



INSTITUTE FOR CLINICAL  
SYSTEMS IMPROVEMENT

**Health Care Guideline:**

# **Venous Thromboembolism Diagnosis and Treatment**

**Twelfth Edition  
January 2012**

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.

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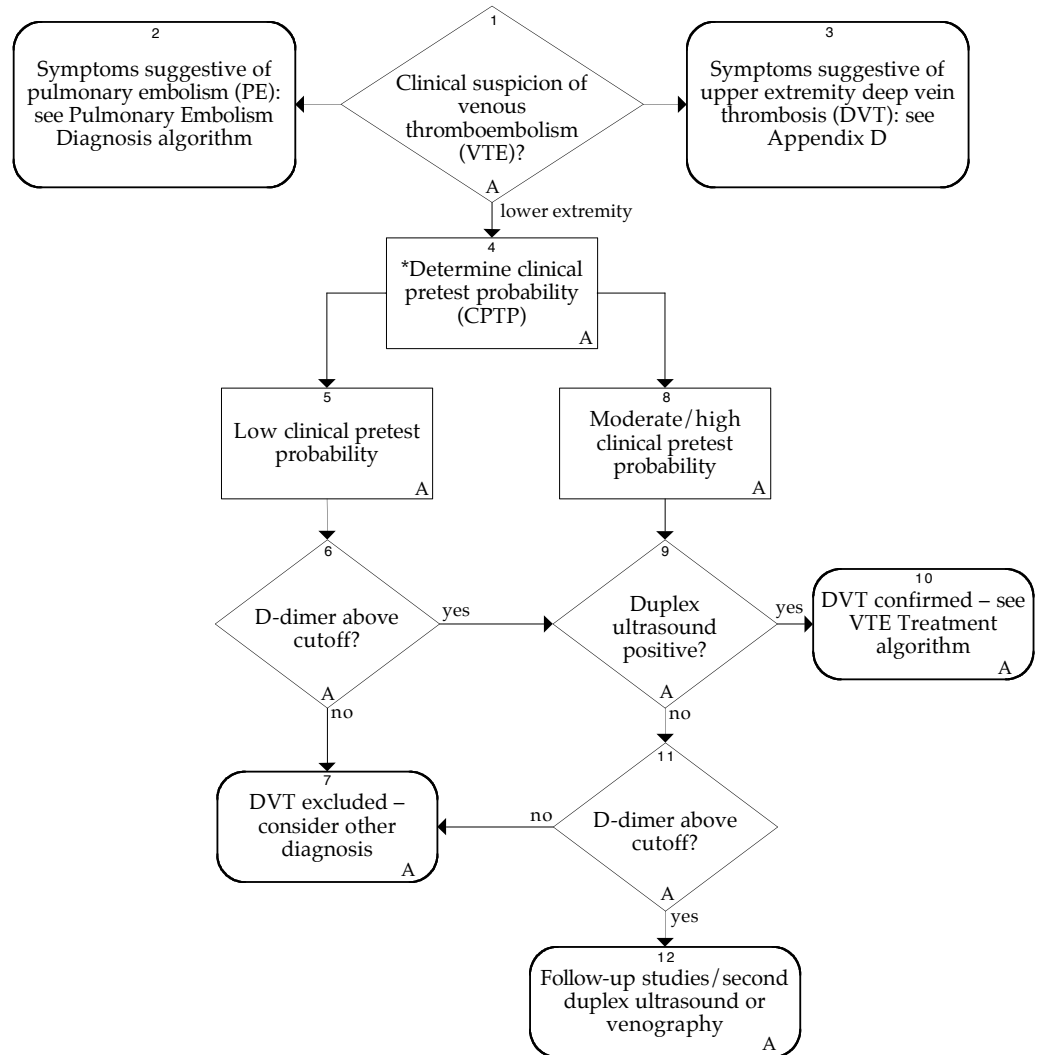
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All algorithm boxes with an "A" and those that refer to other algorithm boxes link to annotation content.

Text in blue throughout the document also provides links.

### Deep Vein Thrombosis (DVT) Diagnosis Algorithm



A = Annotation

\*4.

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
Localized tenderness along the distribution of the deep venous system	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

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**High DVT Risk = 3+**  
**Moderate DVT Risk = 1-2**  
**Low DVT Risk = ≤ 0**

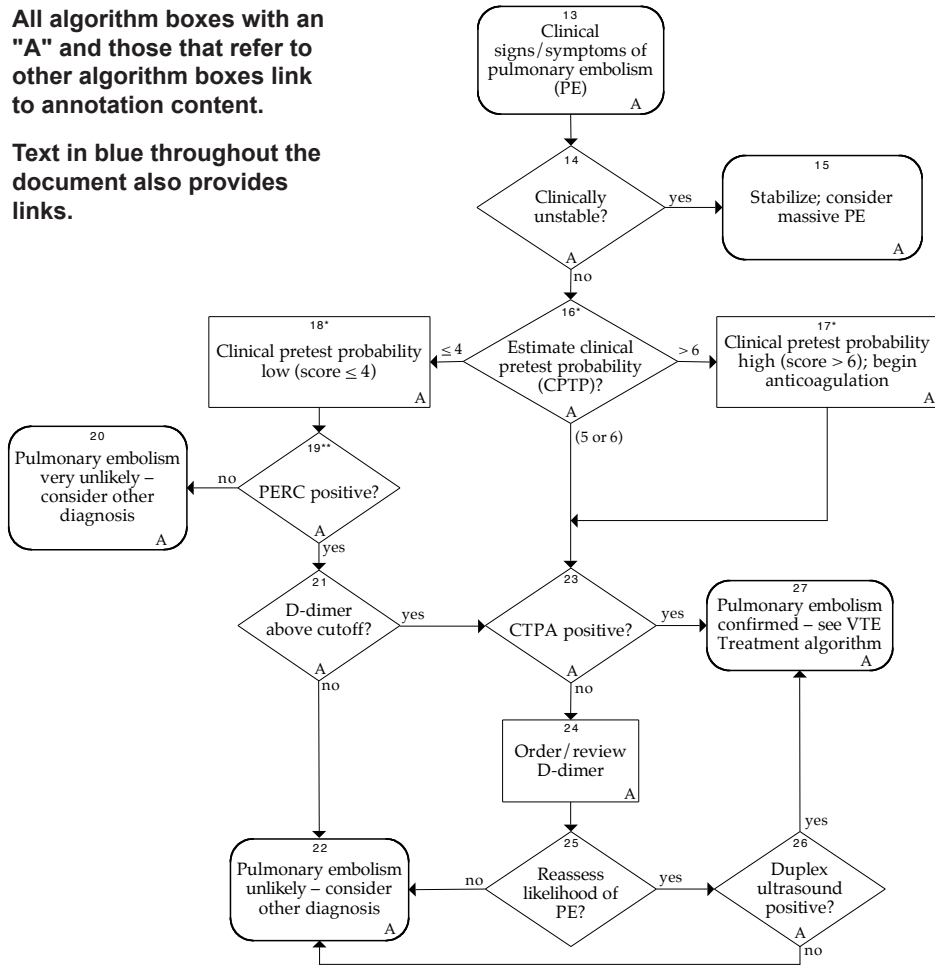
*If both legs are symptomatic, score the more severe leg.*

# Pulmonary Embolism (PE) Diagnosis Algorithm

A = Annotation

All algorithm boxes with an "A" and those that refer to other algorithm boxes link to annotation content.

Text in blue throughout the document also provides links.



<sup>16, 17, 18</sup>  
**Assess Clinical Pretest Probability of Pulmonary Embolism**  
Clinical Pretest Probability (CPTP - modified Wells PE Score)

Clinical Signs	3
Alternative Dx unlikely	3
Heart rate > 100	1.5
Immobilization previous 4 days	1.5
Previous DVT/PE	1.5
Hemoptysis	1
Malignancy (on treatment for last 6 mo)	1

**PE Less Likely ≤ 4**  
**PE Likely > 4**

- Assess Pulmonary Embolism Rule-Out Criteria**  
\*\*If any of these questions is answered yes, then the patient is considered PERC positive:
1. Is the patient older than 49 years?
  2. Is the patient's pulse > 99 beats per minute?
  3. Is the patient's pulse oximetry reading < 95% while breathing room air?
  4. Does the patient have hemoptysis?
  5. Is the patient on exogenous estrogen?
  6. Does the patient have prior diagnosis of VTE?
  7. Has the patient had surgery or trauma (requiring endotracheal intubation or hospitalization in the previous four weeks)?
  8. Does the patient have unilateral leg swelling at the calves?  
(Fesmire, 2011)

**Abbreviations**  
CPTP = Clinical pretest probability  
CTPA = CT pulmonary angiogram  
PE = Pulmonary embolism  
PERC = Pulmonary embolism rule-out criteria  
VTE = Venous thromboembolism

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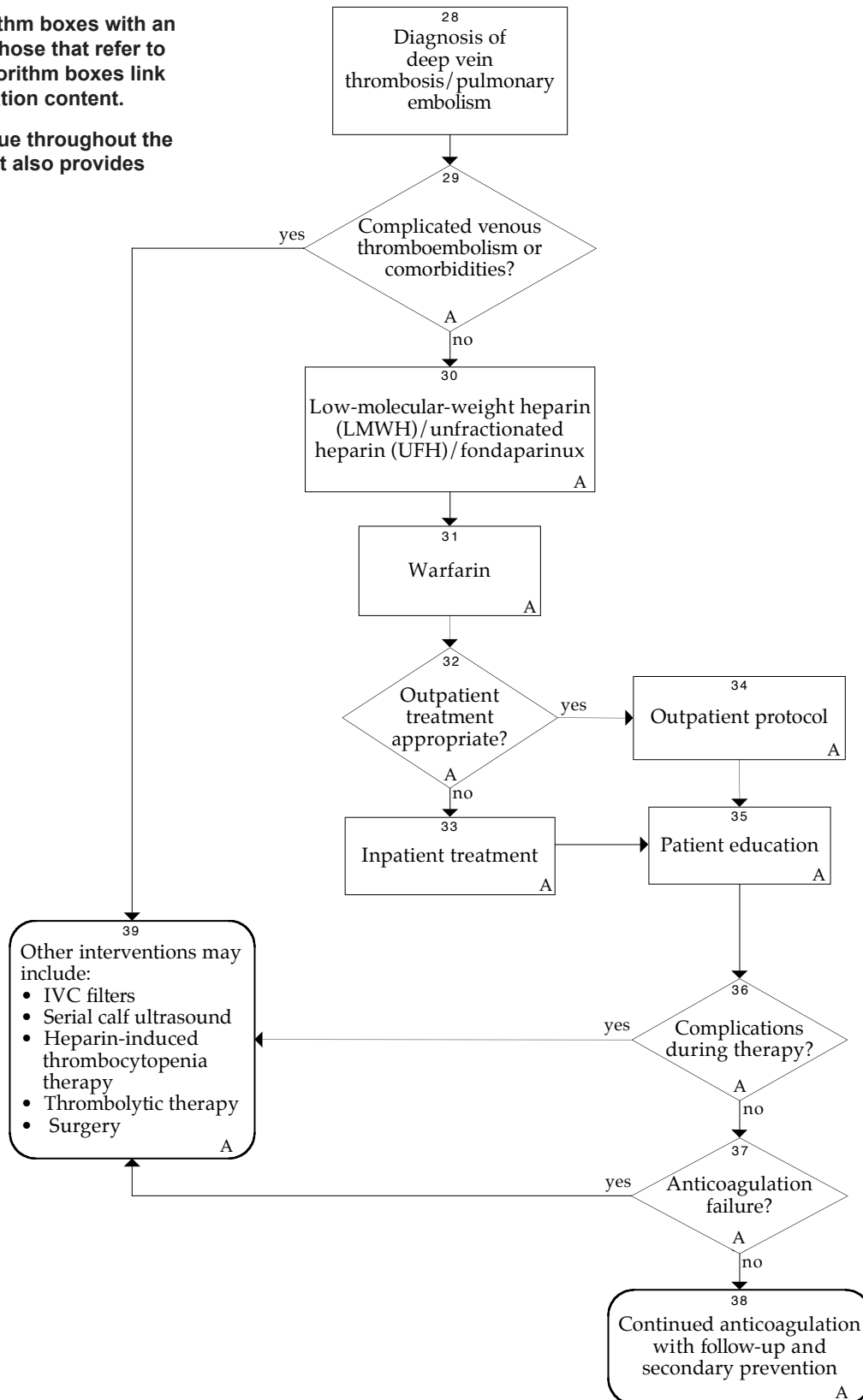
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## Venous Thromboembolism (VTE) Treatment Algorithm

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A = Annotation



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### Work Group Leader

Denise Dupras, MD  
*Internal Medicine, Mayo Clinic*

### Work Group Members

#### Family Practice

Terry A. Johnson, MD  
*Allina Medical Clinic*

#### Internal Medicine

Cindy Felty, NP  
*Mayo Clinic*  
Tarek Hamieh, MD  
*HealthPartners Medical Group and Regions Hospital*  
Seema Maddali, MD, MHA  
*HealthEast Care System*

#### Pharmacy

Peter Marshall, PharmD  
*HealthPartners Health Plan*

#### Vascular Surgery

Mark Melin, MD  
*Park Nicollet Health Services*

#### Facilitator

Myounghee Hanson, BA  
*ICSI*

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## Disclosure of Potential Conflict of Interest

In the interest of full disclosure, ICSI has adopted a policy of revealing relationships work group members have with companies that sell products or services that are relevant to this guideline topic. It is not assumed that these financial interests will have an adverse impact on content. They are simply noted here to fully inform users of the guideline.

Mark Melin, MD serves on the Medica Physician Advisory Panel, Varicose Veins.

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

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## Description of Evidence Grading

A consistent and defined process is used for literature search and review for the development and revision of ICSI guidelines. Literature search terms for the current revision of this document include venous thromboembolism (VTE) treatment / duration, pulmonary embolism (PE) diagnosis/treatment, new drugs for VTE and PE, CT scan and radiation/ways to reduce, D-dimer/predicting risk of deep vein thrombosis and risk of recurrence of DVT, patient decision aid to take warfarin (Coumadin), risks/benefits of anticoagulation as chronic therapy – statistics, outpatient treatment and home therapy for VTE and DVT, upper extremity deep vein thrombosis and heparin-induced thrombocytopenia from 2010 to August 2011. PubMed and Cochrane were the databases that were searched. Inclusion criteria included English language, adults, randomized controlled trials, guidelines, meta-analysis and systematic reviews. Excluded were pregnancy and non-human studies.

Following a review of several evidence rating and recommendation writing systems, ICSI has made a decision to transition to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

GRADE has advantages over other systems including the current system used by ICSI. Advantages include:

- Developed by a widely representative group of international guideline developers
- Explicit and comprehensive criteria for downgrading and upgrading quality of evidence ratings
- Clear separation between quality of evidence and strength of recommendations that includes a transparent process of moving from evidence evaluation to recommendations
- Clear, pragmatic interpretations of strong versus weak recommendations for clinicians, patients and policy-makers
- Explicit acknowledgement of values and preferences
- Explicit evaluation of the importance of outcomes of alternative management strategies

At ICSI we have established a GRADE Implementation Team to provide overall direction for this transition. We intend to complete the transition in phases. In 2011 the following work to transition to GRADE was done:

- Select documents that will undergo complete implementation of GRADE
- For all other documents, including Venous Thromboembolism Diagnosis and Treatment, beginning March 2011:
  - All original ICSI Class A (RCTs) and ICSI Class B (Cohort) studies were reviewed by work group members and the quality of evidence assessed using GRADE. Other literature was labeled by ICSI staff according to Crosswalk between ICSI Evidence Grading System and GRADE.
  - New literature was reviewed and graded by work group members using the new ICSI GRADE system.
  - Key Points in all documents become Recommendations.

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Description of Evidence Grading

Crosswalk between ICSI Evidence Grading System and GRADE

Design of Study Current ICSI System	ICSI GRADE System
<b>Class A:</b> Randomized, controlled trial	<b>High</b> , if no limitation <b>Moderate</b> , if some limitations <b>Low</b> , if serious limitations
<b>Class B:</b> [observational] Cohort study	<b>High</b> , if well done with large effect <b>Moderate</b> , if well done with effect <b>Low</b> , most studies
<b>Class C:</b> [observational] Non-randomized trial with concurrent or historical controls Case-control study Population-based descriptive study Study of sensitivity and specificity of a diagnostic test	<b>Low</b> <b>Low</b> <b>*Low</b>
* Following individual study review, may be elevated to Moderate or High depending upon study design	
<b>Class D:</b> [observational] Cross-sectional study Case series Case report	<b>Low</b>
<b>Class M:</b> Meta-analysis Systematic review Decision analysis Cost-effectiveness analysis	<b>Meta-analysis</b> <b>Systematic Review</b> <b>Decision Analysis</b> <b>Cost-Effectiveness Analysis</b>
<b>Class R:</b> Consensus statement Consensus report Narrative review Guideline	<b>Low</b> <b>Low</b> <b>Low</b> <b>Guideline</b>
<b>Class X:</b> Medical opinion	<b>Low</b>
<b>Class Not Assignable</b>	<b>Reference</b>

**Evidence Definitions:**

**High Quality Evidence** = Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate Quality Evidence** = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low Quality Evidence** = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate or any estimate of effect is very uncertain.

**Supporting Literature:**

In addition to evidence that is Graded and used to formulate recommendations, additional pieces of literature will be used to inform the reader of other topics of interest. This literature is not given an evidence grade and is instead identified as a **Reference** throughout the document.

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# Foreword

## Introduction

It is estimated that over one million patients are identified as having an acute venous thrombotic event in the United States annually. This includes patients with deep vein thrombosis and pulmonary embolism and is estimated to result in more than 100,000 deaths each year.

The ICSI Venous Thromboembolism Diagnosis and Treatment guideline was developed to assist providers and institutions with an evidence-based approach to the diagnosis and acute management of the majority of these patients. Though the guideline algorithm is focused on the evaluation and management of the stable patient, we also include insights into the management of those patients who may not fit into this category.

Key to the evaluation of patients with suspected venous thromboembolism is the use of the provider's clinical evaluation with the help of pretest probability tools as well as judicious use of objective diagnostic tests. Our recommendations for acute treatment of venous thrombosis are determined by the patient's clinical circumstances and range from a safe approach to outpatient treatment of deep vein thrombosis through emergent evaluation and treatment of life-threatening massive pulmonary embolism. Our hope is that we have supplemented providers' clinical acumen and assisted them and their health systems in developing best practice approaches to this ever-increasing population of patients.

The venous thromboembolism work group welcomes your input on how improvements might be made on this guideline in the future.

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## Scope and Target Population

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

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## Aims

1. Improve accurate diagnosis and treatment of venous thromboembolism (VTE). (*Annotations #13, 27*)
2. Prevent progression or recurrence of thromboembolic disease. (*Annotation #38*)
3. Safely use anticoagulants to reduce the likelihood of patient harm and complications of anticoagulation therapy. (*Annotations #30, 31, 32, 37, 38, 39*)
4. Increase the percentage of patients who are evaluated for medication reconciliation upon change in level of care and/or upon discharge. (*Annotations #36, 37, 38*)

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## Clinical Highlights

- A clinical pretest probability assessment should be completed in patients with suspected venous thromboembolism. (*Annotations #4, 16; Aim #1*)
- D-dimer can be used as a negative predictor to eliminate need for further testing. (*Annotations #6, 11, 21; Aim #1*)
- Confirm diagnosis of lower extremity deep vein thrombosis (DVT) with imaging study, preferably duplex ultrasound (with compression). (*Annotation #4; Aim #1*)

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## Foreword

- In patients with a high clinical pretest probability for pulmonary embolism (PE), begin anticoagulation without delay. (*Annotation #17; Aim #1*)
- Achieve rapid, effective anticoagulation. (*Annotation #30; Aim #2*)
- In patients with acute VTE, heparin (UFH or LMWH) or fondaparinux should be given for at least five days and until the INR  $\geq$  2.0 for two consecutive days. (*Annotations #30, 31; Aim #2*)
- Arrange for home therapy in appropriate patients. (*Annotation #34; Aim #4*)

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## Implementation Recommendation Highlights

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. (*2011 Joint Commission/National Safety Goal*)
2. Clinics and Hospitals: develop systems for monitoring the effects of anticoagulation to include monitoring of outpatient therapy.
  - Use of standardized practices/protocols that include patient involvement. (*2011 Joint Commission/National Safety Goal*)
3. When unfractionated heparin is administered intravenously and continuously, the organization should use programmable infusion pumps. (*2011 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. (*2011 Joint Commission/National Safety Goal*)
5. Develop a policy for providing organizational education regarding anticoagulation therapy to prescriber(s), staff, patients and families. (*2011 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. (*2011 Joint Commission/National Safety Goal*)

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## Related ICSI Scientific Documents

### Guidelines

- [Antithrombotic Therapy Supplement](#)
- [Venous Thromboembolism Prophylaxis](#)

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# Algorithm Annotations

## Deep Vein Thrombosis (DVT) Diagnosis Algorithm Annotations

### 1. Clinical Suspicion of Venous Thromboembolism (VTE)?

#### Recommendation:

- Perform a thorough physical examination and obtain a complete history to evaluate for deep vein 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 [Low Quality Evidence]*).

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 #39, "Other Interventions."](#)

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 [Guideline]*).

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### 4. Determine Clinical Pretest Probability (CPTP)

#### Recommendation:

- 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.

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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 [Low Quality Evidence]). In high-risk patients with negative ultrasound, further tests should be considered.

Additional studies reported lower specificity when the pretest probability model was used by primary care providers (Douketis, 2005 [Guideline]; Goodacre, 2005 [Meta-analysis]; Oudega, 2005 [Low Quality Evidence]). Careful review and application of the pretest probability model by all providers are recommended.

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## 5. Low Clinical Pretest Probability

### Recommendation:

- In patients with low clinical pretest probability of deep vein thrombosis, obtain a D-dimer.

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. If D-dimer is negative, duplex ultrasound (with compression) can be omitted, and repeat ultrasound is not needed in one week unless new or progressive clinical symptoms occur (Fünfsinn, 2001 [Low Quality Evidence]; Aschwanden, 1999 [Low Quality Evidence]).

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## 6. D-dimer Above Cutoff?

### Recommendations:

- High sensitivity D-dimer assays have high negative predictive value for patients with a low pretest probability of deep vein thrombosis or pulmonary embolism.
- The D-dimer test is most helpful 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, cancer and those in post-partum period.

Depending on 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. 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 (e.g., 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 immunoassay methods are more sensitive than semiquantitative latex agglutination methods) and the assay discriminate (i.e., "cutoff") level (Stevens, 2005 [Low Quality Evidence]; Fünfsinn, 2001 [Low Quality Evidence]; Heit, 2000 [Low Quality Evidence]; Aschwanden, 1999 [Low Quality Evidence]; Heit, 1999 [Low Quality Evidence]). The assay discriminate level varies by assay vendor; no universal "cutoff" level (e.g., less than 300 or less than 500 ng/mL) exists, but ELISA is used by nearly all labs. It is also less predictive for patients with recent surgery, trauma, cancer and those in the postpartum period (see [Annotation #21, "D-dimer Above Cutoff?"](#) for more information).

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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 [Low Quality Evidence]*). For patients with suspected deep vein thrombosis, D-dimer may decrease the need for initial and subsequent imaging.

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## 7. Deep Vein Thrombosis Excluded – Consider Other Diagnosis

Patients with a low clinical pretest probability of deep vein thrombosis and a negative 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 evaluation unless warranted by new or progressive clinical symptoms (*Aschwanden, 1999 [Low Quality Evidence]*).

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## 8. Moderate/High Clinical Pretest Probability

### Recommendations:

- Venous duplex ultrasound (with compression) should be the first test in patients with moderate or high clinical pretest probability.
- If the duplex ultrasound (with compression) is negative, obtain a D-dimer to guide further testing needs.

Patients with moderate or high clinical to 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.

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## 9. Duplex Ultrasound Positive?

### Recommendation:

- Duplex ultrasound (with compression) is considered to be the primary diagnostic test for evaluation of proximal deep vein thrombosis.

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.

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, "Clinical Suspicion of Venous Thromboembolism \[VTE\]?"](#))

### Proximal (Popliteal Vein and Above)

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

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Ultrasonography has been demonstrated in a large number of studies to be 87% sensitive and between 86% and 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 [Low Quality Evidence]; Heijboer, 1993 [High Quality Evidence]*).

### **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 [Low Quality Evidence]*).

(*Polak, 2005 [Low Quality Evidence]*)

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## **10. Deep Vein Thrombosis Confirmed – See Venous Thromboembolism Treatment Algorithm**

### **Recommendations:**

- Proximal thrombosis should be treated with anticoagulation unless contraindicated.
- Calf vein thrombosis may be treated with anticoagulation or 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 [Guideline]*). (See [Annotation #29, "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 (*Lohr, 1995 [Low Quality Evidence]; Philbrick, 1988 [Low Quality Evidence]; Lagerstedt, 1985 [Moderate Quality Evidence]*). If not treated, these patients should be followed by serial duplex ultrasounds to rule out proximal progression of thrombus to popliteal vein. Short term treatment with LMWH and compression stockings was not shown superior to compression alone in a randomized controlled trial (*Schwarz, 2010 [High Quality Evidence]*).

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 (*Hull, 1989 [Low Quality Evidence]; Philbrick, 1988 [Low Quality Evidence]; Huisman, 1986 [Low Quality Evidence]*).

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## **11. D-dimer Above Cutoff?**

### **Recommendation:**

- Do not administer anticoagulation to patients with a negative ultrasound and two negative high sensitivity D-dimers.

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

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## 12. Follow-Up Studies/Second Duplex Ultrasound or Venography

### Recommendations:

- Consider venography or repeat ultrasound in three to seven days if there is high pretest probability of a deep vein thrombosis in the setting of a positive D-dimer and negative duplex ultrasound.

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 [Low Quality Evidence]; Heijboer, 1993 [High Quality Evidence]*). 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 diagnostic techniques, spiral contrast CT and magnetic resonance venography, have shown excellent results in preliminary studies. Currently these techniques could be considered in patients with unusual diagnostic situations, including suspected ilio caval clots or in patients with contraindications for venography (*Balducci, 1996 [Low Quality Evidence]; Dupas, 1995 [Low Quality Evidence]; Evans, 1993 [Low Quality Evidence]*).

- **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, limited 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.

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## Pulmonary Embolism (PE) Diagnosis Algorithm Annotations

### 13. Clinical Signs/Symptoms of Pulmonary Embolism (PE)

#### Recommendation:

- Consider pulmonary embolism in patients who present with 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:

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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 ( $\Delta S_2P$ ), 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 (Stein, 2006a [High Quality Evidence]; Stein, 2006b [Low Quality Evidence]; Hull, 1995 [Low Quality Evidence]; Stein, 1991 [Low Quality Evidence]).

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## 14. Clinically Unstable?

Patients who are clinically unstable may have massive pulmonary embolism (PE), which is associated with up to a tenfold increase in mortality. Massive PE should be considered when any of the following clinical signs are present: hemodynamic instability (including systolic blood pressure less than 90 mmHg, or a drop in 40 mmHg), syncope, severe hypoxemia or respiratory distress. Massive PE can also be identified with severely abnormal imaging studies: computed tomographic pulmonary angiogram (CTPA) or ventilation/perfusion (V/Q) scan that shows 50% or more absent perfusion or an echocardiogram showing right ventricular (RV) failure or strain. Furthermore, elevated troponin and BNP levels are associated with RV strain, and elevations of both have been associated with increased mortality, even in the absence of overt hemodynamic compromise (Jaff, 2011 [Guideline]).

The challenge is to identify the group of patients with an increased risk of mortality and consider whether they are candidates for thrombolytic therapy. Since thrombolytic therapy has not been clearly shown to improve mortality in any group of patients, its use is always a clinical judgement. Nevertheless, most experts consider thrombolytic therapy lifesaving if the patient is clinically unstable as defined above (Fesmire, 2011 [Guideline]). Other groups of patients who are candidates for consideration of thrombolytic therapy are those with a high clot burden on imaging studies and/or RV failure or strain on echocardiogram (Konstantinides, 2002 [High Quality Evidence]). Lastly, a preliminary recommendation would be to measure a BNP and/or troponin in any patient with a clinical presentation that is concerning (Kline, 2008b [Low Quality Evidence]; Klok, 2008 [Meta-analysis]; Laporte, 2008 [Low Quality Evidence]; Becattini, 2007 [Meta-analysis]; Pieralli, 2006 [Low Quality Evidence]), in order to identify apparently stable patients at higher risk for poor outcome.

(Fesmire, 2011 [Guideline]; Jaff, 2011 [Guideline]; Meyer, 1998 [Low Quality Evidence])

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## 15. Stabilize; Consider Massive Pulmonary Embolism

See Annotation #29, "Complicated Venous Thromboembolism or Comorbidities?" for more information.

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## 16. Estimate Clinical Pretest Probability (CPTP)?

### Recommendation:

- Calculate the clinical pretest probability of pulmonary embolism.

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

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

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inheritable thrombophilic disorder or personal history of acquired thrombophilia (e.g., antiphospholipid antibody, cancer, estrogen, pregnancy or myeloproliferative disorder).

- **Estimate pretest probability.** The work group continues to recommend the Wells' criteria, but other prediction rules exist, none having proved itself superior to Wells (*Fesmire, 2011 [Guideline]; Douma, 2011 [Low Quality Evidence]*). 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 [Low Quality Evidence]*). 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 [Low Quality Evidence]*). A recent prospective study of 3,306 patients presented a validated simplified algorithm based on the earlier work of Wells (*Dalen, 2006 [Low Quality Evidence]; Stein, 2006b [Low Quality Evidence]; Writing Group for the Christopher Study Investigators, 2006 [Low Quality Evidence]*).

Other studies reported lower specificity when the pretest probability model was used by primary care providers (*Douketis, 2005 [Guideline]; Goodacre, 2005 [Meta-analysis]; Oudega, 2005 [Low Quality Evidence]*). Careful review and application of the pretest probability model by all providers are recommended.

- **Chest x-ray, arterial blood gases, electrocardiogram (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<sub>2</sub> 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<sub>1</sub>Q<sub>3</sub>T<sub>3</sub> 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 [Guideline]; Stein, 1991 [Low Quality Evidence]*). A study performed in emergency room physicians supported the effectiveness of the application of a computerized decision support system to improve the diagnoses of PE (*Drescher, 2010 [Low Quality Evidence]*).

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## 17. Clinical Pretest Probability High (Score > 6); Begin Anticoagulation

### Recommendation:

- Begin anticoagulation without delay, unless contraindicated, if the clinical pretest probability score is high (six or more on Wells' criteria).

If the clinical pretest probability score is high, begin unfractionated heparin (UFH) promptly (a tool for determining pretest probability is shown in annotation [Appendix B, "Model for Predicting Clinical Pretest Probability for Pulmonary Embolism"](#)). LMWH is an option but has less favorable pharmacokinetics. Factors favoring UFH are faster onset and shorter half-life. For a patient with HIT, consider fondaparinux.

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## 18. Clinical Pretest Probability Low (Score $\leq$ 4)

### Recommendation:

- Only if the clinical pretest probability score is less than or equal to four, then apply the PERC rule. (See Annotation #19, "Pulmonary Embolism Rule-Out Criteria [PERC] Positive?")

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## 19. Pulmonary Embolism Rule-Out Criteria (PERC) Positive?

### Recommendation:

- Perform PERC assessment to identify group at very low risk of pulmonary embolism (PE).

If any of these questions is answered yes, then the patient is considered PERC positive:

- Is the patient older than 49 years?
- Is the patient's pulse  $>$  99 beats/minute?
- Is the patient's pulse oximetry reading  $<$  95% while breathing room air?
- Does the patient have hemoptysis?
- Is the patient on exogenous estrogen? Does the patient have prior diagnosis of venous thromboembolism?
- Has the patient had surgery or trauma (requiring endotracheal intubation or hospitalization) in the previous four weeks?
- Does the patient have unilateral leg swelling at the calves?

(Fesmire, 2011 [Guideline])

There is concern that since D-dimer testing is not very specific for the diagnosis of pulmonary embolism (PE), use of this test in very low risk populations leads to a high false-positive rate and subsequently exposure of low-risk persons to testing that likely includes ionizing radiation. In lieu of this fact, there has been effort to consider ways to limit advanced testing to those who have a higher CPTP.

In 2004, Kline, et al. published an article that identified eight variables from an original list of 21 that can be used to distinguish the likelihood of pulmonary embolism from a sample of 3,148 patients at 10 U.S. hospitals (Kline, 2004 [Moderate Quality Evidence]). In the same article, they prospectively validated this decision rule on 382 patients who presented with dyspnea but were not suspected of having a PE. They found the prevalence of PE to be 1.4% (confidence interval [CI]: 0.5-3.0%) in this group. This has been labeled the Pulmonary Embolism Rule-out Criteria (PERC).

In 2008, Kline, et al. published another validation of this decision rule in 8,138 patients at 13 centers. In this study they found that there was a 1.0% rate of any VTE or death in patients who had a low clinical suspicion by gestalt and a negative PERC rule (CI: 0.6-1.6%) (Kline, 2008a [Moderate Quality Evidence]).

Since then there have been other studies that have validated the PERC rule (Wolf, et al. [100% sensitivity], and Dachs, et al. [100% sensitivity]). Both of these studies were retrospective in design (Dachs, 2010 [Low Quality Evidence]; Wolf, 2008 [Low Quality Evidence]). Both of these studies were done prospectively, but the rule was applied retrospectively.

There also has been a systematic review of PERC by Carpenter, et al. that concluded the rule was validated by the evidence (Carpenter, 2008 [Systematic Review]).

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There has also been a prospective study that applied the PERC rule retrospectively in 1,675 patients who had the Geneva score used to determine PTP (*Hugli, 2011 [Moderate Quality Evidence]*). It showed 6.4% (CI: 3.7-10.8%) of the patients who were PERC negative and Geneva low risk to subsequently have a PE.

In June of 2011 the American College of Emergency Physicians (ACEP) published a revision of their clinical policy on evaluation and management of PE. In this clinical policy revision, they asked six questions in regard to evaluation and management of PE. One of the questions they asked was "What is the utility of the PERC in evaluation of patients with suspected PE?" Their level B recommendation was that the PERC could be considered to exclude the diagnosis of PE using history and physical examination alone, after finding the patients clinical pretest probability to be low. This was level B evidence, as the studies cited applied the rule retrospectively, so the strength of the evidence was felt to be limited (*Fesmire, 2011 [Guideline]*).

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## 20. Pulmonary Embolism Very Unlikely – Consider Other Diagnosis

Studies have shown that if the "clinical gestalt" of the provider evaluating the patient indicates low likelihood of PE, if the CPTP by the Wells rule is low and the PERC is negative, then the likelihood of PE is < 2% (*Fesmire, 2011 [Guideline]*; *Kline, 2008a [Moderate Quality Evidence]*; *Kline, 2004 [Moderate Quality Evidence]*).

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## 21. D-dimer Above Cutoff?

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 (*Gimber, 2009 [Low Quality Evidence]*; *Wells, 1998a [Low Quality Evidence]*; *Stein, 1995 [Low Quality Evidence]*; *Stein, 1993 [Low Quality Evidence]*). In this group it is safe to withhold anticoagulation therapy and follow these patients clinically.

The specificity of the D-dimer may be reduced if the duration of symptoms or signs of venous thromboembolism exceed two or three days prior to testing. The sensitivity may be reduced if the patient has been receiving heparin therapy or has had a recent procedure, trauma or surgery. In these settings, as well as the postpartum time, there may be increases in the plasma D-dimer level. 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) may be more effective. Studies have also suggested that the negative predictive value of D-dimer may be lower in patients with cancer (*Lee, 1999 [Low Quality Evidence]*), distal DVTs (*Escoffre-Barbe, 1998 [Low Quality Evidence]*) and previous DVTs (*LeGal, 2006 [Low Quality Evidence]*).

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

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## 22. Pulmonary Embolism Unlikely – Consider Other Diagnosis

### Recommendations:

- Evaluate patients for other diagnoses when pulmonary embolism has been excluded.
- No additional workup is needed in patients with an unlikely clinical pretest probability with a positive D-dimer and negative CTPA.

Patients with a negative D-dimer and PE Less Likely Clinical Pretest Probability have a low incidence of pulmonary embolism (*Stein, 2006a [High Quality Evidence]*; *Stein, 2006b [Low Quality Evidence]*; *Writing*

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Group for the Christopher Study Investigators, 2006 [Low Quality Evidence]; Wells, 1998a [Low Quality Evidence]; Stein, 1995 [Low Quality Evidence]; Stein, 1993 [Low Quality Evidence]). It is safe to withhold anticoagulation therapy and follow these patients clinically (Lucassen, 2011 [Systematic Review]).

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 [Low Quality Evidence]; Stein, 2006a [High Quality Evidence]; Stein, 2006b [Low Quality Evidence]; Writing Group for the Christopher Study Investigators, 2006 [Low Quality Evidence]).

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 VTE 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.

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## 23. Computed Tomographic Pulmonary Angiography (CTPA) Positive?

### Recommendation:

- Perform computed tomographic pulmonary angiography (CTPA) as the next diagnostic test.
- Consider the pretest probability and D-dimer results to guide additional testing in patients with a non-diagnostic or negative CTPA.

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

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. In some institutions, CTPA 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.

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 (Dalen, 2006 [Low Quality Evidence]; Remy-Stein, 2006a [High Quality Evidence]; American Thoracic Society, 1999 [Guideline]; PIOPED Investigators, The; 1990 [Low Quality Evidence]).

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In some institutions, CTPA is easier to obtain than a V/Q (ventilation/perfusion) scan than other diagnostics. CT pulmonary angiography has a high sensitivity and specificity for central clots. The sensitivity and specificity drop substantially for peripheral clots. 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. Computed tomographic angiography showing positive results for segmental/subsegmental embolism should be followed up with additional testing, due to the increase in false-positives. 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 [Guideline]; Stein, 2006a [High Quality Evidence]; Writing Group for the Christopher Study Investigators, 2006 [Low Quality Evidence])*

*(Stein, 2006b [Low Quality Evidence]; Mullins, 2000 [Systematic Review]; Rathbun, 2000 [Systematic Review]; Remy-Jardin, 1998 [Low Quality Evidence]; Greaves, 1997 [Low Quality Evidence]; Remy-Jardin, 1997 [Low Quality Evidence])*

Recent evidence convincingly demonstrates that a negative CTPA effectively rules out pulmonary embolism. When current generation multi-detector CT scanning is used, three months after negative CTPA, the incidence of recurrent VTE is 1.2% (Mos, 2009 [Systematic Review]). This compares very favorably to the 1.7% recurrence rate at three months of standard pulmonary angiography, the long recognized gold standard. 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 [Low Quality Evidence]; Stein, 2006a [High Quality Evidence]; Stein, 2006b [Low Quality Evidence]; Writing Group for the Christopher Study Investigators, 2006 [Low Quality Evidence])*

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. 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 (DVT).

*(Dalen, 2006 [Low Quality Evidence]; Stein, 2006a [High Quality Evidence]; Stein, 2006b [Low Quality Evidence])*

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 immunoassay (ELISA) and rapid ELISA methods, are not acceptable for use in excluding PE in patients with clinical suspicion of PE.

*(Berland, 2006 [Guideline])*

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 (Salaun, 2011 [Low Quality Evidence]).

A positive ultrasound usually confirms the diagnosis of deep vein thrombosis and requires treatment regardless of the presence or absence of pulmonary embolism. 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.

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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. (Stein, 2006b [Low Quality Evidence]; Matteson, 1996 [Low Quality Evidence]; Beecham, 1993 [Low Quality Evidence]; Killewich, 1993 [Low Quality Evidence]; Oudkerk, 1993 [Cost Effectiveness Analysis]; Schiff, 1987 [Low Quality Evidence])

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## 24. Order/Review D-dimer

If D-dimer has not yet been obtained, order the test at this point.

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## 26. Duplex Ultrasound Positive?

### Recommendation:

- Use duplex ultrasound (with compression) to assess for VTE 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 (Salaun, 2011 [Low Quality Evidence]).

A positive ultrasound usually confirms the diagnosis of deep vein thrombosis and requires treatment regardless of the presence or absence of pulmonary embolism. 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.

(Stein, 2006b [Low Quality Evidence]; Matteson, 1996 [Low Quality Evidence]; Beecham, 1993 [Low Quality Evidence]; Killewich, 1993 [Low Quality Evidence]; Oudkerk, 1993 [Cost-Effectiveness Analysis]; Schiff, 1987 [Low Quality Evidence])

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## 27. Pulmonary Embolism Confirmed – See Venous Thromboembolism Treatment Algorithm

### Recommendation:

- Treat symptomatic and asymptomatic pulmonary embolism (PE) and/or deep vein thrombosis (DVT) according to the Venous Thromboembolism (VTE) Treatment Algorithm.

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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 (*Stein, 2006a [High Quality Evidence]; Stein, 2006b [Low Quality Evidence]; American Thoracic Society, 1999 [Guideline]; Wells, 1998b [Low Quality Evidence]*).

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 [Low Quality Evidence]*). 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 [Guideline]*).

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## Venous Thromboembolism (VTE) Treatment Algorithm Annotations

### 29. Complicated Venous Thromboembolism or Comorbidities?

#### Recommendation:

- Treatment should be individualized for patients with complicated venous thromboembolism or specific comorbidities (see below).

#### Massive Pulmonary Embolism

Massive pulmonary embolism (PE) has up to a tenfold greater mortality than standard PE; thus, the evaluation and treatment are individualized. Massive PE should be considered in a patient with any hemodynamic instability, severe hypoxemia or respiratory distress. Computed tomographic pulmonary angiography (CTPA), V/Q scan, or standard pulmonary angiography that shows occlusion of 50% or more of the pulmonary vasculature should prompt consideration of massive pulmonary embolism, as well. In this group of patients, brain natriuretic peptide (BNP) and troponin testing, combined with echocardiography, can help identify patients who are at high risk of deterioration and thus would be candidates for thrombolytic therapy. 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 (*Jaff, 2011 [Guideline]; Konstantinides, 2002 [High Quality Evidence]; Arcasoy, 1999 [Systematic Review]; Meyer, 1998 [Low Quality Evidence]; Dalen, 1997 [Low Quality Evidence]; Kanter, 1997 [Low Quality Evidence]; Kasper, 1997 [Low Quality Evidence]; Konstantinides, 1997 [Low Quality Evidence]*).

Patients with severe hemodynamic compromise may require immediate thrombolytic therapy. In this group of unstable patients, bedside echocardiography can be used as the only diagnostic tool, and thrombolytic therapy can be given without imaging the pulmonary arteries. When thrombolytic therapy is contraindicated, patients should be considered for thrombectomy (either catheter-directed or open) or inferior vena cava (IVC) filter placement.

#### 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 [High Quality Evidence]; Fihn, 1996 [Systematic Review]*).

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 #39, "Other Interventions."](#)) Please refer to the [ICSI Antithrombotic Therapy Supplement](#) for more information on contraindications to anticoagulation.

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### 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 [Low Quality Evidence]*).

Patients with HIT should not be treated with either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). Fondaparinux may be an option; it has little or no antiplatelet 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 #39, "Other Interventions."](#)) 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 anticoagulation 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 [#39, "Other Interventions."](#))

### Pregnancy

Pregnancy is out of the scope of this guideline.

### Familial Bleeding Disorders

Because of the complexity and controversy surrounding the use of standard anticoagulation to treat deep vein thrombosis (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. Significant adjustments need to be made for these patients. Pharmacy consultation is recommended.

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

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

### Recommendations:

- Initial treatment of pulmonary embolism includes unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) or fondaparinux.
- Initial anticoagulation for most patients with deep vein thrombosis include LMWH and fondaparinux.

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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  $\geq 2.0$  for two consecutive days.

### Low-Molecular-Weight Heparin (LMWH)

Treatment for venous thromboembolism with LMWH provides reliable anticoagulation levels when given subcutaneously on a weight-based 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 pulmonary embolism (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 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 (*Hull, 2000 [High Quality Evidence]; Raskob, 1999 [Low Quality Evidence]; Charland, 1998 [Low Quality Evidence]; Columbus Investigators, The, 1997 [Moderate Quality Evidence]; Simonneau, 1997 [Moderate Quality Evidence]*).

For patients with underlying cancer, LMWH may be the preferred initial anticoagulant and has been shown to decrease the risk of recurrent VTE when used long term compared to vitamin K antagonists (*Akl, 2011a [High Quality Evidence]; Akl 2011b [High Quality Evidence]*).

Please note that LMWH may not be appropriate for patients with renal insufficiency (creatinine clearance less than 30 mL/min) because studies have shown modestly delayed clearance in patients with chronic renal failure. The clinician should weigh this evidence when considering outpatient therapy (*Cadroy, 1991 [Low Quality Evidence]*). (See [Annotation #29, "Complicated Venous Thromboembolism or Comorbidities?"](#))

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 [Guideline]*)

### Unfractionated Heparin (UFH)

Unfractionated heparin (UFH) is administered by continuous intravenous infusion following a bolus dose. Heparin-induced thrombocytopenia is a recognized complication of UFH therapy. (See [Annotation #39, "Other Interventions."](#))

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 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 (*Pineo, 1994 [Low Quality Evidence]; Hull, 1992 [Low Quality Evidence]; Hirsch, 1991 [Low Quality Evidence]; Hull, 1986 [High Quality Evidence]*).

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

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 (*Shalansky, 1996 [Low Quality Evidence]*; *Raschke, 1993 [High Quality Evidence]*; *Cruickshank, 1991 [Low Quality Evidence]*). 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 [High Quality Evidence]*).

(*Snow, 2007 [Guideline]*)

### Fondaparinux

Fondaparinux, a sodium pentasaccharide, is administered by subcutaneous injection once daily for the treatment of deep vein thrombosis and pulmonary embolism. Fondaparinux 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. Antibodies to fondaparinux rarely interact with Platelet Factor 4. There are several reports of heparin-induced thrombocytopenia (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. Several agents are FDA approved:

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lepirudin, argatroban and most recently, bivalirudin (*Warkentin, 2003 [Low Quality Evidence]; Warkentin, 2004a [Low Quality Evidence], Warkentin, 2004b [Guideline]*).

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 (*Warkentin, 2004b [Guideline]*). (See [Annotation #39, "Other Interventions,"](#) for more information.)

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

## 31. Warfarin

### Recommendations:

- The initial dose of warfarin should not exceed 5 mg.
- A goal INR of 2.5 (range 2.0-3.0) is recommended for patients with venous thromboembolism.
- Start heparin/fondaparinux and warfarin at the same time. Heparin (UHF or LMWH) and/or fondaparinux should be given for a minimum of five days and continued until INR  $\geq$  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 [Low Quality Evidence]*).

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 [Low Quality Evidence]*).
- 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 [Low Quality Evidence]*). 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 [Moderate Quality Evidence]; Harrison, 1997 [Low Quality Evidence]*).

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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 [Low Quality Evidence]*). Heparin (UFH or LMWH) and warfarin may be started at the same time. Heparin (UFH or LMWH) and/or fondaparinux should be given for a minimum of five days. Continue heparin until INR  $\geq$ 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 (UFH or LMWH) and/or fondaparinux 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 [Low Quality Evidence]*).

The ICSI [Antithrombotic Therapy Supplement](#) contains additional information on warfarin therapy.

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## 32. Outpatient Treatment Appropriate?

### Recommendations:

- Patients with uncomplicated venous thromboembolism may be considered for outpatient therapy with low-molecular-weight heparin and warfarin.
- Patients presenting with **symptomatic** pulmonary embolism should initially be treated in-hospital.

Inclusion criteria for outpatient therapy:

- Patient has good cardiorespiratory reserve.
- Patient has no excessive bleeding risks.
- Patient's creatinine clearance is greater than 30 mL/minute.

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.

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.

(*Snow, 2007 [Guideline]; Harrison, 1998 [Low Quality Evidence]; Wells, 1998b [Low Quality Evidence]; Koopman, 1996 [High Quality Evidence]; Levine, 1996 [High Quality Evidence]*)

A Cochrane review found home management cost effective and preferable for some patients (*Othieno, 2011 [Systematic Review]*).

Recent studies suggest that selected patients with symptomatic PE may be treated as outpatients (*Aujesky, 2011 [Moderate Quality Evidence]; Erkens, 2011 [Low Quality Evidence]*).

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Patient-focused care would include shared-decision making between patient, family and the physician when deciding upon outpatient treatment.

According to the MN Shared Decision-Making Collaborative:

Shared Decision-Making is a process in which patients and providers collaborate to clarify all acceptable options, ensure the patient is well-informed, and choose a course of care consistent with patient values and preferences and the best available medical evidence.

Please refer to [Appendix E, "ICSI Shared Decision-Making Model."](#)

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### 33. Inpatient Treatment

Therapy is discussed in [Annotation #30, "Low-Molecular-Weight Heparin \(LMWH\)/Unfractionated Heparin \(UFH\)/Fondaparinux,"](#) and in [Annotation #31, "Warfarin."](#)

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### 34. Outpatient Protocol

#### Recommendation:

- Graduated compression stockings (not Teds) should be prescribed and provide more rapid resolution of pain and swelling.

#### 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 (DVT) patients

- If the criteria in [Annotation #32, "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-phlebotic syndrome. Stockings are contraindicated for patients with peripheral artery disease.
- Graduated compression stockings (not Teds) combined with early ambulation do not cause any increase in pulmonary embolism and give 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 \[High Quality Evidence\]](#); [Brandjes, 1997 \[Moderate Quality Evidence\]](#); [Partsch, 1997 \[Low Quality Evidence\]](#)).

A study of consecutive patients demonstrated the safety of graduated compression stockings and mobilization did not increase in pulmonary embolism (PE) incidence for 1,289 patients treated. The resolution of pain and swelling was significantly faster when the patient ambulated with graduated compression stockings ([Partsch, 2000 \[Moderate Quality Evidence\]](#)). For management of patients with chronic post-thrombotic syndrome, please see [Annotation #38, "Continued Anticoagulation with Follow-Up and Secondary Prevention."](#)

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Please refer to the ICSI [Antithrombotic Therapy Supplement](#) for a discussion of complications during anticoagulation therapy.

(*Snow, 2007 [Guideline]*)

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## 35. Patient Education

### Recommendation:

- Instruct patients 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 Quality Improvement Support section.)

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## 36. Complications during Therapy?

### Recommendations:

- Treatment should be individualized for patients who develop complications.
- Suspect heparin-induced thrombocytopenia if platelets drop 50% or more from baseline.

Patients with complications of therapy should be identified and treated individually rather than by a standard guideline.

Patients who develop 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.

Please refer to the ICSI [Antithrombotic Therapy Supplement](#) for more information on potential complications of anticoagulation therapy.

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## 37. Anticoagulation Failure?

### Recommendations:

- Determination of anticoagulation failure requires objective confirmation.
- Fondaparinux should be considered if a patient fails on warfarin or heparin therapy (UFH or LMWH).
- Consider inferior vena cava filter in selected cases.

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

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

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 [Moderate Quality Evidence]*).

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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 (*Khamashta, 1995 [Low Quality Evidence]*; *Hull, 1982 [Low Quality Evidence]*).

In certain circumstances, alternate treatment such as an inferior vena cava (IVC) filter may be indicated. If a patient fails on warfarin therapy, heparin (UFH or LMWH) or fondaparinux may need to be reinstated. 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 [Guideline]*)

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## 38. Continued Anticoagulation with Follow-Up and Secondary Prevention

### Recommendations:

- The duration of anticoagulation therapy should be individualized.
- Graduated compression stockings are recommended to decrease the risk for post-phlebotic syndrome.

### 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 3-6 months with LWMH and then with anticoagulation therapy indefinitely or until the cancer is resolved.

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- Patients with two or more episodes of documented DVT should receive anticoagulation therapy indefinitely.

(Boutitie, 2011 [Meta-analysis]; Kearon, 2008 [Guideline]; Snow, 2007 [Guideline])

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), three months; for idiopathic/unprovoked, three to six months; for recurrent disease, indefinite anticoagulation may be appropriate. [Conclusion Grade II: See Conclusion Grading A – Annotation #38 (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 six months; for recurrent disease in patients who are carriers of thrombophilia genes, six months to indefinite. [Conclusion Grade II: See Conclusion Grading A – Annotation #38 (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 [Moderate Quality Evidence]).

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 [Guideline]).

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 [Moderate Quality Evidence]). 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 [Meta-analysis]). The increased risk is seen whether or not the cause of VTE is idiopathic and includes recurrent pulmonary embolism (White, 2006 [Low Quality Evidence]; Baglin, 2004 [Low Quality Evidence]; Kyrle, 2004 [Low Quality Evidence]). A recent patient-level meta-analysis suggests that the increased risk associated with male gender may be limited to unprovoked VTE (Douketis, 2011 [Systematic Review]).

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 (Prandoni, 2008 [Low Quality Evidence]; Diuguid, 1997 [Low Quality Evidence]).

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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. A recent study found similar case-fatality rates of recurrent VTE and major bleeding during the initial period of anticoagulation (*Carrier, 2010 [Systematic Review]*). This supports earlier findings that the absolute risk of recurrent VTE decreases after appropriate anticoagulation while the bleeding risk is unchanged (*Hutten, 2006 [Systematic Review]*).

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%. The increased risk is not affected by the timing of the D-dimer testing, age or assay cut point (*Douketis, 2010 [Meta-analysis]*). When anticoagulation therapy is resumed, the combined rate of recurrence and bleeding was 2.9% (p=0.005) (*Verhovsek, 2008 [Systematic Review]*; *Palareti, 2006 [Low Quality Evidence]*).

(*Hron, 2006 [Low Quality Evidence]*)

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 [Moderate Quality Evidence]*). Another study found that residual venous obstruction was not associated with increased risk in patients with unprovoked clot after a course of anticoagulation OR 1.24 (CI 0.9-1.7) (*Carrier, 2011 [Meta-analysis]*).

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 [Guideline]*)

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 non-cardioembolic stroke
- Chronic renal/hepatic disease
- Concomitant antiplatelet therapy
- Serious other illness

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- Poor anticoagulant control
- Suboptimal monitoring of therapy

(Kearon, 2008 [Guideline])

### 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 [Low Quality Evidence]; Poller, 1993 [Moderate Quality Evidence]; Ellis, 1992 [Low Quality Evidence]).

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 [High Quality Evidence]; Ridker, 2003 [High Quality Evidence]).

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.

### Prevention of Post-Thrombotic Syndrome (Post-Phlebotic Syndrome)

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 under treated 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 (Meissner, 2007 [Low Quality Evidence]; Kahn, 2006 [Low Quality Evidence]). 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 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 [Low Quality Evidence]).

Standardized treatment includes initiation of 30-40 mm Hg weight knee-high or thigh-high compression stockings (not TEDS) for management of the acute symptoms, and continued for a minimum of two years or longer if patients have persistent symptoms of PTS (Kearon, 2008 [Guideline]; Kakkos, 2006 [Systematic Review]). 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

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body mass index (BMI) and participation in a regular exercise regime that maintains an adequate calf muscle pump function.

**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 [Moderate Quality Evidence]*).

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. In a study by Cornuz, those without abnormalities on these initial screens did not develop cancer. 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 [Low Quality Evidence]*).

**Thrombophilia**

Certain patients may be tested for thrombophilia. If done, this testing should be done two weeks after discontinuation of anticoagulation (*Griffin, 1996 [Low Quality Evidence]*). A Cochrane database systematic review found no evidence supporting the routine application of these tests following a VTE (*Cohn, 2009 [Systematic Review]*). 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**

<p>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:</p> <ul style="list-style-type: none"> <li>• 25% Elevated factor VIII: C above 150% of normal (<i>Koster, 1995 [Low Quality Evidence]</i>)</li> <li>• 21% Factor V Leiden (resistance to activated protein C) (<i>Bertina, 1994 [Low Quality Evidence]</i>; <i>Koster, 1993 [Low Quality Evidence]</i>)</li> <li>• 19% Factor XI elevation above 90<sup>th</sup> percentile (<i>Meijers, 2000 [Low Quality Evidence]</i>)</li> <li>• 14% Lupus anticoagulant (in non-systemic lupus erythematosus patients) (<i>Ginsberg, 1995 [Low Quality Evidence]</i>)</li> <li>• 10% Hyperhomocystinemia and stronger in women and increased age (diagnostic studies may be unreliable) (<i>Den Heijer, 1996 [Low Quality Evidence]</i>)</li> <li>• 6.2% Prothrombin gene 20210 A allele (<i>Poort, 1996 [Low Quality Evidence]</i>)</li> <li>• 2.8% Antithrombin III deficiency</li> <li>• 2.5% Protein C deficiency</li> <li>• 1.3% Protein S deficiency (<i>Pabinger, 1992 [Low Quality Evidence]</i>)</li> </ul>
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### 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 [Moderate Quality Evidence]*).

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

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## 39. Other Interventions\*

\* Other interventions may include inferior vena cava (IVC) filters, serial calf ultrasound, heparin-induced thrombocytopenia therapy, thrombolytic therapy and surgery.

### Recommendations:

- Consider inferior vena cava filters, thrombolytic therapy or surgical thrombectomy in selected patients.
- Treat heparin-induced thrombocytopenia with direct thrombin inhibitors.
- Serial ultrasound should be used to follow untreated calf thrombosis.

### 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 (*Kearon, 2008 [Guideline]; Decousus, 1998 [High Quality Evidence]; Mohan, 1996 [Low Quality Evidence]*).

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 (*Kearon, 2008 [Guideline]; Decousus, 1998 [High Quality Evidence]*).

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,

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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 [Low Quality Evidence]*). Filter placement does not provide treatment for existing VTE. When safe, anticoagulation should be considered.

### **Intravenous Thrombolytic Therapy**

Lytic therapy has been used in patients with extensive iliofemoral disease who demonstrate evidence of vascular compromise (phlegmasia). Lytic therapy has the potential to reduce the long-term post-phlebotic consequences of proximal DVT through early thrombolysis, restoration of patency, and preservation of venous valve function. Catheter-directed lytic therapy is preferred over systemic lytic therapy. This therapy may be 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 (*Kearon, 2008 [Guideline]*; *Comerota, 2001 [Low Quality Evidence]*; *Mewissen, 1999 [Low Quality Evidence]*; *Semba, 1994 [Low Quality Evidence]*).

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 (*Dong, 2009 [Systematic Review]*; *Arcasoy, 1999 [Systematic Review]*; *Urokinase, 1970 [High Quality Evidence]*). 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 [Systematic Review]*; *Kanter, 1997 [Low Quality Evidence]*).

### **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-phlebotic syndrome development (*Juhan, 1997 [Low Quality Evidence]*; *Meissner, 1996 [Low Quality Evidence]*). Management should be individualized. The morbidity and mortality associated with this surgical procedure deem it be a procedure of last choice.

### **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 [Moderate Quality Evidence]*).

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 (*Masuda, 1998 [Low Quality Evidence]*; *Lohr, 1992 [Low Quality Evidence]*; *Philbrick, 1988 [Low Quality Evidence]*).

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 [Guideline]*; *Wells, 1999 [Low Quality Evidence]*; *Birdwell, 1998 [Low Quality Evidence]*; *Cogo, 1998 [Low Quality Evidence]*; *Wells, 1998b [Low Quality Evidence]*; *Heijboer, 1993 [High Quality Evidence]*; *Stein, 1995 [Low Quality Evidence]*).

### **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 [Low Quality Evidence]*).

Please refer to the ICSI [Antithrombotic Therapy Supplement](#) for more information on HIT.

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

The subdivisions of this section are:

- Aims and Measures
  - Measurement Specifications
- Implementation Recommendations
- Resources
- Resources Table

## Aims and Measures

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

Measures for accomplishing this aim:

- a. Percentage of adult patients with suspected venous thromboembolism (VTE) who have a clinical pretest probability assessment completed.
- b. 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.
- c. Percentage of adult patients diagnosed with venous thromboembolism (VTE) who meet the criteria for low-molecular-weight heparin (LMWH) and for whom shared decision-making is used prior to implementing therapy.

2. Prevent progression or recurrence of thromboembolic disease.

Measures for 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  $\geq 2.0$  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  $\geq 2.0$  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 with venous thromboembolism (VTE) who develop pulmonary embolism.
- e. Percentage of patients who have a high clinical pretest probability (score  $> 6$ ) for pulmonary embolism (PE), who received anticoagulation prior to diagnostic evaluation.
- f. Percentage of hospitalized patients with venous thromboembolism who receive warfarin on day one of heparin therapy.

3. Safely use anticoagulants to reduce the likelihood of patient harm and complications of anticoagulation therapy.

Measures for accomplishing this aim:

- a. Percentage of patients with VTE 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 with VTE 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 with VTE who are prescribed heparin and low-molecular-weight heparin (LMWH), who have baseline laboratory tests documented in their medical record INR; blood count including platelets; creatinine; weight; baseline PTT.
- d. Percentage of patients with VTE who are prescribed heparin and low-molecular-weight heparin (LMWH), who have appropriate laboratory tests (INR, platelets, PTT for those on unfractionated heparin) available to monitor and adjust therapy.

**Aims and Measures**

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

Measure for accomplishing this aim:

- a. Percentage of patients with any of these diagnosis – venous thromboembolism, pulmonary embolism, deep vein thrombosis – 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. (*2011 Joint Commission/National Safety Goal: Inpatient and Outpatient*)

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## Measurement Specifications

### Measurement #1a

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

### Population Definition

Patients age 18 years and older with suspected VTE.

### Data of Interest

$$\frac{\text{\# of patients with clinical pretest probability assessment completed}}{\text{\# of patients with suspected VTE}}$$

### Numerator/Denominator Definitions

Numerator: Number of patients age 18 years and older and suspected VTE who have clinical pretest probability assessment completed.

Denominator: Number of patients age 18 years and older with suspected VTE.

### Method/Source of Data Collection

Review medical records for patients age 18 years and older with suspected VTE. Determine whether patients have completed clinical pretest probability assessment.

### Time Frame Pertaining to Data Collection

Monthly.

### Notes

This is a process measure, and improvement is noted as increase in the rate.

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**Aims and Measures**

**Measurement #1b**

Percentage of 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**

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

**Data of Interest**

# of patients who had leg duplex ultrasound with compression performed, despite a low clinical pretest probability and a negative D-dimer test

---

# of patients suspected with DVT

**Numerator/Denominator Definitions**

Numerator: Number of patients age 18 years and older 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: Number of patients age 18 years and older suspected of a deep vein thrombosis who have a low clinical pretest probability and a negative D-dimer.

**Method/Source of Data Collection**

Review records for patients age 18 years and older suspected of deep vein thrombosis who have a low clinical pretest probability and a negative D-dimer. Determine whether patients underwent a leg duplex ultrasound with compression.

**Time Frame Pertaining to Data Collection**

Monthly.

**Notes**

This is an outcome measure, for which the inappropriate use of leg compression ultrasound Low rate is desirable.

See [Appendix A, "Wells Model of the Clinical Pretest Probability of Deep Vein Thrombosis."](#)

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## Aims and Measures

### Measurement #1c

Percentage of patients diagnosed with venous thromboembolism (VTE) who meet the criteria for low-molecular-weight heparin (LMWH) and for whom shared decision-making was used prior to implementing therapy.

### Population Definition

Patients age 18 years and older diagnosed with venous thromboembolism (VTE) who meet the criteria for low-molecular-weight heparin (LMWH).

### Data of Interest

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

### 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  $\geq 2.0$  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

Monthly.

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## Aims and Measures

### Measurement #2a

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.

### Population Definition

Adults age 18 years and older treated for VTE.

### Data of Interest

# of patients who receive heparin treatment for at least five days after the initiation of warfarin therapy and until INR  $> 2.0$  for two consecutive days

---

# of patients with VTE treated with low-molecular-weight heparin (LMWH)

### Numerator/Denominator Definitions

Numerator: Number of patients age 18 years and older and with 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 INR  $> 2.0$  for two consecutive days.

Denominator: Number of patients age 18 years and older and with VTE, treated with low-molecular-weight heparin (LMWH).

### Method/Source of Data Collection

Review medical records for patients age 18 years and older and treated for VTE with low-molecular-weight heparin. Determine from the records whether patients received heparin treatment for at least five days after the initiation of warfarin therapy and until INR  $> 2.0$  for two consecutive days.

### Time Frame Pertaining to Data Collection

Monthly.

### Notes

This is a process measure, and improvement is noted as increase in the rate.

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**Aims and Measures**

**Measurement #2b**

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.

**Population Definition**

Adults age 18 years and older treated for VTE.

**Data of Interest**

# of patients who receive heparin treatment for at least five days after the initiation of warfarin therapy and until INR > 2.0 for two consecutive days

---

# of patients with VTE treated with unfractionated heparin (UFH)

**Numerator/Denominator Definitions**

Numerator: Number of patients age 18 years and older and with VTE, treated with unfractionated heparin (UFH) who receive heparin treatment for at least five days after the initiation of warfarin therapy and until INR > 2.0 for two consecutive days.

Denominator: Number of patients age 18 years and older and with VTE, treated with unfractionated heparin (UFH).

**Method/Source of Data Collection**

Review medical records for patients age 18 years and older and treated for VTE with unfractionated heparin. Determine from the records whether patients received heparin treatment for at least five days after the initiation of warfarin therapy and until INR > 2.0 for two consecutive days.

**Time Frame Pertaining to Data Collection**

Monthly.

**Notes**

This is a process measure, and improvement is noted as increase in the rate.

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## Aims and Measures

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### Measurement #2c

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

### Population Definition

Patients age 18 years and older diagnosed with deep vein thrombosis.

### Data of Interest

$$\frac{\text{\# of patients who have been assessed for the need for graduated compression stockings (not Teds)}}{\text{\# of patients with deep vein thrombosis}}$$

### Numerator/Denominator Definitions

Numerator: Number of patients age 18 years and older and diagnosed with deep vein thrombosis, who have been assessed for the need for graduated compression stockings (not Teds).

Denominator: Number of patients age 18 years and older and diagnosed with deep vein thrombosis.

### Method/Source of Data Collection

Review medical records for patients age 18 years and older and diagnosed with deep vein thrombosis. Determine whether patients have been assessed for the need for graduated compression stockings (not Teds).

### Time Frame Pertaining to Data Collection

Monthly.

### Notes

This is a process measure, and improvement is noted as increase in the rate.

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**Aims and Measures**

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**Measurement #2d**

Percentage of patients with venous thromboembolism (VTE) who develop pulmonary embolism.

**Population Definition**

Patients age 18 years and older, diagnosed with VTE.

**Data of Interest**

$$\frac{\text{\# of patients who develop pulmonary embolism}}{\text{\# of patients with VTE diagnosis}}$$

**Numerator/Denominator Definitions**

Numerator: Number of patients age 18 years and older and diagnosed with VTE who develop pulmonary embolism.

Denominator: Number of patients age 18 years and older and diagnosed with VTE.

**Method/Source of Data Collection**

Review medical records for patients age 18 years and older and diagnosed with VTE. Determine whether patients developed pulmonary embolism.

**Time Frame Pertaining to Data Collection**

Monthly.

**Notes**

This is an outcome measure, and the goal is zero events of pulmonary embolism.

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**Aims and Measures**

**Measurement #2e**

Percentage of patients who have a high clinical pretest probability (score > 6) for pulmonary embolism (PE) who received anticoagulation prior to diagnostic evaluation.

**Population Definition**

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

**Data of Interest**

# of patients who receive anticoagulation prior to diagnostic evaluation

# of patients with high CPTP of pulmonary embolism

**Numerator/Denominator Definitions**

Numerator: Number of patients age 18 years and older who have a high clinical pretest probability for pulmonary embolism who receive anticoagulation prior to diagnostic evaluation.

Denominator: Number of patients age 18 years and older who have a high clinical pretest probability for pulmonary embolism.

**Method/Source of Data Collection**

Review records of patients age 18 years and older who have a high clinical pretest probability for pulmonary embolism. Review records to determine whether patients received low-molecular-weight heparin (LMWH) during evaluation.

**Time Frame Pertaining to Data Collection**

Monthly.

**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

This is a process measure, and improvement is noted as increase in the rate.

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## Aims and Measures

### Measurement #2f

Percentage of hospitalized patients with venous thromboembolism who receive warfarin on day one of heparin therapy.

### Population Definition

Patients age 18 years and older diagnosed with venous thromboembolism and hospitalized.

### Data of Interest

$$\frac{\# \text{ of patients who receive warfarin on day one of heparin therapy}}{\# \text{ of patients with venous thromboembolism and hospitalized}}$$

### Numerator/Denominator Definitions

Numerator: Number of patients age 18 years and older and diagnosed with venous thromboembolism and hospitalized who receive warfarin on day one of heparin therapy.

Denominator: Number of patients age 18 years and older and diagnosed with venous thromboembolism and hospitalized.

### Method/Source of Data Collection

Review medical records for patients age 18 years and older and diagnosed with venous thromboembolism and hospitalized. Determine whether patients received warfarin on day one of heparin therapy.

### Time Frame Pertaining to Data Collection

Monthly.

### Notes

This is a process measure, and improvement is noted as increase in the rate.

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## Aims and Measures

### Measurement #3a

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

### Population Definition

Patients age 18 years and older diagnosed with VTE.

### Data of Interest

# of patients who are initially prescribed anticoagulation therapy with documentation in the medical record indicating a baseline INR was obtained

---

# of patients with VTE diagnosis

### Numerator/Denominator Definitions

Numerator: Number of patients age 18 years and older and diagnosed with VTE who are initially prescribed anticoagulation therapy with documentation in the medical record indicating a baseline INR was obtained.

Denominator: Number of patients age 18 years and older and diagnosed with VTE.

### Method/Source of Data Collection

Review medical records for patients age 18 years and older and diagnosed with VTE. Determine whether patients were initially prescribed anticoagulation therapy with documentation in the medical record indicating a baseline INR was obtained.

### Time Frame Pertaining to Data Collection

Monthly.

### Notes

This is a process measure, and improvement is noted as increase in the rate.

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**Aims and Measures**

**Measurement #3b**

Percentage of patients with VTE 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.

**Population Definition**

Patients age 18 years and older diagnosed with VTE.

**Data of Interest**

# of patients who receive ongoing anticoagulation therapy with documentation in the medical record, indicating a current INR is available and is used to monitor and adjust therapy

---

# of patients with VTE diagnosis

**Numerator/Denominator Definitions**

Numerator: Number of patients age 18 years and older and diagnosed with VTE who receive ongoing anticoagulation therapy with documentation in the medical record, indicating a current INR is available and is used to monitor and adjust therapy.

Denominator: Number of patients age 18 years and older and diagnosed with VTE.

**Method/Source of Data Collection**

Review medical records for patients age 18 years and older and diagnosed with VTE. Determine whether patients received ongoing anticoagulation therapy with documentation in the medical record, indicating a current INR is available and is used to monitor and adjust therapy.

**Time Frame Pertaining to Data Collection**

Monthly.

**Notes**

This is a process measure, and improvement is noted as increase in the rate.

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**Aims and Measures**

**Measurement #3c**

Percentage of patients with VTE who are prescribed unfractionated heparin and/or low-molecular-weight heparin (LMWH), who have baseline laboratory tests documented in their medical record INR; blood count including platelets; creatinine; weight; baseline PTT.

**Population Definition**

Patients age 18 years and older diagnosed with VTE and prescribed unfractionated heparin and/or low-molecular-weight heparin.

**Data of Interest**

# of patients who have baseline laboratory tests documented in the medical record INR; blood count including platelets; creatinine; weight; baseline PTT.

---

# of patients with VTE diagnosis who are prescribed unfractionated heparin and/or low-molecular-weight heparin (LMWH)

**Numerator/Denominator Definitions**

Numerator: Number of patients age 18 years and older with VTE diagnosis who are prescribed unfractionated heparin and/or low-molecular-weight heparin (LMWH) who have baseline laboratory tests documented in the medical record INR; blood count including platelets; creatinine; weight; baseline PTT.

Denominator: Number of patients age 18 years and older diagnosed with VTE who are prescribed unfractionated heparin and/or low-molecular-weight heparin (LMWH).

**Method/Source of Data Collection**

Review medical records for patients age 18 years and older and diagnosed with VTE who are prescribed heparin and low-molecular-weight heparin (LMWH). Determine whether patients had baseline laboratory tests documented in the medical record INR; blood count including platelets; creatinine; weight; baseline PTT.

**Time Frame Pertaining to Data Collection**

Monthly.

**Notes**

This is a process measure, and improvement is noted as increase in the rate.

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## Aims and Measures

### Measurement #3d

Percentage of patients with VTE who are prescribed heparin and low-molecular-weight heparin (LMWH), who have appropriate laboratory tests (INR; platelets; PTT for those on UFH) available to monitor and adjust therapy.

### Population Definition

Patients age 18 years and older diagnosed with VTE.

### Data of Interest

# of patients who have appropriate laboratory tests (INR; platelets; PTT for those on UFH) available to monitor and adjust therapy

---

# of patients with VTE diagnosis who are prescribed heparin and low-molecular-weight heparin (LMWH)

### Numerator/Denominator Definitions

Numerator: Number of patients age 18 years and older and diagnosed with VTE who are prescribed heparin and low-molecular-weight heparin (LMWH) who have appropriate laboratory tests (INR; platelets; PTT for those on UFH) available to monitor and adjust therapy.

Denominator: Number of patients age 18 years and older and diagnosed with VTE who are prescribed heparin and low-molecular-weight heparin (LMWH).

### Method/Source of Data Collection

Review medical records for patients age 18 years and older and diagnosed with VTE who are prescribed heparin and low-molecular-weight heparin (LMWH). Determine whether patients had appropriate laboratory tests (INR; platelets; PTT for those on UFH) available to monitor and adjust therapy.

### Time Frame Pertaining to Data Collection

Monthly.

### Notes

This is a process measure, and improvement is noted as increase in the rate.

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## Aims and Measures

### Measurement #4a

Percentage of patients with any of these diagnosis – venous thromboembolism, pulmonary embolism, deep vein thrombosis – indicating a complete list of medications 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. (2011 Joint Commission/National Safety Goal: Inpatient and Outpatient)

### Population Definition

Patients age 18 years and older with any of following diagnoses: venous thromboembolism, pulmonary embolism, deep vein thrombosis.

### Data of Interest

# of patients for which a complete list of medications was communicated to the next provider of service when the patient was referred or transferred to another care setting

---

# of patients with any of the following diagnoses: VTE, DVT and pulmonary embolism

### Numerator/Denominator Definitions

Numerator: Number of patients age 18 years and older and diagnosed with VTE, DVT or pulmonary embolism for which a complete list of medications was communicated to the next provider of service when the patient was referred or transferred to another care setting.

Denominator: Number of patients age 18 years and older and diagnosed with any of the following diagnoses: VTE, DVT or pulmonary embolism.

### Method/Source of Data Collection

Review medical records for patients age 18 years and older who were diagnosed with any of the following: VTE, DVT or pulmonary embolism. Review the records to determine whether a complete list of medications was communicated to the next provider of service when the patient was referred or transferred to another care setting.

### Time Frame Pertaining to Data Collection

Monthly.

### Notes

This is a process measure, and improvement is noted as increase in the rate. It is also a 2011 Joint Commission/National Safety Goal for inpatient and outpatient settings.

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## Implementation Recommendations

Prior to implementation, it is important to consider current organizational infrastructure that address the following:

- System and process design
- Training and education
- Culture and the need to shift values, beliefs and behaviors of the organization

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. *(2011 Joint Commission/National Safety Goal)*
2. Clinics and Hospitals: Develop systems for monitoring the effects of anticoagulation to include monitoring of outpatient therapy.
  - Use of standardized practices/protocols that include patient involvement. *(2011 Joint Commission/National Safety Goal)*
3. When unfractionated heparin is administered intravenously and continuously, the organization should use programmable infusion pumps. *(2011 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. *(2011 Joint Commission/National Safety Goal)*
5. Develop a policy for providing organizational education regarding anticoagulation therapy to prescriber(s), staff, patients and families. *(2011 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. *(2011 Joint Commission/National Safety Goal)*

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## Resources

### Criteria for Selecting Resources

The following resources were selected by the 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 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 Resources, go to [http://www.icsi.org/improvement\\_resources](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.

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## Resources Table

* 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	<a href="http://www.veinforum.org/patients/what-is-vein-disease/deep-vein-thrombosis.aspx">http://www.veinforum.org/patients/what-is-vein-disease/deep-vein-thrombosis.aspx</a>
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	<a href="https://www.healthinfotranslations.org/">https://www.healthinfotranslations.org/</a>
* Institute for Clinical Systems Improvement	Development of Anticoagulation Programs at Seven Medical Organizations (#29, 12/04)	Health Care Professionals	<a href="http://www.icsi.org">http://www.icsi.org</a>
* Institute for Clinical Systems Improvement	Family Health Systems Minnesota Improvement Case Report on Anticoagulation Therapy (#12, 11/99)	Health Care Professionals	<a href="http://www.icsi.org">http://www.icsi.org</a>
Mayo Clinic	Overview of deep vein thrombosis.	Patients and Families	<a href="http://www.mayoclinic.com/health/DiseasesIndex/DiseasesIndex">http://www.mayoclinic.com/health/DiseasesIndex/DiseasesIndex</a>
Medicine.net	General information helpful to patients, including educational piece on deep vein thrombosis.	Patients and Families	<a href="http://www.medicinenet.com/deep_vein_thrombosis/article.htm">http://www.medicinenet.com/deep_vein_thrombosis/article.htm</a>
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	<a href="http://www.stoptheclot.org/">http://www.stoptheclot.org/</a>
National Heart, Lung, and Blood Institute	Overview of heart, lung and blood disorders. Provides educational resources and information of ongoing research.	Health Care Professionals	<a href="http://www.nhlbi.nih.gov">http://www.nhlbi.nih.gov</a>
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	<a href="http://www.nlm.nih.gov/medlineplus/ency/article/001109.htm">http://www.nlm.nih.gov/medlineplus/ency/article/001109.htm</a>
* Park Nicollet Health Services	Deep Vein Thrombosis: brochure	Patients and Families	<a href="http://www.icsi.org">http://www.icsi.org</a>
Pub Med	Database of medical literature.	Health Care Professionals	<a href="http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001209/">http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001209/</a>

\* Available to ICSI members only.

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**Resources Table**

*	Author/Organization	Title/Description	Audience	Web Sites/Order Information
	Vascular Disease Foundation	A non-profit educational organization dedicated to increasing awareness of prevention, diagnosis and management of vascular diseases.  This Web site is dedicated to reducing death and disability from vascular diseases and improving vascular health.	Health Care Professionals	<a href="http://www.vdf.org">http://www.vdf.org</a>

\* Available to ICSI members only.

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The subdivisions of this section are:

- Conclusion Grading Worksheet Summary
  - Conclusion Grading Worksheets
- References
- Appendices

## Conclusion Grading Worksheet Summary

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  $\emptyset$  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.

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## Conclusion Grading Worksheet A – Annotation #38 (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), three months; for idiopathic/unprovoked three to six 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 six months; for recurrent disease in patients who are carriers of thrombophilia genes, six months to indefinite.

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

Author/ Year	Design Type	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/ <i>Work Group's Comments (italicized)</i>
Verhovsek et al, 2008	Systematic Review and meta-analysis	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.	<p>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.</p> <p>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 result were associated with a 3.5% (2.7-4.3) annual risk for recurrent disease, whereas a positive D-dimer results were associated with 8.9% (95% CI 5.8-11.9) annual risk for recurrence.</p>	<p>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.</p> <p>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.</p>

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Author/ Year	Design Type	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	Patients with residual venous 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.	<p>Study outcomes were recurrent VTE and/or major bleeding.</p> <p>Patients with RVT were more likely to have idiopathic DVT in comparison with those without RVT.</p> <p>Thrombosis recurred in 23.3% of patients with RVT compared to 1.3% of those with RVT.</p> <p>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 were 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.</p> <p>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).</p>	<p>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.</p>

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Author/ Year	Design Type	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/ <i>Work Group's Comments (italicized)</i>
Ruiz-Gimenez et al, 2008	Prospective cohort study of patients with DVT	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.	<p>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.</p> <p>In the derivation group, 314 (2.4%) patients had major bleeding. Multivariate analysis showed that only age &gt;75 years, recent bleeding, cancer, abnormal creatinine levels, anemia and pulmonary embolism at baseline were independently associated with an increased risk of major bleeding.</p> <p>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.</p>	<p>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 &gt; 1.2 mg/dl, anemia, cancer, clinically overt PE, age &gt;75 years).</p>
Rodger et al, 2008	Prospective cohort study	646 participants with a first, unprovoked major VTE were enrolled and followed for a mean of 18 months.	<p>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.</p> <p>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.</p> <p>52% of women had 0 or 1 of the following characteristics: hyperpigmentation, edema or redness of either leg, D-dimer <math>\geq 250</math> <math>\mu\text{g/L}</math> while taking warfarin, body mass index <math>\geq 30</math> <math>\text{kg/m}^2</math> or age <math>\geq 65</math> 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).</p>	<p>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.</p>

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Conclusion Grading Worksheet A –  
Annotation #38 (Duration of Anticoagulation)

Author/ Year	Design Type	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/ <i>Work Group's Comments (italicized)</i>
Agnelli and Becattini, 2008	Narrative review	n/a	This review dealt with the results of studies on the long-term course of VTE and provided background for the currently recommended long-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	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. [ <i>Thrombophilia is an independent risk factor for VTE; this study was not able to address it adequately.</i> ]  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.

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**Conclusion Grading Worksheet A –  
Annotation #38 (Duration of Anticoagulation)**

Author/Year	Design Type	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/ <i>Work Group's Comments (italicized)</i>															
Schulman et al. 1995	RCT	<p>-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</p> <p>-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; &gt;1 thromboembolic event</p> <p>-After enrollment they excluded from analysis patients with congenital deficiency of antithrombin, protein C or S</p> <p>-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)</p> <p>-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</p> <p>-Follow-up at 1.5, 3, 6, 9, 12 and 24 months after target prothrombin time was reached</p>	<p>-Principal endpoints were major hemorrhage during oral anticoagulation and death or recurrent VTE during 2-year follow-up period</p> <p>-5 patients were removed from the analysis after enrollment because of protein C deficiency (initial group had been 902)</p> <p>-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</p> <p>-There were 39 deaths and 44 dropouts during 2 years of follow-up</p> <p>-Results:</p> <table border="0"> <tr> <td>6 weeks</td> <td>6 months</td> <td>p</td> </tr> <tr> <td>Major hemorrhage</td> <td>1 (0.2%)</td> <td>5 (1.1%)</td> <td>0.23</td> </tr> <tr> <td>Recurrence</td> <td>80 (18.1%)</td> <td>43 (9.5%)</td> <td>&lt;0.001</td> </tr> <tr> <td>Death</td> <td>22 (5.0%)</td> <td>17 (3.7%)</td> <td>0.46</td> </tr> </table> <p>-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.</p>	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	<p>-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.</p> <p><i>Work Group's Comments:</i></p> <p><i>-Known protocol violations were disclosed</i></p> <p><i>-Used registries for deaths and hospitalizations so that few events were missed</i></p>
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																

**Conclusion Grading Worksheet A –  
Annotation #38 (Duration of Anticoagulation)**

Author/Year	Design Type	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/ <i>Work Group's Comments (italicized)</i>
Schulman et al, 1997	RCT	-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, 1999	Review	-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.

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**Conclusion Grading Worksheet A –  
Annotation #38 (Duration of Anticoagulation)**

Author/Year	Design Type	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/ <i>Work Group's Comments (italicized)</i>
Kearon et al, 1999	RCT	<p>-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</p> <p>-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 &lt; 2 years, initially given uncensored LMWH, unable to complete follow-up</p> <p>-Randomized (after stratification) to either warfarin or placebo (with INR results used to adjust warfarin dose)</p> <p>-Assessment of symptoms and signs of VTE every 3 months</p> <p>-Ultrasonography if suspected DVT; ventilation-perfusion scan if suspected PE</p>	<p>-Recruitment of patients stopped in response to interim analysis that showed benefit of warfarin</p> <p>-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)</p> <p>-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</p> <p>-14 in warfarin group and 13 in placebo group chose not to continue treatment</p> <p>-Of 79 in warfarin group, 1 with confirmed VTE</p> <p>-Of 83 in placebo group, 17 with confirmed VTE (including one death)</p> <p>-Cumulative probability of recurrent VTE differed between groups (p&lt; 0.001): 1.3% per patient year in warfarin group and 27.4% per patient year in placebo group</p> <p>-All episodes of recurrent VTE were idiopathic</p> <p>-3 major bleeding episodes in warfarin group (0 in placebo group)</p> <p>-1 death in the warfarin group (pneumonia) and 3 deaths in the placebo group (PE, CAD and leukemia)</p> <p>-Presence of lupus anticoagulant was only clinical or laboratory variable assessed that was significantly (p=0.03) associated with recurrent VTE</p>	<p>-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.</p> <p>-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.</p> <p>-Further studies are needed to determine when anticoagulation therapy can be safely stopped.</p> <p>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</p>

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Conclusion Grading Worksheet A –  
Annotation #38 (Duration of Anticoagulation)

Author/Year	Design Type	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/ <i>Work Group's Comments (italicized)</i>
Agnelli et al, 2001	RCT	<p>-267 patients with first episode of idiopathic proximal deep venous thrombosis; completed 3 months of oral anticoagulant therapy (97% warfarin) without recurrence or bleeding</p> <p>-Excluded: prolonged anticoagulant therapy for other than VTE, major psychiatric disorders, life expectancy &lt; 2 yrs, unable to return for follow-up</p> <p>-Randomized to discontinue oral anticoagulant therapy or continue for 9 additional months; dose adjusted to achieve INR between 2 and 3</p> <p>-Blinded assessment of outcomes</p> <p>-Follow-up at 3, 6 and 12 mos after randomization and every 6 mos. thereafter</p>	<p>-Recruitment stopped after 267 enrolled because difference in risk of recurrence was &lt;25% (thromboembolic events in 16 of 123 [13.0%] in discontinue group, 15 of 123 [12.2%] of continue group)</p> <p>-Groups similar in age, gender, initial use of LMWH</p> <p>-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</p> <p>-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)</p> <p>-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)</p> <p>-4 (3%) in continue group had nonfatal major bleeding; 2 (1.5%) in discontinue group had fatal bleeding; 14 deaths (7 per group)</p>	<p>-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.</p>
<p>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%, <math>\alpha=0.05</math>); 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</p>				

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**Anticoagulation for recurrent events in cancer patients.**

**Conclusion Grade: II**

Author/ Year	Design Type	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/ <i>Work Group's Comments (italicized)</i>
Noble et al, 2008	Syste- matic review and meta- analysis	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.	<p>The primary objective of this paper was to perform a systematic review to help develop guidelines applicable to patients with advanced cancer.</p> <p>Of 5,884 references identified, 35 papers were further reviewed and only 19 met criteria for inclusion.</p> <p>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).</p> <p>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).</p>	<p>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.</p> <p>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.</p> <p>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.</p>

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Author/ Year	Design Type	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/ <i>Work Group's Comments (italicized)</i>
Akl et al, 2008a	Systematic review	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 of 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, 95% CI 0.81-1.14) but a statistically significant reduction in VTE (HR = 0.47, 95% 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	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, unfractionated 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 unfractionated 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 unfractionated 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-phlebotic syndrome.	Based on the meta-analyses of these data from RCTs, low-molecular-weight heparin is likely to be superior to unfractionated 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.

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

Author/ Year	Design Type	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/ <i>Work Group's Comments (italicized)</i>
Prandoni et al, 2008	Retro-spective cohort study	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).	<p>The primary endpoint of this study was recurrent VTE.</p> <p>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.</p>	<p>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.</p>

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## 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

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## 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
<b>Score</b>	
PE Less Likely: $\leq 4$ PE Likely: $> 4$ Score of 6 <sup>+</sup> – Start heparin will continuing clinical and diagnostic evaluation	

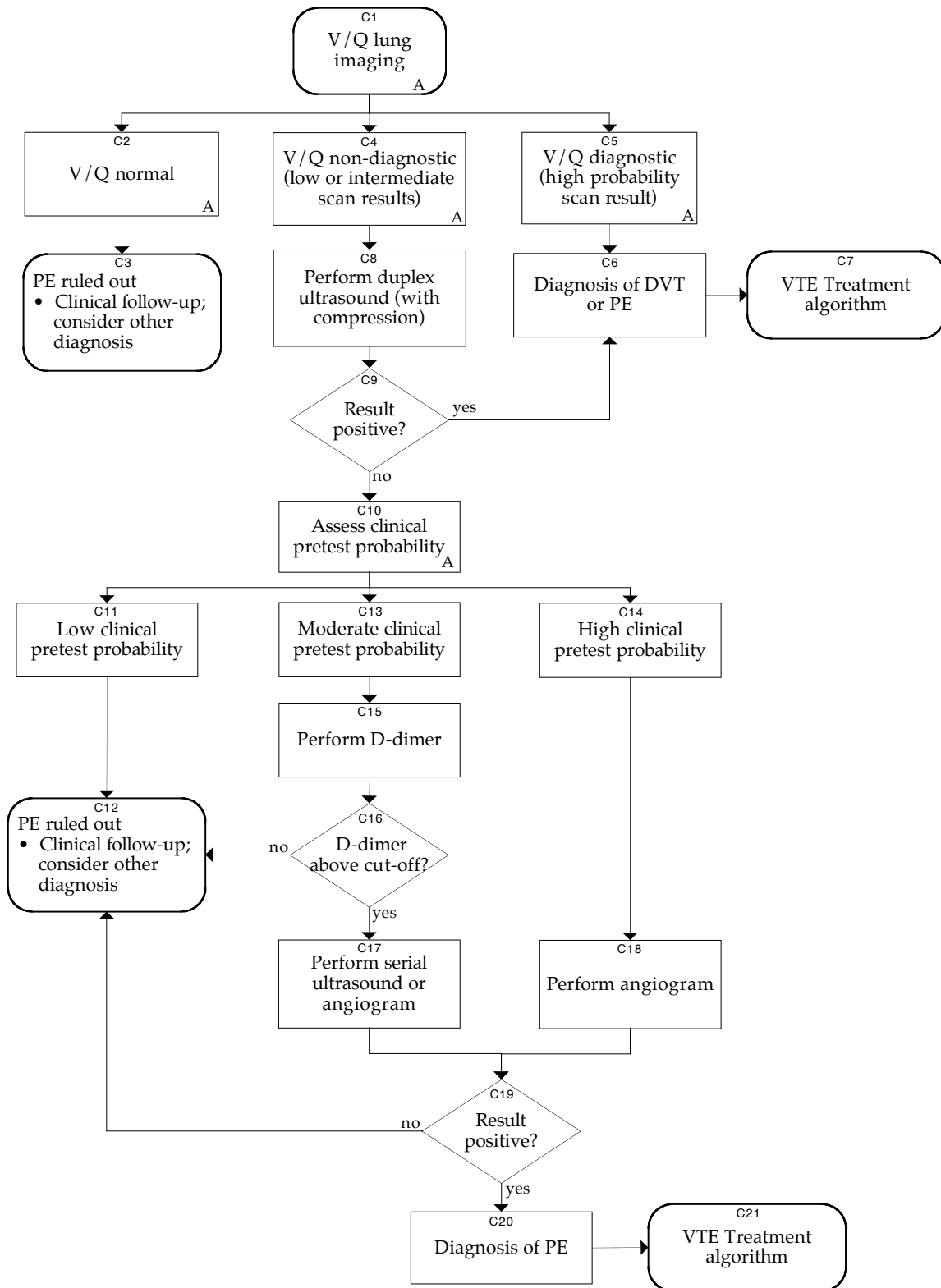
Reproduced with permission of Schattauer and Wells PS.

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.

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[BACK](#)

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



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## 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 [Low Quality Evidence]*).

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, 1995 [Low Quality Evidence]; Hull, 1985 [Low Quality Evidence]*)

## 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 [Guideline]; Goldhaber, 1998 [Low Quality Evidence]; Hull, 1990 [Low Quality Evidence]*).

## 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 (*PIOPED Investigators, The; 1990 [Low Quality Evidence]; Hull, 1985 [Low Quality Evidence]*).

## 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 #29, "Complicated Venous Thromboembolism or Comorbidities?")

(*American Thoracic Society, 1999 [Guideline]; Wells, 1998b [Low Quality Evidence]*)

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## 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 [Low Quality Evidence]*).

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.

### 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, "Deep Vein Thombosis Confirmed - See Venous Thromboembolism Treatment Algorithm."](#)

### 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.

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**BACK**

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

### Recommendation:

- Do not remove the central venous catheter if there is associated deep vein 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 [Guideline]). 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 1-9% of patients, half of whom may be symptomatic (Levy, 2011 [Low Quality Evidence; Mai, 2011 [Low Quality Evidence]). Chronic complications include a recurrence rate of 2-8% (Flinterman, 2008 [Low Quality Evidence]) and post-thrombotic syndrome (PTS), which may occur in varying degrees of severity in 7-44% of patients (Kucher, 2011 [Low Quality Evidence]).

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 [Low Quality Evidence]; Flinterman, 2008 [Low Quality Evidence]; Spencer, 2008 [Low Quality Evidence]). 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 [Low Quality Evidence]).

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 [Guideline]). 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 (Kucher, 2011 [Low Quality Evidence]; Kearon, 2008 [Guideline]).

For patients with UEDVT associated with a central venous catheter, the catheter should not be removed if it is functional and there is a persistent medical requirement for catheter use (Kucher, 2011 [Low Quality Evidence]; Kearon, 2008 [Guideline]). 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 [Guideline]).

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 [Guideline]).

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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## Appendix E – ICSI Shared Decision-Making Model

The technical aspects of Shared Decision-Making are widely discussed and understood. **Decisional conflict** occurs when a patient is presented with options where no single option satisfies all the patient's objectives, where there is an inherent difficulty in making a decision, or where external influencers act to make the choice more difficult. **Decision support** clarifies the decision that needs to be made, clarifies the patient's values and preferences, provides facts and probabilities, guides the deliberation and communication, and monitors the progress. **Decision aids** are evidence-based tools that outline the benefits, harms, probabilities and scientific uncertainties of specific health care options available to the patient.

However, before decision support and decision aids can be most advantageously utilized, a Collaborative Conversation™ should be undertaken between the provider and the patient to provide a supportive framework for Shared Decision-Making.

### Collaborative Conversation™

A collaborative approach toward decision-making is a fundamental tenet of Shared Decision-Making (SDM). The Collaborative Conversation™ is an inter-professional approach that nurtures relationships, enhances patients' knowledge, skills and confidence as vital participants in their health, and encourages them to manage their health care. Within a Collaborative Conversation™, the perspective is that both the patient and the provider play key roles in the decision-making process. The patient knows which course of action is most consistent with his/her values and preferences, and the provider contributes knowledge of medical evidence and best practices. Use of Collaborative Conversation™ elements and tools is even more necessary to support patient, care provider and team relationships when patients and families are dealing with high stakes or highly charged issues. A diagnosis of a life-limiting illness presents such a circumstance.

The overall framework for the Collaborative Conversation™ approach is to create an environment in which the patient, family and care team work collaboratively to reach and carry out a decision that is consistent with the patient's values and preferences. A rote script or a completed form or checklist does not constitute this approach. Rather it is a set of skills employed appropriately for the specific situation. These skills need to be used artfully to address all aspects involved in making a decision: cognitive, affective, social and spiritual.

**Key communication skills** help build the Collaborative Conversation™ approach. These skills include many elements, but in this appendix only the questioning skills will be described. (For complete instruction, see O'Connor, Jacobsen "Decisional Conflict: Supporting People Experiencing Uncertainty about Options Affecting Their Health" [2007], and Bunn H, O'Connor AM, Jacobsen MJ "Analyzing decision support and related communication" [1998, 2003].)

#### 1. Listening skills:

**Encourage** patient to talk by providing prompts to continue such as *go on, and then?, uh huh*, or by repeating the last thing a person said, *It's confusing*.

**Paraphrase content of messages shared by patient** to promote exploration, clarify content and to communicate that the person's unique perspective has been heard. The provider should use his/her own words rather than just parroting what he/she heard.

**Reflection of feelings** usually can be done effectively once trust has been established. Until the provider feels that trust has been established, short reflections at the same level of intensity expressed by the patient without omitting any of the message's meaning is appropriate. Reflection in this manner communicates that the provider understands the patient's feelings and may work as a catalyst for further problem solving. For example, the provider identifies what the person is feeling and responds back in his/her own words like this: *"So, you're unsure which choice is the best for you."*

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**Summarize the person's key comments** and reflect them back to the patient. The provider should condense several key comments made by the patient and provide a summary of the situation. This assists the patient in gaining a broader understanding of the situations rather than getting mired down in the details. The most effective times to do this are midway through and at the end of the conversation. An example of this is, "*You and your family have read the information together, discussed the pros and cons, but are having a hard time making a decision because of the risks.*"

**Perception checks** ensure that the provider accurately understands a patient or family member, and may be used as a summary or reflection. They are used to verify that the provider is interpreting the message correctly. The provider can say "*So you are saying that you're not ready to make a decision at this time. Am I understanding you correctly?*"

## 2. Questioning Skills

**Open and closed questions** are both used, with the emphasis on open questions. Open questions ask for clarification or elaboration and cannot have a yes or no answer. An example would be "*What else would influence you to choose this?*" Closed questions are appropriate if specific information is required such as "*Does your daughter support your decision?*"

Other skills such as summarizing, paraphrasing and reflection of feeling can be used in the questioning process so that the patient doesn't feel pressured by questions.

Verbal tracking, referring back to a topic the patient mentioned earlier, is an important foundational skill (Ivey & Bradford-Ivey). An example of this is the provider saying, "*You mentioned earlier...*"

## 3. Information-Giving Skills

**Providing information** and **providing feedback** are two methods of information giving. The distinction between providing information and giving advice is important. Information giving allows a provider to supplement the patient's knowledge and helps to keep the conversation patient centered. Giving advice, on the other hand, takes the attention away from the patient's unique goals and values, and places it on those of the provider.

**Providing information** can be sharing facts or responding to questions. An example is "*If we look at the evidence, the risk is...*" **Providing feedback** gives the patient the provider's view of the patient's reaction. For instance, the provider can say, "*You seem to understand the facts and value your daughter's advice.*"

## Additional Communication Components

Other elements that can impact the effectiveness of a Collaborative Conversation™ include:

- Eye contact
- Body language consistent with message
- Respect
- Empathy
- Partnerships

Self-examination by the provider involved in the Collaborative Conversation™ can be instructive. Some questions to ask oneself include:

- Do I have a clear understanding of the likely outcomes?
- Do I fully understand the patient's values?

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- Have I framed the options in comprehensible ways?
- Have I helped the decision-makers recognize that preferences may change over time?
- Am I willing and able to assist the patient in reaching a decision based on his/her values, even when his/her values and ultimate decision may differ from my values and decisions in similar circumstances?

### When to Initiate a Collaborative Conversation™

A Collaborative Conversation™ can support decisions that vary widely in complexity. It can range from a straightforward discussion concerning routine immunizations to the morass of navigating care for a life-limiting illness. Table 1 represents one health care event. This event can be simple like a 12 year-old coming to the clinic for routine immunizations, or something much more complex like an individual receiving a diagnosis of congestive heart failure. In either case, entering the clinic or receiving a diagnosis of a life-limiting illness is the catalyst that starts the process represented in this table. There are cues for providers and patient needs that exert influence on this process. They are described below. The heart of the process is the Collaborative Conversation™. The time the patient spends within this health care event will vary according to the decision complexity and the patient's readiness to make a decision.

Regardless of the decision complexity there are cues applicable to all situations that indicate an opportune time for a Collaborative Conversation™. These cues can occur singularly or in conjunction with other cues.

### Cues for the Care Team to Initiate a Collaborative Conversation™

- **Life goal changes:** Patient's priorities change related to things the patient values such as activities, relationships, possessions, goals and hopes, or things that contribute to the patient's emotional and spiritual well-being.
- **Diagnosis/prognosis changes:** Additional diagnoses, improved or worsening prognosis.
- **Change or decline in health status:** Improving or worsening symptoms, change in performance status or psychological distress.
- **Change or lack of support:** Increase or decrease in caregiver support, change in caregiver, change in caregiver status, change in financial standing, difference between patient and family wishes.
- **Change in medical evidence or interpretation of medical evidence:** Providers can clarify the change and help the patient understand its impact.
- **Provider/caregiver contact:** Each contact between the provider/caregiver and the patient presents an opportunity to reaffirm with the patient that his/her care plan and the care the patient is receiving are consistent with his/her values.

Patients and families have a role to play as decision-making partners, as well. The needs and influencers brought to the process by patients and families impact the decision-making process. These are described below.

### Patient and Family Needs within a Collaborative Conversation™

- **Request for support and information:** Decisional conflict is indicated by, among other things, the patient verbalizing uncertainty or concern about undesired outcomes, expressing concern about choice consistency with personal values, exhibiting behavior such as wavering, delay, preoccupation, distress or tension. Generational and cultural influencers may act to inhibit the patient from actively participating in care discussions, often patients need to be given "permission" to participate as partners in making decisions about his/her care.

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**Appendix E – ICSI Shared Decision-Making Model**

Support resources may include health care professionals, family, friends, support groups, clergy and social workers. When the patient expresses a need for information regarding options and his/her potential outcomes, the patient should understand the key facts about options, risks and benefits, and have realistic expectations. The method and pace with which this information is provided to the patient should be appropriate for the patient's capacity at that moment.

- **Advance Care Planning:** With the diagnosis of a life-limiting illness, conversations around advance care planning open up. This is an opportune time to expand the scope of the conversation to other types of decisions that will need to be made as a consequence of the diagnosis of a life-limiting illness.
- **Consideration of Values:** The personal importance a patient assigns potential outcomes must be respected. If the patient is unclear how to prioritize the preferences, value clarification can be achieved through a Collaborative Conversation™ and by the use of decision aids that detail the benefits and harms of potential outcomes in terms the patient can understand.
- **Trust:** The patient must feel confident that his/her preferences will be communicated and respected by all caregivers.
- **Care Coordination:** Should the patient require care coordination, this is an opportune time to discuss the other types of care-related decisions that need to be made. These decisions will most likely need to be revisited often. Further, the care delivery system must be capable of delivering coordinated care throughout the continuum of care.
- **Responsive Care System:** The care system needs to support the components of patient- and family-centered care so the patient's values and preferences are incorporated into the care he/she receives throughout the care continuum.

The Collaborative Conversation™ Map is the heart of this process. The Collaborative Conversation™ Map can be used as a stand-alone tool that is equally applicable to providers and patients as shown in Table 2. Providers use the map as a clinical workflow. It helps get the Shared Decision-Making process initiated, and once on its way, provides navigation for the process. Care teams can use the Collaborative Conversation™ to document team best practices and to formalize a common lexicon. Organizations can build fields from the Collaborative Conversation™ Map in electronic medical records to encourage process normalization. Patients use the Map to prepare for decision-making, to help guide them through the process and to share critical information with their loved ones.

### Evaluating the Decision Quality

Adapted from O'Connor, Jacobsen "Decisional Conflict: Supporting People Experiencing Uncertainty about Options Affecting Their Health" [2007].

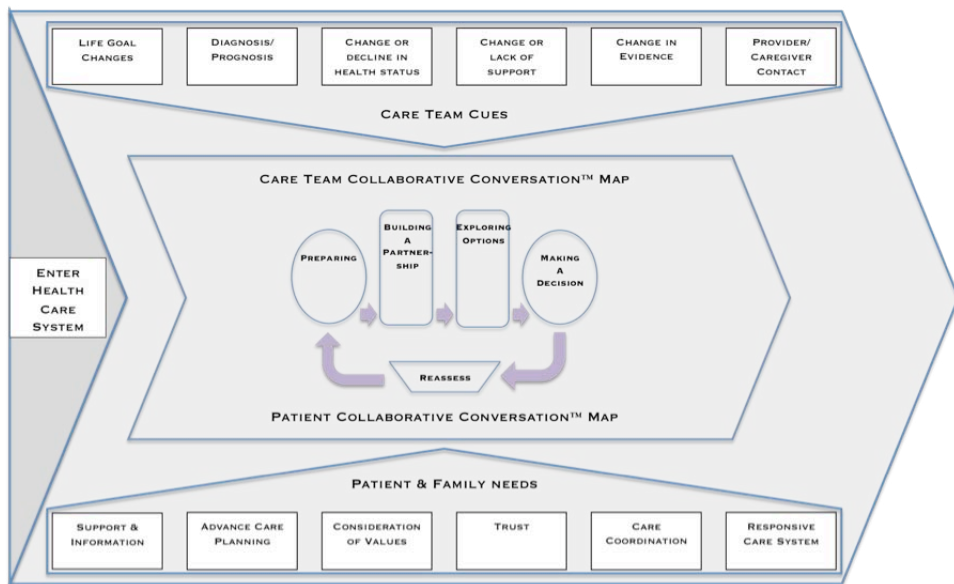
When the patient and family understand the key facts about the condition and his/her options, a good decision can be made. Additionally, the patient should have realistic expectations about the probable benefits and harms. A good indicator of the decision quality is whether or not the patient follows through with his/her chosen option. There may be implications of the decision on patient's emotional state such as regret or blame, and there may be utilization consequences.

Decision quality can be determined by the extent to which the patient's chosen option best matches his/her values and preferences as revealed through the Collaborative Conversation™ process.

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Appendix E – ICSI Shared Decision-Making Model

Table One

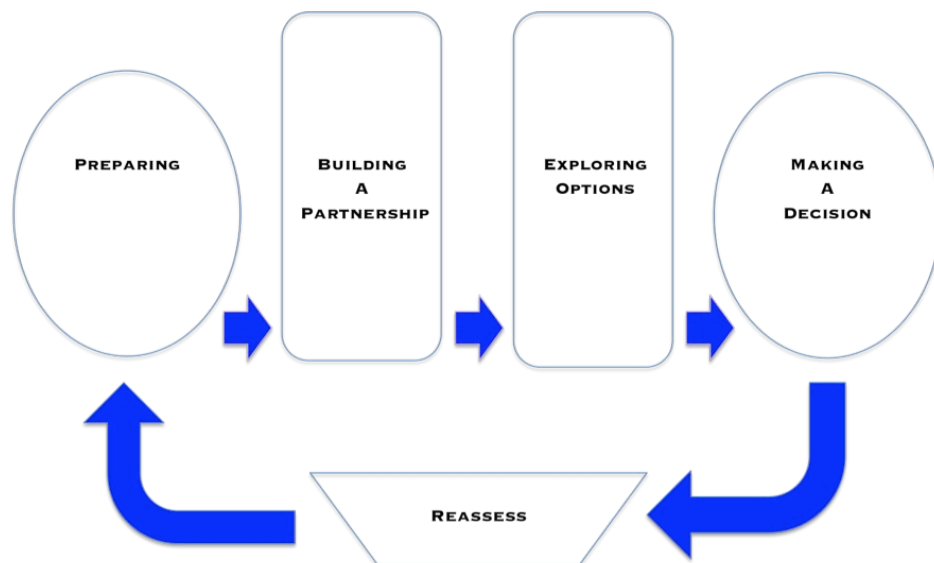


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Table Two

SDM COLLABORATIVE CONVERSATION™ MAP



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Support for this project was provided in part by a grant from the Robert Wood Johnson Foundation.

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Document Drafted  
Dec 1996 – Mar 1997

First Edition  
Jun 1998

Second Edition  
Jun 1999

Third Edition  
Feb 2002

Fourth Edition  
Apr 2003

Fifth Edition  
Mar 2004

Sixth Edition  
May 2005

Seventh Edition  
Mar 2006

Critical Review  
Mar 2007

Eighth Edition  
Jul 2007

Ninth Edition  
Mar 2009

Tenth Edition  
Mar 2010

Eleventh Edition  
Apr 2011

Twelfth Edition  
Begins Feb 2012

### 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**

Released in January 2012 for Twelfth Edition.  
*The next scheduled revision will occur within 12 months.*

- 2012 a partial GRADE approach was implemented

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#### Contact ICSI at:

8009 34th Avenue South, Suite 1200; Bloomington, MN 55425; (952) 814-7060; (952) 858-9675 (fax)  
Online at <http://www.ICSI.org>



## ICSI Document Development and Revision Process

### Overview

Since 1993, the Institute for Clinical Systems Improvement (ICSI) has developed more than 60 evidence-based health care documents that support best practices for the prevention, diagnosis, treatment or management of a given symptom, disease or condition for patients.

### Document Development and Revision Process

The development process is based on a number of long-proven approaches. ICSI staff first conducts a literature search to identify pertinent clinical trials, meta-analysis, systematic reviews, regulatory statements and other professional guidelines. The literature is reviewed and graded based on the ICSI Evidence Grading System.

ICSI facilitators identify gaps between current and optimal practices. The work group uses this information to develop or revise the clinical flow and algorithm, drafting of annotations and identification of the literature citations. ICSI staff reviews existing regulatory and standard measures and drafts outcome and process measures for work group consideration. The work group gives consideration to the importance of changing systems and physician behavior so that outcomes such as health status, patient and provider satisfaction, and cost/utilization are maximized.

Medical groups, who are members of ICSI, review each guideline as part of the revision process. The medical groups provide feedback on new literature, identify areas needing clarification, offer recommended changes, outline successful implementation strategies and list barriers to implementation. A summary of the feedback from all medical groups is provided to the guideline work group for use in the revision of the guideline.

### Implementation Recommendations and Measures

Each guideline includes implementation strategies related to key clinical recommendations. In addition, ICSI offers guideline-derived measures. Assisted by measurement consultants on the guideline development work group, ICSI's measures flow from each guideline's clinical recommendations and implementation strategies. Most regulatory and publicly reported measures are included but, more importantly, measures are recommended to assist medical groups with implementation; thus, both process and outcomes measures are offered.

### Document Revision Cycle

Scientific documents are revised every 12-24 months as indicated by changes in clinical practice and literature. Each ICSI staff monitors major peer-reviewed journals every month for the guidelines for which they are responsible. Work group members are also asked to provide any pertinent literature through check-ins with the work group mid-cycle and annually to determine if there have been changes in the evidence significant enough to warrant document revision earlier than scheduled. This process complements the exhaustive literature search that is done on the subject prior to development of the first version of a guideline.

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