ICSI

INSTITUTE FOR CLINICAL SYSTEMS IMPROVEMENT

Health Care Guideline:

Venous Thromboembolism Diagnosis and Treatment

Tenth Edition
February 2010

The information contained in this ICSI Health Care Guideline is intended primarily for health professionals and the following expert audiences:

- physicians, nurses, and other health care professional and provider organizations;
- health plans, health systems, health care organizations, hospitals and integrated health care delivery systems;
- health care teaching institutions;
- health care information technology departments;
- medical specialty and professional societies;
- researchers;
- federal, state and local government health care policy makers and specialists; and
- employee benefit managers.

This ICSI Health Care Guideline should not be construed as medical advice or medical opinion related to any specific facts or circumstances. If you are not one of the expert audiences listed above you are urged to consult a health care professional regarding your own situation and any specific medical questions you may have. In addition, you should seek assistance from a health care professional in interpreting this ICSI Health Care Guideline and applying it in your individual case.

This ICSI Health Care Guideline is designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and is not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition. An ICSI Health Care Guideline rarely will establish the only approach to a problem.

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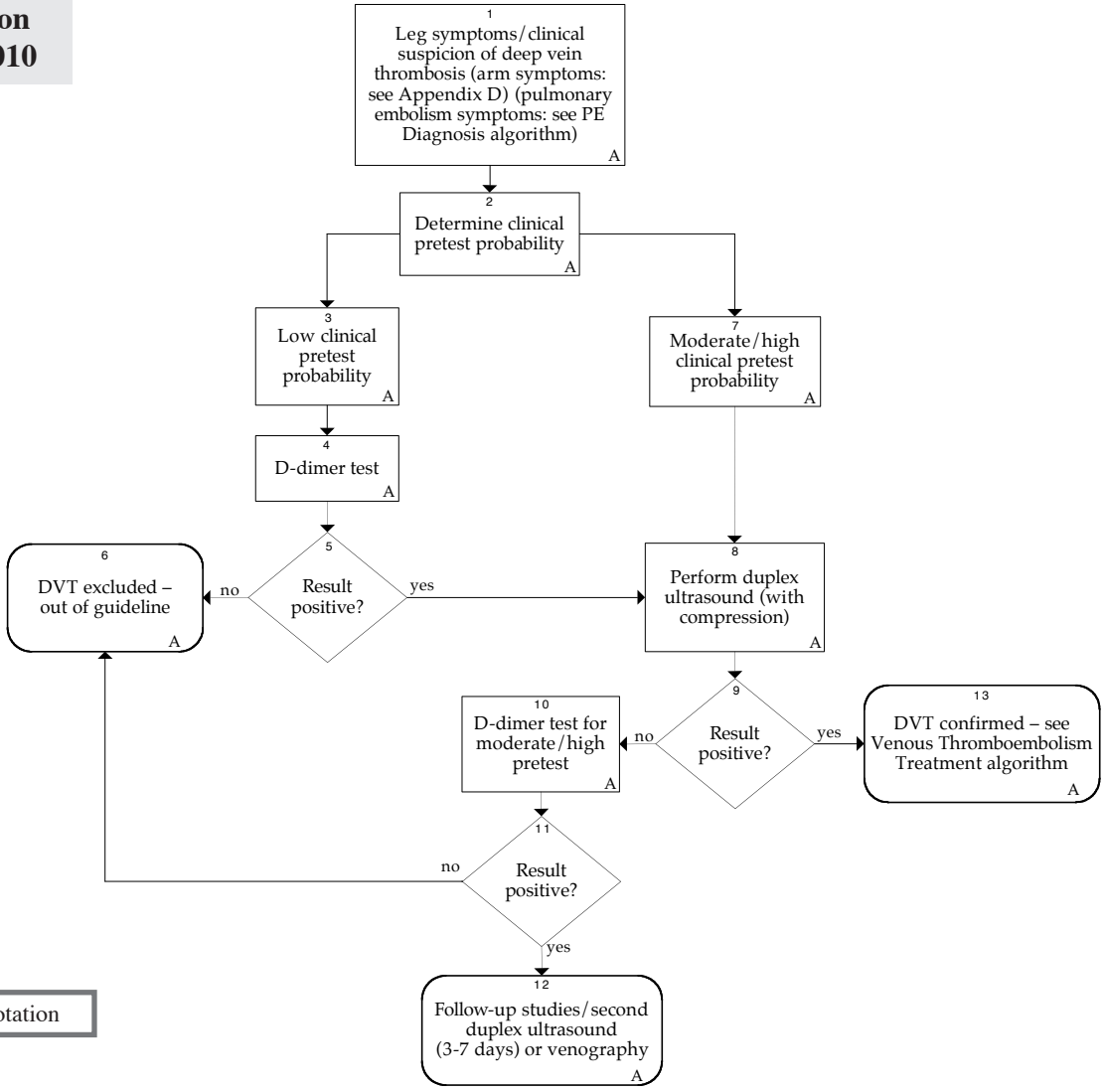
Deep Vein Thrombosis (DVT) Diagnosis Algorithm



A = Annotation

2.

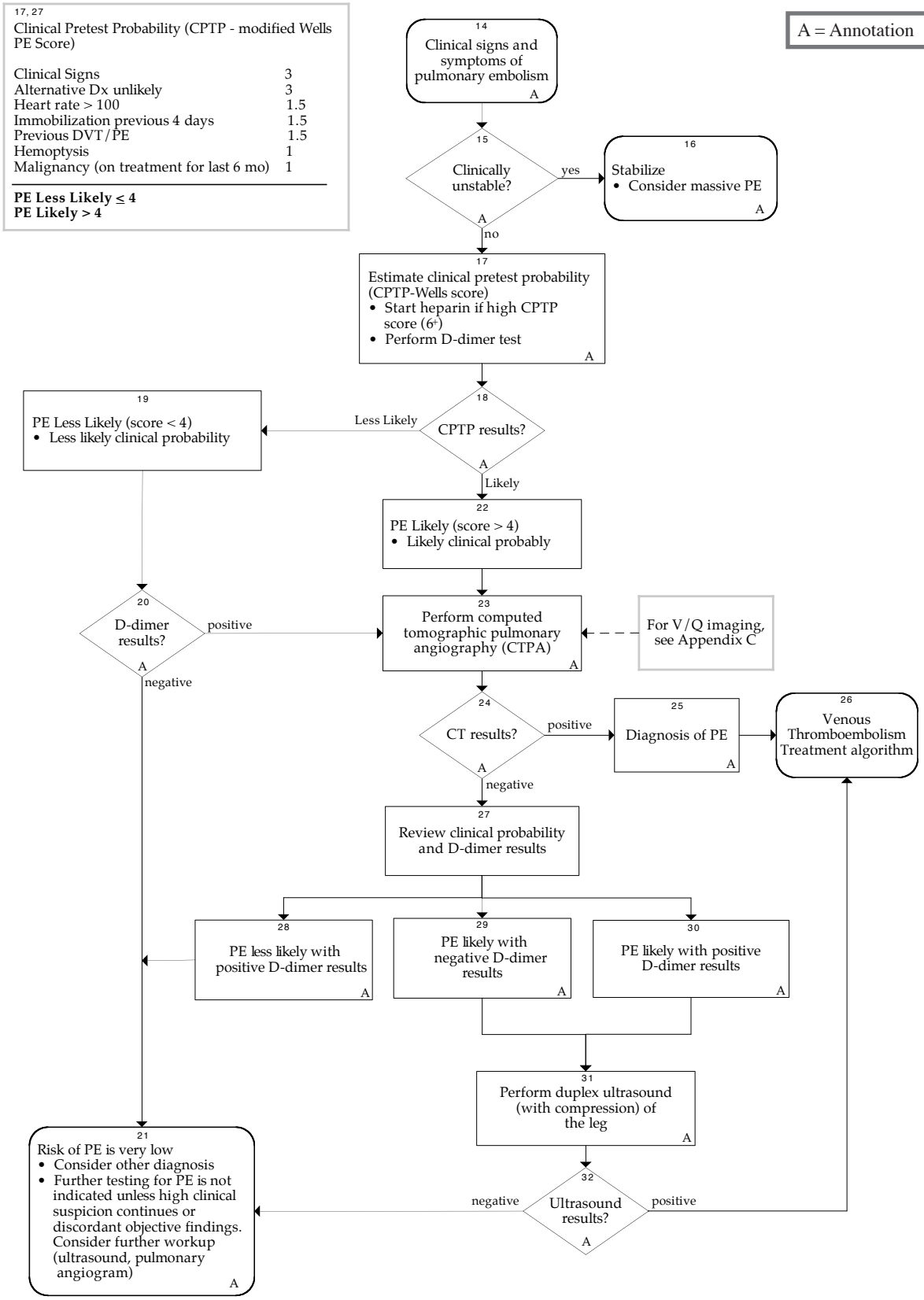
Clinical Pretest Probability (CPTP - Wells DVT Score) – See Appendix A

Active cancer (on treatment for last 6 months or palliative)	1
Paralysis, paresis or plaster immobilization of lower extremity	1
Immobilization previous 4 days or major surgery within 4 weeks	1
Entire leg swollen	1
Calf swollen by more than 3 cm	1
Pitting edema	1
Collateral superficial veins (non-varicose)	1
Probable alternative diagnosis	- 2

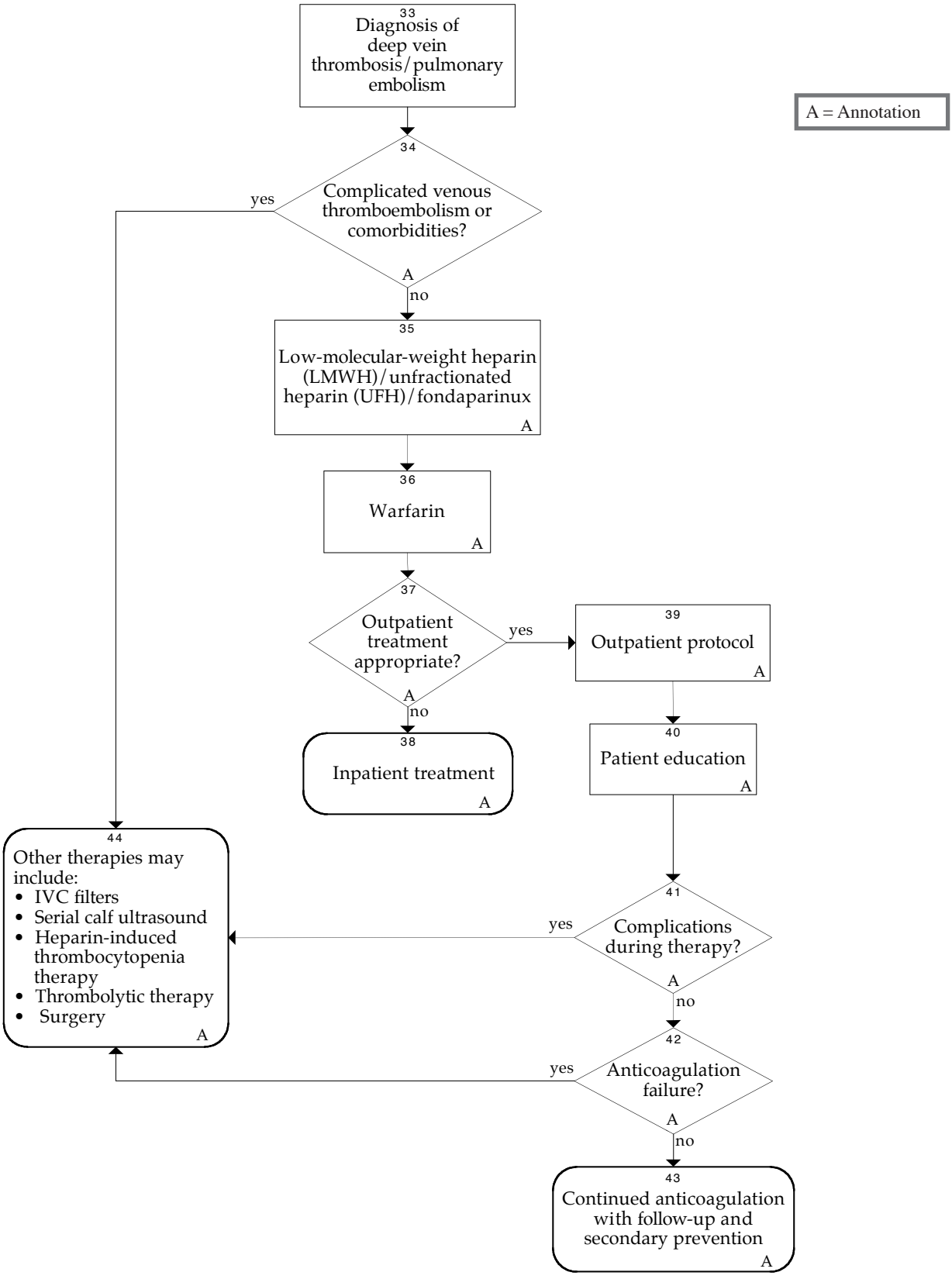
High DVT Risk = 3+
Moderate DVT Risk = 1-2
Low DVT Risk = < 1

If both legs are symptomatic, score the more severe leg.

Pulmonary Embolism (PE) Diagnosis Algorithm



Venous Thromboembolism (VTE) Treatment Algorithm



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Work Group Leader
Bruce Burnett, MD
Internal Medicine, Park Nicollet Health Services

Work Group Members
Family Medicine
Mary Michener, MD
Winona Clinic

Internal Medicine
Denise Dupras, MD
Mayo Clinic
Seema Maddali, MD, MPH
Fairview Health Services

Pharmacy
Peter Marshall, PharmD
HealthPartners Health Plan

Pulmonology
Keith Harmon, MD
Park Nicollet Health Services

Vascular Surgery
Mark Melin, MD
Park Nicollet Health Services

Facilitators
Kerin Hanson, MA
ICSI
Myounghee Hanson
ICSI

Foreword

Scope and Target Population

Adult patients age 18 and over with venous thromboembolism (VTE), excluding those with familial bleeding disorders or pregnancy.

Clinical Highlights and Recommendations

- A clinical pretest probability assessment should be completed in patients with suspected venous thromboembolism. *(Annotations #2, 17; Aim #4)*
- D-dimer can be used as a negative predictor to eliminate need for further testing. *(Annotations #4, 10, 17; Aim #4)*
- Confirm diagnosis of deep vein thrombosis (DVT) with imaging study, preferably duplex ultrasound (with compression). *(Annotation #13; Aim #4)*
- In patients with a high clinical pretest probability for pulmonary embolism (PE), begin anticoagulation without delay. *(Annotation #17; Aim #4)*
- Computed tomographic angiography combined with clinical pretest probability scoring and D-dimer testing has the predictive value to safely diagnose or rule out pulmonary embolism in patients. Additional diagnostic testing is necessary only when clinical symptoms persist or progress. *(Annotation #17; Aim #4)*
- Achieve rapid effective anticoagulation with low-molecular-weight heparin (LMWH)/fondaparinux. *(Annotation #35; Aim #1)*
- In patients with acute VTE, heparin (UFH, LMWH or fondaparinux) should be given for at least five days and until the INR $\geq$ 2.0 for two consecutive days. (*Annotations #35, 36; Aim #1)*
- Arrange for home therapy in appropriate patients. *(Annotation #39; Aim #5)*
- Graduated compression stockings may help prevent post-phlebotic syndrome. All patients should be assessed for the need for graduated compression stockings (not Teds). *(Annotation #43; Aim #1)*
- Patient to be treated three to six months for acute thrombosis followed by re-evaluation of ongoing risks to determine the need for ongoing anticoagulation therapy to prevent recurrent events. *(Annotation #43; Aim #3)*

Priority Aims

1. Prevent progression or recurrence of thromboembolic disease. *(Annotations #13, 43)*
2. Reduce the risk of complications from anticoagulation therapy. *(Annotation #43)*
3. Improve the safety of using medications by reducing the likelihood of patient harm associated with the use of anticoagulation therapy. *(Annotations #35, 36, 37, 42, 43, 44)*
4. Improve accurate diagnosis and treatment of venous thromboembolism (VTE). *(Annotations #14, 25)*
5. Increase the percentage of patients who are evaluated for medication reconciliation upon change in level of care, and/or upon discharge. *(Annotations #41, 42, 43)*

Key Implementation Recommendations

The following system changes were identified by the guideline work group as key strategies for health care systems to incorporate in support of the implementation of this guideline.

1. Implement a defined anticoagulation management program to individualize the care provided to each patient receiving (anticoagulation) therapy. *(2010 Joint Commission/National Safety Goal)*
2. (Clinics and Hospitals): Develop systems for monitoring the effects of anticoagulation therapy (heparin, low-molecular-weight heparin, warfarin and other anticoagulants) to include monitoring of outpatient therapy.
    - Use of standardized practices/protocols that include patient involvement. *(2010 Joint Commission/National Safety Goal)*
3. When heparin is administered intravenously and continuously, the organization should use programmable infusion pumps. *(2010 Joint Commission/National Safety Goal)*
4. Develop systems for providing patient/family education that includes the importance of follow-up monitoring, compliance issues, dietary restrictions, and potential adverse drug reactions and interactions.
    - Patient education to include documentation of the patient's own awareness of his/her risk for venous thromboembolism (VTE) signs and symptoms of venous thromboembolism and when/how to seek treatment, and demonstrated understanding of the prescribed anticoagulation regimen. *(2010 Joint Commission/National Safety Goal)*
5. Develop a policy for providing organizational education regarding anticoagulation therapy to prescriber(s), staff, patients and families. *(2010 Joint Commission/National Safety Goal)*
6. Develop protocols for the initiation and maintenance of anticoagulation therapy appropriate to the medication used, to the condition being treated, and to the potential for drug interactions. *(2010 Joint Commission/National Safety Goal)*

Related ICSI Scientific Documents

Guidelines

- Antithrombotic Therapy Supplement
- Venous Thromboembolism Prophylaxis

Order Sets

- Venous Thromboembolism Prophylaxis for the Medically Ill Patient Order Set

Disclosure of Potential Conflict of Interest

ICSI has adopted a policy of transparency, disclosing potential conflict and competing interests of all individuals who participate in the development, revision and approval of ICSI documents (guidelines, order sets and protocols). This applies to all work groups (guidelines, order sets and protocols) and committees (Committee on Evidence-Based Practice, Cardiovascular Steering Committee, Women's Health Steering Committee, Preventive & Health Maintenance Steering Committee and Respiratory Steering Committee).

Participants must disclose any potential conflict and competing interests they or their dependents (spouse, dependent children, or others claimed as dependents) may have with any organization with commercial, proprietary, or political interests relevant to the topics covered by ICSI documents. Such disclosures will be shared with all individuals who prepare, review and approve ICSI documents.

No work group members have potential conflicts of interest to disclose.

Introduction to ICSI Document Development

This document was developed and/or revised by a multidisciplinary work group utilizing a defined process for literature search and review, document development and revision, as well as obtaining input from and responding to ICSI members.

For a description of ICSI's development and revision process, please see the Development and Revision Process for Guidelines, Order Sets and Protocols at http://www.icsi.org.

Evidence Grading System

A. Primary Reports of New Data Collection:

Class A: Randomized, controlled trial

Class B: Cohort study

Class C: Non-randomized trial with concurrent or historical controls
Case-control study
Study of sensitivity and specificity of a diagnostic test
Population-based descriptive study

Class D: Cross-sectional study
Case series
Case report

B. Reports that Synthesize or Reflect Upon Collections of Primary Reports:

Class M: Meta-analysis
Systematic review
Decision analysis
Cost-effectiveness analysis

Class R: Consensus statement
Consensus report
Narrative review

Class X: Medical opinion

Citations are listed in the guideline utilizing the format of *(Author, YYYY [report class])*. A full explanation of ICSI's Evidence Grading System can be found at http://www.icsi.org.

Algorithm Annotations

Deep Vein Thrombosis Diagnosis Algorithm Annotations

1. Leg Symptoms/Clinical Suspicion of Deep Vein Thrombosis

Key Points:

- Clinical evaluation and examination and patient history are important to the diagnosis of deep vein thrombosis.
- Clinical findings alone are poor predictors of the presence or severity of thrombosis.

Among patients with pain and swelling of the leg, some will have deep vein thrombosis (DVT). Recent unilateral swelling and pain above or below the knee without explanatory bone or joint trauma is suspicious for deep vein thrombosis *(Jorgenson, 1993 [D])*. If patient has arm symptoms, refer to Appendix D, "Diagnosis and Treatment of Upper Extremity Deep Vein Venous Thrombosis."

As part of the evaluation, record onset, location and character of patient's leg pain and swelling.

Factors increasing risk include:

- patient's history of past venous thromboembolism (VTE), family history of VTE;
- pregnancy, postpartum or current estrogen use;
- recent trauma or surgery;
- immobilization;
- presence of cancer;
- varicosities; and
- airline flight longer than eight hours.

Exam findings may include erythema, warmth and superficial thrombophlebitis with a palpable tender cord over a superficial vein. In the most severe form, plegmasia cerulia dolens, the venous drainage of the lower extremity is acutely and severely obstructed, threatening limb viability. This may require other treatment. See Annotation #44, "Other Therapies."

It is well known that clinical findings are poor predictors of the presence or severity of thrombosis; therefore, determining pretest probability is necessary to managing the diagnostic process *(Hirsh, 1986 [R])*.

The work group feels that patients with signs and symptoms of pulmonary embolism (PE) should be evaluated according to the Pulmonary Embolism Diagnosis algorithm. Please refer to Annotation #14, "Clinical Signs and Symptoms of Pulmonary Embolism."

2. Determine Clinical Pretest Probability

Key Points:

- Use a formal protocol to determine a patient's clinical pretest probability of deep vein thrombosis.

The work group recommends the use of a formal protocol to determine a patient's clinical pretest probability of deep vein thrombosis. This can guide the choice of test(s) needed to triage patients for this condition,

which can have minimal signs and symptoms but leads to serious consequences if left untreated. Please refer to Appendix A, "Wells Model of the Clinical Pretest Probability of Deep Vein Thrombosis" for an example of a clinical pretest probability model protocol.

The Wells scale of Clinical Pretest Probability of deep vein thrombosis divides patients into low-, medium- and high-risk groups. In the 1997 study, it was used prospectively on 593 patients:

- Of 329 low-risk, 10 (3%) had deep vein thrombosis diagnosed. The positive predictive value was 82%. The negative predictive value of ultrasound was 99.7%, implying that low-risk patients with normal ultrasound results do not need further testing.
- Of 193 moderate-risk, 32 (16.6%) proved to have deep vein thrombosis.
- Of 71 high-risk, 53 (75%) had deep vein thrombosis diagnosed. In high-risk patients, the negative predictive value of ultrasound was only 82% at best (95% CI 59.7-94.8) *(Wells, 1997 [B])*. In high-risk patients with negative ultrasound, further tests should be considered.

A recent study reported lower specificity when the pretest probability model was used by primary care providers *(Douketis, 2005 [R]; Goodacre, 2005 [M]; Oudega, 2005 [C])*. Careful review and application of the pretest probability model by all providers is recommended.

3. Low Clinical Pretest Probability

Key Points:

- Patients with low clinical pretest probability of deep vein thrombosis and negative D-dimer are considered to have deep vein thrombosis ruled out and no further testing is needed.

Patients with a low clinical pretest probability of deep vein thrombosis, such as a score of zero on Wells scoring, can be safely managed by testing for D-dimer before ordering duplex ultrasound (with compression) of the leg. If D-dimer is negative, ultrasound can be omitted, and repeat ultrasound is not needed in one week as previously recommended unless new or progressive clinical symptoms occur *(Aschwanden, 1999 [C]; Fünfsin, 2001 [C])*.

4. D-dimer Test

Key Points:

- D-dimer assays with high sensitivity have been shown to have high negative predictive value for patients with a low pretest probability of deep vein thrombosis or pulmonary embolism.
- The greatest utility of the D-dimer test is in outpatients with suspected deep vein thrombosis or pulmonary embolism. The "negative predictive value" of the D-dimer is lower in patients with recent surgery, trauma and cancer.

The plasma fibrin D-dimer is a product created from fibrinolysis of cross-linked fibrin. Depending on the assay method, the duration of venous thromboembolism symptoms and possibly the duration of heparin therapy, the D-dimer has a high sensitivity for the presence of an acute thrombosis within virtually any vascular territory. While sensitive, the D-dimer is not specific for venous thromboembolism. In the correct circumstances, the D-dimer may be useful for excluding the diagnosis of acute venous thromboembolism. Among patients with a low clinical pretest probability of deep vein thrombosis or pulmonary embolism, a "negative" D-dimer has a very high negative predictive value for (i.e., essentially excludes the diagnosis of)

acute venous thromboembolism. However, several caveats regarding the D-dimer must be borne in mind. For example, the sensitivity of the D-dimer is dependent on the assay method (i.e., quantitative enzyme linked immunoassy methods are more sensitive than semiquantitative latex agglutination methods) and the assay discriminate (i.e., "cutoff") level *(Aschwanden, 1999 [C]; Fünfsinn, 2001 [C]; Heit, 1999 [C]; Heit, 2000 [C]; Stevens, 2005 [C])*. The assay discriminate level varies by assay vendor; no universal "cutoff" level (e.g., less than 300 or less than 500 ng/mL) exists.

Moreover, the sensitivity of the D-dimer may be reduced if the duration of symptoms or signs of venous thromboembolism exceeds two or three days prior to testing. Likewise, the sensitivity may be reduced if the patient has been receiving heparin therapy. Because a procedure or surgery increases the plasma D-dimer level, the clinical utility of the D-dimer is greatest for evaluation of outpatients. Usually, suspected venous thromboembolism patients with recent trauma or surgery are inappropriate for D-dimer testing and should proceed directly to a diagnostic imaging study for deep vein thrombosis or pulmonary embolism (e.g., duplex ultrasound [with compression] of the leg, high resolution chest computed tomographic angiography). Studies have also suggested that the negative predictive value of the D-dimer may be lower in patients with cancer *(Lee, 1999 [M])* distal DVTs *(Escoffre-Barbe, 1998 [C])* and previous DVTs *(Le Gal, 2006 [C])*. There is insufficient data about the utility of D-dimer in patients who are pregnant.

In summary, D-dimer testing is most appropriate in ambulatory care settings and for patients with recent onset of symptoms who are not currently on anticoagulation therapy *(Schutgens, 2002 [C])*. For patients with suspected deep vein thrombosis, D-dimer may decrease the need for initial and subsequent radiological investigation. The usefulness is dependent on the method used for D-dimer determination.

6. Deep Vein Thrombosis Excluded – Out of Guideline

Patients with a low clinical pretest probability of deep vein thrombosis and a negative (reliable) D-dimer assay have a very low (less than 2%) risk of subsequent finding of deep vein thrombosis. These patients can be followed clinically with no further radiologic evaluation unless warranted by new or progressive clinical symptoms *(Aschwanden, 1999 [C])*.

7. Moderate/High Clinical Pretest Probability

Key Points:

- Patients with moderate or high clinical pretest probability should have a venous duplex ultrasound (with compression) ordered as the first test.
- D-dimer assay can be used after a negative duplex ultrasound (with compression) result to determine further radiologic testing needs.

Patients with moderate or high clinical pretest probability have a 15%-70% risk of deep vein thrombosis. Because of the high incidence of deep vein thrombosis in this population, venous duplex ultrasound (with compression) should be ordered as the first test, and D-dimer assay can be used after a negative duplex ultrasound result to determine further radiologic testing needs. One study, randomized and controlled with a small sample size, showed a significant benefit to long-term anticoagulation of patients with calf vein thrombosis.

8. Perform Duplex Ultrasound (with Compression)

Key Points:

- Duplex ultrasound (with compression) is considered to be the primary diagnostic device and should be the first radiologic choice for evaluation of proximal deep vein thrombosis.
- The combined use of clinical pretest probability and duplex ultrasound (with compression) is effective in confirming or excluding the diagnosis of DVT.
- Duplex ultrasound (with compression) can find thrombi in the calf; however, a negative test cannot always exclude deep vein thrombosis and further testing may be needed.

Patients with a low clinical pretest probability of deep vein thrombosis and a positive D-dimer assay should receive a duplex ultrasound (with compression) to confirm the diagnosis of DVT. The ability to diagnose DVT may vary depending on the proximity of the suspected DVT site. In addition, the interpretation of the duplex ultrasound can be difficult in patients with a previous history of DVT. Consider consulting with the interpreting physician. See Annotation #12, "Follow-Up Studies/Second Duplex Ultrasound (Three to Seven Days) or Venography."

Patients with a moderate/high clinical pretest probability of DVT should receive a duplex ultrasound (with compression) as the first test to diagnose DVT. A negative result on the venous ultrasound can be followed by D-dimer to determine further radiologic testing needs. A positive result on the ultrasound confirms the diagnosis of DVT.

In 1995, Wells found that 24% of the cases with high clinical pretest probability and negative ultrasound had DVT on venography. Extra testing would be needed in only 20% of high-risk cases, because 80% were diagnosed on ultrasound. The high-risk group represented only 16% of all cases presenting for possible DVT. In low clinical pretest risk cases with negative ultrasound, only 1% had DVT on venography. (See Annotation #1, "Leg Symptoms/Clinical Suspicion of Deep Vein Thrombosis.")

Proximal (Popliteal Vein and Above)

Duplex ultrasound (with compression) is considered to be the primary diagnostic device and should be the first choice for evaluation *(Barnes, 1975 [C]; Zierler, 2001 [R])*.

Ultrasonography has been demonstrated in a large number of studies to be 87% sensitive and between 86%-100% specific when compared to venography. It is painless, portable and easily available. This is the most widely used technique locally. However, the technique is not as accurate for veins above the common femoral vein *(Baker, 1994 [R]; Heijboer, 1993 [A])*.

Calf (Below Popliteal Vein)

Some calf thrombi can be found by duplex ultrasound (with compression). However, a negative test cannot exclude an isolated calf DVT *(Simons, 1995 [C])*.

(Polak, 2005 [R])

10. D-dimer Test for Moderate/High Pretest

Key Points:

- It has been found safe to withhold anticoagulation in outpatients with a moderate to high clinical suspicion, a negative duplex ultrasound, and a negative D-dimer.

It is safe to withhold anticoagulation among outpatients with a negative duplex ultrasound (with compression) and a "negative" D-dimer (measured by whole blood latex agglutination or enzyme linked immunoassy, respectively) *(Bernardi, 1998 [B]; Ginsberg, 1997 [C]; Perrier, 1999 [C])*.

For patients with suspected deep vein thrombosis, D-dimer may decrease the need for initial and subsequent radiological investigation. The usefulness is dependent on the method used for D-dimer determination.

12. Follow-Up Studies/Second Duplex Ultrasound (Three to Seven Days) or Venography

Key Points:

- If deep vein thrombosis is strongly suspected and there is a positive D-dimer despite a negative initial ultrasound, consider venography or repeat ultrasound in three to seven days.

Clinical pretest probability and venous duplex ultrasound are adequate to rule in or rule out deep vein thrombosis in the majority of cases. If DVT is strongly suspected despite a negative initial ultrasound, consider venography or repeat ultrasound in three to seven days. Please refer to Appendix A, "Wells Model of the Clinical Pretest Probability of Deep Vein Thrombosis."

The combined use of clinical pretest probability and duplex ultrasound (with compression) is effective in confirming or excluding the diagnosis of DVT in the majority of cases. If clinical suspicion of DVT is high and ultrasound is negative, consider further testing, such as repeat ultrasound for suspected calf thrombosis, or venography for suspected proximal thrombosis.

- **Serial ultrasonography**

  When calf thrombosis is suspected but the initial ultrasound is negative, serial ultrasound is an acceptable alternative to venography. Furthermore, ultrasonography appears to be superior to impedance plethysmography for this purpose *(Ginsberg, 1996 [R]; Heijboer, 1993 [A])*. If a thrombus is discovered, anticoagulation is recommended.

- **Computed tomographic (CT) venography of the inferior vena cava and the iliac veins**

  This is performed at some institutions to visualize proximal obstructions. The common, superficial and deep femoral veins can be done, as well. CT venography does not include the distal calf veins. Newer techniques include spiral contrast CT and magnetic resonance venography, which have shown excellent results in preliminary studies. This effectiveness has included iliocaval thrombi. Currently these techniques could be considered in patients with unusual diagnostic situations, including suspected iliocaval clots or in patients with contraindications for venography *(Baldt, 1996 [C]; Dupas, 1995 [C]; Evans, 1993 [C])*.

- **Contrast venography (proximal, intra-abdominal)**

  This is generally considered the historical gold standard for the accurate diagnosis. However, it has numerous drawbacks including cost, discomfort to the patient, significant resource use, availability, requirement of foot vein cannulation, use of intravenous contrast, and secondary thrombi. For these

reasons, venography is generally reserved for difficult diagnostic cases. It can help distinguish between old and new clots.

13. Deep Vein Thrombosis Confirmed – See Venous Thromboembolism Treatment Algorithm

Key Points:

- Proximal thrombosis should be treated with anticoagulation unless contraindicated.
- Thrombosis of the calf veins is common and carries significant risk of propagation. Patients benefit from anticoagulation treatment.
- Patients with thrombosis of the calf not treated with anticoagulation should be followed by serial duplex ultrasound to rule out proximal progression.

Proximal Thrombosis (at or above the popliteal vein)

Proximal thrombosis should be treated with anticoagulation unless contraindicated *(Kearon, 2008 [R])*. (See Annotation #34, "Complicated Venous Thromboembolism or Comorbidities?") Additional information can be found in the ICSI Antithrombotic Therapy Supplement.

Calf Thrombosis (below the popliteal vein)

Increasing evidence suggests that patients with **symptomatic** calf deep vein thrombosis benefit from treatment similar to that for proximal DVT. Thrombosis of the calf veins is common and carries significant risk of propagation, including propagation into the proximal deep veins *(Lagerstedt, 1985 [A]; Lohr, 1995 [D]; Philbrick, 1988 [R])*. If not treated, these patients should be followed by serial duplex ultrasounds to rule out proximal progression of thrombus to popliteal vein.

Following patients with **suspected** thrombosis limited to the calf veins and treating with anticoagulation only for proximal extension on serial studies may be an acceptable alternative to anticoagulation. However, the safety of this approach in patients with confirmed symptomatic calf deep vein thrombosis has not been studied *(Huisman, 1986 [D]; Hull, 1989 [C]; Philbrick, 1988 [R])*.

Pulmonary Embolism (PE) Diagnosis Algorithm Annotations

14. Clinical Signs and Symptoms of Pulmonary Embolism

Key Points:

- Pulmonary embolism should be considered in patients who present with the three most frequent signs and symptoms: dyspnea, pleuritic chest pain, and tachypnea.

This Pulmonary Embolism Diagnosis Algorithm does not apply to pregnant patients. Pulmonary embolism (PE) should be considered in patients who present with the three most frequent signs and symptoms: dyspnea, pleuritic chest pain, and tachypnea. Less frequent signs/symptoms are cough, hemoptysis, fever, syncope, diaphoresis, nonpleuritic chest pain, apprehension, rales, increased pulmonic component of the second heart sound (^S_2P), wheezing, hypotension, tachycardia, cyanosis or pleural rub. Massive PE can present with hemodynamic instability or cardiac arrest. Clinical findings are non-specific and should not be used as the only criteria to diagnose PE *(Hyers, 1999 [R]; Stein, 1991 [C]; Stein, 2006a [A]; Stein, 2006b [R])*.

Consultation with a pulmonary specialist or perinatologist to assist in the evaluation of pregnant patients with suspected PE may be helpful.

15. Clinically Unstable?

Patients who are clinically unstable (e.g., hypotension, acute respiratory failure) may have massive pulmonary embolism (PE) and should be considered for thrombolytic therapy. Massive PE should be considered with any of the following: hemodynamic instability (including systolic blood pressure less than 90 mm Hg, or a drop in 40 mm Hg), syncope; severe hypoxemia or respiratory distress; computed tomographic pulmonary angiogram (CTPA), angiogram or ventilation/perfusion scan that suggests 50% or more absent perfusion; an echocardiogram showing right ventricular (RV) failure or strain; and elevated B-type natriuretic peptide (BNP) and troponin. Massive PE has up to a tenfold increase greater mortality; thrombolytic therapy appears to improve outcome. A recent study suggests some benefit in the subgroup of patients with RV strain on echo but hemodynamic stability *(Konstantinides, 2002 [A])*. Elevated troponin and BNP levels are associated with RV strain, and both have been clearly associated with increased mortality, even in the absence of hemodynamic compromise. A preliminary recommendation would be to consider a BNP and troponin in a patient with substantial clot burden, abnormal echocardiogram or a clinical presentation that is concerning *(Becattini, 2007 [M]; Kline 2008 [B]; Klok, 2008 [M]; Laporte, 2008 [D]; Pieralli, 2006 [D])*.

Patients who present signs and symptoms of massive PE (syncope, hypotension, respiratory distress, marked hypoxemia) may require evaluation and treatment different from the guideline. In patients considered to possibly have massive PE, urgent echocardiography, BNP and troponin levels, duplex ultrasound and specialty consultation may assist decision-making about whether to use thrombolytic or standard therapy.

(Meyer, 1998 [B])

16. Stabilize

See Annotation #34, "Complicated Venous Thromboembolism or Comorbidities?" for more information.

17. Estimate Clinical Pretest Probability (CPTP – Wells Score)

Key Points:

- If the clinical pretest probability score is high (six or more), or patient's risk of VTE is high due to comorbidities (e.g., pulmonary hypertension) begin anticoagulation without delay.
- Chest x-ray, arterial blood gases, echocardiogram (EKG) and other tests as indicated for alternative diagnoses considered.

For the purposes of the diagnosis of pulmonary embolism, the work group has combined moderate pretest probability and high pretest probability into the PE Likely category.

If the clinical pretest probability score is high, begin heparin promptly (a tool for determining pretest probability is shown in annotation Appendix B, "Model for Predicting Clinical Pretest Probability for Pulmonary Embolism").

Patients presenting with signs and symptoms of pulmonary embolism (PE) need:

- **Complete history and physical exam.** Risk factor assessment for venous thromboembolic disease plays a role in determining the pretest probability of PE. Risk factors include previous history of venous thromboembolism, recent surgery, immobilization, paresis, personal or family history of inheritable thrombophilic disorder or personal history of acquired thrombophilia (e.g., antiphospholipid antibody, cancer, estrogen, pregnancy or myeloproliferative disorder).

- **Estimate pretest probability.** The clinical evaluation can also lead to suspicion of an alternative diagnosis. Wells' method of assessing the clinical pretest probability of PE from his 1998 article was complex, but safely guided a non-invasive PE workup that avoided angiograms except for cases of discordance between the clinical probability and the V/Q probability of PE *(Wells, 2000 [C])*. The group then used the simplified model for clinical pretest probability in conjunction with SimpliRED D-dimer test in 930 consecutive emergency department patients suspected of PE. They demonstrated the safety of avoiding the V/Q and computed tomographic pulmonary angiography when clinical pretest probability is low and D-dimer is negative *(Wells, 2001 [B])*. A recent prospective study of 3,306 patients presented a validated simplified algorithm based on the earlier work of Wells *(Dalen, 2006 [R]; Stein, 2006b [R]; Writing Group for the Christopher Study Investigators, 2006 [B])*.

  Other studies reported lower specificity when the pretest probability model was used by primary care providers *(Douketis, 2005 [R]; Goodacre, 2005 [M]; Oudega, 2005 [C])*. Careful review and application of the pretest probability model by all providers is recommended.

- **Chest x-ray, arterial blood gases, EKG** and other tests as indicated for alternative diagnoses considered. Although laboratory studies can often be normal, some abnormal findings can heighten one's suspicion of PE. Arterial blood gases can show hypoxemia, hypocapnia and widened (A-a) O_2 difference. Chest x-rays can show atelectasis, pleural based infiltrates or effusions, or, rarely, engorged central pulmonary artery vasculature associated with a paucity of peripheral vessels. EKG can show supraventricular arrhythmia, right axis derivation, $S_1Q_3T_3$ pattern or P-pulmonale.

A simplified clinical pretest probability scoring system may improve diagnostic accuracy by being easy to use consistently and alerting clinicians to the need for further testing *(American Thoracic Society, 1999 [R]; Stein, 1991 [C])*.

18. Clinical Pretest Probability Results?

The new simplified algorithm validates the dichotomized groups proposed by Wells *(Wells, 2000 [C])* and includes patients categorized in an earlier study as low and some of those in the moderate probability group.

PE Less Likely (score ≤ 4)

- Less Likely Clinical Pretest Probability

The Christopher Study Investigators found that in patients with a less likely score for pulmonary embolism (PE), D-dimer levels should be measured and can provide diagnostic information to rule out PE.

PE Likely (score > 4)

- Likely Clinical Pretest Probability

The data from Wells and the Christopher Study Investigators found that in patients likely to have a PE, a computed tomographic scan should be the next test and can safely exclude a PE.

* For the purposes of the diagnosis of pulmonary embolism, the work group has combined moderate pretest probability and high pretest probability into PE Likely probability.

(Stein, 2006a [A]; Stein, 2006b [R]; Writing Group for the Christopher Study Investigators, 2006 [B])

20. D-dimer Results?

In patients with PE Less Likely, the Christopher Study Investigators found that patients with negative D-dimer levels could safely be observed without further investigation, as the incidence of non-fatal venous thromboembolism (VTE) was 0.5% in the subsequent three months. This data is consistent with other studies *(Stein, 1993 [R]; Stein, 1995 [C]; Wells, 1998b [B])*. In this group it is safe to withhold anticoagulation therapy and follow these patients clinically.

If the D-dimer is positive, further evaluation is necessary to adequately exclude a pulmonary embolism.

The sensitivity of the D-dimer may be reduced if the duration of symptoms or signs of venous thromboembolism exceeds two or three days prior to testing. Likewise, the sensitivity may be reduced if the patient has been receiving heparin therapy. Because a procedure or surgery increases the plasma D-dimer level, the clinical utility of the D-dimer is greatest for evaluation of outpatients (e.g., emergency department).

Usually, suspected venous thromboembolism patients with recent trauma or surgery are inappropriate for D-dimer testing and should proceed directly to a diagnostic imaging study for deep vein thrombosis or pulmonary embolism (e.g., duplex ultrasound [with compression] of the leg, high resolution chest computed tomographic angiography).

21. Risk of Pulmonary Embolism Is Very Low

Key Points:

- It is important to evaluate patients for other diagnoses when pulmonary embolism has been excluded.

Patients with a negative D-dimer and PE Less Likey Clinical Pretest Probability have a low incidence of pulmonary embolism *(Stein, 1993 [R]; Stein, 1995 [C]; Stein, 2006a [A]; Stein, 2006b [R]; Wells, 1998b [B]; Writing Group for the Christopher Study Investigators, 2006 [B])*. It is safe to withhold anticoagulation therapy and follow these patients clinically.

Patients with a negative computed tomographic angiography and PE Less Likely Clinical Pretest Probability and positive D-dimer results can safely have pulmonary embolism excluded and followed clinically in the outpatient setting *(Dalen, 2006 [R]; Stein, 2006a [A]; Stein, 2006b [R]; Writing Group for the Christopher Study Investigators, 2006 [B])*.

Patients with persistent symptoms or symptoms that progressively worsen should have further diagnostic testing. Ultrasound (with compression) should be used to improve the clinical likelihood of diagnosing disease and avoid more invasive testing.

Patients who have had PE excluded need to have the evaluation for other diagnoses completed and appropriate treatment and follow-up initiated. In particular, pericarditis, myocardial infarction and pneumonia should be excluded in appropriate circumstances. When performed, computed tomographic pulmonary angiography will frequently help identify alternative causes such as pericardial effusion, pneumonia and pleural effusion.

23. Perform Computed Tomographic Pulmonary Angiograph (CTPA)

Key Points:

- Non-invasive pulmonary vascular imaging studies are recommended as the initial radiologic evaluation.

Computed tomographic pulmonary angiography (CTPA) is the first line study of choice unless a contraindication exists, then V/Q (ventilation/perfusion scan) would be preferred.

Computed tomography should be performed with at least a 2.5 mm thickness by 1.25 mm incrementation.

The choice of initial imaging study depends on several factors including how readily available the tests are, the resolution of images obtained, underlying illnesses/conditions including renal status of the patient, and experience of the radiologists. Care should be taken when using dye in patients with renal insufficiency.

Non-invasive pulmonary vascular imaging studies are recommended as the initial diagnostic evaluation in most patients with suspected pulmonary embolism (PE). Both V/Q scans and computed tomographic pulmonary angiography have a relatively high degree of specificity when they are read respectively as "high probability" scan results or "positive" for PE. A negative V/Q scan also has a high degree of specificity. However, either a **non-diagnostic** (intermediate or low radiologic probability scan results) or a negative computed tomographic pulmonary angiogram suffer from lack of sensitivity and usually require further diagnostic studies. In rare instances the CTPA may miss a clot. V/Q scanning is not always readily available and other pulmonary processes such as chronic pulmonary obstructive pulmonary disease and congestive heart failure can influence its specificity *(American Thoracic Society, 1999 [R]; PIOPED Investigators, The; 1990 [C]; Dalen, 2006 [R]; Remy-Jardin; 1997 [R]; Stein, 2006a [A])*.

V/Q imaging follows a different diagnostic algorithm. See Appendix C, "Ventilation/Perfusion (VQ) Lung Imaging Algorithm," for more information.

(Berland, 2006 [R])

24. Computed Tomographic (CT) Results?

Key Points:

- Computed tomographic pulmonary angiography has become the most commonly used radiographic test to evaluate patients for pulmonary embolism.

Computed tomographic (CT) pulmonary angiography offers the clinician a new screening tool for detection of pulmonary embolism. It has been rapidly introduced into clinical practice and, in some institutions, is easier to obtain than a V/Q (ventilation/perfusion) scan. CT pulmonary angiography is also more useful in patients with underlying cardiac disease and chronic obstructive pulmonary disease/asthma. When alternative diagnoses are likely, computed tomographic pulmonary angiography is especially good, as it can rule out pulmonary embolism (PE) and confirm other diagnoses with one test.

CT pulmonary angiography has a high sensitivity and specificity for central clots. The sensitivity and specificity drop substantially for peripheral clots. Technical issues are extremely important. The protocols require appropriate timing from contrast injection to scan acquisition, a prolonged breath-hold (about 20 seconds), and optimized spatial resolution parameter settings. This requires the right equipment and technical sophistication to obtain high-quality images. Computed tomographic angiography showing positive results for sequmental/subsegmental embolism should be followed up with additional testing, due to the increase in false positives.

CT pulmonary angiography may be the initial test if the hospital has state-of-the-art equipment and technical and interpretive expertise. Consultation with a radiologist may be helpful in determining the most appropriate test. With state-of-the-art equipment, the ability to exclude peripheral clots is probably increasing, but the clinical probability must guide the decision to pursue further testing (compression ultrasound or pulmonary angiography).

For patients with CT scan results that cannot clearly confirm or rule out the possibility of PE due to the patient's condition and comorbidities or due to scan technical limitation, clinicians should review the clinical pretest probability and D-dimer results to determine what further workup may be indicated.

(Berland, 2006 [R]; Stein, 2006 [A]; Writing Group for the Christopher Study Investigators, 2006 [B])

(Greaves, 1997 [R]; Mullins, 2000 [M]; Rathbun, 2000 [M]; Remy-Jardin, 1997 [R]; Remy-Jardin, 1998 [R]; Stein, 2006a [A]; Stein, 2006b [R])

25. Diagnosis of Pulmonary Embolism

Patients with a positive computed tomographic (CT) pulmonary angiographic scan and Likely PE clinical pretest probability are essentially confirmed positive for pulmonary embolism. They can be considered for treatment with no further diagnostic testing *(American Thoracic Society, 1999 [R]; Stein, 2006a [A]; Stein, 2006b [R]; Wells, 1998a [C])*.

Pulmonary emboli are noted as incidental findings in 1%-4% of chest CT studies ordered for other reasons. This is more frequent in patients who have studies done for follow-up/staging of malignancies *(Storto, 2005 [D])*. Further testing may be helpful to confirm acute VTE disease such as D-dimer, venous studies, etc. Asymptomatic PE should be treated with the same protocol as outlined for symptomatic PE *(Kearon, 2008 [R])*.

28. Pulmonary Embolism Less Likely with Positive D-dimer Results

In patients with an unlikely pretest probability but positive D-dimer and normal computed tomographic pulmonary angiographic (CTPA), no treatment is necessary. Further work up only if warranted by clinical suspicion.

In the PIOPED II study, patients with a low pretest probability and a negative CTPA alone had a 4% incidence of pulmonary embolism (PE) on angiography. When venous imaging (computed tomographic venography in PIOPED II) was negative, the incidence of PE was 3%. Clinical outcome studies show a lower (less than 1.5%) incidence of PE or deep vein thrombosis.

(Dalen, 2006 [R]; Stein, 2006a [A]; Stein, 2006b [R])

29. Pulmonary Embolism Likely with Negative D-dimer Results

It appears to be safe to withhold anticoagulation while pursuing a non-invasive strategy of serial ultrasonography in order to further evaluate for thromboembolism in this patient population *(Wells, 1998b [B])*.

Irrespective of D-dimer result, venous imaging should be performed.

In PIOPED II patients with either moderate or high pretest probability and negative computed tomographic pulmonary embolism (CTPA), there was a 11%-40% incidence of pulmonary embolism (PE) on angiography. These incidences were lowered to 8%-18% when venous imaging (computed tomographic venography in PIOPED II) was added. Clinical outcome studies showed a much lower (1%-2%) incidence of PE or deep vein thrombosis.

(Dalen, 2006 [R]; Stein, 2006a [A]; Stein, 2006b [R])

The risks associated with a misdiagnosis of PE are typically more severe than those associated with a misdiagnosis of DVT. Higher negative predictive values are required to safely use D-dimer to exclude PE. The evidence, to date, suggests that current assays, with the possible exception of enzyme linked immunoassy (ELISA) and rapid ELISA methods, are not acceptable for use in excluding PE in patients with clinical suspicion of PE.

30. Pulmonary Embolism Likely with Positive D-dimer Results

A significant incidence of PE is found in patients with a negative computed tomographic pulmonary angiography associated with a high clinical pretest probability. Bilateral duplex ultrasound (with compression) of the leg is recommended to improve the diagnosis of VTE without performing invasive tests. Pulmonary angiography can be considered if clinical suspicion remains high or the patient's condition deteriorates.

(Dalen, 2006 [R]; Stein, 2006a [A]; Stein, 2006b [R]; Writing Group for the Christopher Study Investigators, 2006 [B])

31. Perform Duplex Ultrasound (with Compression) of the Leg

Key Points:

- Duplex ultrasound (with compression) should be used to improve clinical likelihood of diagnosing disease and avoid more invasive testing in patients with negative lung imaging results.

In patients with negative computed tomographic pulmonary angiography results and positive D-dimer and a PE Likely clinical probability, further evaluation with duplex ultrasound (with compression) should be used to improve clinical likelihood of diagnosing disease and avoid more invasive testing.

Pulmonary embolism and deep vein thrombosis are part of the same pathologic process. Most patients diagnosed with a pulmonary embolism also have deep vein thrombosis. The diagnosis of lower extremity deep vein thrombosis has been advocated to be an important adjunct to the diagnosis of pulmonary emboli. Venous duplex ultrasonography (DUS) is the most common method for deep vein thrombosis diagnosis. DUS accuracy for lower extremity DVT is as high as 98%, though studies are negative in greater than 50% of pulmonary embolism cases. Total thrombus embolism and proximal migration may account for a number of negative studies. Venous DUS reliability is also limited when evaluating iliac and pelvic veins and the inferior vena cava, which likely accounts for a significant number of negative studies. One study found that when venous DUS is the initial study during evaluation for PE, treatment determination could be made in only 13% of cases.

When DUS is negative, the incorporation of clinical pretest probability can improve diagnostic accuracy and potentially avoid unnecessary pulmonary angiography. Several studies of DUS performed after *non-diagnostic* ventilation/perfusion scans have shown that pulmonary angiography can be avoided in 15%-40% of patients when DVT is identified.

Clinical pretest probability is an important adjunct to DUS at this point. In cases of suspected pulmonary embolism where non-invasive tests do not confirm its presence, pulmonary angiography should be performed.

(Beecham, 1993 [C]; Killewich, 1993 [C]; Matteson, 1996 [D]; Oudkerk, 1993 [M]; Schiff, 1987 [C]; Stein, 2006b [R])

32. Ultrasound Results?

A positive ultrasound usually confirms the diagnosis of deep vein thrombosis and requires treatment regardless of the presence or absence of pulmonary embolism. If the ultrasound is negative, further evaluation may be warranted, dependent upon the patient's clinical pretest probability.

Venous Thromboembolism (VTE) Treatment Algorithm Annotations

34. Complicated Venous Thromboembolism or Comorbidities?

Key Points:

- Patients with complicated venous thromboembolism or certain comorbidities may require therapy that is different than patients with uncomplicated venous thromboembolism. The work group felt that these patients should be identified and treated individually rather than by a standard guideline.
- Complications or comorbidities of venous thromboembolism include massive pulmonary embolism, contraindications to anticoagulation, known history of heparin-induced thrombocytopenia, extensive iliofemoral thrombosis/phlegmasia, pregnancy, familial bleeding disorders, and severe renal dysfunction.

Massive Pulmonary Embolism

Patients who present with symptoms of pulmonary embolism (PE) associated with hemodynamic or respiratory compromise should be evaluated for massive PE. These patients may require treatment other than that discussed in this guideline.

Massive PE should be considered in the following circumstances: any hemodynamic instability, severe hypoxemia or respiratory distress, a ventilation/perfusion scan or angiogram with 50% of the perfusion absent, an echocardiogram showing right heart strain or failure, an elevated pulmonary artery pressure, or a spiral computed tomography scan suggesting severe occlusion. Massive PE has up to a tenfold greater mortality; treatment with thrombolytics appears to favorably affect the outcome. A recent study has also suggested that there may be some benefit for the use of thrombolytics in submassive PE. In this circumstance, specialty consultation and consideration of thrombolytics may be appropriate *(Arcasoy, 1999 [M]; Dalen, 1997 [R]; Kanter, 1997 [D]; Kasper, 1997 [D]; Konstantinides, 1997 [B]; Konstantinides, 2002 [A]; Meyer, 1998 [B])*.

Patients with hemodynamic compromise may require immediate thrombolytic therapy. Normotensive PE patients with right ventricular dysfunction should be treated in-hospital (at least initially), where their vital signs can be closely monitored. Such patients should be considered for thrombectomy (either catheter-directed or open), thrombolysis and/or inferior vena cava (IVC) filter placement if blood pressure support (i.e., pressors and augmentation of intravascular volume) is required, and possibly if hypoxemia cannot be corrected with supplemental oxygen therapy.

Contraindications to Anticoagulation

Absolute contraindications would include patients with active severe hemorrhage or recent intracranial hemorrhage. Relative contraindications include recent or imminent surgery, trauma, anemia (hematocrit less than 30), renal disease, history of gastrointestinal hemorrhage, active peptic ulcer disease, and liver disease *(Campbell, 1996 [A]; Fihn, 1996 [B])*.

These patients require more intense monitoring for bleeding complications if given anticoagulation therapy. If not treated with anticoagulation therapy, serial ultrasounds for untreated calf deep vein thrombosis or IVC filters for proximal deep vein thrombosis are indicated. (See Annotation #44, "Other Therapies.") Please refer to the ICSI Antithrombotic Therapy Supplement for more information on contraindications to anticoagulation.

Known History of Heparin-Induced Thrombocytopenia (HIT)

Thrombocytopenia can complicate heparin therapy. Both a non-immune and a more serious immune-mediated platelet-associated IgG reaction, heparin-induced thrombocytopenia (HIT), have been described. If the patient has previously received heparin, especially within the past three months, thrombocytopenia may occur within hours or days *(Warkentin, 1996 [C])*.

Patients with HIT should not be treated with either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). Though not FDA approved, fondaparinux may be an option; it has little or no anti-platelet effects and has been used successfully to mitigate the effects of HIT. However, several cases of fondaparinux-associated HIT have been reported. Please see the ICSI Antithrombotic Therapy Supplement. Direct thrombin inhibitors (e.g., Refludan or Argatroban) have been used successfully for patients with HIT. (See Annotation #44, "Other Therapies.") Please refer to the ICSI Antithrombotic Therapy Supplement for more information on HIT. Also see the American College of Chest Physicians' 2008 Venous Thromboembolism, Thrombophilia, Antithrombotic Therapy, and Pregnancy guidelines.

Extensive Iliofemoral Thrombosis/Phlegmasia

Patients found to have extensive iliofemoral disease or evidence of phlegmasia will likely require inpatient monitoring and longer course of heparin/low-molecular-weight heparin (LMWH) therapy than patients with uncomplicated deep vein thrombosis. Thrombolytic therapy may be of benefit in these patients for possible reduction of post-thrombotic complications. (See Annotation #44, "Other Therapies.")

Pregnancy

In pregnancy, warfarin is contraindicated because it crosses the placenta and is associated with embryopathy, central nervous system abnormalities, and neonatal bleeding. Subcutaneous UFH, twice daily, has been the standard therapy in pregnancy. LMWH has shown no increased fetal complication and was shown to have fewer bleeding complications than UFH.

The Sanson study was a meta-analysis of 21 studies with 486 pregnancies, in which excess fetal death or complicated prematurity was found associated with comorbid diagnosis of the mother (such as autoantibodies, recurrent fetal loss treatment and preeclampsia), not with the use of LMWH *(Sanson, 1999 [M])*.

In the Pettilä study, in addition to fewer bleeding complications, no difference of venous thromboembolism was noted, but the study was not large enough to detect a difference. In the study, a daily dalteparin dose was initially weight based but was then adjusted to achieve anti-Xa measurement of 0.20 IU/mL three hours after injection, at 20 weeks and 30 weeks gestation, as well as two weeks postpartum *(Pettilä, 1999 [A])*.

Renal clearance of enoxaparin may be increased during pregnancy *(Casele, 1999 [D])*.

Anticoagulation will need to continue four-six weeks after delivery because the postpartum period is itself a high-risk time for thrombosis.

Please refer to the ICSI Antithrombotic Therapy Supplement for more information on anticoagulation therapy during pregnancy.

Familial Bleeding Disorders

Because of the complexity and controversy surrounding the use of standard anticoagulation to treat DVT in patients with familial bleeding disorders, these patients are excluded from the guideline. There is little data that has addressed the use of low-molecular-weight heparin in these patients. Although treatment for these patients may be similar to that found in the algorithm, the work group felt that these patients should be treated individually and not be included in the guideline.

Severe Renal Dysfunction (creatinine clearance less than 30 mL/minute)

These patients require closer monitoring for bleeding complications and dosing adjustments if LMWH is used. Patients with significant renal impairment (creatinine clearance less than 30 mL/min) can accumulate LMWH. The recommended doses in these patients are currently:

- Enoxaparin 1 mg/kg **ONCE** daily for therapeutic (treatment) doses. *(Normal renal function dose is 1 mg/kg twice daily or 1.5 mg/kg once daily.)*
- Enoxaparin 30 mg **ONCE** daily for prophylactic doses. *(Normal renal function dose is 30 mg twice daily or 40 mg once daily.)*

(Cadroy, 1991 [C]; Gerlach, 2000 [B])

Please refer to the ICSI Antithrombotic Therapy Supplement for more information on anticoagulation therapy in patients with renal dysfunction.

35. Low-Molecular-Weight Heparin (LMWH)/Unfractionated Heparin (UFH)/Fondaparinux

Key Points:

- Unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) or fondaparinux should be considered for the initial treatment of pulmonary embolism.
- LMWH and fondaparinux are preferred for the initial anticoagulation for most patients with deep vein thrombosis.
- Heparin-induced thrombocytopenia (HIT) is a recognized complication of heparin therapy.

Unfractionated heparin, low-molecular-weight heparin (LMWH) or fondaparinux should be considered for the initial treatment of pulmonary embolism (PE). LMWH or fondaparinux is preferred for the initial anticoagulation of patients with deep vein thrombosis. LMWH and fondaparinux are as safe and as effective as continuous unfractionated heparin (UFH). Suitable patients can be safely treated with LMWH and fondaparinux in the outpatient setting.

Heparin/fondaparinux should be continued for at least five days after the initiation of warfarin therapy and until International Normalized Ratio (INR) is ≥ 2.0 for two consecutive days.

Low-Molecular-Weight Heparin (LMWH)

LMWH provides reliable anticoagulation levels when given subcutaneously on a weight-determined dosing schedule. No laboratory monitoring of the intensity of anticoagulation is required for LMWH, except in special circumstances. Recent randomized controlled trials of the treatment of PE have shown LMWH to be as effective and safe as UFH. One randomized controlled trial of the treatment of venous thromboembolism (VTE) in 1,021 patients included 271 patients presenting with pulmonary embolism (PE). In this study, there

were no significant differences in outcomes following treatment with UFH versus LMWH. These studies used reviparin and tinzaparin. Two reviews agreed that LMWH may be efficacious in the treatment of PE, but cautioned that the LMWH products may not be equivalent to each other *(Charland, 1998 [R]; Columbus Investigators, The, 1997 [A]; Hull, 2000 [R]; Raskob, 1999 [R]; Simonneau, 1997 [A])*.

Please note that LMWH may not be appropriate for patients with renal insufficiency (creatinine clearance less than 30 mL/min). Studies have shown modestly delayed clearance in patients with chronic renal failure. The clinician should weigh this evidence when considering outpatient therapy *(Cadroy, 1991 [C])*. (See Annotation #34, "Complicated Venous Thromboembolism or Comorbidities?")

- Enoxaparin 1.0 mg/kg subcutaneous twice daily is the recommended treatment for DVT (FDA approved for inpatients and outpatients).
- Enoxaparin 1.5 mg/kg subcutaneous once daily (FDA approved for inpatient venous thromboembolism treatment) *(Merli, 2001 [A])*. Risk factors for therapy failure with once-daily dosing include obesity (greater than 100kg), cancer and chronic kidney disease. Twice-daily dosing (enoxaparin 1 mg/kg subcutaneous, twice daily) is recommended for obese patients and patients with cancer *(Decousus, 1998 [A]; Levine, 1996 [A]; Merli, 2001 [A])*.
- Tinzaparin 175 anti-Xa IU/kg subcutaneous once daily (FDA approved for venous thromboembolism treatment) *(Simonneau, 1997 [A])*.
- Dalteparin 100 IU/kg subcutaneous twice daily (not FDA approved for non-cancer related venous thromboembolism treatment) *(Alhenc-Gelas, 1994 [A]; Holmström, 1992 [A]; Partsch, 1996 [A])*.
- Dalteparin 200 IU/kg subcutaneous once daily (the effectiveness of once-daily dosing is controversial) (not FDA approved for non-cancer related venous thromboembolism treatment) *(Holmström, 1992 [A]; Kovacs, 2000 [B]; Lindmarker, 1994 [A]; Luomanmäki, 1996 [A]; Partsch, 1996 [A])*.

Studies of LMWH have generally excluded pregnant patients. However, neither unfractionated or LMWH crosses the placenta, and pregnant patients are suitable candidates for either form of therapy.

The decision for hospital or home therapy is not mutually exclusive. A patient could be started on LMWH in the hospital and discharged to continue therapy at home at any time during the course of therapy.

(Snow, 2007 [R])

Unfractionated Heparin (UFH)

UFH is administered by continuous intravenous infusion following a bolus dose. Heparin-induced thrombocytopenia is a recognized complication of UFH therapy. (See Annotation #44, "Other Therapies.")

Studies have documented the ability of UFH to decrease the risk of recurrent venous thromboembolism when adequate levels are reached within 24 hours. However, a recent meta-analysis found no difference in the rate of recurrent VTE in patients treated with a bolus of at least 5,000 units of UFH followed by 30,000 units/24 hours. Two prospective studies have determined the adequate level of anticoagulation to correspond to an activated partial thromboplastin time (aPTT) of 1.5 times normal. The therapeutic range of heparin is an aPTT 1.5 to 2.5 times normal, corresponding to a plasma heparin concentration of 200 to 400 units/L determined by protamine titration. An increased risk of bleeding complications associated with an aPTT level greater than 2.5 has not been substantiated in a recent prospective randomized study *(Hirsch, 1991 [R]; Hull, 1986 [A]; Hull, 1992 [A]; Pineo, 1994 [R])*.

Several protocols for managing heparin therapy have been shown to more rapidly achieve therapeutic anticoagulation (as measured by aPTT levels) versus historical controls. This work group favors the protocol developed by Raschke, et al. *(Raschke, 1993 [A])*.

Other acceptable protocols are discussed in the literature. These include a fixed initial maintenance dose, two levels of the initial maintenance dose based on the patient's risk of bleeding, and several levels of the initial maintenance dose based on the patient's body weight *(Cruickshank, 1991 [C]; Raschke, 1993 [A]; Shalansky, 1996 [C])*. Data from a single study of 708 patients suggests that fixed-dose, weight-adjusted unfractionated heparin may be safe and effective in treating acute deep thrombosis *(Kearon, 2006 [A])*.

(Snow, 2007 [A])

Fondaparinux

Fondaparinux, a sodium pentasaccharide, is administered by subcutaneous injection once daily for the treatment of deep vein thrombosis and pulmonary embolism. Fondaparinux (Arixtra®) has a long half-life of 17-21 hours, with no known antidote, and some encourage caution in patients at higher risk of bleeding complications. Other precautions include the elderly, renal insufficiency and patients weighing less than 50 kg. The usual dose is 5 mg once daily for patients less than 50 kg, 7.5 mg once daily for patients 50-100 kg, or 10 mg once daily for patients over 100 kg. Fondaparinux treatment should be continued for a least five days and until a therapeutic oral anticoagulant effect is established (INR 2.0 to 3.0). Warfarin should be initiated as soon as possible, usually within 72 hours.

The heparin assay (anti-factor-Xa) has been used to monitor effects of fondaparinux; however, new calibrators other than heparin will need to be established. A platelet count should be obtained prior to the initiation of fondaparinux and periodically to check for bleeding. Antibodies to fondaparinux rarely interact with Platelet Factor 4. There are several reports of HIT with fondaparinux (see the ICSI Antithrombotic Therapy Supplement). Additional platelet monitoring is not required.

Heparin-Induced Thrombocytopenia (HIT)

Both UFH and LMWH are associated with heparin-induced thrombocytopenia (HIT). HIT is an immune-mediated reaction to heparins. It occurs in 2%-3% of patients treated with UFH and less than 1% of patients treated with LMWH. This syndrome can be associated with paradoxical increased risk for venous and arterial thrombosis. Patients who develop HIT without associated thrombosis will have a significant risk for thrombosis in the subsequent 100 days. Patients with a history of HIT should not be treated with UFH or LMWH.

HIT should be suspected in patients who develop a skin lesion reaction at the injection site, have a systemic reaction to a bolus administration of heparin, or develop a greater than 50% decrease in platelet count from baseline labs while on heparin.

Delayed-onset HIT is an increasingly recognized form of this disorder. Patients with delayed-onset HIT typically present with thromboembolic complications one to two weeks (range 5 to 40 days) after receiving their last dose of LMWH or UFH. They frequently display mild or moderate thrombocytopenia. When HIT is not recognized as the etiology of the thromboembolic complication, the patient is frequently rechallenged with heparin, causing significant worsening of the thrombosis, as well as the thrombocytopenia. These patients typically have very high titers of HIT-related antibodies. The possibility of delayed-onset HIT should be considered in any patient presenting with thromboembolism after a recent hospitalization.

Patients suspected of having any form of HIT should have their heparin stopped while antibody testing for HIT is performed. Patients with a high clinical probability of having HIT should be treated with an appropriate alternative anticoagulant before antibody test results are available. Direct thrombin inhibitors (DTIs) are the alternative anticoagulant of choice for patients with HIT. Three brands are FDA approved: lepirudin, argatroban and most recently, bivalirudin *(Warkentin, 2003 [R]; Warkentin, 2004a [R], Warkentin, 2004b [R])*.

If a patient is receiving warfarin when there is a high clinical probability of HIT, the warfarin should be stopped. The warfarin effect should be reversed with vitamin K, and direct thrombin inhibitor (DTI)

therapy should be initiated. Low-maintenance doses of warfarin can be restarted during DTI therapy after the platelet count has significantly improved and there is clinical improvement in the patient's thrombosis. There should be at least a five-day overlap of the DTIs and warfarin. The DTI therapy should be continued until the platelet count stabilizes *(Warketin, 2004b [R])*. See Annotation #44, "Other Therapies," for more information.

Please refer to the ICSI Antithrombotic Therapy Supplement for more information on low-molecular-weight and unfractionated heparins, synthetic pentasaccharides, and HIT.

36. Warfarin

Key Points:

- A high-loading dose of warfarin (greater than 10 mg) is of no clinical use and should be discouraged.
- A 10 mg initial dose of warfarin has been associated with early over anticoagulation and, when compared to a 5 mg initial dose, was no more effective in achieving a therapeutic international normalized ratio (INR) by day four or five of therapy.
- A therapeutic range of anticoagulation to keep the INR at 2.5 (range 2.0-3.0) is recommended for patients with venous thromboembolism.
- Heparin (UHF or LMWH) and/or fondaparinux should be given for at least five days and until the INR is $\geq$ 2.0 for two consecutive days.

It has been shown that oral anticoagulation with warfarin decreases the complications and recurrence rate of thrombosis *(Hull, 1982 [A])*.

It is recommended that warfarin therapy be initiated with a dose of 5 mg (less in patients with risks for increased sensitivity to warfarin), with dosage adjustments based on results of international normalized ratio (INR) testing.

- A high-loading dose of warfarin (greater than 10 mg) is of no clinical use and should be discouraged. A high-loading dose induces a rapid but excessive reduction in Factor VII activity, predisposing patients to hemorrhage in the first few days of therapy. It fails to achieve a significantly more rapid decline of the other vitamin K dependent coagulation factors (II, IX and X) above that achieved without a loading dose *(O'Reilly, 1968 [B])*.
- A 10 mg initial dose of warfarin has been associated with early over anticoagulation and, when compared to a 5 mg initial dose, was no more effective in achieving a therapeutic INR by day four or five of therapy. Formulas have been devised to predict dosing requirements from the early phase of warfarin therapy. One protocol used an initial 10 mg dose and predicted maintenance dosage based on INR results on the second and third days of therapy *(Fennerty, 1984 [D])*. A communication in the *Annals of Internal Medicine* compared patients initiated on 10 mg versus 5 mg of warfarin. Although the 10 mg group achieved a therapeutic INR sooner (44% at 36 hours versus 8% at 36 hours), there was also a greater incidence of over anticoagulation in patients given the higher initial dose. A follow-up study of similar design showed equal efficacy in achieving a therapeutic INR for patients given 5 mg vs 10 mg initial warfarin dosing *(Crowther, 1999 [A]; Harrison, 1997 [A])*.

A therapeutic range of anticoagulation to keep the INR at 2.5 (range 2.0-3.0) is recommended for patients with venous thromboembolism (VTE). The anticoagulant effect of warfarin is delayed until clotting factors already circulating are cleared. Although Factor VII has a shorter half-life in the blood (six to seven hours), peak anticoagulant activity is delayed for up to 96 hours until factors with longer plasma half-lives (II, IX

and X) have cleared *(Ansell, 1993 [R])*. Therefore, it is recommended that heparin (UFH or LMWH) and/or fondaparinux be given for at least five days and until the INR is ≥ 2.0 for two consecutive days.

In patients with suspected hypercoagulable state (Protein C or Protein S deficiency), the patient should be adequately anticoagulated with heparin before warfarin is started at a low dose (2-5 mg). This is to avoid warfarin-induced skin necrosis or other transient hypercoagulable complications *(Ansell, 1993 [R])*.

The ICSI Antithrombotic Therapy Supplement contains additional information on warfarin therapy, including an appendix on interactions with warfarin.

37. Outpatient Treatment Appropriate?

Key Points:

- Home therapy with low-molecular-weight heparin is as safe and effective as in-hospital therapy with standard unfractionated heparin for patients with uncomplicated venous thromboembolism.
- Because of decreased cardiorespiratory reserve, patients presenting with **symptomatic** pulmonary embolism should initially be treated in-hospital.

Inclusion criteria for outpatient therapy:

- Patient does not have complicated venous thromboembolism (See Annotation #34, "Complicated Venous Thromboembolism or Comorbidities?")
- Patient has good cardiorespiratory reserve
- Patient has no excessive bleeding risks
- Patient's creatinine clearance is greater than 30 mL/minute

Because of decreased cardiorespiratory reserve, patients presenting with **symptomatic** pulmonary embolism should initially be treated in-hospital.

Other considerations include:

- Patients need to be taught how to administer the drug and recognize complications.
- Daily international normalized ratios (INRs) will be needed to guide the institution of warfarin therapy. The warfarin dose will need to be adjusted to the INR.
- Patients will need resources to answer questions and deal with problems.

(Harrison, 1998 [D]; Koopman, 1996 [A]; Levine, 1996 [A]; Snow, 2007 [R]; Wells, 1998a [C])

38. Inpatient Treatment

Therapy is discussed in Annotation #35, "Low-Molecular-Weight Heparin (LMWH)/Unfractionated Heparin (UFH)/Fondaparinux," and in Annotation #36, "Warfarin."

39. Outpatient Protocol

Key Points:

- Patients may need hospitalization during the first 24 hours to start therapy promptly.
- Graduated compression stockings (not Teds) combined with early ambulation does not cause any increase in pulmonary embolism and gives more rapid resolution of pain and swelling.

Because of the need for an organized support system and time-of-day considerations for home care agencies, many patients may need hospitalization during the first 24 hours to start therapy promptly.

All stable venous thromboembolism patients

- Daily self-administered injections, caregiver-administered injections, or daily clinic visits. The patient will need to be geographically accessible to have INRs drawn and receive care for problems that arise.
- Daily INR for transitioning to warfarin treatment after two days of adequate anticoagulation. (For details, see the ICSI Antithrombotic Therapy Supplement.)
- Duration of anticoagulation to be determined by the supervising physician.

Deep vein thrombosis patients

- If the criteria in Annotation #37, "Outpatient Treatment Appropriate?" can be met, DVT treatment can be started in the outpatient setting; otherwise, hospitalize until teaching, medication and close follow-up can be assured.
- For DVT, use graduated compression stockings, at least 30-40 mm Hg (not Teds) on the affected leg to reduce the risk of post-phlebitic syndrome. Stockings are contraindicated for patients with peripheral artery disease.
- Graduated compression stockings (not Teds) combined with early ambulation does not cause any increase in pulmonary embolism and gives more rapid resolution of pain and swelling. A study of 638 consecutive patients with DVT who were allowed to ambulate showed a low incidence of ventilation/perfusion scan-documented pulmonary emboli compared with that reported in the literature, suggesting no increased risk from early ambulation *(Prandoni, 2004 [A]; Brandjes, 1997 [A]; Partsch, 1997 [D])*.

In a study of consecutive patients, the safety of graduated compression stockings and moblization was demonstrated based on no increase in pulmonary embolism (PE) for 1,289 patients treated. The resolution of pain and swelling was significantly faster when the patient ambulated with graduated compression stockings *(Partsch, 2000 [A])*. For management of patients with chronic post-thrombotic syndrome, please see Annotation #43, "Continued Anticoagulation with Follow-Up and Secondary Prevention."

Please refer to the ICSI Antithrombotic Therapy Supplement for a discussion of complications during anticoagulation therapy.

(Snow, 2007 [R])

40. Patient Education

Patients should be instructed on the use of anticoagulants. Please refer to the ICSI Antithrombotic Therapy Supplement for more information on patient education. Patient education materials are also available. (See the Support for Implementation section.)

41. Complications during Therapy?

Key Points:

- Patients with complicated venous thromboembolism or certain comorbidities may require therapy that is different than patients with uncomplicated venous thromboembolism. These patients should be identified and treated individually rather than by a standard guideline.

Patients with complicated venous thromboembolism or certain comorbidities may require therapy that is different than patients with uncomplicated venous thromboembolism. These patients should be identified and treated individually rather than by a standard guideline.

Patients on unfractionated heparin, low-molecular-weight heparin or fondaparinux therapy who have bleeding, thrombocytopenia or osteoporosis may require individual adjustments in therapy. Heparin-induced thrombocytopenia (HIT) should be suspected if the platelet count drops 50% or more from baseline labs.

Patients on warfarin therapy who experience bleeding or skin necrosis, or who become pregnant may require individual adjustments in therapy.

The development of a complication attributable to anticoagulation requires action by the health care team. Sometimes, as with heparin-induced thrombocytopenia (HIT), the drug must be discontinued. The most common complication – bleeding – may require a dosage adjustment, discontinuation of the drug, or further evaluation in the setting of gastrointestinal or genitourinary bleeding. Specific actions are best determined on a case-by-case basis by the clinician, who can appropriately weigh the risks and benefits of continued anticoagulation therapy and who can take into account the timing of the complication.

Please refer to the ICSI Antithrombotic Therapy Supplement for more information on potential complications of anticoagulation therapy.

42. Anticoagulation Failure?

Key Points:

- Recurrent symptomatic deep vein thrombosis or pulmonary embolism during adequate heparin or warfarin treatment represents failure of treatment and needs objective documentation, especially as a new DVT may be difficult to distinguish from post-phlebitic syndrome.
- If a patient fails on warfarin therapy, heparin or low-molecular-weight heparin may need to be reinstituted.

Recurrent symptomatic deep vein thrombosis or pulmonary embolism (PE) during adequate heparin or warfarin treatment represents failure of treatment and needs objective documentation, especially as a new DVT may be difficult to distinguish from post-phlebitic syndrome.

Active cancer is the most common cause of warfarin failure *(Heit, 2000b [B]; Prandoni, 2002 [B])*.

A 4.9% risk of recurrent DVT or PE was found within the first three months of treatment in a series of 355 consecutive DVT patients. This study used venography to detect recurrence of DVT, supplemented by a 125I-fibrinogen leg scan or ultrasonography *(Prandoni, 1996 [B])*.

Antiphospholipid antibodies may be the cause of anticoagulant failure. In these patients, recurrence was most likely in the six months following cessation of warfarin, and higher international normalized ratios of greater than or equal to 3.0 were more effective than 2-3. Aspirin did not help *(Hull, 1982 [A]; Khamashta, 1995 [C])*.

In certain circumstances, alternate treatment such as an inferior vena cava (IVC) filter may be indicated. If a patient fails on warfarin therapy, heparin or LMWH may need to be reinstituted. The work group felt these patients should be identified and treated individually rather than by a standard guideline. The 8th American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy provided the following recommendations regarding placement of an IVC filter:

- For most patients with DVT, the ACCP recommends **against** the routine use of a vena cava filter in addition to anticoagulants.
- In PE or proximal DVT patients with a contraindication or a complication of anticoagulant treatment, as well as those with recurrent thromboembolism despite adequate anticoagulation, the ACCP suggests placement of an inferior vena cava filter.
- Patients with distal (calf vein) thrombosis may have anticoagulation stopped but do not likely need IVC filter given their low risk of embolization.

(Kearon, 2008 [R])

43. Continued Anticoagulation with Follow-Up and Secondary Prevention

Key Points:

- The length of anticoagulation therapy should be individualized to the patient and the circumstances that caused venous thromboembolism (VTE).
- Patients who have had VTE remain at risk for recurrence for up to 10 years.

Graduated Compression Stockings (not Teds)

Knee-high 30-40 mm Hg custom-fitted, graduated compression stockings help alleviate symptoms of edema and pain in patients who have post-phlebitic syndrome. One report showed that graduated compression stockings reduced the incidence of post-phlebitic syndrome by 50% in patients with acute deep vein thrombosis. For chronic or recurrent venous stasis ulcer, consultation with a vascular surgeon should be considered *(Brandjes, 1997 [A]; Ginsberg, 1989 [D]; Pierson, 1983 [C]; Prandoni, 2004 [A])*.

Duration of Anticoagulation

Most VTE episodes are treated adequately with three-to-six months of anticoagulation, after which time an individualized assessment of risk of recurrence should be made. The initial duration of warfarin anticoagulation must be individualized depending on risks of (VTE) recurrence and risk of a complication (e.g., bleeding) due to warfarin therapy. The 8th American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy recommends:

- Transient risk/provoked (e.g., surgery, immobilization, estrogen use, trauma): 3 months. Shorter treatment periods are associated with a higher rate of recurrence and are not recommended.
- Idiopathic risk/unprovoked: 3-6 months.
  - Patients with documented antiphospholipid antibodies or two or more thrombophilic conditions should be treated for 3-6 months and considered for indefinite anticoagulation therapy.
  - Patients with documented deficiency of antithrombin, protein C or S, factor V Leiden, prothrombin 20210 mutation, homocysteinemia or high factor VIII conditions should be treated for 3-6 months and considered for indefinite anticoagulation therapy.

- Recurrent disease or continued risk factors: indefinite.
  - Patients with cancer should be initially treated for 3 to 6 months with LWMH and then with anticoagulation therapy indefinitely or until the cancer is resolved.
  - Patients with two or more episodes of documented DVT should receive anticoagulation therapy indefinitely.

(Kearon, 2008 [R]; Snow, 2007 [R])

The length and duration of anticoagulation should be tailored to the patient dependent on individual circumstances: for transient/provoked cause (e.g., travel, trauma, surgery, oral contraceptives or hormone replacement therapy), 3 months; for idiopathic/unprovoked, 3-6 months; for recurrent disease, indefinite anticoagulation may be appropriate. [*Conclusion Grade II: See Conclusion Grading Worksheet A – Annotation #43 (Duration of Anticoagulation)*]. For patients with cancer and patients with a particular genetic makeup, an alternate schedule may be more appropriate. The length and duration of anticoagulation should be tailored to the patient dependent on individual circumstances: for recurrent disease in cancer patients, low-molecular-weight heparin (preferred over warfarin in this group) for at least 6 months; for recurrent disease in patients who are carriers of thrombophilia genes, 6 months to indefinite. *[Conclusion Grade II: See Conclusion Grading Worksheet A – Annotation #43 (Duration of Anticoagulation)]*

Earlier studies suggested a longer course of anticoagulation therapy imparted greater protection against recurrence, but a study by Agnelli et al. showed equivalent recurrence rates in patients treated for 3 months versus 12 months after warfarin therapy was discontinued *(Agnelli, 2001 [A])*.

In general, the risk of recurrence is highest within the first three-six months after VTE onset. However, VTE patients remain at increased risk for recurrence for at least 10 years, with a 30% 10-year cumulative incidence of recurrence. Fortunately, patients can be stratified into a high or low risk of VTE recurrence. For example, patients with a previous history of VTE have a higher risk of recurrence compared to patients with a first-lifetime VTE. Moreover, patients with a first-lifetime VTE can be further stratified into high and low risk for recurrence based on several baseline characteristics (e.g., risk factors), and by laboratory evidence of an acquired or familial thrombophilia. Such persistent risk factors as active cancer, stroke with extremity paresis, male gender and obesity increase the risk of recurrence. Patients developing VTE in the absence of recognized risk factors (e.g., idiopathic VTE) also appear to be at high risk for recurrence *(Kearon, 2008 [R])*.

In contrast, reversible or transient risk factors are associated with a lower risk of recurrence. These include surgery, estrogen use (oral contraceptives, hormone therapy) and pregnancy or the puerperium. Patients with a lupus anticoagulant or anticardiolipin antibody are at increased risk for recurrence, as are homozygous Factor V R506Q (Leiden) mutation carriers or combined heterozygous carriers for both the Factor V Leiden and Prothrombin 20210 G A mutation *(Heit, 2000b [B])*. See Table 2, "Laboratory Tests for Thrombophilia" later in this annotation. Men appear to be at increased risk of recurrent VTE compared to women, based on observational data and randomized controlled trials. A meta-analysis of 15 studies found the risk to be higher in the observational studies rate of recurrence 2.1 than in the RCTs where the rate of recurrence was 1.3 *(McRae, 2006 [M])*. The increased risk is seen whether or not the cause of VTE is idiopathic and includes recurrent pulmonary embolism *(Baglin, 2004 [B]; Kyrle, 2004 [B]; White, 2006 [B])*.

Patients with idiopathic VTE require at least 3-6 months of warfarin anticoagulation. Whether first-lifetime VTE patients with persistent risk factors (e.g., cancer, stroke with extremity paresis, obesity, homozygous Factor V R506Q carriers, combined heterozygous Factor V R506Q and Prothrombin 20210 G/A carriers) should receive a longer duration of anticoagulation (e.g., lifetime) has not been adequately studied. For the present, this decision must rely on clinical judgment, as well as patient preference. In the absence of contraindications, indefinite anticoagulation is generally recommended for patients with recurrent VTE *(Diuguid, 1997 [R]; Eisher, 2008 [A]; Prandoni, 2008 [B])*.

Balancing the length of anticoagulation therapy with the patient's risk for recurrence has been evolving in the literature. Some patients may receive anticoagulation therapy much longer than necessary while others may need to continue therapy beyond the normal time.

Patients with an abnormal D-dimer result after anticoagulation therapy is stopped show a high rate of recurrence (15.0%). In these studies, patients with a normal D-dimer after anticoagulation therapy is stopped show a recurrence rate of 3.5%-6.2%. When anticoagulation therapy is resumed, the combined rate of recurrence and bleeding was 2.9% (p=0.005) *(Palareti, 2006 [B]; Verhovsek, 2008 [M])*.

(Hron, 2006 [B])

The presence of residual venous clot at three months assessed by ultrasound has also been associated with a high risk of recurrent VTE if anticoagulation is stopped, 23.1% compared to 1.3% in those without residual clot *(Siragusa, 2008 [A])*.

A summary of risk factors for recurrence is listed below.

Table 1. Risk Factors for Recurrent VTE in Patients with Unprovoked DVT

Risk Factor	Relative Risk
Calf versus proximal DVT	0.5
One or more prior VTE	1.5
Negative D-dimer post-anticoagulation	0.4
Antiphospholipid antibody	2.0
Hereditary thrombophilia	1.5
Male versus female	1.6
Asian ethnicity	0.8
Residual thrombosis	1.5

(Kearon, 2008 [R])

In addition to assessing a patient's risk of recurrent thrombosis, a patient's risk for bleeding on chronic anticoagulation needs to be assessed. Risk factors for bleeding on chronic anticoagulation are listed below.

Risk factors for major bleeding during anticoagulation therapy:

- Age more than 75
- Previous GI bleed
- Previous noncardioembolic stroke
- Chronic renal/hepatic disease
- Concomitant antiplatelet therapy
- Serious other illness
- Poor anticoagulant control
- Suboptimal monitoring of therapy

(Kearon, 2008 [R])

Anticoagulation Management

A coordinated effort for follow-up of patients started on warfarin is required to minimize the risks of both hemorrhagic and thrombotic complications while on treatment. In the first several weeks of anticoagulation, international normalized ratios (INRs) need to be checked at least weekly. After stabilization, the interval between INRs can be increased from weekly to biweekly, up to but not beyond four weeks *(Ansell, 1996 [R]; Ellis, 1992 [C]; Poller, 1993 [A])*.

A goal INR target of 2.5 is recommended for the majority of patients who are kept on long-term anticoagulation. Patients who have recurrent VTE on adequate anticoagulation with warfarin may require a higher target INR (e.g., 3.0). One study suggested protection against recurrence in patients who were initially treated for 6-12 months at the target INR of 2.5, then treated to an INR range of 1.5-2.0. However, a recent study comparing long-term anticoagulation at INR 2.5 versus INR 1.5-2.0 showed greater protection against recurrence with the higher target INR of 2.5 *(Kearon, 2003 [A]; Ridker, 2003 [A])*.

Anticoagulation clinics and computerized dosing programs have helped assist in the management and monitoring of patients on warfarin therapy. These areas of anticoagulation therapy are evolving at this time.

Please refer to the ICSI Antithrombotic Therapy Supplement for more information on establishing and maintaining anticoagulation clinics.

Long-Term Complications

The post-thrombotic syndrome (PTS) is the most common complication of lower extremity deep venous thrombosis, occurring in 20-50% of patients. The syndrome is typically an under recognized, under diagnosed, and undertreated condition. Clinically, the symptoms are characterized by chronic leg pain, swelling, fullness and heaviness that can have a significant impact on activities of daily living. Long-term sequelae include development of venous hypertensive ulcerations, which can be recalcitrant to standard treatment and often recurrent. Additional late physical signs include chronic lower extremity edema, hyperpigmentation, lipodermatosclerosis and development of varicose veins *(Kahn, 2006 [R]; Meissner, 2007 [R])*.

The pathophysiology of PTS is related to the direct deep venous valvular damage as a result of deep venous thrombosis, ultimately resulting in valvular incompetence. Persistent occlusive or sub-occlusive residual thrombus increases the occurrence of PTS.

Onset of symptoms after development of a DVT may not occur for 6-24 months after resolution of the acute symptoms. Recurrent DVT within the affected limb markedly increases the risk of PTS development. Subsequent long-term sequelae of venous ulcerations may not occur for 10-20 years after the initial deep venous thrombosis *(Kahn, 2006 [R])*.

Standardized treatment includes initiation of 30-40 mm Hg weight knee-high or thigh-high compression stockings for management of the acute symptoms, and continued for a minimum of two years or longer if patients have persistent symptoms of PTS *(Kakkos, 2006 [M]; Kearon, 2008 [R])*. Subsequent long-term utilization of graduated compression stockings (not Teds) is standard of care for patients who develop chronic PTS symptoms. Additional treatments include obtaining an ideal body mass index (BMI) and participation in a regular exercise regime that maintains an adequate calf muscle pump function.

Without adequate recognition and treatment of PTS, patients may develop significant disabilities and a subsequent inability to perform daily activities of living, including gainful employment. The direct and indirect costs of PTS are significant to the patient, the patient's family and society as a whole, with an estimated treatment cost of greater than $300,000,000 per year in the United States and an estimated 2,000,000 work days lost annually in the United States due to the presence of venous hypertensive ulcerations alone *(Kahn, 2006 [R])*.

Look for Malignancy?

Some patients who present with idiopathic DVT may have occult malignancy. However, extensive workups in asymptomatic patients beyond appropriate cancer screening have not shown benefit *(Prandoni, 1992 [B])*.

In patients with known cancer, risk of DVT is increased. In patients who have idiopathic DVT, there may be cancer present at the time of presentation in 3%-12% of cases. A routine complete medical examination (including history, physical examination [including pelvic, rectal and breast examination], complete blood count, sedimentation rate, renal and liver function tests, urinalysis and chest x-ray) was deemed adequate to detect cancer. Cornuz had no one develop cancer who had not shown abnormalities on these initial screens. This study with 986 consecutive evaluations retrospectively found no difference in cancer incidence over the next 34 months among the 142 DVT patients and those 844 in whom DVT was ruled out *(Cornuz, 1996 [C])*.

Thrombophilia

Certain patients should be tested for thrombophilia. This testing should be done two weeks after discontinuation of anticoagulation *(Griffin, 1996 [R])*. The work group recommends consideration be given to a discussion with a thrombophilia expert for:

- patients who have recurrent thromboembolic disease, and
- patients with first idiopathic DVT who:
  - are less than 50 years of age,
  - have a family history of VTE among one or more first-degree relatives,
  - have an unusual site of spontaneous thrombosis, or
  - have massive venous thrombosis.

Table 2. Laboratory Tests for Thrombophilia

In most circumstances, laboratory tests for thrombophilia should be done at least two weeks after discontinuation of anticoagulation. If levels are found to be low during anticoagulation, they should be confirmed off anticoagulation. The following are listed in decreasing order of prevalence among unselected DVT patients:

- 25% Elevated factor VIII: C above 150% of normal *(Koster, 1995 [C])*
- 21% Factor V Leiden (resistance to activated protein C) *(Bertina, 1994 [D]; Koster, 1993 [C])*
- 19% Factor XI elevation above 90th percentile *(Meijers, 2000 [C])*
- 14% Lupus anticoagulant (in non-systemic lupus erythematosus patients) *(Ginsberg, 1995 [B])*
- 10% Hyperhomocystinemia and stronger in women and increased age (diagnostic studies may be unreliable) *(Den Heijer, 1996 [C])*
- 6.2% Prothrombin gene 20210 A allele *(Poort, 1996 [C])*
- 2.8% Antithrombin III deficiency
- 2.5% Protein C deficiency
- 1.3% Protein S deficiency *(Pabinger, 1992 [B])*

Activity Level

There is no evidence that restriction of activity is of benefit nor is there evidence to determine the appropriate activity level. The physician needs to be guided by individual patient circumstances, including pain and swelling. In a study of consecutive patients, the safety of graduated compression stockings (not Teds) and mobilization was demonstrated based on no increase in PE for 1,289 patients treated. The resolution of pain and swelling was significantly faster when the patient ambulated with graduated compression stockings (not Teds) *(Partsch, 2000 [A])*.

Ambulatory exercise programs are unlikely to exacerbate symptoms and may result in improved leg muscle flexibility *(Kahn, 2003 [C])*.

44. Other Therapies*

* Other therapies may include IVC filters, serial calf ultrasound, heparin-induced thrombocytopenia therapy, thrombolytic therapy and surgery.

Key Points:

- Direct thrombin inhibitors have been used to treat heparin-induced thrombocytopenia successfully.
- Thrombolytic therapy results in a more rapid clot resolution but does not significantly reduce mortality or risk of recurrent pulmonary embolism.

Inferior Vena Cava (IVC) Filters

Treatment is required, due to risk of mortality. Accepted indications for inferior vena caval interruption include:

- patients with pulmonary embolism (PE) or proximal deep vein thrombosis and contraindications to anticoagulation;
- progressive thromboembolism, despite *adequate* anticoagulation; and
- patients with underlying pulmonary hypertension in whom a PE would likely be fatal.

Consultation with a specialist is strongly recommended prior to placement of a filter, as long-term sequelae of filter placement include increased risks of recurrent DVT and PE.

IVC filter is the procedure of choice in patients with a contraindication or complication of anticoagulation who are at high risk for proximal vein thrombosis, who experience recurrent thromboembolism despite adequate anticoagulation, who have chronic recurrent PE with pulmonary hypertension, or who are undergoing pulmonary embolectomy or pulmonary endarterectomy. Although there are no randomized or cohort studies comparing anticoagulation to IVC, a meta-analysis of 2,557 patients who were treated using IVC found the filters to have a low incidence of pulmonary embolization (2%), a rare incidence of fatal complications (0.12%), and an acceptable rate of non-fatal adverse consequences of filter placement *(Decousus, 1998 [A]; Kearon, 2008 [R]; Mohan, 1996 [C])*.

A randomized study of vena caval filters in ***anticoagulated*** patients with proximal DVT showed a significant decrease in the incidence of PE. This was counterbalanced, however, by a significant increase in the rate of late recurrent symptomatic deep vein thrombosis *(Decousus, 1998 [A]; Kearon, 2008 [R])*.

The recent advent of retrievable filters has made short-term placement possible for patients with transient contraindications to anticoagulation therapy. However, the ICSI work group's clinical experience shows retrievable filters, in practice, are removed less than one fourth of the time. An audit at one center found

that follow-up for retrievable filter placements was inadequate. Failure to remove the filter was documented in 15% of the cohort *(Seshadri, 2008 [M])*. Filter placement does not provide treatment for existing VTE. When safe, anticoagulation should be considered.

Serial Ultrasound in Calf Deep Vein Thrombosis

Serial ultrasound (at three and seven days) may be useful to evaluate for propagation of thromboses in two groups of patients:

- Patients with a positive diagnosis of a calf thrombosis, but contraindications to anticoagulation therapy
- Patients with clinical suspicion of calf thrombosis, but initial negative ultrasound. In general, patients with symptomatic calf DVT who do not have contraindications to anticoagulation will do better if treated similarly to those with a proximal DVT *(Lagerstedt, 1985 [A])*.

It is safe to withhold anticoagulation in patients with whom serial compression ultrasound is negative over five to seven days, provided the initial study includes the femoral vein, the popliteal fossa, and scanned to the trifurcation of the calf veins *(Lohr, 1992 [D]; Masuda, 1998 [D]; Philbrick, 1988 [R])*.

Although serial compression ultrasound testing is safe, it is often inconvenient for patients and health care providers, and may not be cost effective. When patient follow-up cannot be guaranteed, serial compression ultrasound protocols should not be utilized *(American Thoracic Society, 1999 [R]; Birdwell, 1998 [B]; Cogo, 1998 [B]; Heijboer, 1993 [A]; Stein, 1995 [C]; Wells, 1999 [R]; Wells, 1998b [B])*.

Treatment of Heparin-Induced Thrombocytopenia (HIT)

Patients developing HIT while on heparin therapy should be taken off all unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH). Direct thrombin inhibitors have been used to treat HIT successfully. Direct thrombin inhibitors approved for the treatment of HIT include lepirudin, argatroban and bivalirudin. Direct thrombin inhibitors must be administered by continuous intravenous infusion necessitating hospitalization. Direct thrombin inhibitor therapy must be monitored by measuring the activated partial thromboplastin time *(Hirsch, 2001b [R])*.

Please refer to the ICSI Antithrombotic Therapy Supplement for more information on HIT.

Intravenous Thrombolytic Therapy

Lytic therapy has been used in patients with extensive iliofemoral disease who demonstrate evidence of vascular compromise (phlegmasia). Lytic therapy has been touted as potentially reducing the long-term post-phlebitic consequences of proximal DVT through early thrombolysis, restoration of patency, and preservation of venous valve function. When utilized, catheter-directed lytic therapy is preferred over systemic lytic therapy. This therapy has been suggested as a means of reducing the incidence of post-thrombotic syndrome. However, long-term randomized studies comparing this therapy to standard anticoagulation have not been performed. Management should be individualized and is most appropriate for patients with massive iliofemoral thrombosis. Consultation with a specialist is strongly recommended prior to initiation of lytic therapy *(Comerota, 2001 [R]; Kearon, 2008 [R]; Mewissen, 1999 [D]; Semba, 1994 [D])*.

Thrombolytic therapy results in more rapid clot resolution, but it does not significantly reduce mortality or the risk of recurrent PE in hemodynamically stable patients *(Arcasoy, 1999 [M]; Urokinase, 1970 [A])*. Pooled data show thrombolytic therapy has an increased incidence of major hemorrhage and intracranial hemorrhage as compared to UFH therapy alone. Elevated diastolic blood pressure is a risk factor for intracranial hemorrhage *(Arcasoy, 1999 [M]; Kanter, 1997 [D])*.

Surgical Thrombectomy

In a highly select group of patients, surgical venous thrombectomy has been utilized. These patients typically have extensive venous thrombosis and have contraindications to anticoagulation and lytic therapy. Surgical thrombectomy has historically been utilized to reduce acute symptomatology in patients with iliofemoral thrombosis and was touted to reduce the risk of post-phlebitic syndrome development *(Juhan, 1997 [D]; Meissner, 1996 [D])*. Management should be individualized. The morbidity and mortality associated with this surgical procedure deems it be a procedure of last choice.

Appendix A – Wells Model of the Clinical Pretest Probability of Deep Vein Thrombosis

A Model of the Clinical Pretest Probability of Deep Vein Thrombosis*	
Score	
1	Active cancer (treatment ongoing or within previous 6 months or palliative)
1	Paralysis, paresis or recent plaster immobilization of lower extremity
1	Recently bedridden for more than three days or major surgery within four weeks
1	Localized tenderness along the distribution of the deep venous system
1	Entire leg swollen
1	Calf swollen by more than 3 cm when compared to asymptomatic leg (measured 10 cm below tibial tuberosity)
1	Pitting edema (greater in the symptomatic leg)
1	Collateral superficial veins (non-varicose)
-2	Alternative diagnosis as likely or greater than that of deep vein thrombosis

If both legs are symptomatic, score the more severe side.

High risk =	scored 3 or more
Moderate risk =	1 or 2
Low risk =	0 or less

* Reprinted from *Lancet* 350:1795-98, Wells PS, Anderson DR, Bormanis J, et al. "Value of assessment of pretest probability of deep vein thrombosis in clinical management." 1326-30, Copyright 1997, with permission from Elsevier.

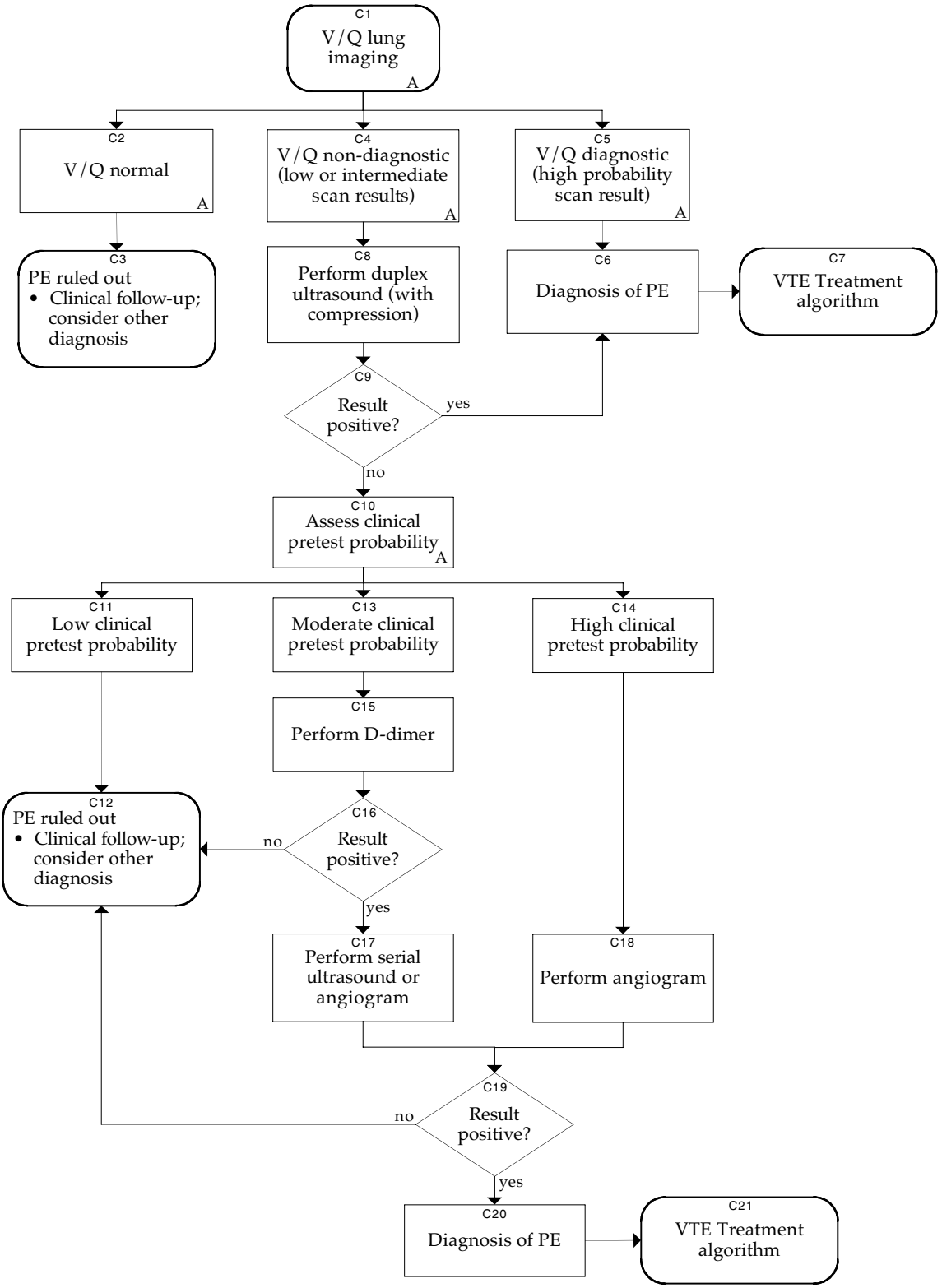
Appendix B – Model for Predicting Clinical Pretest Probability for Pulmonary Embolism

Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3 points
An alternative diagnosis is less likely than PE	3 points
Heart rate greater than 100	1.5 points
Immobilization or surgery in previous four weeks	1.5 points
Previous DVT/PE	1.5 points
Hemoptysis	1 point
Malignancy (on treatment, treated in last six months or palliative)	1 point
Score	
PE Less Likely: ≤ 4 PE Likely: > 4 Score of 6^{+} – Start heparin will continuing clinical and diagnostic evaluation	

Reproduced with permission of Schattauer and Wells PS.

Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost* 2000;83:416-20.

Appendix C – Ventilation Perfusion (V/Q) Lung Imaging Algorithm



C1. Ventilation/Perfusion (V/Q) Lung Imaging

The phraseology of V/Q classification has generated confusion. Low probability scans are not really low clinical probability for pulmonary embolism (PE). Up to 25% of these patients have PE on angiogram. Approximately 40% of patients with intermediate (non-diagnostic) scans have positive angiograms. Thus, these two groups of scans are more properly considered non-diagnostic scans and require further evaluation. In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED), 72% of enrolled patients had non-diagnostic scans. All these patients required further evaluation. In general, normal and high probability scans are considered diagnostic unless the clinical probability strongly suggests otherwise. Low, intermediate and indeterminate readings are considered non-diagnostic and have a probability of PE that ranges from about 15% to 40%. Further testing is usually required. When a contrast load needs to be avoided, such as in patients with renal insufficiency or dye allergy, the V/Q scan is preferred *(PIOPED Investigators, 1990 [C])*.

High probability scans are associated with PE approximately 90% of the time, and unless the clinical situation does not fit, can be considered positive.

(Hull, 1985 [C]; Hull, 1995 [B])

C2. Ventilation/Perfusion Normal

A normal perfusion scan, irrespective of ventilation abnormalities, essentially excludes the diagnosis of pulmonary embolism *(ACCP Consensus Committee on Pulmonary Embolism, 1998 [R]; Goldhaber, 1998 [R]; Hull, 1990a [D])*.

C4. Ventilation/Perfusion Non-Diagnostic (Low or Intermediate Scan Results)

Radiologists typically report non-diagnostic scans as either low probability or intermediate probability. Low probability scans are associated with positive angiograms 15%-25% of the time. Intermediate probability scans are associated with positive angiograms 30%-40% of the time. Therefore, clinicians currently designate these as non-diagnostic scans. Further diagnostic testing combined with the clinical pretest probability will help determine the final diagnosis *(Hull, 1985 [C]; PIOPED Investigators, The; 1990 [C])*.

C5. Ventilation/Perfusion Diagnostic (High Probability Scan Result)

The significance of a high probability (diagnostic) ventilation/perfusion (V/Q) scan depends on the clinical pretest probability of pulmonary embolism (PE). Several clinical studies have demonstrated that high probability scans are associated with PE at least 85% of the time. If the clinical suspicion is likely, this test can be considered a final diagnostic test. However, if the clinical suspicion is actually unlikely, the incidence of pulmonary embolism appears to be 35%-55%. In this circumstance, one should consider further evaluation with a computed tomographic (CT) pulmonary angiogram. A positive CT pulmonary angiogram in central pulmonary arteries has a high degree of specificity and may be considered diagnostic. A positive CT pulmonary angiogram in peripheral vessels may not represent a true positive finding. Depending upon the clinical pretest probability, the patient may need further workup with a standard pulmonary angiogram.

In each patient with a high probability (diagnostic) V/Q scan, the clinician should consider whether this might represent a massive PE. If the patient also has hemodynamic changes or profound hypoxemia, one should consider whether the patient is a candidate for thrombolytic therapy. In this setting, an echocardiogram evaluating right ventricular function can provide additional guidance for the use of thrombolytic therapy. (See Annotation #34, "Complicated Venous Thromboembolism or Comorbidities?")

(American Thoracic Society, 1999 [R]; Wells, 1998b [B])

C10. Assess Clinical Pretest Probability

In patients with an unlikely clinical pretest probability, the ventilation/perfusion (V/Q) lung scan is frequently false positive. In 19% of the population they studied, Wells, et al. found that the incidence of proven pulmonary embolism (PE) in patients with high probability (diagnostic) V/Q scan but an unlikely clinical pretest probability was only 30%. With more than two-thirds of these patients having no PE, it is recommended that further studies be performed to confirm the positive V/Q finding. In this circumstance, pulmonary angiogram to rule in or out PE is the recommended procedure unless the patient has specific contraindications *(Wells, 1998b [B])*.

In patients with a likely clinical pretest probability, a high probability (diagnostic) V/Q scan has 85%-90% sensitivity for PE and can be considered the confirmatory test. Proceed to the Venous Thromboembolism Treatment Algorithm.

Low Clinical Pretest Probability

Patients with a non-diagnostic V/Q scan associated with a negative duplex ultrasound with compression and an unlikely clinical pretest probability have a low incidence of pulmonary embolism. It is safe to withhold anticoagulation therapy and follow these patients clinically. Please refer to Annotation #21, "Risk of Pulmonary Embolism Is Very Low."

Moderate Clinical Pretest Probability

Patients with a non-diagnostic V/Q scan associated with a negative duplex ultrasound with compression but a likely clinical pretest probability have a small but significant incidence of pulmonary embolism.

Follow-up studies such as D-dimer testing or serial duplex ultrasounds with compression are recommended to improve the diagnostic sensitivity for pulmonary emboli while avoiding invasive diagnostic tests. Please refer to Annotation #10, "D-dimer Test for Moderate/High Pretest."

High Clinical Pretest Probability

A significant incidence of PE is found in patients with a non-diagnostic V/Q scan associated with a negative duplex ultrasound with compression and high clinical pretest probability. Pulmonary angiography is recommended in this subgroup.

Appendix D – Diagnosis and Treatment of Upper Extremity Deep Vein Venous Thrombosis

Upper extremity deep venous thrombosis (UEDVT) has become an increasingly recognized source of morbidity and mortality and represents an estimated 1%-4% of all cases of deep venous thrombosis *(Kearon, 2008 [R])*. UEDVT may occur in the subclavian, axillary or brachial veins with clinical symptoms consisting of edema, arm pain or discoloration, or the development of collateral veins involving the affected arm, neck or chest wall. Complications of acute UEDVT include pulmonary embolism, which may occur in up to 33% of patients, half of whom may be symptomatic *(Burns, 2008 [R])*. Chronic complications include a recurrence rate of 2%-8% *(Flinterman, 2008 [R])* and post-thrombotic syndrome (PTS), which may occur in varying degrees of severity in 7%-44% of patients *(Kahn, 2005 [R])*.

Causes of UEDVT are divided into primary and secondary causes. Causes of primary UEDVT include idiopathic thrombosis and thrombosis associated with thoracic outlet syndrome, and Paget-Schrötter syndrome (also known as effort thrombosis). The majority of primary UEDVT cases are related to thoracic outlet syndrome. Secondary UEDVTs are caused by a known identified risk factor, either genetic or acquired. Genetic factors include the well-described hypercoagulable states. Acquired risk factors include peripherally inserted central lines (PIC), central venous catheters (CVC) and pacemaker placement. Malignancy is identified as an important risk factor for development of UEDVT, though this is primarily related with the presence of a CVC *(Burns, 2008 [R]; Flinterman, 2008 [R]; Spencer, 2007 [B])*. Plaster cast of the upper extremity was identified in a single study to place patients at increased risk for UEDVT, and there is no consensus about oral contraceptive use as a risk factor for UEDVT *(Flinterman, 2008 [R])*.

Ultrasound imaging is the preferred means of rendering an affirmation diagnosis. When acute UEDVT is diagnosed, the treatment of patients is initiated in a manner similar to lower extremity DVT with the initiation of therapeutic doses of anticoagulants to prevent thrombus extension and pulmonary emboli *(Kearon, 2008 [R])*. Multiple studies of thrombolytic therapy have been performed; however, it is unclear if this results in improved short-term or long-term outcomes as compared to anticoagulation therapy alone.

Following initial treatment, there is general agreement that patients with symptomatic acute UEDVT require long-term treatment with anticoagulants for a minimum of three months and then clinical reevaluation *(Kearon, 2008 [R])*.

For patients with UEDVT associated with a central venous catheter, it is now recommended that the catheter not be removed if it is functional and there is a persistent medical requirement for catheter use *(Kearon, 2008 [R])*. If the catheter is removed, long-term utilization of oral anticoagulants is recommended for a minimum of three months and then clinical reevaluation. Patients with a malignancy and a central venous catheter are at increased risk for development of UEDVT. Clinical trials have not clearly demonstrated a benefit of low dose (1 mg daily) warfarin compared to no thrombo-prophylaxis for prevention of catheter-related UEDVT *(Geerts, 2008 [R])*.

In selected patients with acute UEDVT who fail anticoagulant therapy, vascular interventional radiologic or surgical evaluation should be considered for consultation of catheter extraction, surgical thrombectomy or thrombolysis. For selected patients who have clear progression of acute UEDVT and anticoagulation contraindications, superior vena cava filter placement should be considered *(Kearon, 2008 [R])*.

Development of post-thrombotic syndrome of the upper extremity is recognized by the existence of persistent edema, heaviness and limb fatigue with upper extremity utilization. Treatment of post-thrombotic syndrome includes elastic bandage or elastic compression sleeve application.

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Original Work Group Members

David Borgstrom, MD
Surgery
Ramsey Clinic

Elizabeth Brackett, MD
Family Practice
HealthPartners

Bruce Burnett, MD
Internal Medicine
HealthSystem Minnesota

Diane Davies, MD
Buyers Health Care Action Group
Pfizer

Kay Dickison, RN
Nursing
HealthPartners

Denise Dupras, MD
Internal Medicine
Mayo Clinic

Jane Erickson, RN
Facilitator
ICSI

Jane Gendron
Measurement Advisor
ICSI

Vic Kelmenson, MD
Pulmonology
HealthPartners

Jeff Larsen, MD
Internal Medicine
River Falls

Peter Marshall, PharmD
Pharmacy
St. Paul Ramsey

Laurie Ritz, RN
Nursing
HealthSystem Minnesota

Jane Rodriguez
Health Education
HealthPartners

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Contact ICSI at:
8009 34th Avenue South, Suite 1200; Bloomington, MN 55425; (952) 814-7060; (952) 858-9675 (fax)
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Brief Description of Evidence Grading

Individual research reports are assigned a letter indicating the class of report based on design type: A, B, C, D, M, R, X.

A full explanation of these designators is found in the Foreword of the guideline.

II. CONCLUSION GRADES

Key conclusions (as determined by the work group) are supported by a conclusion grading worksheet that summarizes the important studies pertaining to the conclusion. Individual studies are classed according to the system defined in the Foreword and are assigned a designator of +, -, or ø to reflect the study quality. Conclusion grades are determined by the work group based on the following definitions:

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results from different studies or because of serious doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

The symbols **+**, **–**, **ø**, and **N/A** found on the conclusion grading worksheets are used to designate the quality of the primary research reports and systematic reviews:

+ indicates that the report or review has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis;

– indicates that these issues have not been adequately addressed;

ø indicates that the report or review is neither exceptionally strong or exceptionally weak;

N/A indicates that the report is not a primary reference or a systematic review and therefore the quality has not been assessed.

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Conclusion Grading Worksheet A – Annotation #43 (Duration of Anticoagulation)

Work Group's Conclusion: The length and duration of anticoagulation should be tailored to the patient dependent on individual circumstances: for transient/provoked cause (e.g., travel, trauma, surgery, oral contraceptives or hormone replacement therapy), 3 months; for idiopathic/unprovoked 3-6 months; for recurrent disease, indefinite anticoagulation may be appropriate.

Work Group's Conclusion: The length and duration of anticoagulation should be tailored to the patient dependent on individual circumstances: for recurrent disease in cancer patients, low-molecular-weight heparin (preferred over warfarin in this group) for at least 6 months; for recurrent disease in patients who are carriers of thrombophilia genes, 6 months to indefinite.

Anticoagulation for recurrent events in the general population.
Conclusion Grade: II

Author/ Year	Design Type	Class	Quality +,–,0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Verhovsek et al, 2008	Systematic Review and meta-analysis	M	+	MEDLINE, EMBASE, CINAHL, and Cochrane databases were searched until March 2008 for prospective cohort or randomized trials that used D-dimer to predict recurrent VTE.	Twenty-nine studies met inclusion criteria and 7 studies with 1888 patients were included in the meta-analysis of the association of D-dimer after at least three months of anticoagulant treatment of unprovoked VTE. In patients who have completed at least 3 months of anticoagulation treatment for a first episode of VTE and after approximately 2 years of follow-up, a negative D-dimer results associated with a 3.5% (2.7-4.3) annual risk for recurrent disease, whereas a positive D-dimer results was associated with 8.9% (95% CI 5.8-11.9) annual risk for recurrence.	The authors conclude that the low risk for recurrence with a negative D-dimer result suggests that long-term anticoagulation treatment may not be necessary in all patients with unprovoked VTE. This rate may not be low enough for some clinicians or patients to stop anticoagulation. The authors note that D-dimer should not be used as a stand-alone test to determine whether to stop or prolong anticoagulation in patients with a first or unprovoked VTE. Ideally, D-dimer should be part of a prediction rule that includes clinical and laboratory features to predict recurrent VTE.

Author/ Year	Design Type	Class	Quality +,–,0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Siragusa et al, 2008	RCT	A	+	Patients with residual veinous thromboembolism (RVT) were randomized to either stop (n=92) or continue (n=88) anticoagulation for 9 additional months. Patients without RVT (n=78) did not continue anticoagulation. Patients were followed for at least one year after stopping anticoagulation.	Study outcomes were recurrent VTE and/or major bleeding. Patients with RVT were more likely to have idiopathic DVT in comparison with those without RVT. Thrombosis recurred in 23.3% of patients with RVT compared to 1.3% of those with RVT. In patients with RVT randomized to stop anticoagulation, there were 25/92 (27.2%) recurrences and in patients randomized to continue anticoagulation there were 17/88 (19.3%) recurrences (p-value comparing groups 0.213). In the group with RVT there was 1/78 recurrence (1.3). In patients with RVT randomized to stop anticoagulation, there 1.92 (1.1%) cases of major bleeding, and in patients randomized to continue anticoagulation there were 2/88 (2/3%) cases of major bleeding (p-value comparing groups 0.534). In the group without RVT, there were 0 cases of major bleeding. Compared to those who were randomized to continue anticoagulation, those who were randomized to stop anticoagulation were 1.58 times more likely to have a recurrent event (hazard ration 1.59, 95% CI 0.85-2.93) after adjusting for age and sex. Compared to patients without RVT, those with RVT who continued anticoagulation had a 15.7 times increased risk of recurrence (95% CI 2.1-118.0) and those who stopped anticoagulation had a 24.9 times greater risk of recurrence (95% CI 3.4-183.6).	The results of this study suggest that RVT assessment is useful for evaluation the features of a DVT of a lower limb. RVT may identify a subset of patients with a lower risk for recurrence. Additionally, the results of this study indicate that absence of RVT identifies patients at low risk of recurrent thrombotic events and that this information may reduce clinical burden for the patient and the health care system. However, this is only one study; further trials are needed to assess the optimal duration of anticoagulation in RVT patients.

Author/ Year	Design Type	Class	Quality +,–,Ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Ruiz-Gimenez et al, 2008	Prospective cohort study of patients with DVT	B	Ø	19,274 consecutive patients with symptomatic, acute DVT were enrolled in RIETE. 13,057 were randomly assigned to a derivation sample and 6,572 were assigned to the validation sample to develop a risk prediction score based on variables that can be obtained before the anticoagulant therapy is instituted.	The primary outcome for this study was the ability to distinguish between patients at low, mild and high risk of experiencing major bleeding during the first 90 days of therapy. In the derivation group, 314 (2.4%) patients had major bleeding. Multivariate analysis showed that only age >75 years, recent bleeding, cancer, abnormal creatinine levels, anemia and pulmonary embolism at baseline were independently associated with an increased risk of major bleeding. In the validation patient group, 159 (2.4%) had major bleeding. When the predictive model was cross-validated in the validation population, the incidence of major bleeding was 0.1% in low-risk patients, 2.8% in mild-risk patients, and 6.2% in high-risk patients.	This study shows that it is possible to classify patients as low, mild or high risk for major bleeding based on 6 clinical variables documents at baseline (recent major bleeding, creatinine levels > 1.2 mg/dl, anemia, cancer, clinically overt PE, age >75 years).
Rodger et al, 2008	Prospective cohort study	**B**	+	646 participants with a first, unprovoked major VTE were enrolled and followed for a mean of 18 months.	The primary objective of this study was to determine the clinical predictors or combinations of predictors that identify patients with an annual risk of VTE of less than 3% after taking anticoagulant for 5-7 months after the first event. 91 episodes of confirmed recurrent VTE were identified during follow-up after discontinuing anticoagulant therapy (annual risk 9.3%, 95% CI 7.7-11.3). Men had a 13.7% (10.8-17.0) annual risk. 52% of women had 0 or 1 of the following characteristics: hyperpigmentation, edema or redness of either leg, D-dimer ≥250 µg/L while taking warfarin, body mass index ≥30 kg/m^2 or age ≥65 years. These women had an annual risk of 1.6% (0.3-04.6). Women who had 2 or more of these findings had an annual risk of 14.1% (10.9-17.3).	These findings suggest that women with 0 or 1 risk factors may safely discontinue anticoagulant therapy after 6 months following a first unprovoked VTE. This criterion does not apply to men. There was no combination of risk factors that satisfied criteria for identifying a low-risk subgroup of men.

Author/ Year	Design Type	Class	Quality +, –, ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Agnelli and Becattini, 2008	Narrative review	**R**	-	n/a	This review dealt with the results of studies on the long term course of VTE and provided background for the currently recommended log-term management of VTE. The authors identified three different groups and their subsequent risk for DVT: idiopathic, transient risk and persistent risk factors.	The authors concluded that all patients should get 3 months anticoagulation except the very transient risks with distal calf DVT. They further suggest that anticoagulation beyond 3 months should be tailored to patient characteristics.
Prandoni et al, 2007	Prospective cohort study	**B**	Ø	All consecutive patients between 1991 and 2003 with clinically symptomatic DVT and/or PE were potentially eligible for this study. Of 3338 eligible patients, 1626 participated and were subsequently examined or telephoned at least every 6 months for up to 10 years to document incidence of recurrent DVT.	The primary objective of this study was to assess the rate of recurrent VTE after withdrawal of vitamin K antagonists and to identify clinical parameters in both the entire cohort and in a subgroup of patients with VTE of unknown origin. After a median follow-up of 50 months, 373 patients (22.9%) had recurrent episodes of VTE. The cumulative incidence of recurrent VTE was 11.0% (95% CI 9.5-12.5) after one year, 19.6% (17.5-21.7) after 3 years, 29.1% (26.3-31.9) after 5 years, and 39.9% (35.4-44.4) after 10 years. The adjusted hazard ratio for recurrent VTE was 2.30 (95% CI 1.82-02.90) in patients whose first VTE was unprovoked, 2.02 (1.52-2.69) in those with thrombophilia, 1.44 (1.03-2.03) in those presenting with primary DVT, 1.39 (1.08-1.80) for patients who received a short (up to 6 months) duration of anticoagulation, and 1.14 (1.06-1.12) for every 10-year increase in age. There was no association with male sex (HR = 1.16, 95% I 0.94-1.43).	These findings suggest that after discontinuing anticoagulation the rate of recurrent VTE increases steadily over time. The authors further add that the results confirm that patients who present with thrombotic episodes of unknown origin have a more than twofold higher risk of recurrences than that observed in patients with temporary risk factors. A potential limitation is the failure to have assessed thrombophilia in all recruited patients. *[Thrombophilia is an independent risk factor for VTE; this study was not able to address it adequately.]* The findings of this study contradict other studies in the literature: 1) this study found similar risk in males and females; 2) the longer duration of anticoagulation lowers the risk of subsequent recurrent VTE.

Author/Year	Design Type	Class	Quality +-Ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Schulman et al. 1995	RCT	A	Ø	-897 patients with a first episode of VTE; ≥15 years old, acute PE or DVT in leg, iliac vein, or both (confirmed); combined PE and DVT was classified as DVT -Excluded: unavailable for follow-up; pregnancy; allergy to warfarin or dicumarol; indication for continuous oral anticoagulation; permanent, total paresis of the affected leg; arterial insufficiency of that leg (class III or worse); current or previous venous ulcer; cancer; >1 thromboembolic event -After enrollment they excluded from analysis patients with congenital deficiency of antithrombin, protein C or S -Randomized at the end of hospitalization to receive oral anticoagulation for either 6 weeks or 6 months (from time of stable prothrombin times in target range) -Initial treatment was with LMWH or UFH for at least 5 days; thrombolytic therapy was allowed; oral anticoagulation (warfarin or dicumarol) usually started with heparin -Follow-up at 1.5, 3, 6, 9, 12 and 24 months after target prothrombin time was reached	-Principal endpoints were major hemorrhage during oral anticoagulation and death or recurrent VTE during 2-year follow-up period -5 patients were removed from the analysis after enrollment because of protein C deficiency (initial group had been 902) -443 were randomly assigned to 6 wks of treatment and 454 to 6 months; groups were similar at baseline except for fewer with previous thrombolytic therapy in the 6-wk group -There were 39 deaths and 44 dropouts during 2 years of follow-up -Results: 6 weeks 6 months p Major hemorrhage 1 (0.2%) 5 (1.1%) 0.23 Recurrence 80 (18.1%) 43 (9.5%) <0.001 Death 22 (5.0%) 17 (3.7%) 0.46 -Subgroup analyses (based on temporary or permanent risk factors, initial PE vs. DVT, family history and effectiveness of oral anticoagulation) indicated that secondary prophylaxis with 6 months instead of 6 weeks of oral anticoagulants reduced the risk of recurrence by approximately 50% in almost every subgroup.	-Six months of prophylactic oral anticoagulation after a first episode of VTE led to a lower recurrence rate than did treatment lasting for 6 weeks. The difference between the two groups occurred between 6 weeks and 6 months after the start of treatment, and the rates of recurrence remained nearly parallel for 1.5 years thereafter. *Work Group's Comments:* *-Known protocol violations were disclosed* *-Used registries for deaths and hospitalizations so that few events were missed*

Author/Year	Design Type	Class	Quality +,–,ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Schulman et al, 1997	RCT	A	**ø**	-227 patients with second episodes of VTE -Inclusion and exclusion criteria and initial treatments same as above (Schulman et al., 1995) -Randomized at end of hospitalization to receive oral anticoagulant for either 6 months or indefinitely -Follow-up intervals the same with the addition of 36 and 48 months	-Principal endpoints were major hemorrhage, recurrent VTE, or death during the 4-year follow-up -111 were assigned to 6 months of treatment and 116 to indefinite treatment; groups were similar at baseline -Over 4 years, 26 died and 14 dropped out -Results: 6 months Indefinite p Major hemorrhage 3 (2.7%) 10 (8.6%) 0.08 Recurrence 23 (20.7%) 3 (2.6%) <0.001 Death 16 (14.4%) 10 (8.6%) 0.21	-Prophylactic anticoagulant therapy that was continued for an indefinite period after a second VTE was associated with a much lower rate of recurrence during 4 years of follow-up than treatment for 6 months; there was a trend toward a higher risk of major hemorrhage when anticoagulation was continued indefinitely. NOTES: attempted to minimize bias in an open study by having test results reviewed by an independent, blinded radiologist
Hyers et al, 1998	Review	R	**N/A**	-A review of studies pertaining to the effectiveness of antithrombotic agents in the treatment of VTE		-Oral anticoagulant therapy should be continued for at least 3 months to prolong the prothrombin time to a target INR of 2.5. -Patients with reversible or time-limited risk factors can be treated for 3 to 5 months; patients with first episode of idiopathic DVT should be treated for at least 6 months; patients with recurrent VTE or continuing risk factors should be treated indefinitely. -Symptomatic isolated calf VT should be treated with anticoagulation for at least 6 months.

Author/Year	Design Type	Class	Quality +,–,ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Kearon et al, 1999	RCT	A	ø	-162 patients; first episode of idiopathic VTE (symptomatic, confirmed proximal DVT or PE in the absence of a major thrombotic risk factor); completed 3 mos of oral anticoagulant therapy after initial UFH or LMWH -Excluded: anticoagulant therapy for other than DVT, need for long-term NSAIDS, familial bleeding diathesis, major psychiatric disorder, pregnant or could become pregnant, allergic to contrast medium, life expectancy < 2 years, initially given unlicensed LMWH, unable to complete follow-up -Randomized (after stratification) to either warfarin or placebo (with INR results used to adjust warfarin dose) -Assessment of symptoms and signs of VTE every 3 months -Ultrasonography if suspected DVT; ventilation-perfusion scan if suspected PE	-Recruitment of patients stopped in response to interim analysis that showed benefit of warfarin -162 of 327 who met criteria for inclusion at time of diagnosis and gave consent to participate randomized (79 in warfarin group and 83 in placebo group) -Mean duration of follow-up 10 months (12 months in warfarin group vs. 9 months in placebo group) – follow-up discontinued if VTE, and with more events in placebo group, the follow-up was shorter -14 in warfarin group and 13 in placebo group chose not to continue treatment -Of 79 in warfarin group, 1 with confirmed VTE -Of 83 in placebo group, 17 with confirmed VTE (including one death) -Cumulative probability of recurrent VTE differed between groups ($p< 0.001$): 1.3% per patient year in warfarin group and 27.4% per patient year in placebo group -All episodes of recurrent VTE were idiopathic -3 major bleeding episodes in warfarin group (0 in placebo group) -1 death in the warfarin group (pneumonia) and 3 deaths in the placebo group (PE, CAD and leukemia) -Presence of lupus anticoagulant was only clinical or laboratory variable assessed that was significantly ($p=0.03$) associated with recurrent VTE	-Patients with a first episode of idiopathic VTE have a high rate of recurrence if anticoagulant therapy is stopped after three months; extended warfarin therapy was effective in preventing recurrent VTE but was associated with an increased risk of major bleeding. -There was a high risk of recurrent VTE in patients without any of the biochemical abnormalities screened for, suggesting that these findings apply to all patients with a first episode of idiopathic VTE. -Further studies are needed to determine when anticoagulation therapy can be safely stopped. NOTES: Extensive precautions to avoid bias: double-blind design, central adjudication of outcomes, standardized approach to diagnosis; stopping early may have led to overestimation of magnitude of benefit from extended warfarin therapy

Author/Year	Design Type	Class	Quality +,–,ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Agnelli et al, 2001	RCT	A	ø	-267 patients with first episode of idiopathic proximal deep venous thrombosis; completed 3 months of oral anticoagulant therapy (97% warfarin) without recurrence or bleeding -Excluded: prolonged anticoagulant therapy for other than VTE, major psychiatric disorders, life expectancy < 2 yrs, unable to return for follow-up -Randomized to discontinue oral anticoagulant therapy or continue for 9 additional months; dose adjusted to achieve INR between 2 and 3 -Blinded assessment of outcomes -Follow-up at 3, 6 and 12 mos after randomization and every 6 mos. thereafter	-Recruitment stopped after 267 enrolled because difference in risk of recurrence was <25% (thromboembolic events in 16 of 123 [13.0%] in discontinue group, 15 of 123 [12.2%] of continue group) -Groups similar in age, gender, initial use of LMWH -Intention-to-treat analysis: 15.7% of continue group and 15.8% of discontinue group had recurrent VTE (with 38 and 37 mos average follow-up, respectively); RR=0.99 (95%CI: 0.57-1.73); none was fatal; average time to recurrence of 11 mos in discontinue group, 16 mos in continue group -Per-protocol analysis: 15.7% of continue and 16.7% of discontinue group had recurrent VTE; RR=0.94 (95%CI: 0.54-1.67) -During first 9 mos of follow-up (intention-to-treat analysis): 4 patients (3%) in continue group and 11 (8.3%) in discontinue group had recurrence (RR=0.36; 95%CI 0.12-1.11) -4 (3%) in continue group had nonfatal major bleeding; 2 (1.5%) in discontinue group had fatal bleeding; 14 deaths (7 per group)	-The clinical benefit achieved during therapy when the 3 month course of anticoagulant therapy is extended to one year is not maintained after the discontinuation of therapy. Prolonged anticoagulant therapy beyond 3 mos delays recurrence until therapy is stopped but does not reduce the risk. NOTES: study was completed at 10 centers in Italy; sample size estimation (based on 15% recurrence rate if treatment discontinued) was 246 per group to detect 50% reduction in recurrence with prolongation of therapy (power= 80%, α=0.05); during first 9 mos of follow-up, only 1 patient (of 4) in continue group had recurrence while receiving active oral anticoagulant therapy; attempted to avoid bias with consecutive patients, central randomization, follow-up of all randomized patients, blinded assessment of outcomes, and objective criteria for recurrence

Anticoagulation for recurrent events in cancer patients.
Conclusion grade for this evidence: II

Author/ Year	Design Type	Class	Quality +,–, 0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Noble et al, 2008	Systematic review and meta-analysis	**M**	+	Papers published between 1966 and 2006 were searched for articles on anticoagulation treatment in patients with cancer with focus on studies of patients with advanced disease.	The primary objective of this paper was to perform a systematic review to help develop guidelines applicable to patients with advanced cancer. Of 5884 references identified, 35 papers were further reviewed and only 19 met criteria for inclusion. The meta-analysis of pooled data from randomized controlled trials showed low-molecular-weight heparin to be more effective than warfarin in the prevention of recurrent VTE (overall RR 0.51, 95% CI 0.35-0.74). Additionally, there was no significant difference in the risk of bleeding between patients on low-molecular-weight heparin or warfarin, with an overall RR of 1.10 (95% CI 0.77-1.58). Data from 7 retrospective cohort studies were pooled for meta-analysis. Adjusted analysis of pooled data showed an overall risk of recurrent VTE on anticoagulant treatment of 0.21 (95% CI 0.15-0.30).	Data from the RCTs included in this systematic review and meta-analysis suggest that long-term low-molecular-weight heparin is more effective than warfarin in decreasing the risk of recurrent VTE in patients with cancer. The optimum duration of treatment with low-molecular-weight heparin is unknown because no study has assessed its use beyond 6 months. There may be a strong argument for indefinite anticoagulation in view of the fact that thrombotic risk will remain and may increase in patients with progressive disease. Ultimately the decision to initiate, continue or stop anticoagulation will need to be made on an individual basis, guided by the available evidence, the patient's circumstances, and the patient's informed preferences.

Author/ Year	Design Type	Class	Quality +,–,Ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Akl et al, 2008a	Systematic review	**M**	+	Medical literature was reviewed for studies of anticoagulation in patients with cancer. Of 3986 references, 57 were potentially eligible for this review, and of those, data from 8 RCTs were included in this review.	The objective this paper was to conduct a systematic review to compare efficacy and safety of low-molecular-weight heparin and oral anticoagulants for the long-term treatment of thromboembolism in patients with cancer. The quality of data was low for death and moderate for recurrent VTE. Compared to vitamin K antagonists, low-molecular-weight heparin provided no statistically significant survival benefit (HR = 0.96, 9%% CI 0.81-1.14) but a statistically significant reduction in VTE (HR = 0.47, (% % CI 0.32-0.71) was observed. There was no statistically significant difference between low-molecular-weight heparin and vitamin K antagonists in bleeding outcomes (HR =0.91, 95% CI 0.64-1.31).	For long-term treatment of VTE in patients with cancer low-molecular-weight heparin reduces thromboembolism but not death compared to vitamin K antagonists. Two other systematic reviews comparing low-molecular-weight heparin and vitamin K antagonists found no statistically significant reduction in recurrent VTE when the analysis was not restricted to cancer patients. It is unclear why there is a differential effect in patients with cancer.
Akl et al, 2008b	Systematic review	**M**	Ø	A comprehensive search for studies of anticoagulation in cancer patients was conducted up to January 2007. Of 3986 citations, 26 RCTs including cancer patients as subgroups fulfilled the inclusion criteria. Data from 11 studies were used in the meta-analysis.	The objective of the review was to compare the efficacy and safety of three types of anticoagulants (low-molecular-weight heparin, unfractioned heparin, and fondaparinux) for initial treatment of VTE in patients with cancer. There was a statistically significant reduction in mortality in patients treated with low-molecular-weight heparin compared to those treated with unfractioned heparin (RR=0.71, 95% CI 0.52-0.98). There was little change in RR after excluding studies of lower methodological quality (RR+0.72, 95% CI 0.52-1.00). Data from three studies were used to compare low-molecular-weight heparin with unfractioned heparin in reducing recurrent VTE; results were inconclusive (RR= 0.78, 95% CI 0.29-2.08). There was no data available for bleeding outcomes, thrombocytopenia or post-phlebetic syndrome.	Based on the meta-analyses of these data from RCTs, low-molecular-weight heparin is likely to be superior to unfractioned heparin in the initial treatment of VTE in patients with cancer. The authors acknowledge that there is a need for more trials to better address the research questions in cancer patients.

Anticoagulation for recurrent events in patients who are carriers of thrombophilia genes.
Grade for this evidence: II

Author/ Year	Design Type	Class	Quality +, –, 0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Prandoni et al, 2008	Retrospective cohort study	**B**	+	714 consecutive patients with a first episode of DVT and/or PE were included in this analysis. Of those, 114 were found to be carriers of a gene for factor V Leiden (83), prothrombin (25) mutation or both (6).	The primary endpoint of this study was recurrent VTE. One or more episodes of recurrent VTE developed in 33 of the 114 (28.9%) carriers of genes for thrombophilia and 105 of 600 (17.5%) non-carriers. The relative risk was 1.70 (95% CI 1.19-2.44). After adjusting for modality of clinical presentation (unprovoked or secondary to transient risk factors for thrombosis), the RR for recurrent VTE was 2.25 (95% CI 1.36-3.74) in carriers compared to non-carriers.	The authors conclude that carriers of factor V Leiden or prothrombotic mutation who have an episode of VTE are likely to have an increased risk of recurrence compared to those who are not carriers of thrombophilia genes, when they receive only 3 months of anticoagulation. The difference is no longer detectable when anticoagulation is administered for at least 6 months.

This section provides resources, strategies and measurement specifications for use in closing the gap between current clinical practice and the recommendations set forth in the guideline.

The subdivisions of this section are:

- Priority Aims and Suggested Measures
  - Measurement Specifications
- Key Implementation Recommendations
- Knowledge Resources
- Resources Available

Priority Aims and Suggested Measures

1. Prevent progression or recurrence of thromboembolic disease.

   Possible measures of accomplishing this aim:

   a. Percentage of patients with venous thromboembolism (VTE) treated with low-molecular-weight heparin (LMWH) who receive heparin treatment for at least five days after the initiation of warfarin therapy and until international normalized ratio (INR) is ≥ 2.0 for two consecutive days.

   b. Percentage of patients with venous thromboembolism (VTE) treated with unfractionated heparin (UFH) who receive heparin treatment for at least five days after the initiation of warfarin therapy and until international normalized ratio (INR) is ≥ 2.0 for two consecutive days.

   c. Percentage of patients with deep vein thrombosis who have been assessed for the need for graduated compression stockings (not Teds).

   d. Percentage of patients who develop pulmonary embolism after a diagnosis of venous thromboembolism (VTE).

   e. Percentage of patients who have a high clinical pretest probability for pulmonary embolism (PE), who received low-molecular-weight heparin (LMWH) during evaluation.

   f. Percentage of inpatients with deep vein thrombosis who receive warfarin on day one of heparin therapy.

2. Reduce the risk of complications from anticoagulation therapy.

   Possible measures of accomplishing this aim:

   a. Percentage of patients with venous thromboembolism (VTE) receiving heparin therapy who have a baseline platelet count before starting heparin, and then a platelet count every other day for at least the first three days of therapy.

   b. Percentage of patients who require hospital readmission within 30 days of discharge for conditions related to deep vein thrombosis (including complications).

3. Improve the safety of using medications by reducing the likelihood of patient harm associated with the use of anticoagulation therapy.

   Possible measures for accomplishing this aim:

   (2010 Joint Commission National Safety Measure: Inpatient)

   a. Percentage of patients who are initially prescribed anticoagulation therapy with documentation in the medical record, indicating a baseline international normalized ratio (INR) was obtained.

   b. Percentage of patients who receive ongoing anticoagulation therapy with documentation in the medical record, indicating a current international normalized ratio (INR) is available and is used to monitor and adjust therapy.

   c. Percentage of patients who are prescribed heparin and low-molecular-weight heparin (LMWH), who have appropriate baseline laboratory tests documented in their medical record.

   d. Percentage of patients who are prescribed heparin and low-molecular-weight heparin (LMWH), who have appropriate ongoing laboratory tests available to monitor and adjust therapy.

e. Percentage of patients who have been treated with anticoagulation therapy for three to six months, having been re-evaluated for ongoing risk factors to determine the need for ongoing therapy.

4. Improve accurate diagnosis and treatment of venous thromboembolism (VTE).

   Possible measures for accomplishing this aim:

   a. Percentage of patients with suspected venous thromboembolism (VTE) with clinical pretest probability assessment completed.

   b. Percentage of patients diagnosed with venous thromboembolism (VTE) who have had a D-dimer test.

   c. Percentage of adult patients suspected of DVT who have leg duplex ultrasound with compression performed, despite a low clinical pretest probability and a negative D-dimer test.

   d. Percentage of patient diagnosed with venous thromboembolism (VTE) who meet the criteria for low-molecular-weight heparin (LMWH) and for whom low-molecular-weight heparin (LMWH) is used.

   e. Percentage of patients with deep vein thrombosis who are treated in an outpatient setting.

5. Increase the percentage of patients who are evaluated for medication reconciliation upon change in level of care, and/or upon discharge.

   Possible measure for accomplishing this aim:

   (2010 Joint Commission/National Safety Goal: Inpatient and Outpatient)

   a. Percentage of patients with a confirmed diagnosis of venous thromboembolism, pulmonary embolism, deep vein thrombosis with documentation in their medical record, indicating a complete list of medication was communicated to the next provider of service when the patient is referred or transferred to another setting, service, practitioner or level of care within or outside the organization.

Measurement Specifications

Possible Success Measure #1c

Percentage of adult patients treated for venous thromboembolism (VTE) who have been assessed for the need for graduated compression stockings (not Teds).

Population Definition

Adults age 18 years and older treated for VTE.

Data of Interest

Documentation in the medical record of an assessment for graduated compression stockings (not Teds).

Numerator/Denominator Definitions

Numerator: Total number of adult patients treated for venous thromboembolism (VTE) with a completed graduated compression stocking assessment in the medical record.

Denominator: Total number of adult patients treated for venous thromboembolism (VTE).

Method/Source of Data Collection

A list of all adult patients treated for venous thromboembolism (VTE) during the previous target period. The medical records can be reviewed to determine the documentation of a completed assessment for graduated compression stockings (not Teds).

Time Frame Pertaining to Data Collection

Data may be collected semiannually.

Possible Success Measure #1e

Percentage of patients who have a high clinical pretest probability for pulmonary embolism (PE) who received low-molecular-weight heparin (LMWH) during evaluation.

Population Definition

Adults age 18 years and older suspected of having a pulmonary embolism (PE).

Data of Interest

Documentation in the medical record of low-molecular-weight heparin (LMWH) given during evaluation for pulmonary embolism (PE).

Numerator/Denominator Definitions

Numerator: Total number of adult patients with a documented high clinical pretest probability for pulmonary embolism (PE) receiving low-molecular-weight heparin (LMWH) during the evaluation for pulmonary embolism (PE).

Denominator: Total number of adult patients with a documented high clinical pretest probability of pulmonary embolism (PE).

Method/Source of Data Collection

A list of all adult patients with a documented high clinical pretest probability for pulmonary embolism (PE) during the previous target period. The medical records can be reviewed to determine if low-molecular-weight heparin (LMWH) was used during evaluation.

Time Frame Pertaining to Data Collection

Data may be collected semiannually.

Notes

Model for Predicting Clinical Pretest Probability for Pulmonary Embolism (PE)

Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3 points
Alternative diagnosis is less likely	3 points
Heart rate greater than 100	1.5 points
Immobilization or surgery in previous four weeks	1.5 points
Previous DVT/PE	1.5 points
Hemoptysis	1 point
Malignancy (active or treated in the last six months or palliative)	1 point

SCORE:
Score less than 2 = low clinical pretest probability
Score 2-6 = moderate clinical pretest probability
Score more than 6 = high clinical pretest probability

Possible Success Measure #2a

Percentage of patients with venous thromboembolism (VTE) receiving heparin therapy who have a baseline platelet count before starting heparin, and then a platelet count every other day for at least the first three days of therapy.

Population Definition

Adults ages 18 years and older receiving heparin therapy for venous thromboembolism (VTE).

Data of Interest

Documentation in the medical record of a baseline platelet count and platelet count obtained every other day for at least the first three days of therapy.

Numerator/Denominator Definitions

Numerator: Total number of adult patients receiving heparin for venous thromboembolism (VTE) with a baseline platelet count and a platelet count obtained every other day documented in the medical record.

Denominator: Total number of adult patients receiving heparin therapy for venous thromboembolism (VTE).

Method/Source of Data Collection

A list of all adult patients receiving heparin therapy for venous thromboembolism (VTE) during the previous target period. The medical records can be reviewed to determine the documentation of a baseline platelet count and a platelet count obtained every other day for at least the first three days of therapy.

Time Frame Pertaining to Data Collection

Data may be collected semiannually.

Possible Success Measure #4c

Percentage of adult patients suspected of DVT who have leg duplex ultrasound with compression performed, despite a low clinical pretest probability and a negative D-dimer test.

Population Definition

Adults age 18 years and older evaluated for possible deep vein thrombosis.

Data of Interest

Documentation in the medical record of a low clinical pretest probability, negative D-dimer and the performance of a leg compression ultrasound.

Numerator/Denominator Definitions

Numerator: Total number of adult patients suspected of deep vein thrombosis who have a low clinical pretest probability and a negative D-dimer who undergo a leg duplex ultrasound with compression.

Denominator: Total number of adult patients suspected of a deep vein thrombosis who have a low clinical pretest probability and a negative D-dimer.

Method/Source of Data Collection

A list of all adult patients evaluated for deep vein thrombosis during the previous target period. The medical records can be reviewed to determine the documentation of a low clinical pretest probability, negative D-dimer and the performance of a leg compression ultrasound.

Time Frame Pertaining to Data Collection

Data may be collected semiannually.

Notes

This measure is for the inappropriate use of leg compression ultrasound and a low number is desirable.

See Appendix A, "Wells Model of the Clinical Pretest Probability of Deep Vein Thrombosis."

Possible Success Measure #4d

Percentage of patients diagnosed with venous thromboembolism (VTE) who meet the criteria for low-molecular-weight heparin (LMWH) and for whom low-molecular-weight heparin (LMWH) is used.

Population Definition

Patients diagnosed with venous thromboembolism (VTE) who meet the criteria for low-molecular-weight heparin (LMWH).

Data of Interest

$$\frac{\text{\# of people with a diagnosis of venous thromboembolism (VTE) who are treated with low-molecular-weight heparin (LMWH)}}{\text{\# of people diagnosed with venous thromboembolism (VTE) who meet the criteria for low-molecular-weight heparin (LMWH)}}$$

Numerator/Denominator Definitions

Numerator: Patients treated with low-molecular-weight heparin (LMWH) (listed with GCN code 7542). Include only patients who meet the criteria for the denominator.

Denominator: Patients diagnosed with lower extremity venous thromboembolism (VTE) as identified by the following ICD-9 codes: 451.11, 451.19, 451.2, 453.8.

Patients are excluded for any of the following conditions:

- Any venous thromboembolism (VTE) other than lower extremity
- Suspected or confirmed pulmonary embolus (PE)
- Contraindications to anticoagulation
- Familial bleeding or clotting disorders
- History of heparin-induced thrombocytopenia
- Pregnancy
- Phlegmasia/extensive iliofemoral disease
- Renal dysfunction requiring dialysis

Method/Source of Data Collection

Identify patients diagnosed with venous thromboembolism (VTE) using the above diagnosis codes. Some medical groups will be able to identify the population of patients through patient computer records of ICD-9 codes. If this is not possible, a list of patients may be generated from the laboratory log for compression ultrasounds with a diagnosis of venous thromboembolism (VTE).

The medical record of each patient is reviewed to determine if the patient meets any of the exclusion criteria. If none of the exclusions is met, the chart is further reviewed for administration of low-molecular-weight heparin (LMWH).

During review, additional information on the number of days of treatment, and whether treatment was continued until the international normalized ratio (INR) was ≥ 2.0 for two consecutive days. In addition, some medical groups may want to track the percent of patients treated with low-molecular-weight heparin (LMWH) who receive treatment in an outpatient setting.

Time Frame Pertaining to Data Collection

The suggested time period is a calendar month.

Possible Success Measure #4e

Percentage of patients with deep vein thrombosis who are treated in an outpatient setting.

Population Definition

Patients age 18 years and older diagnosed with deep vein thrombosis who meet the criteria for low-molecular-weight heparin (LMWH).

Data of Interest

$$\frac{\text{\# of low-molecular-weight heparin (LMWH) eligible patients with deep vein thrombosis treated as outpatients}}{\text{\# of low-molecular-weight heparin (LMWH) eligible patients with deep vein thrombosis treated with low-molecular-weight heparin (LMWH)}}$$

Numerator/Denominator Definitions

Numerator: Patients who do not have an inpatient admission within seven days of diagnosis. (Do not consider stays in observation units as inpatient admission.)

Denominator: Patients diagnosed with lower extremity deep vein thrombosis as identified by the following ICD-9 codes: 451.11, 451.19, 451.2, 453.8.

Patients are excluded for any of the following conditions:

- Any deep vein thrombosis other than lower extremity
- Suspected or confirmed pulmonary embolus
- Contraindications to anticoagulation
- Familial bleeding or clotting disorders
- History of heparin-induced thrombocytopenia
- Pregnancy
- Phlegmasia/extensive iliofemoral disease
- Renal dysfunction requiring dialysis

Patients treated with low-molecular-weight heparin (LMWH) (listed with GCN code 7542)

Method/Source of Data Collection

Identify patients diagnosed with deep vein thrombosis using the above diagnosis codes. Some medical groups will be able to identify the population of patients through patient computer records of ICD-9 codes. If this is not possible, a list of patients may be generated from the radiology records for compression ultrasounds with a diagnosis of deep vein thrombosis.

The medical record of each patient is reviewed to determine if the patient meets any of the exclusion criteria. If none of the exclusions is met, the chart is further reviewed for administration of low-molecular-weight heparin (LMWH).

Finally, the chart is reviewed for an inpatient admission within seven days of the diagnosis of deep vein thrombosis.

Time Frame Pertaining to Data Collection

The suggested time period is a calendar month.

Key Implementation Recommendations

The following system changes were identified by the guideline work group as key strategies for health care systems to incorporate in support of the implementation of this guideline.

1. Implement a defined anticoagulation management program to individualize the care provided to each patient receiving (anticoagulation) therapy. *(2010 Joint Commission/National Safety Goal)*
2. (Clinics and Hospitals): Develop systems for monitoring the effects of anticoagulation therapy (heparin, low-molecular-weight heparin, warfarin and other anticoagulants) to include monitoring of outpatient therapy.
    - Use of standardized practices/protocols that include patient involvement. *(2010 Joint Commission/ National Safety Goal)*
3. When heparin is administered intravenously and continuously, the organization should use programmable infusion pumps. *(2010 Joint Commission/National Safety Goal)*
4. Develop systems for providing patient/family education that includes the importance of follow-up monitoring, compliance issues, dietary restrictions, and potential adverse drug reactions and interactions.
    - Patient education to include documentation of the patient's own awareness of his/her risk for venous thromboembolism (VTE) signs and symptoms of venous thromboembolism and when/how to seek treatment, and demonstrated understanding of the prescribed anticoagulation regimen. *(2010 Joint Commission/National Safety Goal)*
5. Develop a policy for providing organizational education regarding anticoagulation therapy to prescriber(s), staff, patients and families. *(2010 Joint Commission/National Safety Goal)*
6. Develop protocols for the initiation and maintenance of anticoagulation therapy appropriate to the medication used, to the condition being treated, and to the potential for drug interactions. *(2010 Joint Commission/National Safety Goal)*

Knowledge Resources

Criteria for Selecting Resources

The following resources were selected by the Venous Thromboembolism Diagnosis and Treatment guideline work group as additional resources for providers and/or patients. The following criteria were considered in selecting these resources.

- The site contains information specific to the topic of the guideline.
- The content is supported by evidence-based research.
- The content includes the source/author and contact information.
- The content clearly states revision dates or the date the information was published.
- The content is clear about potential biases, noting conflict of interest and/or disclaimers as appropriate.

Resources Available to ICSI Members Only

ICSI has a wide variety of knowledge resources that are ***only*** available to ICSI members (these are indicated with an asterisk in far left-hand column of the Resources Available table). In addition to the resources listed in the table, ICSI members have access to a broad range of materials including tool kits on CQI processes and Rapid Cycling that can be helpful. To obtain copies of these or other Knowledge Resources, go to http://www.icsi.org/improvement_resources. To access these materials on the Web site, you must be logged in as an ICSI member.

The resources in the table on the next page that are not reserved for ICSI members are available to the public free-of-charge.

Resources Available

*	Author/Organization	Title/Description	Audience	Web Sites/Order Information
	American Venous Forum/Venous Educational Institute of America (VEIN)	Provides a general overview of the condition, a clinical discussion group, referral center and links to other resources.	Health Care Professionals; Patients and Families	http://www.dvt.info.com
	Health Information Translations or Ohio State University Medical Center, Ohio Health, Mount Carmel Foundation, Nationwide Children's Hospital	Site contains downloadable print education materials on cardiovascular and other topics in a wide range of languages.	Health Care Professionals; Patients and Families	http:www.healthinfotranslations.com
*	Institute for Clinical Systems Improvement	Development of Anticoagulation Programs at Seven Medical Organizations (#29, 12/04)	Health Care Professionals	http://www.icsi.org
*	Institute for Clinical Systems Improvement	Family Health Systems Minnesota Improvement Case Report on Anticoagulation Therapy (#12, 11/99)	Health Care Professionals	http://www.icsi.org
	Mayo Clinic	Overview of deep vein thrombosis.	Patients and Families	http://www.mayoclinic.com (Select D under Diseases and Conditions)
	National Alliance for Thrombosis and Thrombophilia ("NATT")	A patient-led advocacy organization that includes many of the nation's foremost experts on blood clots and blood clotting disorders.	Patients and Families	http://stoptheclot.org/
	National Heart, Lung, and Blood Institute	Overview of heart, lung and blood disorders. Provides educational resources and information of ongoing research.	Health Care Professionals	http://www.nhlbi.nih.gov
	National Library of Medicine-Medline Plus	Overview of varicose veins and related conditions, diagnosis, causes and treatment. Connects to additional DVT resources.	Patients and Families	http://www.nlm.nih.gov/medlineplus/ency/article/001109.htm
*	Park Nicollet Health Services	Deep Vein Thrombosis: brochure	Patients and Families	http://www.icsi.org
	Vascular Disease Foundation	A non-profit educational organization dedicated to increasing awareness of prevention, diagnosis and management of vascular diseases.	Health Care Professionals	http://www.vdf.org
	Vascular Disease Foundation (VDF)	This Web site is dedicated to reducing death and disability from vascular diseases and improving vascular health.	Health Care Professionals	http://www.vdf.org

* Available to ICSI members only.