

## Venous Thromboembolism (VTE)

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These guidelines should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific clinical procedure or treatment must be made by the physician in light of the circumstances presented by the patient.

**Patient population:** Adults with suspected acute deep venous thrombosis (DVT) of the lower extremity, pulmonary embolus (PE), or both. Prophylaxis and upper-extremity thrombosis are beyond the scope of this document.

**Objectives:** (1) Improve the recognition of VTE and selection of appropriate testing. (2) Shorten resolution time for clinical symptoms. (3) Reduce incidence of pulmonary embolism. (4) Reduce mortality. (5) Reduce bleeding and other complications. (6) Reduce cost of hospitalization.

### Key Points

**Initiate treatment immediately.** Patients without contraindications to heparin should begin full-dose heparinization at once [IA\*]. If PE is clinically likely, initiation 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. Warfarin should be initiated on day 1 of treatment, after heparin loading is complete.

### Diagnosis

#### Deep venous thrombosis

Clinical likelihood estimation. Symptoms and signs alone are not adequately sensitive or specific for diagnosis or exclusion of VTE, but clinical likelihood estimation based on symptoms and signs is a necessary step in the testing strategy. [IA]

Lower extremity DVT. Venous color duplex Doppler ultrasound imaging is the standard for diagnosis [IA]. Depending on the clinical likelihood estimate, high-sensitivity D-dimer testing can exclude DVT without imaging (see text and Table 1).

#### Pulmonary embolism

Lab tests inadequate. D-dimer testing must be interpreted in the context of pretest probability. [IC] D-dimer testing alone is not adequately sensitive or specific to diagnose or exclude PE. [IIIC]

Diagnostic testing determined by clinical likelihood estimation. The diagnostic approach differs depending on prior probability (see Figure 1, Tables 4, 5, & 6). 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) preferred. LMWH is preferred over unfractionated heparin (UFH) for both safety and cost reasons [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 (afebrile, normotensive, without tachycardia or tachypnea) patients who are not at elevated risk due to comorbidities can manage DVT entirely in the outpatient setting using LMWH.

Unfractionated heparin. If UFH is used, it should be initiated and dosed in a structured manner (see Appendix A) to achieve therapeutic levels quickly, without excessive adjustment of dosing [IIA].

Minimum time period. Heparin (LMWH or UFH) must be continued until INR is > 2.0, but always for at least five days to minimize the risk of extension of thrombosis or occurrence or recurrence of embolism [IB].

If heparin contraindicated. Patients who are not candidates for heparin anticoagulation due to risk of major bleeding or to drug sensitivity (heparin-induced thrombocytopenia, or HIT) may be candidates for one of the new non-heparin anticoagulant agents (e.g., lepirudin, argatroban). [IIB] Those who cannot use any anticoagulant should have an inferior vena cava filter placed to prevent pulmonary embolization [IIB].

**Warfarin.** Patients should begin warfarin on day 1 of heparin therapy after heparin loading is complete, and INRs must be > 2.0 before discontinuation of heparin [IA,B]. Start warfarin at the anticipated therapeutic dose [IC]; loading doses are no longer considered appropriate. [IIC]

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.

**Aggressive therapy.** Patients with extensive 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. [IID]

#### \*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 trials; D = opinion of expert panel.

**Table 1. Wells Criteria for Likelihood Estimation of Lower Extremity Deep Venous Thrombosis**

Clinical Characteristic	Score
Active cancer (patient receiving treatment for cancer within the previous 6 mo or currently receiving palliative treatment)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days or more, or major surgery within the previous 12 wk requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Previously documented deep-vein thrombosis	1
Alternative diagnosis at least as likely as deep-vein thrombosis	-2

A score of < 2 is considered low probability for DVT  
From Wells et al., N Engl J Med 2003;349:1227-35.

**Table 2. Clinical Findings Possibly Associated with Pulmonary Embolism\***

Clinical situation	Elderly or chronically ill, e.g. malignancy Prolonged immobility Post-operative state Trauma Prior venous thromboembolism Prothrombic disorder (e.g. factor V Leiden, prothrombin (Factor II) variant 20210 G to A, hyperhomocystinuria, protein C or S deficiency, antithrombin III deficiency)
Symptoms	Dyspnea Chest pain (pleuritic) Hemoptysis Syncope Apprehension Cough Diaphoresis
Signs	Tachypnea Tachycardia Evidence of lower extremity DVT Hypotension Fever Crackles Loud P2 Gallop rhythm
Chest X-ray	Elevated hemidiaphragm (loss of lung volume) Infiltrate Pleural effusion Atelectasis
Electrocardiogram**	Sinus tachycardia S1Q3T3 Rightward QRS axis Transient RBBB T wave inversion, ST segment depression in right precordial leads P pulmonale pattern ST segment elevation in lead III
Arterial Blood Gases (ABGs)***	Hypoxia Hypocapnia Increased A-a gradient

\* Within each category findings are listed in approximate order of positive predictive value (expert opinion).

\*\* Changes found in fewer than 10% of cases of PE.

\*\*\* Cannot use normal ABGs to exclude PE. In one study, for patients with suspected PE and with normal paO<sub>2</sub>, paCO<sub>2</sub>, and P(A-a)O<sub>2</sub>, 38% were found to have PE.

**Table 3. Wells' Criteria for Assessment of Pretest Probability for Pulmonary Embolism**

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

**Interpretation of Point Total**

Score	Mean Probability	Risk
<2 points	3.6	Low
2 to 6 points	20.5	Intermediate
>6 points	66.7	High

From Wells et al., Ann Int Med 2001;135:98-107.

**4. Tests Useful in Diagnosis of Pulmonary Embolism**

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

**Table 5. Test Characteristics of Multidetector Helical CT Angiography for PE**

CTA Findings By Prior Probability	Predictive Values, %
<i>High Prior Probability</i>	
CTA only, PPV	96
CTA+CTV, PPV	96
CTA only, NPV	60
CTA+CTV, NPV	82
<i>Intermediate Prior Probability</i>	
CTA only, PPV	92
CTA+CTV, PPV	90
CTA only, NPV	89
CTA+CTV, NPV	92
<i>Low Prior Probability</i>	
CTA only, PPV	58
CTA+CTV, PPV	57
CTA+/-CTV, PPV for main/lobar	97
CTA+/-CTV, PPV for segmental	68
CTA+/-CTV, PPV for subsegmental	25
CTA only, NPV	96
CTA+CTV, NPV	97

From Stein et al., N Engl J Med 2006;354:2317-27.

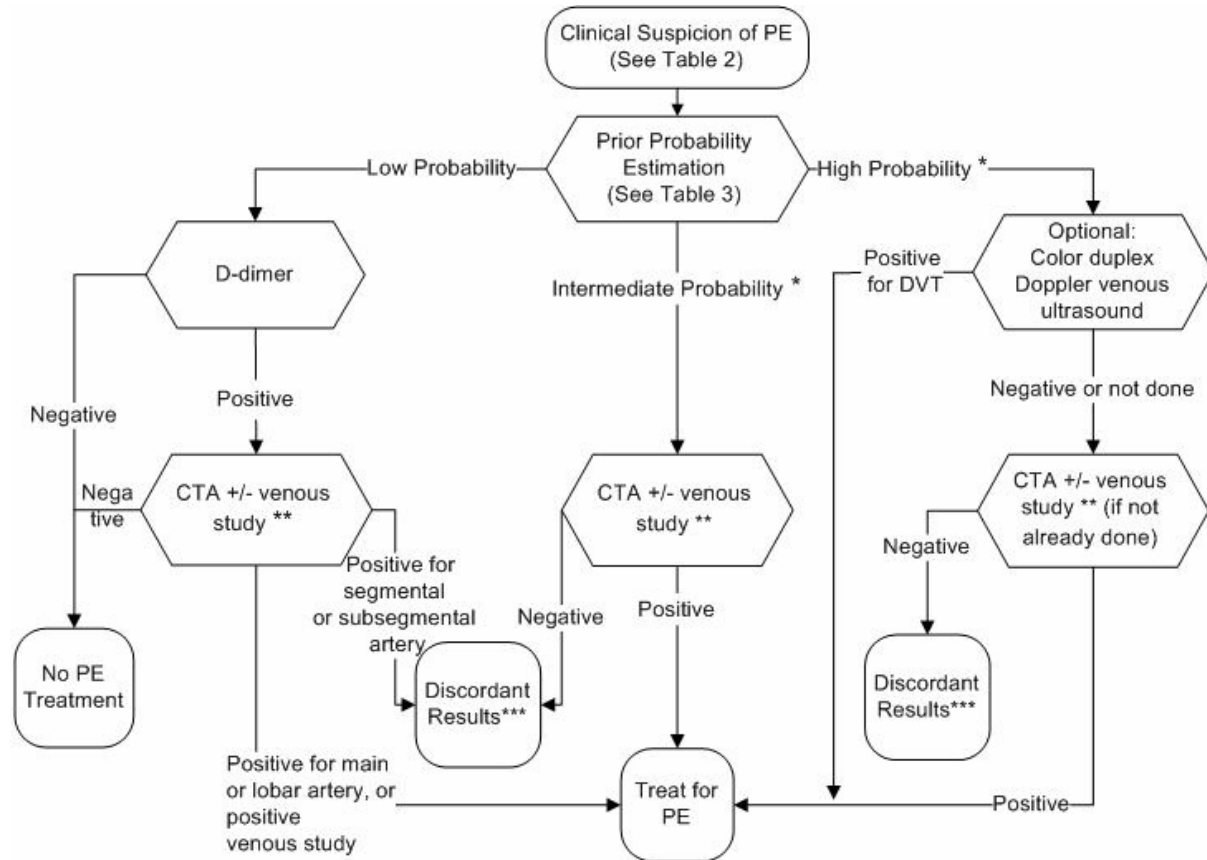
**Table 6. V/Q Scanning, Pretest Probability for PE\*, and Incidence of PE**

Scan Report	Incidence of PE
<i>Overall performance</i>	
Normal scan	<<1%
Low probability scan	14%
Intermediate probability scan	30%
High probability scan	90%
<i>Low clinical likelihood</i>	
Normal scan	<<1%
Low probability scan	4%
Intermediate probability scan	16%
High probability scan	80%
<i>High clinical likelihood</i>	
Normal scan	<1%
Low probability scan	14%
Intermediate probability scan	66%
High probability scan from PIOPED data	>90%

\* For pretest probability, see Table 3.

**Figure 1. Algorithm for the Diagnosis of Pulmonary Embolism**

(see Table 4 for Wells score for PE, Table 5 and 6 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 7. Duration of Anticoagulant Therapy: Clinical Considerations**

Patient Subgroup	Recommendation
Calf-vein thrombosis with no previous venous thromboembolism and reversible time-limited cause	3 months of anticoagulant therapy
First event proximal DVT with reversible or time-limited risk factors (patient may have underlying heterozygous Factor V Leiden or prothrombin gene variant 20210A)	3-6 months of anticoagulant therapy
Proximal DVT or pulmonary embolism with no previous venous thromboembolism, without reversible or time-limited risk factor	3-6 months of full-dose anticoagulant therapy, optionally followed by low-intensity (INR 1.5-2) or conventional-intensity warfarin indefinitely
VTE in the setting of metastatic cancer	6 months of anticoagulant therapy, or long-term anticoagulation (warfarin or LMWH; see text)
Congenital or acquired risk factor present <sup>a</sup>	6 months of anticoagulant therapy, or long-term anticoagulation
Recurrent venous thromboembolism	1 year, optionally followed by long-term anticoagulation
Venous thromboembolism during pregnancy	SQ full-dose low-molecular-weight heparin until delivery, then warfarin for 4-6 weeks post-partum

Adapted with modification from Ginsberg JS. Management of Venous Thromboembolism. *N Engl J Med.* 1996;335:1816-1828 and Hyers TM et al. Antithrombotic Therapy for Venous Thromboembolic Disease. *Chest* 2001(1):176S-193S.

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.

<sup>a</sup> Thrombophilic risk factors include homozygous factor V Leiden; homozygous prothrombin (factor II) variant 20210 G to A; hyperhomocystinemia; congenital deficiencies of protein C, protein S, antithrombin III, or plasminogen; and antiphospholipid antibodies.

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# 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 postphlebotic syndrome. Historically, prior to the widespread use of heparin, approximately 12% of all patients with clinically evident DVT died, most often from PE.

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

Management of heparinization has historically been variable. Over- and undershooting target levels with UFH is common and extends hospital stays. Some patients are not able to receive warfarin, and some cannot receive any anticoagulation at all, complicating management of their VTE. LMWH has supplanted UFH for most indications, and use of LMWH in fixed doses determined by body weight has improved management of heparinization.

Throughout this document DVT of the veins distal to the knee is not distinguished from proximal DVT. There has been an informal clinical tradition of regarding below-knee DVT as not requiring treatment, or being amenable to observation. However, 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 greatly so, and not enough to merit less serious treatment.

## Rationale for Recommendations

### Diagnosis of Deep Venous Thrombosis

**Clinical recognition of DVT.** The clinical diagnosis of DVT is challenging and characterized by uncertainty. DVT may be suspected in the “clinical situations” in Table 2, but is by no means limited to these settings. Typical symptoms and signs include swelling and tenderness of the calf, and Homan’s sign (slight pain at the back of the knee or calf when the ankle is slowly and gently dorsiflexed, with the knee bent). However, half of significant DVTs are without clinical symptoms or signs, so these may not be relied on for diagnosis. Superficial thrombophlebitis may closely resemble DVT, as may ruptured Baker’s cyst, gastrocnemius-soleus muscle injuries, and other conditions. The diagnosis cannot be made or excluded on clinical grounds, therefore threshold for testing should be low. (Formal criteria, e.g., Table 1, 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.** Venous color duplex imaging is standard, although D-dimer may be considered in low probability settings.

Venous color duplex Doppler ultrasound imaging. The current standard clinical practice for the diagnosis of deep venous thrombosis is venous color duplex Doppler ultrasound imaging. The positive and negative predictive values for gray-scale imaging are inferior to color imaging.

The high negative predictive value (NPV) of color duplex Doppler ultrasound both above and below the knee supports withholding anticoagulation on the basis of a good quality negative study, and clinical data also support that strategy. Positive predictive value is high for symptomatic patients, but below the knee in the absence of symptoms may fall as low as 75%. 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.

D-dimer and low probability exclusion. 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 1) 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, Doppler studies must be done; D-dimer cannot exclude DVT for non-low-probability patients.

Phlebography. Phlebography carries appreciable local morbidity, the risk of contrast administration, and is technically inadequate in 7-20% of studies. It is seldom indicated any longer.

**Recurrence of DVT.** Recurrence of DVT is not uncommon. The diagnosis of recurrent DVT can be difficult, since the postphlebotic syndrome (pain and edema without recurrent thrombosis) can mimic recurrent DVT. However, careful clinical assessment, including venous duplex imaging, usually is sufficient to diagnose recurrent DVT.

Characteristics on duplex imaging may be generally helpful in differentiating acute from chronic thrombosis. With acute thrombi, the vein is enlarged in size, echolucent, and there is a lack of well-formed collaterals present. With chronic thrombi, the vein is shrunken, echodense, and there is the presence of well-formed collaterals.

### Diagnosis of Pulmonary Embolism

**Clinical recognition of PE.** No set of bedside diagnostic findings are definitive. Clinicians select patients for testing

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for PE based on a high index of suspicion and awareness of clinical findings of PE illustrated in Table 2. As is the case with DVT, formal criteria (Table 3) 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 2, 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 3) 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 approach to diagnosis of PE has changed substantially since the last version of this guideline. As illustrated in Figure 1, testing begins with prior probability estimation for all patients (Table 3). D-dimer testing is used for low-probability patients. Patients with both low probability and negative D-dimer require no further investigation; all others should be imaged. Multidetector helical CT angiography (CTA) is the primary imaging modality, though V/Q scanning remains viable (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 can establish the diagnosis without lung imaging. Table 4 lists these and other tests that may be relevant for PE.

**D-dimer testing.** D-dimer testing is used to exclude PE for patients with low prior probability (i.e., Wells < 2; Table 3). *D-dimer testing has no role in diagnosis if prior probability is not 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. A negative D-dimer in a low-probability patient has an NPV of 99%.

**CT Angiography.** Multidetector helical CT angiography (CTA) is the primary imaging modality for patients not excluded by probability and D-dimer. Its test characteristics are detailed in Table 5. CTA establishes the diagnosis of PE if it is positive in an intermediate- or high-probability patient, or in a low-probability patient with finding of a mainstem or lobar embolus. It excludes the diagnosis of PE in low-probability patients with negative scans. It may be combined with CT venography or Doppler venous imaging, as shown in Table 5. If the patient's estimated GFR is below normal or if the patient is receiving potentially nephrotoxic medications, consultation with the radiologist is recommended.

**Discordance Between Prior Probability and CTA Findings**  
Patients with low prior probabilities but CTAs positive for sub- or segmental embolism and patients with high or intermediate prior probability but negative CTA results

require further investigation. A prudent initial step is to obtain a second expert reading of the CTA images. 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. Expert consultation should be considered.

**V/Q scan.** A normal V/Q scan effectively excludes PE (see Figure 1 and Table 6). For other than normal tests, V/Q scanning returns a probability statement as a result, that must be evaluated in conjunction with the clinical findings (see Table 2 and Table 6). V/Q scanning can be useful in further evaluating patients with discordant CTA and probability findings, particularly for patients who do not have underlying lung disease that would degrade the interpretability of the V/Q images (for whom it may optionally be chosen instead of CTA as a primary test). 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 B.

**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.** Pulmonary angiography is widely considered the reference standard for the diagnosis of pulmonary embolism. Without a higher standard to appeal to, we cannot discuss specificity and sensitivity of pulmonary angiography, using commonly accepted definitions of these terms. Instead, the accuracy of pulmonary angiography is discussed in terms of interobserver variability in the reading of pulmonary angiograms obtained in the context of large multicenter trials. Studies demonstrate that the larger the embolus, the larger the interobserver agreement. For segmental and larger emboli, agreement exceeds 95%. For subsegmental emboli, agreement is considerably less.

**Future developments in testing.** Magnetic resonance (MRI) angiography is still investigational at this time.

## Heparin Anticoagulation

**Demonstration of efficacy.** 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. There was no

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reduction in incidence of bleeding complications 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 A.

**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. Dalteparin is used 120 anti-Xa units/kg SQ q12hr to treat VTE.

**Outpatient 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.

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.

**Aggressive treatment in exceptional cases.** These general guidelines are appropriate for most patients. Occasional patients with extensive proximal DVT producing severe limb swelling and pain may benefit in both immediate and long-term symptom relief from more aggressive initial therapy than solely anticoagulation with LMWH and warfarin. Such patients should be discussed with a vascular consultant, to determine whether they may be candidates for thrombolytic therapy or surgical thrombectomy; no specific data are available to guide patient selection. For PE, thrombolytic therapy has not

been proven to reduce mortality when compared to standard anticoagulant therapy in controlled clinical trials. However, for patients with massive pulmonary embolism producing shock or systemic hypoperfusion, thrombolytic therapy with tissue-type plasminogen activator (t-PA, 100 mg IV administered over 2 hours) is an option. Such patients should be discussed emergently with a consultant (typically in cardiology or pulmonary medicine).

**Optimal duration.** 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 increase in adverse events and avoids difficult warfarin management resulting from variable food intake.

**Monitoring 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 or when there is a fall in platelet count to <100,000 or a decline by  $\geq 50\%$  from baseline counts during heparin therapy, or the appearance of venous or arterial thrombi. 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 and consult with a specialist for testing and treatment options.

### Overlap of Heparin and Warfarin

Heparin and warfarin therapy should overlap during the acute management of venous thrombosis. 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  $\geq 5$  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.

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## Warfarin Anticoagulation

**Efficacy.** 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.** Warfarin should be started early, usually within the first 24 hours of heparin therapy after heparin is therapeutic. *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 <http://www.med.umich.edu/hcp/anticoag/initiate.htm>). 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. 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. 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). This equates to a major bleeding risk of 6%/yr in this patient population. Some patients, such as those with venous thrombosis and 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.

**Duration.** The optimal duration of full-dose warfarin therapy after DVT or PE depends upon clinical circumstances (see Table 7), and must be discussed and decided together with the patient. Natural history studies suggest that after a first DVT the risk of recurrent thrombosis (PE or DVT) is 17.5% at 2 years, 25% at 5 years, and 30% at 8 years. Patients with continuing risk factors for thrombosis, such as malignancy, cardiomyopathy, 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 3-6 months of full-dose warfarin (Table 7).

Given the low risk of major bleeding during properly monitored warfarin therapy (particularly in patients with transient risk factors for thrombosis), we recommend at least 3 months of full-dose warfarin after confirmed venous 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.

Duration of therapy must be determined individually taking into consideration risks for bleeding and thromboembolism. Prospective clinical trials addressing the optimal duration of warfarin therapy in patients with a first episode of venous thrombosis and an irreversible risk factor considered to place the patient at high risk of recurrence (e.g. malignancy, identifiable thrombophilia such as factor V Leiden) are lacking. However, recent studies suggest that certain patients within this heterogeneous group are at high risk of recurrent DVT. For example, patients who are homozygous for Factor V Leiden or prothrombin gene variants require prolonged anticoagulation, while heterozygotes are at substantially lesser risk of recurrence. Those who are heterozygous for two or more mutations are also at high risk for recurrence. Therefore, some patients with a first episode of DVT and an irreversible thrombotic risk factor should be considered for indefinite full-dose warfarin therapy.

If long-term anticoagulation is desired, full-dose warfarin should be used. Two recent 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. The ELIATE trial found however 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.

**Discontinuation.** One study has 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%. The use of repeat lower extremity ultrasound has also been proposed as a test for whether to continue anticoagulation beyond the usual timeframe. Neither approach is well enough studied yet to establish its place in practice.

**Other considerations.** Additional aspects of care should be considered.

**Monitoring frequency.** The frequency of monitoring warfarin anticoagulation has not been rigorously studied. The frequency needed varies with both the patient's clinical condition and the stability of the PT level achieved. Frequent INR monitoring is necessary at the onset of therapy (e.g. at least 2 checks in the first week of therapy, and at least weekly checks for the next few weeks). In the long-run, monthly checks are performed on stable patients, though erratic INR results should prompt more frequent testing. For patients on low-intensity warfarin (target INR

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1.5-2.0), intervals of up to 6 weeks between INR checks may be appropriate for stable patients.

**Diet and drug interactions.** Patients taking warfarin should also be aware of the effect of both diet and drug interactions on their anticoagulation status. Information on dietary sources of vitamin K which can reduce the effect of warfarin should be provided as part of patient education, as should warning about OTC vitamin supplementation. Since the list of medications that interact with warfarin is lengthy, anticoagulated patients should be advised to ask their physician's advice 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).

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

**Testing for thrombophilias.** Several genetic thrombophilias are now known, including Factor V Leiden mutation; antithrombin, protein C, and protein S deficiencies; hyperhomocysteinemia; and prothrombin gene mutation. At present, it does not appear indicated to screen for these disorders nor test for them in all VTE patients. Testing is prudent for patients who develop VTE in pregnancy, who have a first episode with no identifiable precipitating cause, and those with strong family histories of VTE. It may be useful to test patients with second episodes of VTE, if negative results could obviate lifelong anticoagulation.

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

**Considerations in 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 (~90%) 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 thrombophilias: up to 60% of pregnant women with first VTE episodes may have factor V Leiden, and other thrombophilias are also common. Antithrombin, protein C, and protein S deficiency do not appear strongly associated, but prothrombin gene mutation, hyperhomocysteinemia, and antiphospholipid antibodies do. In one study of women with previous pregnancy-associated VTE, none of 44 patients without prothrombotic syndrome but 3 of 51 (6%) with the syndrome had a recurrence in subsequent pregnancies.

Warfarin for VTE should be discontinued in favor of LMWH when pregnancy is planned or discovered. LMWH can be continued throughout pregnancy. Renal clearance of LMWH is increased during pregnancy, so some experts recommend monitoring anti-factor Xa levels every one to

three months. However, no outcomes data address benefit or lack thereof, and a therapeutic range is not clearly established. Neither UFH nor LMWH cross the placenta. Though heparin anticoagulation could increase the risk of abruption, it causes neither teratogenicity nor fetal bleeding. Warfarin does cross the placenta. 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 some carefully considered circumstances (e.g., artificial heart valves or other arterial thromboembolism risks), with expert consultation, warfarin might be re-instituted after 12 weeks, but should be re-evaluated close to term. Warfarin does not cross into breast milk in active form, and may be used during nursing.

## 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 are:

- Contraindication to anticoagulation
    - Fresh surgical wound
    - Active GI or other bleeding (not occult blood)
    - Recent hemorrhagic CVA
    - Multiple/major trauma
    - Recent neurosurgery
    - Inability or unwillingness to comply with oral anticoagulation
  - Complications of anticoagulation
    - Major bleeding
    - Heparin-induced thrombocytopenia\*
    - Warfarin-induced skin necrosis
  - Failure of anticoagulation
  - Pulmonary embolectomy
- \*Agatroban or lepirudin are primary treatment; IVC filters may be used in addition.

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.

The advent of removable filters allows for retrieval if the risk factor(s) no longer exist. Removal guidelines do not

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yet exist, so consultation on a case-by-case basis is required.

**Complications.** 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
- 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.

## New Anticoagulants

The narrow therapeutic range and high bleeding risk of current anticoagulants has spurred a search for new, safer agents. Two new classes of agents for venous thrombosis treatment are the direct thrombin inhibitors and specific Factor Xa inhibitors. Lepirudin and argatroban are direct thrombin inhibitors that have been approved for VTE treatment in patients with HIT. Dabigatran etexilate is a direct thrombin inhibitor currently in clinical trials for use in post-operative VTE prophylaxis.

Fondaparinux is an indirect Xa inhibitor whose clinical application is most like LMWH. It has a half-life of 17 hours, compared to 4 hours for LMWH. However, no antidote is readily available. It does not produce thrombocytopenia. Fondaparinux has been approved for the treatment of DVT/PE, thrombosis prophylaxis in total hip, total knee and hip fracture patients and in the extended prophylaxis of hip fracture patients. This drug is given based on body weight: 5mg SQ daily for patients < 50kg; 7.5mg for those 50 to 100kg; and 10mg for those >100kg.

New oral anti-factor Xa agents are being developed. Rivaroxaban and apixaban are the two agents furthest along in development. Other antithrombotic agents being evaluated including oral heparins, other direct thrombin inhibitors such as bivalirudin; defibrating agents such as ancrod; anti-inflammatory agents such as P-selectin inhibitors; Factor VIIa inhibitors; tissue factor pathway inhibitor; and activated Protein C.

## Prevention of Post-Thrombotic Syndrome

Post-thrombotic syndrome 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. A Cochrane meta-analysis found a strong effect (OR 0.31) for prevention of PTS using graduated compression stockings beginning within two weeks of onset of DVT. Stockings of 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.

## 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.

**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.

## Strategy for Literature Search

The initial prospective literature searches for this project were performed in 1996, 1997, and 2002. The current update is based on a supplemental literature search performed in January 2008. For diagnostic topic, literature published since the 2002 was searched. For treatment topics, the team accepted the literature search performed through May 2006 for the American College of Chest Physicians guideline on antithrombotic therapy for venous thromboembolic disease (see Kearon et al, 2008). Literature published since May 2006 was searched.

The 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: duplex venous scan, pulmonary angiography, V/Q scan, arterial blood gasses (O<sub>2</sub> saturation), computed tomography, CT angiography, CT venography, magnetic resonance imaging, D-dimer, recurrent pulmonary embolism, pulmonary hypertension – embolism, and pregnancy and VTE diagnosis. Additional search terms for treatment were: low molecular weight heparin, heparin, warfarin, international normalized ratio, prothombin time, argatroban, lepirudin, bivalirudin, vena cava filter, temporary filter, massive pulmonary embolism (anatomic embolism removal, ECMO, thrombolytic: pharmaceutical and mechanical), pregnancy and VTE treatment, and failure of therapy. 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 clinical 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.

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## Appendix A

### Use of Unfractionated Heparin (UFH)

#### Body Weight-Based IV Heparin Dosing Nomogram <sup>a</sup>

aPTT (seconds) <sup>b</sup>	Dose Change, units/kg/h	Additional Action	Next aPTT, h
<39	+4	Rebolus with 80 units/kg	6
39-49	+2	Rebolus with 40 units/kg	6
50-83	0	None	Next AM <sup>c</sup>
84-99	-2	None	6
>99	-3	Stop infusion 1 hr	6

<sup>a</sup> **Initial dosing:** loading = 80 units/kg; maintenance = 18 units/kg/h. Check 1st aPTT 6 hours after loading dose. Suggested concentration of heparin infusion = 100 units/mL (25,000 units in 250 mL of D<sub>5</sub>W)

<sup>b</sup> Observed aPTT (in seconds) **Note:** The control and therapeutic ranges (in seconds) of the aPTT can vary between different clinical laboratories, depending on the commercial reagents used. The values change with each new lot of reagents. Each clinical lab should determine the aPTT values (in seconds) that correspond to heparin concentrations of 0.2-0.4 units/mL by protamine titration or 0.3-0.7 antifactor Xa units/ml, and this range should be the target during heparin therapy.

<sup>c</sup> If patient's clinical status is unstable, consider more frequent (e.g. q 6-12 hour) monitoring of aPTT during 1st 24 hours of heparin Rx, even if initial aPTT (i.e. 6 hours after starting heparin) is in therapeutic range. When two consecutive aPTT are in the therapeutic range, obtain aPTT next morning and then every morning.

*Modified from Raschke et al. Ann Intern Med 1993;119:874-81.*

**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 hr 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.

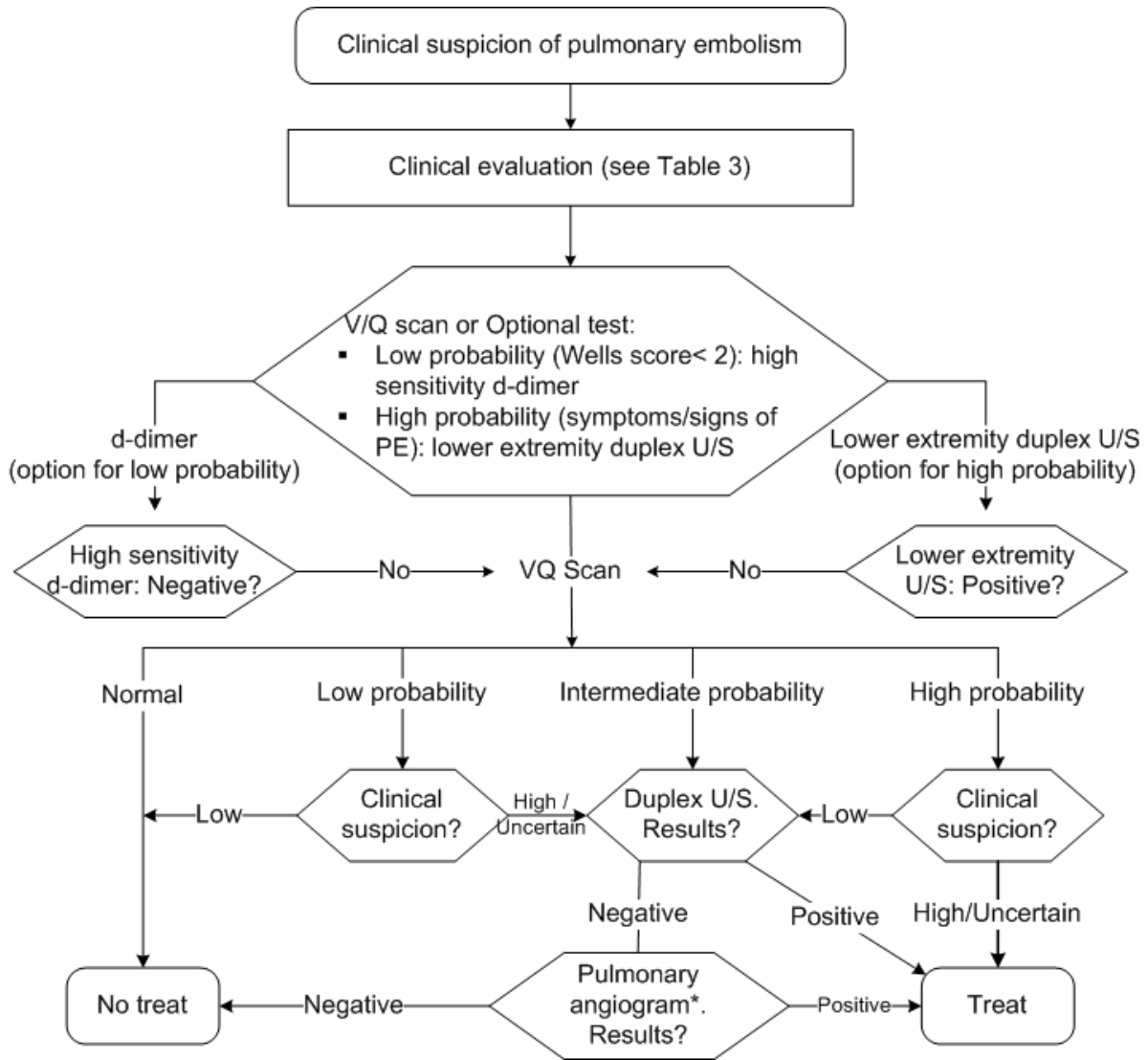
UFH can be administered as continuous IV infusion, intermittent IV boluses, or SQ boluses. Continuous infusion is more readily monitored and adjusted, and probably achieves therapeutic levels more rapidly; hence it is the standard in our institution. There is only a single small study of patient preferences, 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. Table 2 is one such nomogram, in which initial heparin dose is based on patient weight (the best predictor of heparin requirements), and subsequent dose changes are based on the aPTT.

**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 UHF therapy should be carried out as for LMWH.

## APPENDIX B

### Algorithm For Use Of V/Q Scan In PE Diagnosis



\* CT angiography may be used for patients in whom CT is not contraindicated