension requiring inotropic support.

In cases of hemodynamic instability, consider systemic thrombolysis in the absence of a high risk of bleeding (t-PA 100mg over 2 hours or 50mg over ≤15 minutes). In selected patients with submassive PE (evidence of RV strain on echocardiogram, worsening clinical status after anticoagulation instituted, and/or relative hypotension with SBP drop >40mmHg), systemic thrombolysis can be considered if the patient is at very low risk of bleeding. If thrombolysis is considered, emergent consultation with a specialist in thrombotic therapy (typically in cardiology, interventional radiology, or pulmonology) should be initiated as quickly as possible.

**Thrombectomy.** Surgical removal of an embolus is an emergency procedure indicated in the case of massive PE and/or limb threatening iliofemoral DVT. Patients with this situation are best managed in the inpatient setting.

**Secondary Prevention and Prophylaxis**

**Long-term secondary prevention after discontinuing anticoagulation.** In general, patients whose VTE was provoked by a major reversible risk factor, such as surgery or major trauma, have a low risk of recurrence. The risk becomes higher in patients with VTE provoked by minor reversible risk factors (e.g. minor trauma, estrogen therapy, prolonged air travel, pregnancy) and is highest in patients with unprovoked (idiopathic) VTE. As stated earlier in this guideline, the key tenet of secondary prevention of VTE is determining the optimal duration of anticoagulant therapy.

In most patients, the risk of bleeding associated with indefinite anticoagulation for the purposes of preventing VTE recurrences outweighs the benefits. This has inspired research into alternative strategies for long-term secondary prevention of VTE after discontinuation of traditional anticoagulation. The two main agents that have been investigated thus far are aspirin and the HMG-CoA reductase inhibitors (statins).

**Aspirin.** Based on the limited data available, low-dose aspirin provides long-term benefit in secondary VTE prevention. The benefit is primarily in adult patients following a first episode of unprovoked (idiopathic) VTE after optimal duration anticoagulation and without an indication for indefinite anticoagulation. Additionally, aspirin is both inexpensive and widely available.

Results from the WARFASA trial demonstrated that low-dose aspirin (100mg daily) reduced the rate of VTE recurrence by 40% in adult patients following a first episode of unprovoked VTE, without any increase in the rate of bleeding. The second main trial investigating aspirin for this purpose, ASPIRE, demonstrated a non-significant decrease in rate of VTE recurrence with low-dose aspirin (4.8% vs. 6.5% per year respectively). However, low-dose aspirin still had a net clinical benefit by reducing major vascular events (VTE, MI, CVA, cardiovascular death).

**Statins.** At present, data are insufficient to recommend routine use of statins for long-term secondary prevention of VTE. However, if a patient is taking a statin for an approved indication (e.g. prior cardiovascular event, dyslipidemia), it is important to continue this medication following a VTE event since it will also likely reduce the risk of VTE recurrence. Fibrates should be used with caution in patients with prior VTE given the increased VTE risk associated with these medications.

HMG-CoA reductase inhibitors (statins) have been used to treat dyslipidemia since the 1980’s. A growing body of evidence demonstrates considerable overlap between atherosclerotic disease and venous thromboembolism and that statins may be effective in preventing VTE recurrences. The non-lipid lowering anti-inflammatory and immunomodulatory properties of statins influence antithrombotic activity.
The JUPITER trial was the first randomized, placebo controlled trial to specifically test whether statins prevent VTE. This trial demonstrated that rosuvastatin 20mg daily reduced the risk of VTE by 43% in healthy older adults with elevated high sensitivity C-reactive protein and normal LDL cholesterol. This trial excluded patients less than age 50 and those taking hormone replacement therapy, as well as those with co-morbidities such as diabetes, uncontrolled hypertension, or cancer within the prior 5 years.

Whether statins would provide the same benefit in a higher risk patient population or in younger patients is unknown. Also unknown is whether this is a class effect, with conflicting results reported with other statins. Optimal dosing is also unknown based on currently available data. The protective effect is specific to statins as compared to non-statin lipid lowering medications.

**Prevention of post-thrombotic syndrome.** Previous studies had demonstrated that prevention of post-thrombotic syndrome could be achieved with use of compression stockings. However, one recent RCT of more than 800 patients failed to show this benefit. Even though there is no long term benefit, calf-length compression stockings provide symptom relief. For symptomatic relief use of at least 20-30mm gradient or more should be recommended to most patients with DVT, for a minimum of two years post-DVT, and longer if they have symptoms of post-thrombotic syndrome. Evidence exists for both intermittent compression and exercise training also reducing symptoms of post-thrombotic syndrome.

Post-thrombotic syndrome (PTS) results from loss of competence of the venous valves as a result of DVT. It can cause significant morbidity in the form of pain, swelling, skin breakdown and ulcerations. The incidence of PTS is highest with iliocaval thrombosis, and diminishes with more peripheral DVT.

In patients with post-thrombotic syndrome, evaluation for persistent iliac vein occlusion is recommended. When present, percutaneous iliac vein recanalization has been shown to be highly effective in providing relief even many years after the initial thrombosis. Whether early thrombolysis results in reduced incidence of PTS after iliofemoral DVT is the focus of current clinical investigation.

**Testing for thrombophilias.** Identifying thrombophilias can guide assessment of risk for future VTE events and therapeutic decisions regarding duration of anticoagulation. Guidelines and expert opinions suggest testing in some of the following populations:

- Idiopathic/unprovoked VTE – some suggest only in those with strong family history of clotting disorder or age <50
- VTE in unusual sites, i.e. cerebral/mesenteric
- Recurrent pregnancy loss
- Recurrent VTE

- Asymptomatic patients with a strong family history of VTE/thrombophilia in whom COCs/Hormone Replacement therapy (HRT) with estrogen is being considered. The risk may be even higher among smokers in this subset of patients.
- VTE in pregnancy
- Strong family history for VTE

Several genetic thrombophilias are now known, including Factor V Leiden and prothrombin gene mutations; antithrombin, protein C, and protein S deficiencies; hyperhomocysteinemia. Acute thrombosis and pregnancy can transiently reduce the levels of antithrombin, proteins C and S. Therefore, these assays should be delayed at least 6 weeks from the acute event or similar time into the post-partum phase. Heparin treatment can reduce antithrombin activity and antigen levels and interfere with interpretation of clot-based assays for a lupus anticoagulant. Warfarin treatment can increase antithrombin levels and will reduce protein C and S levels as they are vitamin K-dependent factors. The effect from warfarin may persist for up to 6 weeks after discontinuation. ELISAs for antiphospholipid antibodies and molecular diagnostic testing for factor V Leiden and prothrombin gene mutations are not affected by anticoagulation may be performed anytime.

**Prophylaxis during long-distance travel.** Prolonged air travel results in a small increase in risk for development of VTE. Thrombosis risk also appears to be increased for prolonged travel by car, train or bus. The association between travel and VTE risk is strongest for flights > 8 to 10 hours in duration. The risk increases in the presence of other VTE risk factors (e.g., prior VTE, thrombophilia, malignancy, pregnancy, estrogen use). While not definitive, dehydration has also been implicated in travel related VTE. Immobility during travel, particularly in obese individuals, can increase the risk of VTE.

Patients with prior VTE history should consider compression stockings 15-30mmHg while in-flight and should get up frequently to ambulate during long flights, perform calf muscle exercises and select an aisle seat whenever possible. A meta-analysis of 9 randomized trials demonstrated that compression stockings (15-30mmHg) reduced the rate of asymptomatic DVT from 3.6% to 0.2%.

Evidence is insufficient to recommend routine use of pharmacologic prophylaxis in travelers, even those with a prior VTE event. Based on the limited evidence available, decisions regarding pharmacologic thromboprophylaxis for travelers considered to be at particularly high risk for VTE should be made on an individual basis, balancing the individual patient risk factors against both the risks and benefits of pharmacologic prophylaxis. One controversial small study (LONFLIT3) evaluated no prophylaxis, aspirin 400mg once daily starting 12 hours prior to flight and taken for 3 consecutive days, and a single dose of weight-adjusted (1mg/kg) enoxaparin given 2-4 hours prior to flight for the purposes of VTE prevention in high risk patients (prior VTE, known thrombophilia, severe obesity, mobility limitation due to bone or joint problems, cancer within the previous 2
years, or large varicose veins). Of the 82 patients with no prophylaxis, four (4.82%) had a subsequent DVT. In the aspirin group, 3 of 84 (3.6%) had a subsequent DVT. In the enoxaparin group, zero of 82 subjects had a subsequent DVT detected by ultrasound, suggesting that a single dose of weight-based enoxaparin administered 2-4 hours prior to long flights is protective against VTE in high risk patients.

**Smoking cessation.** Since smoking cessation for general health benefits is non-controversial, it is reasonable to place an emphasis on smoking cessation following a VTE event for patients who smoke. Data are conflicting on whether smoking status represents an independent risk factor for VTE.

### Related Treatment Issue: Superficial Venous Thrombosis.

Treatment of superficial thrombophlebitis depends on the extent and location of thrombus burden.

- **Mild forms** of superficial thrombophlebitis may be treated with conservative measures that include non-stereoidal anti-inflammatory drugs (NSAIDs), elastic compression and elevation. If NSAIDs are selected, avoid use in patients with heart disease or its risk factors as NSAID use increases overall risk of heart attack or stroke.

- **Moderate thrombus burden** (thrombus measuring at least 5 cm in length and at least 3 cm distal to the saphenofemoral junction.) is treated by anti-coagulation, with 2.5 mg fondaparinux (prophylactic dose) favored over prophylactic low-molecular weight heparin.

- **Moderate thrombus burden** for which anticoagulation is contraindicated (e.g., great saphenous vein [GSV] disconnection and ligation) and those with documented venous insufficiency and associated varicose veins (e.g., GSV ablation and phlebectomy) are treated surgically.

- **Associated DVT or PE development** is treated with therapeutic anticoagulation.

### What the Patient Should Know

**Serious condition.** Venous thromboembolism is a serious condition caused by a blood clot forming in the deep venous system.

**Blood thinner.** Treatment requires the use of blood thinners. A balance must be made between blood clotting so easily that veins are blocked or blood not clotting enough to stop bleeding. Patients may be hospitalized while determining the amount of blood thinner they need. Any blood thinner, oral or injectable, must be taken every day as directed. Failure to do so can result in increased risk for a recurrent thromboembolism.

**Other medicines.** If you are on warfarin (Coumadin), always consult your doctor before beginning any new medication, even over the counter medications.

**Check regularly.** Have your blood tested as regularly as your doctor recommends.

**Abnormal bleeding.** Call your doctor if you have any abnormal bleeding while on warfarin (Coumadin).

**Emergency: chest pain or breathing problem.** Seek emergency care if you develop sudden chest pain or shortness of breath.

**Pregnancy.** Warfarin can cause birth defects. Notify your doctor if you are pregnant.

### Related National Guidelines

This guideline is consistent with the following national guidelines:

  - Diagnosis of DVT
  - Antithrombotic Therapy for VTE Disease


### Measures of Clinical Performance

National programs that have clinical performance measures for care for hypertension include the following.

- Centers for Medicare & Medicaid Services:
  - Physician Quality Reporting Measures for Group Practice Reporting Option (GPRO)
  - Clinical Quality Measures for financial incentives for Meaningful Use of certified Electronic Health Record technology (MU)
  - Quality measures for Accountable Care Organizations (ACO)

These program's clinical performance measures VTE are summarized below. When programs have relevant measures, some measures may be similar, although specific details vary (e.g., population inclusions and exclusions).

- **Monthly INR for beneficiaries on warfarin.** The percentage of monthly intervals in which Part D beneficiaries with claims for warfarin do not receive an INR test during the measurement period. (ACO)

- **Platelet monitoring on unfractionated heparin (inpatient).** The percent of patients diagnosed with confirmed VTE who received intravenous UFH therapy dosages and had their platelet counts monitored using defined parameters such as a nomogram or protocol. (MU)

- **Anticoagulation overlap therapy (inpatient).** The percent of patients diagnosed with confirmed VTE who received an overlap of parenteral (intravenous or subcutaneous) anticoagulation and warfarin therapy. For patients who
received less than five days of overlap therapy, they must be discharged on both medications. Overlap therapy must be administered for at least five days with an international normalized ratio \( \geq 2 \) prior to discontinuation of the parenteral anticoagulation therapy or the patient must be discharged on both medications. (MU)

VTE discharge instructions (inpatient). Percent of patients diagnosed with confirmed VTE that are discharged with written discharge instructions that address all four criteria: compliance issues, dietary advice, follow-up monitoring, and information about the potential for adverse drug reactions/interactions. (MU)

**Strategy for Literature Search**

The initial prospective literature searches for this project were performed on Medline in 1996, 1997, 2002, and 2008. The current update is based on a supplemental literature search performed on Medline in May 2013. Literature published since January 2008 was searched. The team also reviewed the overlapping literature search results published in the American College of Chest Physician evidence-based clinical practice guidelines: “Diagnosis of DVT” and “Antithrombotic therapy for VTE disease” published in 2012.

The specified population was adults. Major key words were: pulmonary embolism and deep venous thrombosis thrombophlebitis (includes venous thromboembolism, thromboembolism, venous thrombosis), guidelines, controlled trials, meta-analyses. Additional search terms for diagnosis were: primary risk factors (hereditary predisposition for clotting, estrogen [women], tobacco, etc.), acquired risk factors (malignancy, antiphospholipid antibody syndrome, etc.), duplex venous scan, pulmonary angiography, V/Q scan, arterial blood gasses (O2 saturation), computed tomography, CT angiography, CT venography, magnetic resonance imaging, risk scores for DVT, risk scores for PE, D-dimer, pulmonary hypertension – embolism, and pregnancy and VTE diagnosis. Additional search terms for treatment were: low molecular weight heparin, heparin, warfarin, oral factor Xa inhibitors (rivaroxaban, apixaban, dabigatran), direct thrombin inhibitors (argatroban, bivalirudin), fondaparinux, idraparinux, factor 10 testing, international normalized ratio, prothrombin time, vena cava filter, temporary filter, emergency room treatment, indications for anegeographic embolism removal, indications for ECMO, indications for thrombolytic, indications for iliofemoral DVT thrombolysis, pregnancy and VTE treatment, non-pharmalogic modalities of DVT treatment (e.g., sequential compression device, compression stockings/hose, physical therapy), DVT and PE prophylaxis after treatment (secondary prevention), treatment of late complications: pulmonary hypertension and post-thrombotic syndrome (edema). Detailed search terms and strategy are available upon request.

The search was conducted in components each keyed to a specific causal link in a formal problem structure (available upon request). The search was supplemented with very recent clinical trials known to expert members of the panel. Negative trials were specifically sought. The search was a single cycle. Conclusions were based on prospective randomized controlled trials if available, to the exclusion of other data; if RCTs were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was used to estimate effect size.

**Disclosures**

The University of Michigan Health System endorses the Guidelines of the Association of American Medical Colleges and the Standards of the Accreditation Council for Continuing Medical Education that the individuals who present educational activities disclose significant relationships with commercial companies whose products or services are discussed. Disclosure of a relationship is not intended to suggest bias in the information presented, but is made to provide readers with information that might be of potential importance to their evaluation of the information.
Drafts of this guideline were reviewed in clinical conferences and by distribution for comment within departments and divisions of the University of Michigan Medical School to which the content is most relevant: Cardiology, Emergency Medicine, Family Medicine, General Medicine, Nuclear Medicine, Pulmonary & Critical Care Medicine, Radiology, Surgery, and Vascular Surgery. The final version was endorsed by the Clinical Practice Committee of the University of Michigan Faculty Group Practice and the Executive Committee for Clinical Affairs of the University of Michigan Hospitals and Health Centers.

Acknowledgements

The following individuals are acknowledged for their contributions to previous versions of this guideline.

1998:  Lee A. Green, MD, MPH, William P. Fay, MD, R. Van Harrison, PhD, Mary D. Wahl, MD, Thomas W. Wakefield, MD, John G. Weg, MD, David M. Williams, MD.

2004:  Lee A. Green, MD, MPH, William P. Fay, MD, Kirk A. Frey, MD, PhD, R. Van Harrison, PhD, Mary D. Kleaveland, MD, Thomas W. Wakefield, MD, John G. Weg, MD, David M. Williams, MD.

2009:  Lee A. Green, MD, MPH, Kirk A. Frey, MD, PhD, James B. Froehlich, MD, R. Van Harrison, PhD, Mary D. Kleaveland, MD, Steven Kronick, MD, Thomas W. Wakefield, MD, John G. Weg, MD, David M. Williams, MD.

Selected References


Goodman LR, Stein PD, Matta F, et al. CT venography and compression sonography are diagnostically equivalent: data from PIOPED II. AJR Am J Roentgenol. 2007;189:1071-6


Appendix A

Diagnostic Stratification Scoring Tools for DVT and PE

Multiple validated scoring tools have been developed to facilitate both diagnosis and management options. Presented below are some tools not specifically discussed in the text of the guideline, but are known to be clinically useful.

- The Revised Geneva Score can be applied to determine pre-test probability for VTE diagnosis.
- The Wells DVT Criteria, as with the Geneva score, can be applied to determine pre-test probability specific to DVT (not PE). (The modified Wells Criteria, Table 5 is specific to PE.)
- The PERC criterion is a decision tool to minimize need for diagnostic testing for PE for patients meeting the criteria.

Revised Geneva Score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression Coefficients</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt; 65 y</td>
<td>0.39</td>
<td>1</td>
</tr>
<tr>
<td>Previous DVT or PE *</td>
<td>1.05</td>
<td>3</td>
</tr>
<tr>
<td>Surgery (under general anesthesia) or fracture (of the lower limbs within 1 month)</td>
<td>0.78</td>
<td>2</td>
</tr>
<tr>
<td>Active malignant condition (solid or hematologic malignant condition, currently active or considered cured &lt; 1 year)</td>
<td>0.45</td>
<td>2</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral lower-limb pain</td>
<td>0.97</td>
<td>3</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>0.74</td>
<td>2</td>
</tr>
<tr>
<td>Clinical Signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75-94 beats/minute</td>
<td>1.20</td>
<td>3</td>
</tr>
<tr>
<td>≥ 95 beats/minute</td>
<td>0.67</td>
<td>5</td>
</tr>
<tr>
<td>Pain on lower-limb deep venous palpation and unilateral edema</td>
<td>1.34</td>
<td>4</td>
</tr>
<tr>
<td>Clinical probability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0-3 total</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>4-10 total</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>≥ 11 total</td>
<td></td>
</tr>
</tbody>
</table>

* DVT = deep venous thrombosis; PE = Pulmonary embolism


PE Rule-out Criteria [PERC]

The PERC criteria negative [PERC(-)] requires the clinician to answer no to the following eight questions:
1. Is the patient older than 49 years of age?
2. Is the pulse rate above 99 beats min)?
3. Is the pulse oximetry reading <95% while the patient breathes room air?
4. Is there a present history of hemoptysis?
5. Is the patient taking exogenous estrogen?
6. Does the patient have a prior diagnosis of venous thromboembolism (VTE)?
7. Has the patient had recent surgery or trauma? (Requiring endotracheal intubation or hospitalization in the previous 4 weeks.)
8. Does the patient have unilateral leg swelling? (Visual observation of asymmetry of the calves.)
Appendix B

Use of Unfractionated Heparin (UFH)

Weight-Adjusted Heparin Nomogram

<table>
<thead>
<tr>
<th>Anti-Xa (units/mL)</th>
<th>Repeat Heparin Bolus Dose</th>
<th>Hold Infusion (minutes)</th>
<th>Rate Change</th>
<th>Repeat Anti-Xa level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 0.2 *</td>
<td>80 units/kg</td>
<td>0</td>
<td>Increase 1.5 units/kg/h</td>
<td>6 hours</td>
</tr>
<tr>
<td>0.2-0.29</td>
<td>40 units/kg</td>
<td>0</td>
<td>Increase 1 units/kg/h</td>
<td>6 hours</td>
</tr>
<tr>
<td>0.3-0.7</td>
<td>None</td>
<td>0</td>
<td>No change</td>
<td>6 hours**</td>
</tr>
<tr>
<td>0.71-0.8</td>
<td>None</td>
<td>30 min</td>
<td>Decrease 1 units/kg/h</td>
<td>6 hours</td>
</tr>
<tr>
<td>0.81-0.89</td>
<td>None</td>
<td>60 min</td>
<td>Decrease 1.5 units/kg/h</td>
<td>6 hours</td>
</tr>
<tr>
<td>Greater than or equal to 1 *</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Notify physician if 2 consecutive Anti-Xa values are in this range

** When 2 consecutive Anti-Xa values are in therapeutic range (0.3-0.7 units/mL), obtain Anti-Xa assay the next morning and every 24 hours thereafter

Ensure physician has not selected “No bolus ever” option above

Dosing UFH. Careful monitoring of UFH therapy must be performed at regular intervals to ensure that this agent is effective and safe; see “Monitoring Therapy” below. Six hours after initiation of standard heparin therapy for VTE approximately 1/3 of patients will have a sub-therapeutic aPTT, 1/3 will have an aPTT within the therapeutic range, and 1/3 will have a supratherapeutic aPTT. Failure to achieve a therapeutic aPTT is associated with a marked increase in recurrent thrombotic events. If heparin is administered in adequate amounts to patients with DVT, symptomatic PE will occur in only 5% of patients, and fatal PE will occur in < 0.5%. Combined analysis of 7 studies in which patients with VTE received a 5000 U bolus of heparin and a continuous infusion of 30,000-40,000 U/24 hour indicates that the risk of recurrent thrombosis is 5.7%.

Route of administration. Full dose UFH can be administered either by continuous intravenous (IV) infusion or by intermittent subcutaneous (SQ) injection. However, analyses of multiple randomized trials suggest that SQ UFH is as effective as IV UFH in the treatment of DVT, provided that an initial IV bolus dose (5-10,000 U) is given, large doses of heparin are administered (usually > 17,500 U SQ BID), and heparin therapy is monitored closely.

UFH can be administered as continuous IV infusion, intermittent IV boluses, or SQ boluses. Continuous infusion is more readily monitored and adjusted, and probably achieves therapeutic levels more rapidly; hence it is the standard in our institution. There is only a single small study of patient preferences, which found that most patients preferred SQ administration, but IV equipment was not portable in that study.

The effectiveness of UFH therapy is usually monitored by the activated partial thromboplastin time (aPTT). The aPTT is readily available and relatively inexpensive. Several studies have shown that anticoagulation guided by nomograms is superior to individual physician-guided therapy, which varies significantly. Published nomograms have been based on the aPTT which can be used in place of anti-Xa above, but have been shown to have a higher error rate, require more frequent blood draws, and may result in an increased time to therapeutic anticoagulation.

Monitoring therapy. An aPTT time of 50 to 83 seconds is generally considered therapeutic. In patients whose baseline aPTT is prolonged (e.g. due to lupus-type inhibitor), anti-factor Xa should be considered instead of aPTT for monitoring heparin therapy. The aPTT or anti-FXa is usually measured every 6 hours until stable anticoagulation is achieved, then each morning. In patients receiving SQ heparin every 12 hours, clotting times are measured 6 hours after injection. Platelet count monitoring for HIT for UFH therapy should be carried out as for LMWH.
Appendix C

University of Michigan Health System
Anticoagulation Program

Guideline for Initiating Oral Warfarin in Adult Inpatients

Purpose: The purpose of this guideline is to provide dosing assistance for initiating warfarin therapy in patients that have not previously been on warfarin.

Loading doses of warfarin (e.g., 10 mg on days 1 and 2) are no longer recommended.

Several controlled studies have shown that starting patients on 5 mg of warfarin daily achieves a therapeutic anticoagulant effect as rapidly as 10 mg loading regimens while causing fewer supratherapeutic INRs. The following algorithm by Crowther and colleagues should guide the dosing of warfarin during the first several days of therapy.

### Nomogram for Starting Patients on Warfarin*

<table>
<thead>
<tr>
<th></th>
<th>INR</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 mg**</td>
<td></td>
</tr>
<tr>
<td>DAY 1</td>
<td>A baseline INR must be obtained prior to starting warfarin</td>
<td>5 mg**</td>
</tr>
<tr>
<td>DAY 2</td>
<td>&lt; 1.5</td>
<td>5 mg</td>
</tr>
<tr>
<td></td>
<td>1.5 - 1.9</td>
<td>2.5 mg</td>
</tr>
<tr>
<td></td>
<td>2.0 - 2.5</td>
<td>1 - 2 mg</td>
</tr>
<tr>
<td></td>
<td>&gt; 2.5</td>
<td>0 mg</td>
</tr>
<tr>
<td>DAY 3</td>
<td>&lt; 1.5</td>
<td>5 - 10 mg</td>
</tr>
<tr>
<td></td>
<td>1.5 - 1.9</td>
<td>2.5 - 5 mg</td>
</tr>
<tr>
<td></td>
<td>2.0 - 3.0</td>
<td>0 - 2.5 mg</td>
</tr>
<tr>
<td></td>
<td>&gt; 3.0</td>
<td>0 mg</td>
</tr>
<tr>
<td>DAY 4</td>
<td>&lt; 1.5</td>
<td>10 mg</td>
</tr>
<tr>
<td></td>
<td>1.5 - 1.9</td>
<td>5 - 7.5 mg</td>
</tr>
<tr>
<td></td>
<td>2.0 - 3.0</td>
<td>0 - 5 mg</td>
</tr>
<tr>
<td></td>
<td>&gt; 3.0</td>
<td>0</td>
</tr>
<tr>
<td>DAY 5</td>
<td>&lt; 1.5</td>
<td>10 mg</td>
</tr>
<tr>
<td></td>
<td>1.5 - 1.9</td>
<td>7.5 - 10 mg</td>
</tr>
<tr>
<td></td>
<td>2.0 - 3.0</td>
<td>0 - 5 mg</td>
</tr>
<tr>
<td></td>
<td>&gt; 3.0</td>
<td>0</td>
</tr>
<tr>
<td>DAY 6</td>
<td>&lt; 1.5</td>
<td>7.5 - 12.5 mg</td>
</tr>
<tr>
<td></td>
<td>1.5 - 1.9</td>
<td>5 - 10 mg</td>
</tr>
<tr>
<td></td>
<td>2.0 - 3.0</td>
<td>0 - 7.5 mg</td>
</tr>
<tr>
<td></td>
<td>&gt; 3.0</td>
<td>0</td>
</tr>
</tbody>
</table>

*This algorithm can be used in patients currently receiving unfractionated heparin or low molecular weight heparin (LMWH).

**In select patients (e.g., very large or frail patients, those on medications known to interact with warfarin, elderly, and those with heart failure or liver failure), a Day 1 warfarin dose different from 5mg may be appropriate.

Due to the uncertain clinical benefit and cost of the pharmacogenetic tests, their routine use is not recommended to guide warfarin dose initiation or adjustment.

References:

Authors: Anticoagulation Subcommittee
Approved: Anticoagulation Subcommittee (1/11/2010)
P&T Committee (3/16/2010)
CT angiography may be used for patients in whom CT is not contraindicated