Evidence Report/Technology Assessment
Number 68

Diagnosis and Treatment of Deep Venous Thrombosis and Pulmonary Embolism

Agency for Healthcare Research and Quality

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Diagnosis and Treatment of Deep Venous Thrombosis and Pulmonary Embolism

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 6010 Executive Blvd., Suite 300, Rockville, MD 20852.

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Structured Abstract

Objectives. Venous thromboembolism (VTE), thrombosis in the venous vasculature, causes considerable morbidity and mortality, and diagnosis and treatment are challenging. In this report we sought to summarize evidence on the following questions: 1) What are the efficacy and safety of low molecular weight heparin (LMWH) compared to unfractionated heparin (UFH) for treatment of deep venous thrombosis (DVT)? 2) What are the efficacy and safety of LMWH compared to UFH for treatment of pulmonary embolism (PE)? 3) What are the efficacy, safety, and cost-effectiveness of outpatient versus inpatient treatment of DVT with LMWH or UFH? 4) What is the optimal duration of treatment for DVT and PE? 5) How accurate are clinical prediction rules used for the diagnosis of DVT or PE? 6) What are the test characteristics of ultrasonography for diagnosis of DVT? 7) What are the test characteristics of helical computerized tomography (CT), magnetic resonance imaging (MRI), and magnetic resonance angiography (MRA) for diagnosis of PE? 8) What are the test characteristics of D-dimer for diagnosis of VTE?

Search Strategy. The Johns Hopkins University Evidence-based Practice Center (EPC) team searched electronic databases for literature from January 1966 to April 2002. The team identified additional articles by hand-searching relevant journals and reference lists, and by querying experts.

Selection Criteria. Paired investigators reviewed the abstracts of identified citations to select original studies and systematic reviews that addressed the questions, reported on human subjects, and were written in English. Each question had additional eligibility criteria.

Data Collection and Analysis. Paired reviewers assessed the quality of each eligible study and abstracted data.

Main Results. The search identified 64 original studies and 29 systematic reviews that addressed the questions. Results were as follows: 1) The evidence indicated that LMWH was more efficacious than UFH in reducing thrombus extension and recurrence in patients with DVT, with less risk of major bleeding and death. 2) Evidence was limited but supported the efficacy and safety of LMWH for the treatment of PE. 3) LMWH for outpatient treatment of DVT was safe and effective in carefully selected patients. LMWH was either cost-saving or cost-effective compared with inpatient treatment with UFH. 4) The evidence indicated that the optimal duration of oral anticoagulation after a first DVT is between three and six months. A longer duration may be necessary for patients with thrombophilic risk factors or PE. 5) Clinical prediction rules had high negative predictive values for excluding DVT, and moderately high predictive values for excluding PE. 6) Ultrasonography had high sensitivity and specificity for diagnosing proximal DVT, but was less accurate for diagnosis of calf vein thrombosis. 7) Helical CT was fairly sensitive and had high specificity for detecting PE. MRA was accurate in detecting PE of the lobar and segmental branches of pulmonary arteries. 8) The literature was too varied to make conclusions about the accuracy and role of D-dimer for diagnosis or exclusion of VTE.

Conclusions. Relatively strong evidence exists to support the efficacy, safety, and cost-effectiveness of LMWH for treatment of DVT, as an inpatient or outpatient therapy. Moderate evidence exists to define the optimal duration of oral anticoagulation for patients with DVT. Less evidence exists regarding duration of treatment for PE. Strong evidence indicates that ultrasonography is accurate for diagnosing proximal DVT, while moderate evidence exists to support a role for clinical prediction rules for diagnosis of DVT or PE, and for helical CT or MRA for diagnosis of PE.

Diagnosis and Treatment of Deep Venous Thrombosis and Pulmonary Embolism

Summary

Overview

Venous thromboembolism (VTE) refers to all forms of pathologic thrombosis occurring on the venous side of the circulation, the most common of which is deep venous thrombosis (DVT) of the lower extremities. The most life-threatening manifestation of VTE is embolization of venous thrombi to the pulmonary circulation—pulmonary embolism (PE). The occurrence of VTE is generally triggered by a confluence of environmental and constitutional risk factors.

VTE and its complications are a common cause of morbidity and mortality in the United States. Researchers have estimated that the average annual incidence of isolated DVT is 50 per 100,000 people and for PE, with or without DVT, the incidence is 70 per 100,000. Others estimate the incidence as being higher and suggest that 450,000 cases of DVT (350,000 cases of non-fatal PE, and 250,000 cases of fatal PE) may occur annually in the United States.

The reference standard for VTE diagnosis remains clot visualization with contrast venography or pulmonary angiography. However, the invasiveness and the risks of these modalities have led to a steady increase in the use of non-invasive or minimally invasive VTE testing. All of these tests are optimally used after clinical examination and estimation of the pre-test likelihood of disease.

When VTE has been diagnosed, acute management usually involves anticoagulation with intravenous unfractionated heparin (UFH), or more recently, subcutaneous low molecular weight heparin (LMWH), to prevent further clot formation and allow endogenous thrombolysis to proceed. Thrombolytic therapy with intravenous

tissue plasminogen activator, urokinase, or streptokinase typically has been reserved for patients with life threatening pulmonary embolism. Once adequate anticoagulation is achieved with heparin, patients switch to oral anticoagulants (e.g., warfarin) for months to years to decrease the risk of recurrent VTE. Although anticoagulants are effective in treating VTE, they are also associated with an increased risk of serious bleeding complications.

Reporting the Evidence

With recent technological advances in diagnosis of VTE and the availability of new pharmacological therapies, a number of questions require careful evaluation of the evidence to guide clinical practice and policy-making. This report addresses the following questions regarding the diagnosis and treatment of VTE.

Treatment

1. **What are the efficacy and safety of LMWH compared with UFH for the treatment of DVT?**

    The main outcomes of interest were death, recurrent VTE, and bleeding complications.

2. **What are the efficacy and safety of LMWH compared with UFH for treatment of PE?**

    The outcomes of interest were the same as for question 1.

3a. **What are the efficacy and safety of outpatient versus inpatient treatment of DVT with LMWH or UFH?**

    The clinical outcomes of interest were the same as for question 1.

3b. What is the cost-effectiveness of outpatient versus inpatient treatment of DVT with LMWH or UFH?

The outcomes of interest included all costs to society in addition to the above mentioned clinical outcomes.

4. What is the optimal duration of treatment for DVT and PE in patients without known thrombophilic disorders and in patients with thrombophilic disorders?

The main outcomes of interest again were death, recurrent VTE, and bleeding complications.

Diagnosis

5. How accurate are clinical prediction rules used for the diagnosis of DVT or PE?

The review focused on prediction rules that were based on at least two of the following types of clinical information: medical history, physical examination, and blood tests.

6a. What are the test characteristics of ultrasonography for diagnosis of DVT?

The review focused on the sensitivity, specificity, and predictive values of ultrasonography.

6b. Are calf vein thromboses adequately identified with ultrasound?

The review for this question also focused on the sensitivity, specificity, and predictive values of ultrasonography.

7a. What are the test characteristics of helical computed tomography (CT) for diagnosis of PE relative to ventilation/perfusion (V/Q) scanning or standard angiography?

7b. What are the test characteristics of magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) for diagnosis of PE relative to V/Q scanning and/or standard angiography?

The review focused on the sensitivity, specificity, and predictive values of these radiologic tests (7a and 7b).

8. What are the test characteristics of D-dimer for diagnosis of VTE?

The review focused on the sensitivity, specificity, and predictive values of this blood test.

Methodology

The Johns Hopkins University Evidence-based Practice Center (EPC) assembled a team of physicians from diverse specialties including general internal medicine, hematology, radiology, and pulmonary and critical care medicine. The EPC team then recruited 16 technical experts and peer reviewers to provide input regarding the choice of key questions and/or to review a draft of the evidence report. These included investigators active in thrombosis research, representatives of major professional organizations, experts in research

methodology, an allied health professional, and representatives of private and governmental payers.

Literature Search

The EPC team searched several literature indexing systems to identify articles relevant to the review. These included MEDLINE®, MICROMEDEX®, the Cochrane Controlled Trials Register, and the Cochrane Database of Systematic Reviews. To ensure a comprehensive literature search and identification of all relevant articles, the EPC team also examined the reference lists from articles identified through the electronic searching, queried the technical experts, and reviewed the table of contents of recent issues of relevant journals.

Two members of the EPC team independently reviewed the abstracts identified by the search to exclude those that did not meet the eligibility criteria. Primary studies were eligible if they addressed one of the key questions, included original human data, were not limited to prevention of VTE, were not case reports, and were written in the English language. Reviews were eligible for inclusion in the report if they used a systematic approach to searching and synthesizing the literature on one of the key questions. Individual key questions had additional exclusion criteria. When two reviewers agreed that an abstract was not eligible, it was excluded from further review.

The EPC team discovered that the primary literature had been systematically reviewed in some detail for questions 1, 2, 6a, 6b, 7a, and 8. To avoid replication of earlier work, team members systematically reviewed the reviews on these questions. They extracted the results of the reviews and reported the aggregate effect measures. For questions 3a, 3b, 4, 5, and 7b, they reviewed the primary studies found in the literature search. Team members also reviewed selected primary studies on question 7a, even though some systematic reviews had addressed this question.

To focus the evidence report on the studies that would be most valuable in addressing the key questions, they used the following additional eligibility criteria:

- For key questions 3a and 4, they excluded studies that did not include a comparison group.
- For key question 5, the EPC team excluded studies that did not use an appropriate reference test to make the diagnosis of VTE or that did not specify a priori the plans for testing of the clinical prediction rule.
- For key question 7b, they excluded studies that did not use pulmonary angiography or V/Q scanning as the reference test for diagnosing PE.

Review Process

Paired reviewers assessed the quality of each eligible article. Differences between the paired reviewers were resolved by face-to-face discussion. The systematic reviews received points for the adequacy of the authors' reporting of search strategies (3 items), the description of the inclusion criteria for the primary

studies (3 items), the adequacy of the quality assessment of the primary studies (2 items), the validity of the methods for combining the results (2 items), and the degree to which conclusions were supported by the evidence (2 items). The primary studies received points for the degree to which they described the patients included in the study (4 items), designed the study to minimize bias in the results (3 items), the description of the intervention or evaluation (2 items), the adequacy of followup (5 items), and the reporting of appropriate statistical methods (4 items). The cost-effectiveness studies (question 3b) received points for nine items. The score for each category of study quality was the percentage of the total points available in each category for that study, and could range from 0 to 100 percent. The overall quality score reported was the mean of the five categorical scores.

One reviewer in each pair was the primary reviewer who abstracted data from the article, and the second reviewer confirmed the accuracy of the first reviewer's work.

Evidence Grades

Five members of the EPC team independently graded the strength of evidence on each key question. If the team members disagreed about an evidence grade, the final grade given was based on the majority opinion. They graded the strength of evidence on each question as strong (Grade A), moderate (Grade B), weak (Grade C), or insufficient (Grade I).

Findings

1. **What are the efficacy and safety of LMWH compared with UFH for the treatment of DVT?**

2. **What are the efficacy and safety of LMWH compared with UFH for the treatment of PE?**

   - Fourteen systematic reviews have addressed these questions.

   - Eleven of these 14 reviews reported either that LMWH was more efficacious than UFH at reducing thrombus recurrence within the subsequent 3 or 6 months, or that the data was trending in that direction.

   - Five of six reviews reported that thrombus extension was less with LMWH than with UFH.

   - Nine of ten reviews reported less major bleeding with LMWH compared with UFH.

   - Nine of 11 reviews reported fewer deaths within the followup period among patients who received LMWH compared with UFH.

   - The more recent reviews (from 1998 to 2000) tended to report smaller magnitudes of benefit than the older reviews (recurrence of VTE: relative risk [RR] 0.7 to 0.8; major bleeding: RR 0.6 to 0.7; mortality: RR 0.7 to 0.8).

   - The evidence suggested that for treatment of DVT, LMWH is more efficacious than UFH for reducing the rate of VTE recurrence, thrombus extension, and death—and LMWH causes less major bleeding than UFH (Evidence Grade: A).

   - The evidence suggested that for treatment of PE, LMWH was likely to be as effective and safe as UFH (Evidence Grade: B).

3a. **What are the efficacy and safety of outpatient versus inpatient treatment of DVT with LMWH or UFH?**

3b. **What is the cost-effectiveness of outpatient versus inpatient treatment of DVT with LMWH or UFH?**

   - Eight trials compared LMWH as an outpatient to UFH as an inpatient, and two trials compared LMWH as an outpatient to LMWH as an inpatient.

   - Nine studies analyzed the costs or cost-effectiveness of LMWH compared with UFH.

   - The randomized trials that tested LMWH as an outpatient, or with early discharge, compared with UFH did not demonstrate a difference in adverse outcomes between groups, and showed a major reduction in duration of hospitalization and associated costs.

   - The comparisons between LMWH in the hospital or at home revealed no difference in outcomes, but found a major savings in hospitalization costs.

   - No study alone was adequately powered to detect small differences in rates of adverse events between groups.

   - These studies primarily enrolled patients who were selected as being appropriate for outpatient therapy, and the results may not be applicable to all patients presenting with VTE.

   - Overall, the evidence indicated that outpatient treatment of DVT with LMWH is likely to be efficacious and safe (Evidence Grade: B).

   - The cost effectiveness studies suggested that LMWH is either cost-saving or cost-effective compared to UFH (Evidence Grade: B).

4. **What is the optimal duration of treatment for DVT and PE in patients without known thrombophilic disorders and in patients with thrombophilic disorders?**

   - Twelve randomized trials and one cohort study addressed this question.

   - For a first episode of idiopathic DVT, outcomes were best if warfarin was given for 3 to 6 months. The benefit to risk ratio declined after 6 months.

   - For patients with VTE and temporary risk factors, 3 months of therapy may be sufficient.

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- For symptomatic calf vein thrombosis, outcomes were best if warfarin was given for 6 weeks.

- No randomized studies focused exclusively on duration of treatment for patients with PE. For patients with any first VTE, which included some patients with PE, 6 months of therapy was superior to 6 weeks.

- Indefinite treatment was most efficacious for patients with a second episode of VTE or patients with a thrombophilic condition, although the evidence was sparse.

- The evidence regarding duration of therapy for patients with idiopathic DVT or DVT with only temporary risks was relatively consistent (Evidence Grade: B); for patients with VTE and a thrombophilic condition or a second DVT, the evidence was sparse (Evidence Grade: I). Little evidence was found on treatment duration for patients with PE (Evidence Grade: I).

5. **How accurate are clinical prediction rules used for the diagnosis of DVT or PE?**

   - Nineteen studies addressed this topic for diagnosis of DVT, and five studies addressed this for PE diagnosis.

   - The most frequently tested clinical prediction rule for diagnosing DVT was the one developed by Wells and colleagues in 1995.

   - Studies were relatively consistent in showing that the Wells model is useful for identifying patients that have no more than a 10 percent chance of having a DVT, and is useful for identifying patients with a high enough risk of DVT to warrant additional testing (Evidence Grade: B).

   - For detection of proximal DVT, the area under the Receiver Operating Characteristic curve (AUC) ranged from 0.79 to 0.92, whereas for distal DVT, the AUCs ranged only from 0.65 to 0.79, suggesting that the Wells model is more accurate for the diagnosis of proximal DVT than for distal DVT.

   - Addition of the D-dimer assay to the model improved the diagnostic performance.

   - The clinical prediction rules for diagnosing PE were tested less throughly and were less accurate than those used for diagnosing DVT. The Wells model had negative predictive values ranging from 72 percent to 98 percent when a lower score cutoff was used and from 64 percent to 89 percent when a higher score cutoff was used (Evidence Grade: C).

6a. **What are the test characteristics of ultrasonography for diagnosis of DVT?**

6b. **Are calf vein thromboses adequately identified with ultrasound?**

   - Seven systematic reviews addressed this topic.

   - The evidence was consistent in showing that ultrasonography has relatively high sensitivity and specificity for diagnosis of proximal lower extremity DVT in symptomatic patients (Evidence Grade: A). With a false negative rate across studies ranging from 0 percent to 6 percent, a negative ultrasound cannot absolutely exclude disease. For diagnosis of VTE in asymptomatic patients, ultrasonography retained its high specificity, but its sensitivity was markedly reduced to as low as 37 percent.

   - Upper extremity DVT, even if symptomatic, was often missed with ultrasound alone, although this was evaluated in few studies (Evidence Grade: C). Recent studies suggested that its efficacy may be higher than previously thought.

   - For diagnosis of calf vein thrombosis, three reviews found that ultrasound had sensitivity as low as 29 percent in both asymptomatic and symptomatic patients (Evidence Grade: B).

   - In the high quality studies, duplex and color Doppler modalities offered no important advantage over compression ultrasound in diagnosing proximal DVT.

7a. **What are the test characteristics of helical CT for diagnosis of PE?**

7b. **What are the test characteristics of MRI and MRA for diagnosis of PE?**

   - Six systematic reviews addressed the use of helical CT for diagnosis of PE.

   - Eight original studies met strict eligibility criteria for the EPC review of use of helical CT for diagnosis of PE.

   - Seven studies met eligibility criteria for the review of use of MRI/MRA for diagnosis of PE.

   - In the examination of both systematic reviews and primary studies, the EPC team found a moderate amount of variation in reported sensitivity of helical CT for the diagnosis of PE, ranging from 45 to 100 percent; reported specificity ranged from 78 to 100 percent (Evidence Grade: B). Based on a focused review of the primary literature, the best overall estimate of sensitivity was 86 percent (95 percent confidence interval [CI], 80 percent to 90 percent), and the team's best overall estimate of specificity was 92 percent (95 percent CI, 88 percent to 95

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percent). Interpretation of these estimates should be done with caution due to potential selection bias and heterogeneity in the reviewed studies.

- Variation in the reported sensitivity of contrast-enhanced helical CT for the diagnosis of PE cannot be entirely explained by variation in study design or by the level of pulmonary arteries (segmental or subsegmental) included in CT interpretation.

- MRA was sensitive and specific in detecting acute PE of the lobar and segmental branches of pulmonary arteries in patients presenting with clinical suspicion for PE, although the studies were small (Evidence Grade: B).

- Accuracy of detecting smaller emboli was reduced substantially for emboli distal to the lobar segment of the arteries.

8. **What are the test characteristics of D-dimer for diagnosis of VTE?**

- Only two systematic reviews have addressed this issue.

- One review evaluated studies of D-dimer in patients with normal ultrasonography; the other evaluated 29 studies that used D-dimer and reported on its sensitivity and specificity for diagnosing DVT.

- The major determinants for specificity of D-dimer tests were the type of assay, the cut-off values, and the spectrum of clinical characteristics of enrolled patients free of thromboembolic disease.

- The lack of standardization of the various D-dimer assays, variable cut-off levels, and specimen-type variation (whole blood or plasma) made summarizing this literature challenging (Evidence Grade: C).

- D-dimer tests generally had greater specificity than sensitivity in VTE diagnosis.

- Specificities were higher for outpatients than for inpatients, and for patients without comorbidity, for both Enzyme Linked Immunosorbent Assay and agglutination assays.

Future Research

Efficacy and Safety of LMWH for DVT and PE

Future research is needed to address the relative risks and benefits of specific LMWH preparations and their efficacy in subpopulations of patients with VTE (e.g., PE only) and unique patient populations (e.g., patients with malignancies, or other thrombophilic conditions).

Outpatient Versus Inpatient Treatment of DVT

Additional studies are needed to evaluate the use of outpatient therapy among a less restricted group of patients, or specifically in high-risk subgroups such as patients with malignancies or known hereditary thrombophilias. Also needed are high quality trials designed as equivalency studies to confirm that LMWH as an outpatient is equivalently effective and safe relative to UFH in the hospital. Additional trials are needed of LMWH as an outpatient for stable patients with PE. LMWH needs to be evaluated for outpatients with symptomatic calf vein thrombosis.

Duration of Treatment for VTE

Further research is needed regarding the optimal duration of therapy after PE. The results of ongoing randomized studies of low dose warfarin for long duration prophylaxis will help clarify whether prevention of VTE can be achieved with greater safety. Additional trials regarding duration of therapy in patients with permanent thrombotic risk factors are needed.

Clinical Prediction Rules

Further research is needed for refinement of the clinical prediction rules to optimize their performance characteristics and to test the addition of laboratory testing. Research is also needed to clarify the optimal role for clinical prediction rules. Are they to be used to aid in interpretation of radiologic tests or can they supplant further testing? Researchers will need to identify the most efficacious way to move these rules into general practice.

Radiologic Tests

Future research needs to clarify the role of ultrasonography for diagnosis of upper extremity DVT. Studies should incorporate discussion of the importance or lack of importance of diagnosis of calf vein thrombosis in studies that address the sensitivity and specificity of testing modalities. Additional systematic reviews of this topic could explore the heterogeneity between studies and alternative ways to present the aggregate data.

The question about the use of helical CT would benefit from more high quality prospective studies in which helical CT is compared to pulmonary arteriography for detecting PE. Future studies of MRI/MRA need to be standardized in terms of speed, image acquisition, number of breath holds, presence or absence of cardiac gating, and dose of contrast to yield precise estimates of test characteristics. The feasibility of MRI/MRA in patients with symptomatic PE (with tachypnea and tachycardia) needs to be studied.

D-dimer

Future research is needed with attention to the clinical spectrum of the patients, the duration of symptoms, the clinical setting, age, and comorbid conditions of the patients. Another

important point not addressed adequately in the literature is the role of abnormal D-dimer levels in patients with calf vein thrombosis.

Overall Areas of Future Research

Clinicians need to know the role of newer agents (including lepirudin, argatroban, or fondaparinux) in the treatment of VTE. Studies should examine the role of systemic thrombolytics in the treatment of PE and DVT for patients without a life-threatening burden of clot. Additional work also needs to be done in clarifying the optimal treatment of patients with thrombophilias such as malignancies and prothrombotic mutations, including duration of treatment, prothrombin time requirements, and prophylactic regimens.

Availability of Full Report

The full evidence report from which this summary was taken was prepared for AHRQ by the Johns Hopkins University Evidence-based Practice Center under contract number 290-97-0007. It is expected to be available in early 2003. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requestors should ask for Evidence Report/Technology Assessment No. 68, *Diagnosis and Treatment of Deep Venous Thrombosis and Pulmonary Embolism*. When available, Internet users will be able to access the report online through AHRQ's Web site at: www.ahrq.gov.

Chapter 1: Introduction

Definition of Venous Thromboembolism

Venous thromboembolism (VTE) refers to all forms of pathologic thrombosis occurring on the venous side of the circulation. When it occurs in its most common location, the deep veins of the leg, it is referred to as deep venous thrombosis (DVT). Less common sites include the veins of the upper extremities, pelvis, abdomen and cerebral venous sinuses. The most life-threatening manifestation of VTE is embolization of venous thrombi to the pulmonary circulation, pulmonary embolism (PE). Up to 30 percent of patients with DVT suffer a symptomatic PE and another 40 percent have asymptomatic PE demonstrated on objective radiological tests.[1,2] Other complications associated with VTE include recurrent thromboembolism and post-phlebitic syndrome. Recurrent DVT occurs in about 20 percent of patients at 5 years and 30 percent after 10 years of followup.[3,4] Post-phlebitic syndrome is characterized by the development of lower extremity pain and swelling, stasis dermatitis, and venous ulceration due to the disrupted venous outflow after a DVT. Almost 30 percent of patients with DVT develop post-phlebitic syndrome after 20 years of followup.[5] Patient presentation varies markedly with some patients being entirely asymptomatic with a small calf vein thrombosis, and others having sudden death from hemodynamic compromise resulting from a large PE.

Epidemiology

VTE and its complications are a common cause of morbidity and mortality in the United States. Data from the Rochester Epidemiology Project estimate that the annual age and sex-adjusted incidence of isolated DVT is 48 per 100,000 people and the incidence of PE , with or without DVT, is 69 per 100,000, respectively.[6] Others estimate the incidence as being higher and suggest that 450,000 cases of DVT, 350,000 cases of non-fatal PE and 250,000 cases of fatal PE may occur annually in the United States.[7]

Etiology

The occurrence of VTE is generally triggered by a confluence of environmental and constitutional risk factors. Environmental risk factors for thrombosis include trauma, surgery, or immobility. Constitutional risk factors for thrombosis may be genetic or acquired. Genetic risk factors include deficiencies of endogenous anticoagulant proteins (such as antithrombin III, protein C or protein S); excessive function of procoagulant proteins (such as is associated with the factor V Leiden or prothrombin 20210 mutations), or elevated levels of factors VIII, IX and XI.[8] Although disturbances of normal fibrinolytic function (e.g., tissue plasminogen activator (TPA) deficiency, excessive levels of plasminogen activator inhibitor 1 (PAI-1) or a_2-antiplasmin, or factor XII deficiency) would be expected to contribute to a hypercoaguable state, clinical evidence of such is lacking.[9-11] Rarely, dysfibrinogenemia is associated with an increased tendency toward clot formation.[12] Hyperhomocysteinemia is associated with an

increased risk for both venous and arterial thrombosis and can result from inherited enzymopathies, or from acquired disorders of homocysteine metabolism including renal failure or folate or vitamin B12 deficiency.[13] Hyperhomocysteinemia has diverse effects on the coagulation cascade; it induces acquired resistance to activated protein C, up regulates tissue factor production and damages the vascular endothelium.[13-15]

Systemic illnesses, particularly cancer, nephrotic syndrome, paroxysmal nocturnal hemoglobinuria, and the antiphospholipid syndrome greatly increase the risk of VTE. Patients with myeloproliferative disorders, such as polycythemia vera and essential thrombocythemia are at an increased risk of thrombosis.[8] Congenital anemias, including sickle cell anemia and thalassemia, also heighten the risk of VTE.[16] Oral contraceptives or estrogen therapy raises the risk for VTE, as does pregnancy.[8] Heparin-induced thrombocytopenia is associated with venous or arterial thrombosis in up to 50 percent of patients in whom it develops.[17]

Diagnostic Approaches

The reference standard for VTE diagnosis remains clot visualization with contrast venography or pulmonary angiography. However, the invasiveness and the risks of these modalities have led to a steady increase in the use of non-invasive or minimally invasive VTE testing. Once popular, impedance plethysmography has become considerably less important in recent years since studies demonstrated its inferiority to duplex ultrasound in the diagnosis of DVT.[18] New methods of venography are now being investigated.[19,20]

Clinicians have relied heavily upon ventilation/perfusion (V/Q) scanning for the diagnosis of PE although they are using helical computed tomography (CT) more and more. Investigators are now examining the usefulness of magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) for diagnosis of PE, as well as the usefulness of coagulation tests (particularly D-dimer assays). All of these tests are optimally used after clinical examination and estimation of the pre-test likelihood of disease.

Therapeutic Approaches

The optimal approach to VTE is prevention. Much effort, with considerable success, has been devoted to VTE prophylaxis in patients known to be at high risk, such as surgical patients and patients with prior VTE. These approaches have included minimization of other contributing risks, such as discontinuing estrogen perioperatively, early ambulation, the use of physical systems to reduce blood stasis (such as sequential venous compression devices and foot pumps), and use of anticoagulant medications perioperatively.[21]

Once VTE has occurred, management is divided into acute and maintenance therapy. Generally, acute management involves anticoagulation with intravenous unfractionated heparin (UFH) or, more recently, subcutaneous low molecular weight heparin (LMWH) to prevent further clot formation and to allow endogenous thrombolysis to proceed. Thrombolytic therapy with intravenous tissue plasminogen activator, urokinase, or streptokinase to rapidly reduce clot burden has typically been reserved for patients with life threatening PE. The benefits of expanding the indications for systemic thrombolytic therapy to include patients with smaller

pulmonary emboli and the use of catheter-directed thrombolysis for DVT are unclear. Once adequate anticoagulation is achieved with heparin, oral vitamin K antagonists such as warfarin are initiated. Warfarin therapy is continued for a variable duration depending upon the clinical situation.

Purpose of Evidence Report

Despite VTE being a very common disease with relatively few diagnostic and treatment options, there remains significant uncertainty about optimal patient management. The purpose of this report is to review and synthesize the evidence on key issues in the diagnosis and treatment of VTE. The report should be a resource for clinicians and policy makers who must make decisions about the management of patients with VTE.

Chapter 2: Methodology

Recruitment of Experts

The EPC team identified a group of 16 experts to provide input at key points during the project (see Appendix A). These experts included representatives from our partner organization, the American Academy of Family Physicians (AAFP), and other relevant professional associations, as well as clinical specialists and allied health representatives.

The EPC team involved a core group of the experts in defining the key questions (see Identifying the Specific Questions, below) and asked the entire group of experts to participate in review of the draft report (see Peer Review Process, below).

Target Population

The main targeted users of the report are clinicians, including family physicians, internists, cardiologists, and other specialists managing patients with VTE.

Identifying the Specific Questions

The AAFP generated a list of key questions to be addressed. The EPC team conducted preliminary literature searches and formulated the questions in specific terms that would focus the review process on the most relevant published studies. The team then sent the draft questions to the core experts, asking them to rank the questions in terms of *importance* and *uncertainty* about the answers.   After reviewing the experts' ratings and comments, the EPC team established the final list of key questions to address in this Evidence Report. Because some of the questions have been addressed in previous systematic reviews, each question was designated to be addressed either through review of previous systematic reviews, through review of primary literature, or through a combination of the two. This strategy enabled the EPC team to address more questions than if it had relied solely on a primary review of all original studies on each question.

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Key Questions

The EPC team sought to address the following key questions as they pertained to management of DVT.

Q1. What are the efficacy and safety of LMWH compared to UFH for the treatment of DVT?
Q2. What are the efficacy and safety of LMWH compared to UFH for treatment of PE?

The experts indicated that these two questions were associated with little uncertainty but remained important questions. Given that many systematic reviews had already been done on this topic, the EPC team decided to review the quality and content of the earlier *systematic reviews.*

Q3a. What are the efficacy and safety of outpatient versus inpatient treatment of DVT with LMWH or UFH?
Q3b. What is the cost-effectiveness of outpatient versus inpatient treatment of DVT with LMWH or UFH?

The experts identified these questions as a high priority. For these questions, the EPC team decided to review the *primary literature* as well as any existing meta-analyses and cost-effectiveness analyses on this topic.

Q4. What is the optimal duration of treatment for DVT and PE in patients without known thrombophilic disorders and in patients with known thrombophilic disorders?

The experts indicated that this question was important and was associated with uncertainty. The EPC team decided to review the *primary literature* to answer this question.

Q5. How accurate are clinical prediction rules used for the diagnosis of DVT or PE?

The experts generally indicated that this question was at least moderately important and was associated with considerable uncertainty. The EPC team decided to review the *primary literature* to determine the accuracy of validated clinical prediction rules for diagnosing DVT or PE.

Q6a. What are the test characteristics of ultrasonography for diagnosis of DVT?
Q6b. Are calf vein thromboses adequately identified with ultrasound?

The experts reported that use of ultrasound was an important topic that was associated with moderate uncertainty. Because this topic has been addressed in a number of systematic reviews, the EPC team decided to review the quality and content of the *systematic reviews.*

Q7a. What are the test characteristics of helical CT for diagnosis of PE relative to V/Q scanning or standard angiography?

Q7b. What are the test characteristics of MRI and MRA for diagnosis of PE relative to V/Q scanning and/or standard angiography?

The experts reported that these two questions were very important and were associated with uncertainty. There have been systematic reviews on this topic, particularly regarding CT. For these questions, the EPC team decided to review published *systematic reviews* and update these with a review of the *primary literature* that used the most appropriate reference tests.

Q8. What are the test characteristics of D-dimer for diagnosis of VTE?

The experts indicated that this question was relatively important and was associated with moderate uncertainty. Instead of reviewing the large diffuse body of literature on this topic, the EPC team decided to review previous *systematic reviews.*

Causal Pathway

To show how the key questions relate to the overall management of patients with VTE, the EPC team developed a description of a causal pathway (Figure 1)*.* The causal pathway depicts the diagnostic and treatment course for a patient with venous thrombosis and the types of outcomes that need to be considered in management decisions. The pathway also provides a conceptual framework for linking the responses to our key questions and for identifying gaps in our knowledge about management of VTE.

Literature Search Methods

The literature search consisted of several steps: identifying sources, formulating a search strategy for each source, and executing and documenting each search.

Sources

Electronic literature sources were used to identify all studies potentially relevant to the research questions and included both electronic database searching and manual searching. Preliminary searches were performed in January to March, 2002, with followup searches in April, 2002. The following databases were searched.

MEDLINE®

MEDLINE, or MEDLARS on-line, is a database of bibliographic citations and author abstracts from approximately 3,900 current biomedical journals published in the United States and 70 foreign countries, dating back to 1966. MEDLINE was accessed through PubMed, the Internet access to the database provided by the National Library of Medicine (NLM).

Cochrane

The Cochrane Database of Systematic Reviews includes full text articles reviewing the effects of healthcare. The reviews are highly structured and systematic, with evidence included or excluded on the basis of explicit quality criteria, to minimize bias.

To ensure a comprehensive literature search, the team examined the reference lists from our database of reference material previously identified through the electronic searching, queried our technical reviewers and reviewed the tables of contents from journals cited most frequently in the literature searches (see Appendix B). The team reviewed the tables of contents of these journals published between October 2001 and March 2002.

MICROMEDEX®

The Micromedex worldwide editorial team reviews and edits all information compiled from the most current sources available. The unbiased documents are thoroughly researched, evaluated, and referenced based on the world's leading literature. Healthcare and environmental safety professionals rely on Micromedex information in over 8,000 facilities in more than 90 countries.

Search Terms and Strategies

The search strategies were designed to maximize sensitivity and were developed in consultation with Johns Hopkins University Welch Medical Library staff and team members. Preliminary strategies were developed to identify key articles. Using key articles determined to be eligible for review, search strategies were developed and refined in an iterative process. A strategy was first developed for PubMed. This strategy was then modified to create separate search strategies for the Cochrane and Micromedex electronic databases (see Appendix C).

Organization and Tracking of Literature Search

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The results of the searches were downloaded from electronic sources, where possible, or manually entered into a ProCite database. (ProCite, ISI Research Soft, Berkeley, CA)The duplication check in the bibliographic software was used to eliminate articles already retrieved. This ProCite database was used to store citations and track search strategies and sources. The use of this software also allowed for the tracking of the abstract review process.

Abstract Review

As a first step in the review process, two members of the study team independently reviewed the abstracts identified by the search to exclude those that did not meet our eligibility criteria. At this step we excluded citations when: the articles did not apply to a key question, the article reported only on prevention of VTE (not treatment), the articles were not written in English, the articles did not include human data, or the articles reported on a meeting only (i.e., no full article to review). In addition, for those questions for which we reviewed primary literature, we excluded articles that did not include any original data or were case reports. For our key questions relying on review of systematic reviews, we excluded articles that did not include a systematic review, meta-analysis or cost effectiveness analysis.

The EPC team used abstract review forms appropriate for the search processes (See Appendices D and E). The forms were based on those used in previous EPC reports. Each abstract was circulated to two members of the study team who independently reviewed the abstract and indicated which of the key questions the article addressed. For those articles found not eligible, the reviewers indicated a reason for exclusion. When there was no abstract or when the reviewers could not determine from the abstract whether the article met the eligibility criteria, the team obtained a full copy of the article to review. Investigators met face-to-face to adjudicate when there were disagreements between them on study eligibility. Our process emphasized arriving at agreement on which studies met our pre-established criteria.

Qualitative and Quantitative Data Abstraction

The study team developed article review forms that were pilot tested and revised before use. These included both a quality assessment and a content abstraction form. Due to the different types of questions addressed, the team had four sets of quality and content forms (see Appendices F, G, H, and I): one set addressed key questions 3a and 4, treatment questions, and one set addressed the diagnostic testing questions, questions 5 and 7. The team developed a third set of quality and content forms to address question 3b on cost-effectiveness. The review of published systematic reviews (questions 1, 2, 6, 7, and 8) required a fourth set of forms, which were created based on our review of several systems for evaluating systematic reviews.[22-27] To make sure that all articles met eligibility criteria, the study quality form began with a check of

the eligibility criteria (see Abstract Review, above). For questions 3 and 4, the team limited the review to studies with a comparison group and a minimum sample size of five.

The quality assessment forms for diagnosis and treatment studies included items about study quality in the following categories: representativeness of study population; bias and confounding; description of therapy/testing; outcomes or test interpretation; and statistical quality and interpretation. The items in these categories were derived from study quality forms used in previous EPC projects[28,29] and were modified for this project. Because of the variety of issues covered by our key questions, not all items were required for each of the key questions.

The study team responded to each question with a score of zero (criteria not met), one (criteria partially met), or two (criteria fully met). The score for each category of study quality was the percentage of the total points available in each category for that study and therefore

could range from zero to 100 percent. As there is presently no consensus on reporting quality scores, we have reported scores by category, giving each category equal weighting. Therefore the overall quality score was the average of the five categorical scores.

The quality assessment forms for cost-effectiveness studies and systematic reviews had fewer items without category scores. The overall quality score for these articles was based on the average of the scores on the individual items.

The content abstraction form for the review of the original studies included items that described the type of study, geographical location, the definition of study groups, the specific aims, the inclusion and exclusion criteria, characteristics of tests and interactions, demographic, social and clinical characteristics of subjects, and outcomes or results related to each of the key questions.

Article Review Process

The team reviewed each eligible article identified by the abstract review process. Two reviewers independently reviewed each article. One team member was responsible for completing both the quality assessment and content abstraction forms, and the second reviewed and confirmed the material abstracted. Differences between the two reviewers in either quality or content abstraction were resolved at face to face meetings. Reviewers were not masked to author or journal names because previous work has shown that masking is unlikely to make a significant difference in the results of the data abstraction.[30]

The team developed a database to collect, maintain, and analyze the quality assessment and content abstraction data. The evidence tables were built in Microsoft Access 2000 (Copyright © 1992-9 Microsoft Corporation), with a data-entry front end developed in Delphi© (Borland Delphi, Scotts Valley, CA).

Evidence Tables

For each key question, the EPC team created a set of evidence tables. Each set of tables contained basic information about study aims and eligibility criteria, assessments of study quality, selected characteristics of study participants, and results most pertinent to the key question.

For two of the questions, we abstracted data from the studies to fill in contingency tables, and from these, calculated true positive (TPR) and false positive rates (FPR). If this primary data was not presented in an article, we abstracted only the summary statistics reported, including sensitivity, specificity, positive predictive value, negative predictive value and area under the receiver operating characteristic (ROC) curve. If the data were available, we calculated test characteristics separately for each strata of pretest probability, or for each test cutoff for which data was provided. The area under the ROC curve was measured using ROCFIT©, (Chicago,

IL).

For the question regarding the utility of clinical prediction rules, we plotted the true positive rates and false positive rates from several studies to create a summary ROC curve. For this analysis, we used as a cutoff the score that separated patients with a low pretest probability of DVT from those in the moderate and high categories. In our analyses of the utility of CT and MRI, we also prepared a summary ROC curve. We specified that the TPR and FPR be from analyses that used data from all the participants in the study and be data points which represented the best test performance of cutoffs studied.

Evidence Grades

Five members of the EPC team independently graded the strength of the evidence on each key question. If the team members disagreed about an evidence grade, the final grade given was based on the majority opinion. The grading scheme was derived from the scheme used in previous EPC projects.[28,29,31] For questions 1, 2, 3, and 4 the grades were as follows:

Grade A (strong): Appropriate data available, including at least one well done randomized controlled trial; study population sufficiently large; adequate controls; data consistent across studies; intervention clearly superior, equivalent or inferior to another strategy;

Grade B (moderate): Appropriate data available; study population sufficiently large; adequate controls; data reasonably consistent across studies; intervention likely to be superior, equivalent, or inferior to another but not enough evidence to conclude definitively;

Grade C (weak): Some data available; study population reasonably large; data indicate trend supporting benefit (or no benefit) of one intervention compared to another; not enough evidence to conclude that intervention is likely to be superior, equivalent or inferior to another;

Grade I (insufficient): Appropriate data not available or insufficient number of patients studied.

For questions 5, 6, 7, and 8 the evidence grades were as follows:

Grade A (strong): Appropriate data available, including at least one high quality study; study population sufficiently large; adequate reference standard; data consistent across studies; test definitely is or is not useful;

Grade B (moderate): Appropriate data available; study population sufficiently large;

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adequate reference standard; data reasonably consistent across studies; data indicate test is likely to be or is likely not to be useful but not enough evidence to conclude definitively;

Grade C (weak): Some data available; study population reasonably large; data indicates trend supporting or not supporting usefulness of the test; not enough evidence to conclude that test is or is not likely to be useful;

Grade I (insufficient): Appropriate data not available or insufficient number of patients studied.

Peer Review Process

The EPC team sent a copy of the draft report to the core experts and the peer reviewers, as listed in Appendix A. The reviewers were asked to comment on the form and content of specific sections of the report, according to their areas of expertise and interest, and were invited to comment on other parts as well. The EPC team incorporated the reviewers' comments into the final report.

Figure 1: Causal pathway for diagnosis and treatment of venous thromboembolism as it relates to our key questions

Predictors/Precipitants:

non-genetic

genetic

Disease Studies:

Pulmonary embolism

Deep venous thrombosis

Outcomes:

Questions 1, 2, 3

Recurrence

Bleeding

Death

Costs

Quality of life

Diagnosis:

Questions 5,6,7,8

Clinical exam

Imaging tests

Laboratory tests

Influencing response to treatment:

Question 4

Duration of therapy

Intensity of maintenance therapy

Patient characteristics

Treatment:

Questions 1,2,3

Heparin

Inpatient/outpatient

Low molecular weight heparin

Warfarin

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Chapter 3: Results

Literature Search and Abstract Review

Systematic reviews

The literature search process identified 463 unique citations potentially relevant to key questions for which the EPC team evaluated *systematic reviews.* During the review of abstracts, 86 percent (399 articles) were found not to meet the criteria for inclusion. Articles were excluded for the following reasons: the article was not in English (62); the article did not include human data (3); the article was a review but did not include a systematic review, meta-analysis, or cost-effectiveness analysis (84); the article was not a review (49); reports primary data only (49); the article focused on prevention only (86); and the article did not apply to a key question designated to be addressed by systematic reviews (153). The total number of exclusions exceeded the number of articles reviewed because some articles were excluded for more than one reason.

Primary Literature

The literature search process identified 1786 unique citations potentially relevant to key questions for which the EPC team evaluated *primary literature*. During the review of abstracts, 92 percent (1638 articles) were found not to meet the criteria for inclusion. Abstracts were excluded for the following reasons: the article was not in English (99); the article did not include human data (18); the citation was a meeting abstract only (3); the study was limited to prevention of VTE (126); the article was a case report (26); the article contained no original data (354); the article did not apply to a key question designated to be addressed by review of primary literature (956) or all data in the article were presented elsewhere (2). For articles relating only to key questions 3 or 4, the EPC team excluded 18 studies that did not involve a comparison group or did not include a cost-effectiveness analysis. For articles relating only to key question 5, the team excluded studies that did not include a clinical prediction rule (i.e., at least two of history, physical exam, and/or laboratory testing, used together) (11) or did not specify a reference standard (1). For articles relating only to key question 7, the team excluded studies that did not report test characteristics of CT or MRI for the diagnosis of PE (3) or did not have an appropriate reference standard (21). The total exclusions exceeded the number of articles reviewed because some articles were excluded for more than one reason.

Articles Eligible for Review

Following the abstract review process, 63 reviews and 146 primary studies remained eligible. Of these, 31 reviews were tagged for key question 1 or 2 (LMWH for treatment of DVT or PE), 33 primary studies addressed key question 3 (efficacy and cost-effectiveness of outpatient treatment for DVT), 22 primary studies addressed key question 4 (duration of therapy), 61 primary studies pertained to key question 5 (use of clinical prediction rules), 16 reviews addressed key question 6 (ultrasonography for DVT diagnosis), 9 reviews and 30 primary studies pertained to key question 7 (helical CT or MRI/MRA for PE diagnosis), and 15 reviews addressed key question 8 (D-dimer for thromboembolism diagnosis). Added together, the total number of articles identified as pertaining to key questions exceeded the actual number of articles reviewed because some articles were identified as relevant for more than one key question.

Results of the Key Questions

Q1. What are the efficacy and safety of LMWH compared with UFH for the treatment of DVT?
Q2. What are the efficacy and safety of LMWH compared with UFH for treatment of PE?

Introduction

Because DVT and PE have similar underlying pathophysiology and often occur together, most of the published clinical trials evaluated the use of LMWH in patients with DVT with or without concomitant PE. Also, several systematic reviews of clinical trials have already been published about the efficacy and safety of LMWH for VTE. Therefore, for the purposes of this report, we combined questions 1 and 2 and searched the literature for systematic reviews that have evaluated the efficacy and safety of LMWH versus UFH in patients with VTE, emphasizing the quality and content of these reviews.

Results of Literature Search

Thirty-one articles were identified at article review for possible relevance to key questions 1 or 2. Of these, 17 were excluded: nine did not include a systematic review, one focused on prevention of VTE, three did not apply to any key question, three duplicates were found with different citations, and two did not discuss any relevant outcomes. The number of exclusions exceeded the number of articles reviewed as reviewers could indicate more than one reason for exclusion. After article review, 14 systematic reviews remained eligible for the review on key questions 1 and 2.[32-45]

Characteristics of Reviews

In Evidence Table 1 we have summarized the study aims, number of trials included, and quality scores for the 14 systematic reviews of clinical trials for Questions 1 and 2. The reviews were published between 1994 and 2000; nine included trials that enrolled patients with DVT or PE,[33,36-39,42-45] while five limited their review to trials of patients with DVT only.[32,34,35,40,41] No systematic review published to date has focused exclusively on patients with PE with or without concomitant DVT. The number of randomized controlled trials (RCTs) reviewed in each article varied substantially (mean 13, range 6 to 21) and was not related to either year of publication or whether the review included patients with VTE or those limited to DVT. There was little overlap among the trials included in the systematic reviews of this topic. The most recent reviews. those by van den Belt, et al., and van der Heijeden, et al., included many of the trials that were included in earlier reviews. Most of the systematic reviews included RCTs evaluating the efficacy of many different LMWHs, with the exception of one that focused solely on dalteparin.[36]

Quality of Reviews

The overall quality scores varied substantially (mean 58 percent, range 22 to 92 percent), with more recent studies tending to have higher scores (see Evidence Table 1). Most reviews adequately described the study aims, search strategy, and study inclusion criteria, and provided conclusions consistent with the results of their analyses. Fewer reviews adequately described their methods to pool data across the RCTs. Only four reviews included a formal assessment of the quality of the included RCTs.[33,41,42,44]

Results of Reviews

Evidence Table 2 describes patient populations and outcomes of trials included in the systematic reviews. A few articles limited their review to specific subpopulations of VTE (e.g., first episode of VTE[33] or first episode of DVT[40]). Several reviews analyzed data for all participants in the RCTs combined and then separately for patients with cancer.[33,34,38,41,44] The clinical outcomes most commonly compared between treatment groups were recurrence of VTE, major bleeding, and all-cause mortality. Most reviews reported recurrence of VTE and mortality data at three or six months after VTE diagnosis, although some also examined differences in outcomes at several earlier times (e.g., days 1 to 15, 16 to 90, 1 to 90[33] or during the period of heparin use[44]). Bleeding, however, was generally assessed during the initial period of heparin treatment (LMWH or UFH). A few reviews evaluated other outcomes as well, particularly thrombus extension,[32,34,35,40,43,44] minor bleeding,[33,41,42] and thrombocytopenia.[37,41,42] Four systematic reviews published in 1997[36] and 1998[37,39,40] were only descriptive and did not quantitatively pool results. The remaining 10 systematic reviews provided a summary measure of treatment effect based on a quantitative pooling of data from the RCTs.[32-35,38,41-45]

During the three or six months of followup in the RCTs, the rate of recurrence of VTE among RCT participants was approximately five percent. The systematic reviews relied on the definition of VTE recurrence used in the various RCTs. Of the 10 reviews that quantitatively examined the results of the various RCTs, four reported that LMWH significantly reduced the risk of recurrent thrombosis,[32-34,45] and six indicated a trend toward a protective effect with LMWH.[35,38,41-44] A review published in 1995[33] found that the benefit of LMWH in preventing recurrence of VTE occurred primarily during days 1 to 15 ;[33] a later review reported a similar magnitude of benefits extending up to six months after initiation of therapy.[44] Results of the descriptive reviews were discordant, indicating that LMWH was more effective,[39] that there was no difference between LMWH and UFH,[37,40] or that data were insufficient to answer the question.[36]

Of the six reviews that compared rates of thrombus extension in LMWH and UFH groups,[32,34,35,40,43,44] five reported that LMWH was superior to UFH,[32,34,35,43,44] and one (a descriptive review) suggested no difference.[40]

All reviews compared rates of major bleeding during the initial treatment period with heparin. Authors of the systematic reviews generally relied on the definition of major bleeding used in the various RCTs. The overall rate of major bleeding reported in the systematic reviews was approximately two percent. In eight of the 10 reviews that reported results from the quantitative pooling of the data, patients treated with LMWH had fewer episodes of major bleeding than those treated with UFH.[32-35,38,43-45] Gould et al. reported a significant benefit when using a fixed-effects model, but only a trend toward benefit when using a random-effects model;[41] the remaining review indicated a trend toward less bleeding with LMWH.[42] As with recurrence of VTE, the descriptive reviews either indicated that LMWH was more effective,[39] that there was a lack of difference between LMWH and UFH,[37,40] or that there were insufficient data.[36]

Eleven of the fourteen systematic reviews examined differences in rates of all-cause mortality in patients according to treatment assignment.[33-35,37,38,40-45] The systematic reviews reported a mortality rate of approximately five percent across the RCTs. All nine reviews that employed quantitative pooling for this outcome indicated that LMWH significantly reduced mortality during the three or six months of followup compared to UFH,[33-35,38,41-45] with one review indicating a similar benefit of LMWH in days 1 to 15 and days 16 to 90 after VTE diagnosis.[33] Two descriptive reviews suggested that mortality was no lower with LMWH than with UFH.[37,40] Five reviews[33,34,38,41,44] examined mortality in patients with cancer according to their treatment assignment. Two of these reviews[33,44] concluded that LMWH reduced mortality in patients with cancer, but not in patients without cancer.

In general, published clinical trials evaluating the efficacy of LMWH for VTE enrolled patients with DVT with or without concomitant PE. Only three published trials have been specifically designed to compare LMWH with UFH for patients with PE. These three trials include two smaller pilot studies (fraxiprine versus UFH, 101 patients;[46] (fragmin versus UFH, 60 patients[47]) and a large unblinded multicenter trial (tinzaparin versus UFH, 612 patients[48]) of patients without "massive" PE (i.e., were not in shock, did not receive thrombolytic therapy or embolectomy). One systematic review presented in this report included all three trials of patients with PE,[39] with five systematic reviews only including the tinzaparin versus UFH trial.[37,38,42,44,45]

Only three systematic reviews reported summary results for patients with PE, concluding that LMWH was as effective as UFH in this population.[36,38,44]

Since publication of these systematic reviews, data from a previously published double-blind double-placebo clinical trial of 432 patients with proximal DVT[49] were presented as part of re-analyses comparing LMWH (tinzaprin) versus UFH to patients who also had PE.[50] Perfusion lung scanning was performed on 97 percent of participants with proximal DVT at study entry. Investigators found evidence of PE in about 50 percent of participants (defined as high probability perfusion scans); about half of these patients were asymptomatic for PE. In this population with DVT and concomitant PE, patients assigned LMWH (N=97) were less likely than patients assigned UFH (N=103) to have a recurrence of VTE (0 versus 6.8 percent; 95 percent confidence interval (CI) for difference 1.9 to 11.7 percent) but had similar rates of major bleeding during heparin therapy (1.0 versus 1.9 percent; 95 percent CI for difference was -2.4 to 4.3 percent).[50]

Summary of Reviews

Compared to the five reviews published between 1994 and 1997, the nine reviews published more recently, from 1998 to 2000, tended to report smaller magnitudes of risk reduction from use of LMWH (recurrence of VTE: relative risk (RR) 0.7 to 0.8 versus 0.4 to 0.7; major bleeding: RR 0.6 to 0.7 versus 0.3 to 0.5; mortality: RR 0.7 to 0.8 versus 0.6 to 0.7). These differences could be due to variations in methodological quality, types of LMWH examined, and populations of included patients with VTE.

Overall, these data provided evidence that the efficacy (reduced rate of VTE recurrence, thrombus extension, and mortality) and safety (lower rates of major bleeding) of LMWH are superior to that of UFH for DVT (Evidence Grade: A). The evidence for treatment of submassive PE (with or without DVT) is more limited, but suggests that LMWH is likely to be as effective and safe as UFH (Evidence Grade: B).

Q3a. What are the efficacy and safety of outpatient versus inpatient treatment of DVT with LMWH or UFH?
Q3b. What is the cost-effectiveness of outpatient versus inpatient treatment of DVT with LMWH or UFH?

Introduction

In the first part of this document, we reviewed all published systematic reviews that evaluated the efficacy and safety of LMWH compared with UFH for the treatment of acute DVT. The evidence demonstrated that LMWH is at least as efficacious as UFH for the treatment of DVT, without an increase in major hemorrhagic complications. As with any new medication or technology, the costs associated with its use must be evaluated before it can be recommended for widespread use in a population.

Most of the trials described in these systematic reviews tested LMWH compared to UFH in an inpatient setting. As LMWH does not require intravenous administration, it may be used in an

outpatient setting or at home. If hospital stays are eliminated or shortened by the use of LMWH in place of UFH, the total costs of treatment can be expected to be less, despite higher medication costs. Furthermore, as partial thromboplastin times do not need to be monitored with the use of LMWH, the reduction in laboratory costs can be expected to reduce the total costs.

To better understand the efficacy and safety associated with use of LMWH in an outpatient setting and to address the cost implications of this practice, we reviewed the literature addressing the two study questions noted above.

Results of Literature Search

At article review, 14 articles were excluded from the 33 articles originally identified for possible relevance to key question 3. Of these, two contained no original data, six had no comparison group, one compared only two groups of outpatients, one presented data that were reported elsewhere, and four did not apply to any key question. After article review, 19 primary studies remained eligible for the review on key question 3 including ten on key question 3a and nine on key question 3b.[41,51-68]

Characteristics of Studies

Eight of the identified studies on key question 3a reported on the outcomes of patients with DVT treated with LMWH administered at home compared with outcomes of patients treated with UFH in the hospital[51-58] (see Evidence Table 3). Three of these were randomized trials,[51-53] while the others were cohort studies. An additional two studies compared clinical outcomes and costs for patients receiving LMWH at home to patients receiving LMWH administered in the hospital.[59,60] One of these studies enrolled only patients with PE.[60] We identified nine studies on key question 3b that were cost-effectiveness or cost-minimization studies.[41,61-68]

Outpatient versus Inpatient Therapy

The ten studies on key question 3a were published between 1996 and 2002 (see Evidence Tables 4, 5, and 6). Four of these were randomized controlled trials.[51-53,59] The smallest study enrolled 28 patients in each arm[57] and the largest was a retrospective cohort study with 1850 patients (164 of whom had received LMWH).[58] All of the trials used enoxaparin, nadroparin, or dalteparin during the intervention, and then an oral anticoagulant during the followup period. Enoxaparin was always used at a dosage of 1 mg/kg twice daily, but the dosage of nadroparin varied across studies.

In all of the studies, UFH was given in the hospital, except for one trial in which one group at home used UFH given subcutaneously.[51] In all studies, LMWH was administered at home or was completed at home after a brief in-patient admission. In two studies, however, outpatient LMWH was compared with LMWH administered as an inpatient treatment.[59,60] Among randomized trials, only one study required a visiting nurse to administer the medication.[59] In the trial by Koopman et al., only 15 percent of participants received help at home with drug administration. In the study by Levine et al., the patients administered the drug themselves,[53] and in the trial by Belcaro et al., patients received one home visit by a nurse for instruction and then self-

administered the drug.[51]

    All studies excluded patients with PE except for the study by Kovacs et al. that exclusively enrolled patients with PE.[60] The exclusion criteria were fairly extensive; most studies excluded patients with known thrombophilic conditions, including prior VTE and patients unlikely to comply with outpatient therapy (see Evidence Table 3). Only three of the studies used scheduled, radiological surveillance procedures to detect recurrences.[51,53,59]

Quality of Studies on Outpatient versus Inpatient Therapy

Generally, the quality of the studies was not high. The studies were mostly complete in their description of the patient populations, but weaker in the description of the interventions (particularly regarding the UFH interventions) with little description of the adequacy of anticoagulation during the acute intervention or the followup period. Few studies adequately described whether other therapies, such as aspirin, were allowed or prohibited during the followup period (see Evidence Table 4).

Results of Studies on Outpatient versus Inpatient Therapy

The studies reported few differences in outcomes between study groups (see Evidence Table 6). Across studies, the percentages of recurrent DVT ranged from zero to nine percent. Only one study reported a significant difference between groups in the percentages of patients with recurrences.[58] The single study that enrolled patients with PE also found no difference in adverse event rates; unfortunately, it was a small study and underpowered for seeing a difference in these rates.[60]

The occurrence of PE was rare and not different between arms in any study. Similarly the incidence of major bleeding was very low (from zero to four percent) and not different between arms. The percentage of patients dying during followup ranged from zero to 11 percent, again with no difference between study arms.

The number of inpatient days was fewer in the study arms that used LMWH either entirely at home or after a brief inpatient stay than in the arms that used UFH in the hospital. Few studies reported the statistical significance of these differences. The duration of the hospitalization depended strongly on how the study was designed.

Five of these 10 studies reported on costs[51,54,57-59] (see Evidence Table 6). Although only two studies reported on the statistical significance of the difference in costs between the study arms,[54,59] it seems likely that this difference was also statistically significant in other studies. Huse et al. showed that outpatient costs with LMWH were higher, but stated that the anticipated savings of 2.5 hospital days in this group would save 1,911 U.S. dollars per patient.[58]

Cost-Effectiveness or Cost-Minimization Studies

Nine cost-effectiveness or cost-minimization studies were published between 1997 and 2000 (see Evidence Table 7). Four were designed as cost-effectiveness studies,[41,62,64,66] four were cost-minimization studies,[61,63,65,67] and one used a decision-model but could not be classified as either of the above.[68] A societal perspective was used in quantifying costs in two studies,[41,65] while the other seven took the perspective of a payer.

The modeled comparisons fell into two categories. Four of the studies modeled the use of LMWH compared with UFH, with all drugs administered in the hospital.[41,61,62,67] The other studies modeled the use of LMWH at home compared with UFH in the hospital.[63,65,66,68] Two of these modeled the use of LMWH in patients at home if they were medically eligible to be treated as outpatients, and in the hospital if they were not.[64,66]

The source of the estimates for costs used in the models varied (see Evidence Table 8). Half

of the studies used actual costs measured in the setting of a clinical trial. The others used costs obtained from databases of costs maintained by the government or payer, or used costs abstracted from review of the literature. Similarly, the rates of events included in the models came from actual data observed in trials or from the literature. For the models, two of the studies assumed, on the basis of earlier work, that the rates of recurrent thromboses and adverse events were equivalent for LMWH and UFH.[61,63]

Quality of Studies on Cost-Effectiveness or Cost-Minimization

The overall quality of the studies was good (see Evidence Table 7). According to the quality assessment instrument that we designed, the study quality score ranged from 67 percent to 100 percent. The two questions on which the studies performed worst concerned the adequacy of the sensitivity analysis and the description of the population to whom the results could be expected to apply. Thus, readers of these studies may have some difficulty generalizing the results.

Results of Studies on Cost-Effectiveness or Cost-Minimization

Of the four studies that compared inpatient LMWH treatment to inpatient UFH treatment, two were cost-minimization studies. One projected a 57 percent cost savings with use of nadroparin instead of UFH.[61] The other study found no difference in costs between enoxaparin and UFH. It concluded that, since these costs were accrued in the setting of a clinical trial, some of the laboratory tests were protocol-driven, thus raising the costs in the enoxaparin arm above what would be seen in usual practice[67] (see Evidence Table 9).

One of the cost-effectiveness studies addressing this comparison found that inpatient tinzaparin dominated the UFH arm, i.e. tinzaparin was less costly and more efficacious.[62] This study predicted an 11 percent cost savings with the use of tinzaparin in the hospital in place of UFH. The high-quality cost-effectiveness study by Gould et al. modeled the use of enoxaparin and UFH in the hospital and found that while enoxaparin treatment is more expensive, it can be considered cost-effective compared with UFH because of the gain in quality-adjusted life-years, i.e. gain in years of life adjusted for the quality of those years.[41] In a secondary analysis in which the outcomes modeled that some of the patients on enoxaparin were treated as outpatients, they found that if only eight percent were treated as outpatients, this treatment would be cost-saving.

Of the studies investigating outpatient LMWH treatment compared with inpatient UFH treatment, all found that use of LMWH in outpatients is less costly than hospitalization for UFH. The cost-effectiveness study by Estrada et al. found that use of LMWH at home for clinically stable patients and in the hospital for unstable patients, yields a 10 percent cost savings over use of UFH in the hospital for all patients.[66] The authors noted that the cost savings were largely due to savings on inpatient costs. Rodger et al. similarly found a cost savings of 23 percent when this same comparison was made.[64] The two cost-minimization studies found outpatient LMWH to yield a cost-savings of 57 percent[65] and 64 percent[63] compared with inpatient UFH. The final study by Tillman et al. provided little data on event rates in the UFH arm so that the results were harder to interpret.[68] However, the authors stated that there was a 60 percent cost savings with enoxaparin at home compared with UFH in the hospital, and indicated that this treatment would be cost-saving even if hospitalization costs were to decrease by 77 percent.

Summary of Studies

The randomized trials that compared treatment with LMWH, in outpatients or in inpatients with early discharge, to inpatient treatment with UFH did not demonstrate a difference in adverse outcomes between groups, and showed a major reduction in duration of hospitalization and associated costs. Similarly, the comparison between LMWH in the hospital or at home revealed no difference in outcomes, but did demonstrate a major savings in hospitalization costs. However, no study alone was adequately powered to detect small differences in rates of adverse events between groups. For example, the largest trial had only 12 percent power to detect a difference in the observed rates of recurrent DVT between groups.[53] The frequency of adverse events in all studies was small; a difference in outcomes between groups was not be demonstrated, however equivalency cannot be definitively claimed. Still, the direction of the results suggested that it is unlikely that LMWH at home will be found to be substantially less safe than UFH. The results also suggest a substantial savings in duration of hospitalization and a savings in costs. Overall, we concluded that outpatient treatment of DVT with LMWH is likely to be efficacious and safe (Evidence Grade: B). These studies primarily enrolled patients who were selected as being appropriate for outpatient therapy and the results may not be applicable to all patients presenting with VTE.

The cost‑effectiveness studies were consistent in suggesting that LMWH is either cost‑saving or cost‑effective compared with UFH (Evidence Grade: B). This is the conclusion regardless of whether this drug is administered in the hospital or at home, although the cost savings should be greater if hospitalization can be avoided. Given the different units of benefit and years of the studies, it was difficult to compare the studies directly with one another, but the direction of the benefit was uniform across studies.

Q4. What is the optimal duration of treatment for DVT and PE in patients without known thrombophilic disorders and in patients with thrombophilic disorders?

Introduction

Immediate therapy of symptomatic VTE employs UFH, LMWH or thrombolytic therapy (in severe cases) followed by heparin to inhibit coagulation and promote initial clot lysis. Once therapeutic heparin anticoagulation is achieved, a vitamin K antagonist (warfarin, acenocoumarol, fluindione, etc.) is initiated with the goal of attaining a target INR of at least 2.0 with concomitant use of heparin for an additional four to five days. Longer periods of heparin therapy (ten days) may be appropriate for massive pulmonary emboli or iliofemoral thrombosis.[69] Initial therapy of symptomatic VTE with a vitamin K antagonist alone is associated with a significantly higher incidence of recurrent VTE within three months.[70]

Continuation of warfarin therapy beyond the initial period of heparin anticoagulation permits continued thrombus resolution and reduces the risk of recurrent thrombotic episodes. The

benefits of warfarin therapy must be weighed against the risk of hemorrhagic morbidity and mortality associated with anticoagulation. The risk to benefit ratio is influenced by variables such as the acuity and location of the clot, the intensity, stability and duration of anticoagulation, patient age, comorbidities, and both intrinsic and extrinsic predispositions to thrombus formation. Intrinsic predispositions include inherited and acquired thrombophilic disorders such as Factor V leiden and antiphospholipid antibodies. Extrinsic predispositions include surgery, trauma, and immobility. Since excessive or inadequate anticoagulation can each lead to adverse outcomes, it is important to evaluate of the evidence on the optimal duration of oral anticoagulation therapy for patients with VTE. To this end, we conducted a systematic review of the English language literature that assessed the duration of anticoagulation for VTE. For the purposes of this review, idiopathic VTE is considered to be thrombosis that occurs in the absence of an obvious intrinsic or extrinsic risk factor. Secondary VTE refers to thrombotic events that occur in association with one or more temporary or permanent risk factors.

Results of Literature Search

At article review, 10 articles were excluded from the 23 articles originally identified for possible relevance to key question 4. Of these, seven were not relevant to any key question, three contained no original data, and one had no comparison group. After article review, 13 primary studies remained eligible for the review on key question 4.

Characteristics of Studies

The 13 studies, published between 1972 and 2001, included a total of 4137 patients (range of patients per study: 80 to 897)[71-83] (see Evidence Table 10). Twelve were RCTs;[71-78,80-83] one was a retrospective cohort study.[79] Inclusion criteria varied considerably with recent studies more precisely specifying eligible study subjects.[71,75,80,82,83] Most of these studies excluded subjects at high risk for recurrent thrombosis (known thrombophilia or malignancy) or bleeding (malignancy, recent surgery or trauma).[71-73,75-77,79,80,82,83] Differences in exclusion criteria were common even among more recent studies.

Five studies focused exclusively on patients being treated for a first episode of thrombosis,[71,74,75,80,82] while one evaluated the treatment of patients following a second episode of VTE.[83] Three included patients with isolated calf vein thrombosis,[74,76,80] one of which focused exclusively on this population.[76]

Quality of Studies

Evidence Table 11 summarizes the quality assessment of these studies, with the earlier trials providing less information about the setting and participants' characteristics.[72-74,78,79,81] Recently designed studies were less likely to be at risk of having results affected by confounding and biases. In this regard, studies by Levine et al.[77] and Kearon et al.,[75] which employed placebo-controlled triple-blind designs, were particularly strong. Among older studies, the one by Petitti et al. may be especially vulnerable to bias because of the retrospective cohort design.[79] More complete and precise assessments of patient outcomes characterized the recently published

literature.[71,75,80,82,83]

Unlike the earlier trials, five recent studies used independently-adjudicated, well-defined radiological criteria for the diagnosis of VTE.[71,75,77,82,83] Older studies used several different coagulation assays to monitor the intensity of oral anticoagulation and failed to provide data on the time within the therapeutic range,[72,73,78] whereas more recent studies routinely used the INR and reported data on therapeutic intensity over time.[71,75,77,80,82,83] Statistical analyses were also of higher quality in later reports.[71,75,77,80,82,83] Precise characterizations of the study populations, therapeutic intensity and outcome definitions, as well as randomization, blinded outcome assessment, and appropriate statistical analysis distinguished the highest-quality studies.[71,75,77,82,83]

Results of Studies

The twelve randomized trials enrolled 3767 patients (range of patients per study: 80 to 897) with a mean age of 61.5 years (range of mean ages from 56 to 67.7 years); a mean of 56 percent of participants were men (range of mean percentages from 40 to 75 percent) (see Evidence Table 12).

As shown in Evidence Table 13, most early studies found no evidence of increased benefit with a longer duration of anticoagulation for VTE. This finding, however, was weakened by methodological limitations including small study populations, unblinded assessment of outcomes, and the absence of radiological confirmation of VTE.[72-74,78,79,81]

Recent studies clearly demonstrated that oral anticoagulation effectively prevents recurrent thromboembolism as long as patients remain on treatment.[71,75,77,82,83] Prolonged anticoagulation for patients with a first idiopathic VTE[75] or a second VTE[83] was associated with fewer VTE recurrences but at the expense of a trend toward more bleeding and no difference in survival. Consequently, since the incidence of recurrent VTE decreased as time elapsed from a thrombotic event (recurrence rate 2.1 percent per month between six weeks and six months[82] and 0.45 percent per month between six months and indefinite treatment[83]) while bleeding risk remained constant (two percent per year), the therapeutic benefit of continued anticoagulation may decline over time.

For patients with a first episode of idiopathic DVT, the rate of recurrent VTE after discontinuation of anticoagulation was similar for patients treated for three months (5.1 percent per patient-year) or 12 months (5.0 percent per patient-year).[71] In contrast, six weeks of oral anticoagulation for patients with a first episode of VTE in the absence of malignancy, pregnancy or known thrombophilia was associated with an initially increased rate of recurrence (2.1 percent per month during months 1.5 to 6) compared with patients treated for six months (0.1 percent per month during months 1.5 to 6). After six months, the VTE recurrence rates over the next 18 months were equivalent between treatment groups (0.4 percent per month in the 6 week group versus 0.5 percent per month in the 6 month group).[82]

Agnelli et al. found that the incidence of recurrent VTE within two years of stopping anticoagulation was similar among patients who received three months compared with 12 months of treatment for idiopathic DVT.[71] These studies suggest that at least 3 months of anticoagulation is required for patients with idiopathic DVT.[71,82]

For calf vein thrombosis, three months of oral anticoagulant therapy in addition to five days

of heparin was superior to five days of heparin alone,[76] but, in another study, six weeks was equivalent to three months of oral anticoagulation.[80]

Subgroup analysis among the more methodologically sound trials demonstrated that the presence of permanent risk factors for VTE increased the risk of recurrence[75,77,80,82] Patients with permanent risk factors for VTE may benefit from longer therapy.[75,82] Specific permanent risk factors identified in subgroup analyses included antiphospholipid antibody syndrome[75] and malignancy.[80] In contrast, the presence of Factor V Leiden and the prothrombin mutation did not increase the risk of recurrence.[75] However, a small number of patients in the latter study reduced the certainty of these subgroup analyses and larger prospective clinical trials are needed to validate the findings. Increasing the duration of anticoagulation from six weeks to six months significantly reduced the two-year incidence of recurrence among patients with: a) permanent risk factors, b) a proximal DVT or c) inadequate anticoagulation (INR adequately elevated less than 75 percent of the time).[82] Among patients with these risk factors, the incidence of recurrent VTE was very high during the first 10 weeks after discontinuation of anticoagulation in the six week group.[82]

Conversely, there was no evidence that patients with temporary risk factors benefitted from a longer duration of treatment. Schulman, et al. and Pinede, et al. found no difference in recurrence among VTE patients with temporary risk factors treated for shorter versus longer durations.[80,82] VTE patients with temporary risk factors are significantly less likely to have a recurrence than those with permanent risk factors.[77]

Summary of Studies

For a first episode of idiopathic DVT, the evidence demonstrated that at least three months of oral anticoagulation is optimal, meaning that this duration of therapy reduces the risk of recurrent VTE without an excessive increase in episodes of major bleeding[71,77] (Evidence Grade: B). For symptomatic calf vein thrombosis, six weeks appeared to be sufficient.[76,80] Although no randomized studies focused exclusively on patients with PE, the outcomes of patients with first VTE, including PE, indicated that six months of therapy is superior to six weeks.[82] Although one study suggested that three months may be sufficient,[80] the more persuasive data supported a longer treatment duration.[75] For patients with a first episode of VTE associated with a temporary risk factor, three months of therapy is probably sufficient.[77,80,82]

For patients with an objectively documented second episode of VTE, the evidence suggested that indefinite anticoagulation is highly efficacious, albeit associated with a steady 2 percent per year incidence of major bleeding.[83] Subgroups of patients at exceptionally high risk of recurrent VTE such as those with the antiphospholipid antibody syndrome are particularly likely to benefit from prolonged anticoagulation.[75] However, since the incidence of recurrent VTE appeared to decline over time while the incidence of major bleeding remained constant, indefinite anticoagulation may not benefit all subgroups of patients with a second episode of VTE (Evidence Grade: C).

Q5. How accurate are clinical prediction rules used for the diagnosis of DVT or PE?

Introduction

Optimal use of diagnostic tests requires an appreciation of the pretest probability of disease in a patient. The results of a diagnostic test are best interpreted with knowledge of this pretest probability to yield a posttest probability that the patient actually has the disease. A number of clinical prediction rules have been created to help clinicians estimate accurately the pretest likelihood of disease.

Some of the scoring systems used to generate pretest probabilities of DVT or PE may be accurate enough to serve as diagnostic tests by themselves. If this is so, this approach could eliminate more invasive or expensive testing. Examples are the use of the Ottawa ankle rules,[84] which have markedly reduced the use of radiography of injured ankles, and the use of "strep throat" prediction rules, which have safely reduced the use of throat culture and antibiotics.[85,86]

Thus, we evaluated clinical prediction rules that are used in the diagnosis of DVT or PE.

Results of Literature Search

At article review, 44 articles were excluded from the 63 articles originally identified for possible relevance to key question 5. Of these, 30 did not report on clinical prediction rules as defined by the EPC team (i.e., two of the three from history, physical exam, or laboratory testing), seven were retrospective studies, four contained no original data, two did not address any key question, and one focused on prevention of VTE. After article review, 19 primary studies remained eligible for the review on key question 5 (Evidence Tables 14 to 17).

Characteristics of Studies

The articles were stratified according to the event that the clinical prediction rule was predicting (Evidence Table 14). We identified 14 studies that prospectively evaluated clinical prediction rules for the diagnosis of DVT,[87-103] and five studies evaluating prediction rules for diagnosis of PE.[100,101,104-107] Of the 14 studies using clinical prediction rules for the diagnosis of DVT, 12 were studies in which the Wells prediction model was evaluated.[88] Of these 12 studies, only one included a comparison of the Wells model to other proposed models.[95]

The clinical prediction rules for the diagnosis of DVT were evaluated in a total of 5411 patients. Most of the studies were done in Canada and Europe with only two studies having been done in the United States. Fifty-eight percent of the studies reported that the patients had idiopathic DVT, and most of them excluded patients for whom there was a suspicion of a concomitant PE. Among studies, the mean age for the patients evaluated was between 54 and 68 years. Men accounted for 25 to 62 percent of the subjects in the studies. The most commonly reported risk factors for the development of DVT were surgery and immobilization; only a few patients in each study had a malignancy (5 to 17 percent).

The clinical prediction rules for the diagnosis of PE were evaluated in a total of 3284 patients.[101,104-107] All of the studies were done in Canada or Europe. Among studies, the reported mean age ranged from 51 to 64 years. The risk factors for the development of PE were not consistently reported.

Quality of Studies

We report on the quality of these studies in Evidence Table 15. The population was well described in most of the studies. The low scores in the bias and confounding sections were due to most of the studies not having two independent observers applying the clinical prediction rules to the study subjects, to an absence of blinding in interpretation of the reference test, or to an absence of independent observers interpreting the reference test.

The overall quality of the studies was fairly high and there were no major differences in quality between the studies evaluating clinical prediction rules for the diagnosis of DVT and for PE.

Results of Studies

The Wells model is a scoring system that allocates pretest probability as high, moderate, and low based on a score derived from risk factors and physical findings of DVT (see Table 1).[108] In the 12 studies in which the model was tested, patients who had a high pretest probability based on this model had a prevalence of DVT that ranged between 17 and 81 percent (Evidence Table 17). Those found to be at a moderate pretest probability had a prevalence of DVT between zero and 28 percent; the group with a low pretest probability had a prevalence of DVT between zero and 13 percent.

The negative predictive value is a useful summary statistic in this setting because it indicates what proportion of patients who have a *low* score will truly *not* have thrombosis. These patients may be able to forego further testing or, alternatively, the results of their subsequent radiological tests can be interpreted with this knowledge.

The negative predictive values across the studies evaluating DVT were high. If patients with either moderate or high scores were classified as having DVT, the median negative predictive value was 96 percent with a range from 81 percent to 100 percent. If only patients with the highest category of prediction scores were classified as having DVT, the median negative predictive value was slightly lower, 87 percent, with a range from 75 percent to 100 percent. With a higher cutoff score, a greater number of patients can potentially be spared further testing although there is more misclassification of patients as being free of DVT when they are not.

The positive predictive values were not high indicating that these rules were not as useful for definitively identifying patients who do have thrombosis. Even with a high cutoff score, the positive predictive values rarely exceeded 75 percent.

The Wells model for the prediction of DVT, across all studies, had an area under the ROC curve (AUC) that ranged from 0.74 to 0.90. This indicates that the model has a probability of 0.74 to 0.90 of correctly discriminating a random pair of patients in which one has DVT and one does not. An AUC of 0.50 means that a test has no discriminating ability.[109] For detection of proximal DVT, the AUCs ranged from 0.79 to 0.92, whereas for distal DVT, the AUCs ranged only from 0.65 to 0.79, thereby suggesting that the Wells model is more accurate for the diagnosis of proximal DVT than for distal DVT.

A number of studies tested the addition of a D-dimer assay to the Wells model for improving the performance of the model.[91,92,94,96-99,102] In the majority of these studies the area under the

ROC curve increased with addition of the D-dimer assay indicating better discrimination between patients with and without thrombosis. The predominant conclusion was that a D-dimer assay that is normal (low), in the setting of a low clinical probability of VTE, even further lowers the likelihood of thrombosis.

In the studies evaluating the clinical prediction rules for diagnosis of PE, the percentages of patients that had a PE in the high pretest probability group ranged from 38 to 78 percent, the percentages for the moderate pretest probability group ranged from 16 to 39 percent, and for low pretest probability, percentages ranged from 3 to 28 percent. The Wells model for the prediction of PE had negative predictive values ranging from 72 percent to 98 percent when a lower cutoff was used for classifying patients as having PE, and from 64 percent to 89 percent when a high score cutoff was used.[104-106] By comparison, the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) model had a negative predictive value of 81 percent when a lower cutoff was used, and 73 percent when a high cutoff was used.[105]

Other clinical prediction rules, besides the Wells model, had AUCs that ranged from 0.51 to 0.87; however, the models were each tested in only a single patient population.[87,92,95,105,107] The only direct comparison between the Wells model and any other prediction rule found that the Sant-Andre Hospital rule performed similarly to the Wells model, with negative predictive values of 89 percent for Sant-Andre and 90 percent for Wells when a low score cutoff was used for classifying patients having DVT, and 79 percent and 84 percent, respectively, when a higher cutoff was used.[95,105]

Summary of Studies

Studies were relatively consistent in showing that the Wells clinical prediction rule for diagnosing DVT is useful for generating an estimate of the probability that a patient has a DVT, identifying patients who have no more than a ten percent chance of having a DVT, and identifying patients with a high enough risk of DVT to warrant additional testing (Evidence Grade: B). The evidence indicated that the model is not sufficiently specific for ruling *in* the diagnosis of DVT without further radiological testing. The model performed best if the DVT was proximal, and addition of the D-dimer assay to the model improved the diagnostic performance. Other models performed similarly to the Wells model, but there were not enough data to make conclusive comparisons. The evidence also indicated that the Wells model for PE has less predictive value than the DVT model (Evidence Grade: C).

Q6a. What are the test characteristics of ultrasonography for diagnosis of DVT?
Q6b. Are calf vein thromboses adequately identified with ultrasound?

Introduction

Contrast venography is the test that serves as the reference standard for the diagnosis of DVT. It is, however, a procedure that is avoided when possible because of its invasiveness and the risk of complications including thrombosis, phlebitis, bleeding, and allergic reaction to the

contrast dye. A noninvasive and safe diagnostic test is ultrasonography. Many studies have been done to determine the sensitivity and specificity of ultrasonography for the diagnosis of DVT. In these studies, patients received both ultrasonography and the reference standard, and the resulting diagnoses were compared. We describe here the systematic reviews that have qualitatively and quantitatively summarized this primary literature.

Results of Literature Search

At article review, nine articles were excluded from the 16 articles originally identified for possible relevance to key question 6. Of these, six did not contain a systematic review, and three did not address any key question. After article review, seven systematic reviews remained eligible for the review on key question 6.

Characteristics of Studies

The reviews were published between 1989 and 2002 (see Evidence Table 18). All of the reviews included only studies that compared ultrasonography to venography.

Four of the reviews summarized studies aimed specifically at diagnosing proximal DVT[75,110-112] (see Evidence Table 19). One review included studies of calf vein thrombosis exclusively,[113] and one included studies of upper-extremity DVT diagnosis only.[114] Most reviews specified that the studies must have had a prospective design and enrolled consecutive patients meeting the study entry criteria.

Five reviews included only trials of symptomatic patients,[110-113,115] while the review by Wells et al. focused on studies of asymptomatic, post-operative patients.[112] One review included trials of asymptomatic and symptomatic patients and stratified the results.[18] Two studies stratified the studies into two levels based on study quality.[110,112] Level one studies were prospective and employed blinded interpretation of both diagnostic tests. Level 2 studies failed to meet all criteria for a level 1 designation. Another review carefully assessed study quality but did not stratify on that basis.[115]

Quality of Studies

The description of the search methods used to identify studies for inclusion were reasonably strong although no review contacted experts in the field to identify other studies for inclusion (see Evidence Table 18). Most reviews provided little detail about the included study populations, although it is possible that many of the primary studies provided little clinical information. Two of the reviews made no assessment of the quality of the included studies.[111,113] It was difficult to assess the quality of the methods of combination of the studies as there is no consensus about the ideal way to pool results from diagnostic testing studies. Several studies appropriately avoided a quantitative summary of the data (i.e., did not pool the sensitivities and specificities). Others pooled the data, but stratified it in some way to minimize heterogeneity between studies.

Results of Studies

As the reviews had different criteria for inclusion of trials, the included studies overlapped less than anticipated. The reviews with the most overlap were those by Kearon et al., Cogo et al., and White et al., reviews that focused on studies enrolling patients with symptoms of lower-extremity DVT.[75,110,111] The review by Becker included studies lacking prospective designs and many of these were not included in the later reviews.[115]

All of the reviews used a simple weighted average of the individual sensitivities and specificities to yield aggregate results (see Evidence Table 19). One review incorporated the heterogeneity between the studies in calculating the CI surrounding the estimates of sensitivity and specificity.[112] These authors also included a summary ROC curve for the included studies, which is a useful way to present these data. There is no consensus on the best methodology for combining results of diagnostic tests, and aggregate sensitivities and specificities may not adequately capture the heterogeneity of the included studies.

The reviews that focused on studies of patients with symptoms of lower-extremity DVT reported uniformly high sensitivity and specificity for ultrasonography. The level of ultrasound technology (i.e., use of compression, duplex or Doppler) did not influence the results greatly. In these included studies, the prevalence of DVT was high, roughly 40 to 60 percent, a finding that suggests the positive predictive value of an abnormal ultrasound will be very high. This suggests that the test is useful in a population of patients selected to have a high prevalence of disease (such as with suggestive clinical criteria).

Upper-extremity DVT, even if symptomatic, was often missed with ultrasound alone, although the highest quality study included in the review had a sensitivity of 100 percent and a specificity of 93 percent.[114] The studies included in this review had an extremely high prevalence of upper extremity DVT, thus making the positive predictive value of this test fairly high despite a low sensitivity and specificity.

For diagnosing VTE in asymptomatic patients, ultrasonography retained its high specificity, but its sensitivity was markedly reduced, as shown in two reviews.[18,112]

For diagnosing calf vein thrombosis, three reviews found that ultrasound had low sensitivity in both asymptomatic and symptomatic patients.[18,111,112] One review found fairly high sensitivity for diagnosing calf vein thrombosis among the studies that were included,[113] although the authors noted many indeterminate test results throughout the included studies. The uncertain clinical significance of calf vein thrombosis was not addressed in these systematic reviews.

Looking only at the primary literature as defined by the reviews' authors, ultrasonography for diagnosing proximal DVT in symptomatic patients was sensitive and very specific. In these studies, doppler and color doppler capability offered no important advantage over compression ultrasound alone in diagnosing proximal DVT. In trials of asymptomatic patients, the performance characteristics of ultrasonography were fairly low in the high quality primary studies.

Summary of Studies

We conclude that the evidence was consistent in showing that ultrasonography has relatively high sensitivity and specificity for diagnosis of proximal lower extremity DVT in symptomatic patients (Evidence Grade A). However, with a false negative rate ranging from 0 to 6 percent, a negative ultrasound cannot absolutely exclude disease. The evidence indicated that ultrasound has considerably less utility for diagnosing DVT in asymptomatic patients, such as in a post-operative screening setting. The studies in which screening asymptomatic patients seemed promising were mostly of lower quality than those in which it was less useful.

The evidence was somewhat inconsistent, but suggested that ultrasound had relatively low sensitivity and specificity for diagnosing upper-extremity DVT (Evidence Grade: C). The identification of one successful high quality study suggests that this topic needs further study. Additionally, a high quality primary study was recently published. This recent study suggested that upper extremity DVT can be diagnosed with ultrasound with acceptable accuracy if the ultrasound examination shows venous incompressibility.[116]

The evidence suggested that ultrasound has poor sensitivity for the diagnosis of calf vein thrombosis. The need for diagnosis of calf vein thrombosis was not addressed by these reviews and is a separate issue (Evidence Grade: B).

Q7a. What are the test characteristics of helical CT for diagnosis of PE relative to V/Q scanning and/or standard angiography?
Q7b. What are the test characteristics of MRI and MRA for diagnosis of PE relative to V/Q scanning and/or standard angiography?

Introduction

Imaging is an important component in the diagnostic evaluation of patients who are suspected of having PE (see Evidence Table 20). V/Q scintigraphy is widely used in the initial evaluation for PE, but the usefulness of this test is limited by a substantial proportion of indeterminate exams and the possibility that PE may be present despite a low probability scan. By contrast, pulmonary arteriography is highly accurate in the diagnosis of PE, but it is accompanied by the risks and discomfort associated with an angiographic procedure.

Examination of the pulmonary arteries with contrast-enhanced CT was made possible by the introduction of high-speed helical CT scanners in the early 1990s.[117] The advantages of helical CT include rapid exam times, high availability in emergent clinical settings, non-invasiveness, and relatively low cost. Helical CT scanners have since become widely available, and examination of the pulmonary arteries by helical CT has become a routine practice.[118] Given the high reported accuracy, it is reasonable to consider whether helical CT can replace traditional imaging modalities for detecting PE, namely, V/Q scan and pulmonary arteriography by catheterization. More recently MRI/MRA has been studied for diagnosis of PE. Its benefits include the ability to avoid the use of iodinated contrast material, and faster scanning sequences that have enabled imaging to be done more quickly than older techniques (see Table 2).

This key question was addressed in two parts. In part one, we examined all published systematic reviews of the use of helical CT or MRI/MRA for the diagnosis of PE. In part two, we examined original studies reporting the sensitivity and specificity of helical CT for the diagnosis

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of PE compared to pulmonary arteriography, and the sensitivity and specificity of MRI/MRA for the diagnosis of PE.

Results of Literature Search

At article review, four reviews and 15 primary studies were excluded from the ten reviews and 30 primary studies originally identified for possible relevance to key question 7. The reviews were excluded for not being systematic reviews. For the primary studies, seven did not use a diagnostic testing study design, five did not address any key question, two contained no original data, and two did not use an appropriate reference standard. The total number of reasons for exclusion may exceed the number reviewed as reviewers may indicate more than one reason for exclusion. After article review, six systematic reviews and 15 primary studies remained eligible for the review on key question 7 (eight primary studies for key question 7a and seven for key question 7b).

Part One: Examination of Systematic ReviewsCharacteristics of Studies.

Six systematic reviews have examined the use of helical CT for the diagnosis of PE (see Evidence Table 20).[93,119-123] The most recent systematic review included the literature published before December 2000.[123] A major difference in these systematic reviews was the reference standard against which CT was compared. Two of the reviews[120] examined only studies in which the reference standard was pulmonary arteriography.[119,120] Two reviews defined the reference standard as either pulmonary arteriography or V/Q scan.[122,123] The remaining two reviews did not limit the reference standard to specific imaging modalities.[93,121] Two of the reviews included an article evaluating contrast-enhanced electron beam CT.[119,120] No systematic review addressed the use of MRI/MRA for diagnosis of PE.

Quality of Studies. Evidence Table 21 summarizes our assessment of the quality of the systematic reviews. Except for one review,[122] the quality scores for the reviews had a range from 72 to 78 percent. The articles with the lowest quality evaluation scored lowest in all categories, indicating no single area of weakness.[122,123] Among these systematic reviews, description of search methods received the lowest quality scores, whereas statements of study aims and conclusions received the highest quality scores.

Results of Studies. The findings of the systematic reviews are shown in Evidence Table 22. All of the reviews reported the sensitivity and specificity of helical CT for diagnosing PE as a main index of test performance. In five of the reviews, the sensitivities and specificities of each reviewed study were averaged, weighted according to each study's sample size. The combined sensitivities of CT across reviews ranged from 66 percent to 93 percent, and the combined specificities of CT ranged from 89 percent to 97 percent. In one of the reviews, combined sensitivity and specificity were not reported because the authors felt that the heterogeneity of included studies did not allow mathematical combination.[93] In that review, sensitivity was reported as a range from 53 percent to 100 percent, and specificity was reported as a range from 81 percent to 100 percent.

Part Two: Examination of Primary Studies

Our examination of the published systematic reviews was supplemented by a review of the

primary literature. Our initial aim was to update our analysis of the systematic reviews with pertinent studies published after completion of the systematic reviews. However, because of the wide variation in sensitivities reported by the systematic reviews, we felt a more meaningful approach would be to focus on the strongest evidence, instead of focusing only on the most recent. Therefore, we completed our primary literature review on all prospective studies evaluating helical CT for the diagnosis of PE in which all participants received the optimal reference test to confirm the diagnosis. We excluded studies evaluating electron beam CT because this technology is not routinely available. Our review of the primary studies on MRI/MRA also included all prospective studies that evaluated this modality against an acceptable reference test (pulmonary angiography or V/Q scan).

Characteristics of Studies. Evidence Table 23 summarizes key aspects of the eight eligible studies of CT, which were published between 1994 and 2001.[117,124-130] All studies were diagnostic test evaluations in which all participants received the diagnostic test and the reference test. None were multi-center studies, and none of the reports stated the specific dates of participant recruitment. Although some of the studies were included in the systematic reviews in Part One, none of the systematic reviews reviewed all of the studies selected for our primary literature review.

One study employed dual-detector helical CT, a faster form of helical CT.[128] All of the other studies employed conventional single-detector helical CT, and all studies used pulmonary arteriography as the reference standard. Only one study used explicit clinical findings to define the suspicion of PE.[130] In six of the studies, clinical suspicion of PE was implied as all participants in these studies were referred for imaging.[117,124,126-129] In one study, it was unclear if patients were enrolled because of referral for imaging or because of symptomatology.[125]

We identified seven studies of MRI /MRA for diagnosis of PE; the earliest was published in 1993. Five of these studies used MRA,[131-135] while the other two used perfusion MRI techniques.[136,137] The five MRA studies enrolled consecutive patients with suspicion of PE and required pulmonary angiography as the reference test. One MRI study enrolled nonconsecutive patients with suspected PE referred for either V/Q or angiography.[137] Finally, one study of MRI evaluated two groups of patients for perfusion defects due to either PE or severe emphysema.[136]

Quality of Studies. The study quality scores are given in Evidence Table 24. For the eight studies of CT, the scores ranged from 44 percent to 84 percent. The CT study with the lowest quality score was a brief report describing a study of 10 patients in whom massive PE was clinically suspected.[124] The study with the second lowest quality score was similarly a brief report, and the low scores may be related to the brief format.[125] The two categories with the lowest average quality scores across the eight studies of CT were for the descriptions of the included patients, and for the potential for bias and confounding in the study.

The five MRA studies were of similar and reasonably high quality. Their weakness as a group was incomplete description of the study population and key patient characteristics. The MRI perfusion studies were of lower quality than the MRA studies. Berthezene et al. described two series of patients with suspected perfusion defects, but did not describe the patient populations very well.[136] Erdman et al. enrolled nonconsecutive patients and allowed different reference tests.[137] All MRA studies used some form of blinding during the interpretation of the MRA examinations.

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Results of Studies. The eight studies of CT reported data on a total of 443 individuals with the prevalence of PE ranging from 27 percent to 70 percent. The basic population characteristics for each of the studies are given in Evidence Table 23. The results of each study are summarized in Evidence Table 24. The reported sensitivity of CT ranged from 45 percent to 100 percent, and the reported specificity ranged from 78 percent to 100 percent. The only study reporting a sensitivity of 100 percent was the one that enrolled patients with clinically suspected massive PE, which was also the study with the highest prevalence of PE.[124]

The variability in sensitivity was greater than the variability in specificity, a fact we also noted in the prior systematic reviews. This variability in sensitivity was present in our primary literature review even though it had more stringent study inclusion criteria than did the earlier systematic reviews (i.e., we required that all patients in a study undergo both the diagnostic test and the reference test). This observation suggests that study design may not be an important contributor to the variations in sensitivity and specificity.

To summarize the CT studies graphically, a representative sensitivity and specificity for each study is plotted in Figure 2. We specified that the sensitivity/specificity pair be calculated using data from all the participants in the study and using the cutoff that yielded the best test performance (if several cutoffs were studied). The greater variability in sensitivity relative to the variability in specificity is also apparent in Figure 2. In Figure 3 we examined the relationship between prevalence of PE and the reported sensitivity and specificity. There is no apparent relation between prevalence and test performance. Therefore, the variability in reported sensitivities and specificities did not appear to be related to disease prevalence. However, the variability in disease prevalence is expected to strongly influence the reported positive and negative predictive values.

When the representative sensitivity/specificity pairs from the eight studies were pooled using simple addition, the sensitivity of CT was 86 percent (95 percent CI 80 to 90 percent) and the specificity was 92 percent (95 percent CI 88 to 95 percent). However, such pooling assumes that the studies were similar enough to be pooled, (i.e., each study is assumed to have the same underlying sensitivity and specificity so that random variation is the only source of variance between the results of different investigations). Figure 2 suggests that two of the studies are outliers having sources of variance outside of random variation.[126,130] The study by Velmahos et al. reported the lowest sensitivity and specificity, but theirs was also the only study in which all participants came from a specific clinical setting (a surgical intensive care unit).[130] Therefore, interpretation of the pooled sensitivity and specificity for the reviewed studies must be done with caution because of potential underlying heterogeneity.

Two of the studies suggested that the relatively low sensitivity may be related to whether CT interpretation included the finding of subsegmental clots that were seen on the reference tests. Velmahos et al. included interpretation of subsegmental clot, and their study was associated with the lowest sensitivity of all of the studies reviewed.[130] In the study by Goodman et al., inclusion of subsegmental clot lowered the sensitivity from 86 percent to 64 percent.[127] However, the study by Qanadli et al. differed from this pattern because it reported relatively high sensitivity and specificity despite the inclusion of subsegmental clot.[128] Therefore, in the studies reviewed, there did not appear to be a definite relation between test accuracy and vessel level interpreted.

The sensitivity of helical CT found in our examination of both the primary literature and systematic reviews is generally higher than was found in a recent large study of outpatients,

which reported a sensitivity of 70 percent and a specificity of 91 percent.[138] The latter study incorporated other imaging modalities as well as clinical followup to establish the diagnosis of PE rather than pulmonary arteriography alone, and this difference in study design may at least partially explain the lower sensitivity compared to the literature we reviewed.

The MRA studies demonstrated fairly consistent specificities. Sensitivities ranged across studies from 77 percent to 100 percent. The prevalence of PE across studies ranged from 27 percent to 55 percent. Berthezene et al., who presented aggregate data from two populations of patients (those with suspected PE and those with emphysema), found that sensitivity for picking up perfusion defects was low.[136] Erdman et al. found fairly high sensitivity and specificity and included an analysis of a subgroup of patients with pulmonary angiography as the reference test.[137] In this subpopulation, sensitivity was similar to that observed in other MRA studies; specificity, however, was lower.

Interpretation of our examination of the primary literature should be made with the knowledge of some important limitations in the evidence. First, participants in all but one of the studies [130] were enrolled because of suspicion of PE that led to referral for imaging. This introduced a potential selection bias in the study populations because nothing is known about individuals in whom PE was suspected but who were not referred for imaging. The real effect of this potential selection bias was difficult to determine from the data, however. Individuals referred for imaging may have been selected because of clinically obvious (rather than occult) disease and perhaps have a form of disease that is easier to detect by imaging than the typical case (inflating sensitivity and specificity), as exemplified by the one study in our review that included only patients suspected of having massive PE.[124] On the other hand, referring physicians may have referred only clinically difficult cases which could have more subtle imaging findings than clinically obvious cases.

There is also obvious heterogeneity in the prevalence of PE in the published studies. While disease prevalence strongly influences the positive and negative predictive values of a test, it classically should not affect the sensitivity and specificity of a test. However, if the variation in prevalence is indicative of a variation in disease spectrum or severity, then sensitivity and specficity may be affected. This principle is exemplified by the study of patients suspected of having massive PE.[124]

Summary of Studies

In our examination of both systematic reviews and primary studies, we found a moderate amount of variation in reported sensitivity of helical CT for the diagnosis of PE, ranging from 45 to 100 percent; reported specificity was generally greater than 90 percent with less variability (Evidence Grade: B). Pooled estimates of sensitivity and specificity of helical CT reported by systematic literature reviews should be interpreted with caution due to potential selection bias and heterogeneity in the reviewed studies. The source of the variability in sensitivity was unclear and was not completely explained by differences in study design, prevalence of PE, or smallest arterial level (segmental or subsegmental) interpreted by the radiologists. Potential sources of variability that could not be systematically evaluated from the literature included variations in scanning protocols, timing of contrast injection, scanner technology, and experience of radiologists.

Our review of the evidence also indicated that MRA is sensitive and specific in detecting acute PE of the lobar and segmental branches of pulmonary arteries in patients whose clinical presentation suggests PE (Evidence Grade: B). The accuracy of detecting smaller emboli was reduced substantially as one moves distal to the lobar segment of the arteries.

Q8. What are the test characteristics of D-dimer for diagnosis of VTE?

Introduction

The diagnosis of VTE employs clinical assessment followed by objective testing. Most of the available non-invasive diagnostic tests are radiological procedures that require expensive equipment, technicians, and radiologists for their performance and interpretation. These tests, are costly, time-consuming, and burdensome to patients.

A blood test that is both highly sensitive and specific for the diagnosis of VTE would be ideal. The test that has been most studied for this purpose is the D-dimer assay. D-dimers are fragments of cross-linked fibrin that are generated by fibrinolysis. Thus, elevated D-dimer levels indicate that clot formation and lysis have occurred. Many qualitative and quantitative D-dimer assays are available. Qualitative assays generally rely on the agglutination of latex particles or red cells coated with monoclonal antibodies to detect D-dimers in patient samples. Quantitative assays typically employ enzyme-linked immunosorbent assay (ELISA) to measure precisely the amount of D-dimer present in plasma.[80,139,140]

Over 70 articles in the primary literature have evaluated the characteristics of different D-dimer assays in various patient populations using different criteria for positivity. We sought to determine the usefulness of these assays in the diagnosis of VTE by reviewing systematic reviews of this primary data.

Results of Literature Search

At article review, 13 articles were excluded from the 15 articles originally identified for possible relevance to key question 8. Of these, 11 were not systematic reviews, and two did not apply to any key question. After article review, two systematic reviews remained eligible for the review on key question 8.

Characteristics of Studies

Of the eligible two reviews, the study by Kraaijenhagen et al. addressed multiple questions regarding the diagnosis of VTE, one of which was the role of D-dimer in patients with normal ultrasound exams.[141] The study by Becker et al. evaluated 29 published primary studies and presented detailed characteristics of the various D-dimer assays and their accuracies.[142] There was no overlap in the primary literature included in the two reviews.

Quality of Studies

Both reviews cleared stated the purpose of their study.[141,142] Pertinent English-language literature was identified by electronic and hand searches in both reviews. In the Kraaijenhagen et al. review, this search was supplemented by a query of experts in the field.[141] Inclusion criteria were reported in sufficient detail to allow replication in that review.[141] A validated instrument to assess study quality was used in the Becker review;[142] no instrument was reported in the other.[141] Reproducibility of quality assessments was not reported. Kraaijenhagen et al. pooled their selected studies and found no evidence of significant heterogeneity. Becker et al. found that the heterogeneity among the selected studies precluded pooling. The conclusions of both reviews were supported by the reported analysis. Based on these criteria for assessing the quality of systematic reviews, we assigned a quality score of 71 percent to the review by Kraaijenhagen et al. and 38 percent to the review by Becker et al.

Results of Studies

The two systematic reviews that we evaluated were methodologically very different. As part of a more extensive review, the authors of the review by Kraaijenhagen et al. focused upon two specific clinical questions; the utility of the D-dimer assay in patients with suspected DVT and a normal initial compression ultrasound result, and the utility of the D-dimer assay in patients evaluated with impedance plethysmography (IPG) and a clinical prediction rule.[141] The assays used and the thresholds for defining abnormal results were not reported. Of a total of 1128 patients with normal ultrasounds pooled from two of the primary studies identified by Kraaijenhagen et al., 250 had an abnormal D-dimer result and underwent a second ultrasound at one week. Two-hundred thirty-four patients had normal serial ultrasounds, but 4 (1.7 percent) of these patients developed non-fatal VTE during three months of followup. Only one fatal PE occurred (0.4 percent). Of the 878 patients with a normal initial ultrasound and normal D-dimer result only two (0.2 percent) went on to develop VTE during the three-month followup period. The overall VTE complication rate for this strategy was only 0.6 percent. Only patients with abnormal D-dimer assays had the followup ultrasonography mandated, introducing the likelihood of ascertainment bias, which could make the D-dimer test appear to be more predictive than it really is.

To further discuss the content of the Kraaijenhagen et al. review, we describe the included studies briefly. One of the primary studies, included in the review by Kraaijenhagen et al., evaluated the utility of D-dimer assays in patients evaluated with IPG after application of a clinical prediction rule.[143] Of 401 patients with clinically suspected DVT, 352 had a normal IPG. Seventy-six of these 352 had an abnormal D-dimer and venography confirmed a DVT in one-third of these patients. Of the remaining 276 patients with normal D-dimer levels, 177 patients with low clinical likelihood of DVT were followed without treatment for three months. Only one of these patients developed a VTE. Another patient, with a normal IPG and D-dimer result but a high clinical likelihood of thrombosis developed a DVT during followup. Therefore, the total VTE complication rate for this strategy was low. Again, ascertainment bias was possible because not all patients had clinical followup.

The systematic review by Becker et al., included 29 studies evaluating the test characteristics of D-dimer measurements (12 for diagnosis of DVT, 13 for diagnosis of PE, and four for either).[142] Thirteen of these studies were identified by the review's authors as being of high

quality. These studies employed a reference test, described the patient selection process, and studied test subjects representative of patents with suspected VTE. Marked heterogeneity was present among the studies and, appropriately, the results were not pooled. The authors plotted the studies' true positive and false positive rates on a summary ROC curve, a useful way to summarize this information. The authors identified, on the plot, the cutoffs used to define an abnormal test for each study. They identified at least 10 different cutoffs in these 29 studies.

As expected, the plots showed clearly that the ELISA studies that used very high D-dimer cutoffs (1000 ng/mL or 2000 ng/mL) had low sensitivity (five percent to 90 percent) and higher specificity (50 percent to 99 percent) for identifying patients with VTE. Studies using very low cutoffs (100 ng/mL or 200 ng/ml) had much higher sensitivity (75 percent to 100 percent) and lower specificity (one percent to 70 percent). A similar pattern was seen with the latex agglutination studies, with the summary ROC curve having a similar shape to that generated from the ELISA quantitative studies.

The authors noted that the major determinants of the specificity of D-dimer tests were the type of assay, the cutoff value, and the spectrum of clinical characteristics of enrolled patients free of thromboembolic disease. Overall, specificities were higher for outpatients than for inpatients, and for patients without co-morbidities, for both ELISA and agglutination assays. The authors concluded that D-dimer assays could not yet be used as a diagnostic test for VTE and recommended that further research be done with attention to the clinical spectrum of the patients, the duration of symptoms, the clinical setting, the age, and the comorbidities of the patients.

Summary of Studies

The systematic reviews reported widely varying estimates for sensitivity and specificity for D-dimer in the diagnosis of DVT. The specificities were generally higher than the sensitivities, particularly for outpatients and patients without comorbid diseases. This being so, D-dimer may eventually prove to have a role in risk stratification of patients, particularly when used with clinical prediction rules. However the evidence to date was not strong enough to allow us to draw definitive conclusions (Evidence Grade: C).

Figure 2: Plot of the representative sensitivity of helical computerized tomography for the diagnosis of pulmonary embolism versus one hundred minus the representative specificity reported in the eight studies in the primary literature review.
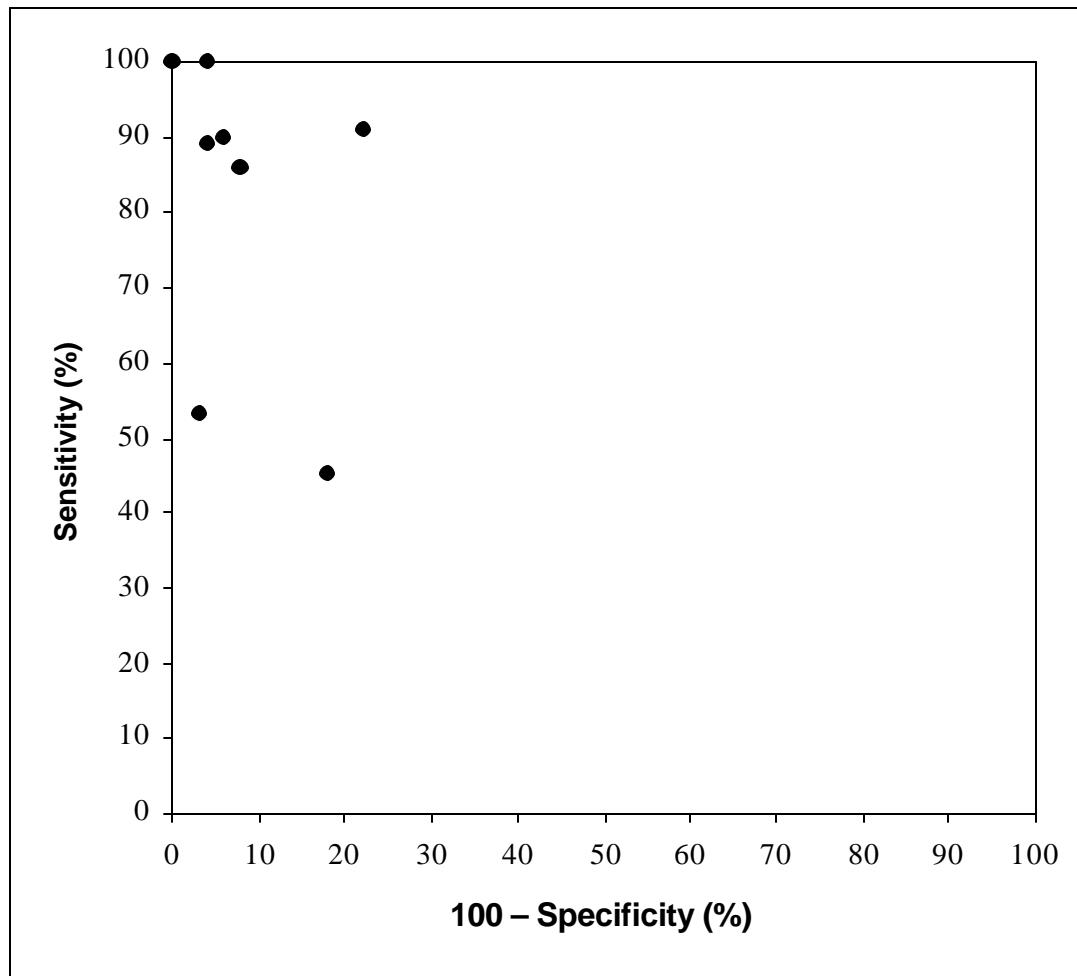
Figure 3: Plot of the

representative sensitivity and specificity of helical computerized tomography for the diagnosis of pulmonary embolism versus the prevalence of pulmonary embolism in the eight studies in the primary literature review.
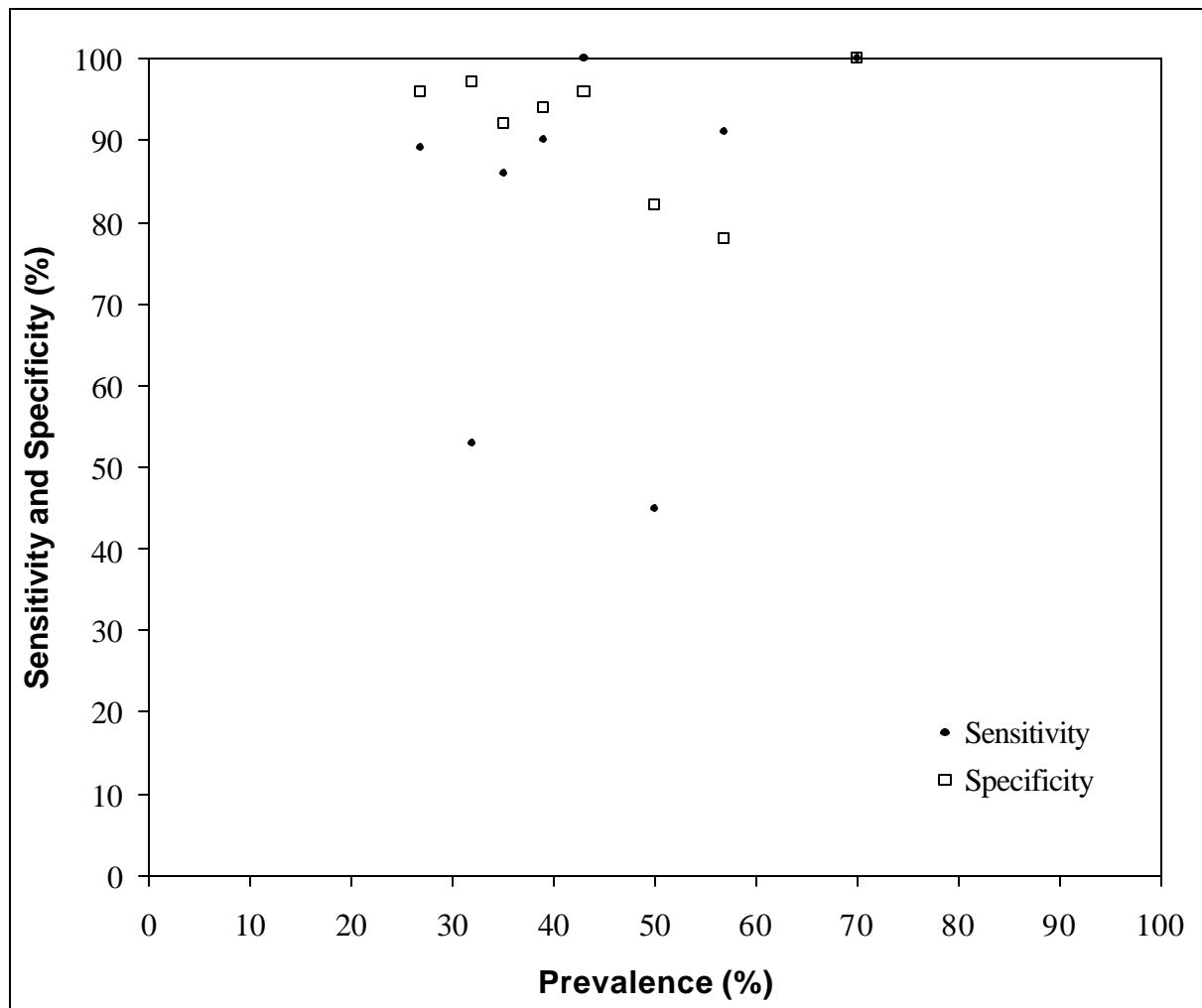
Table 1: Clinical model for predicting pretest probability for deep-vein thrombosis

Checklist
Major Points
Active cancer (treatment ongoing or within previous 6 months or palliative)
Paralysis, paresis, or recent plaster immobilization of the lower extremities
Recently bedridden >3 days and/or major surgery within 4 weeks
Localized tenderness along the distribution of the deep venous system
Thigh and calf swollen (should be measured)
Calf swelling 3 cm >symptomless side (measured 10 cm below tibial tuberosity)
Strong family history of DVT ($\geq$ 2 first degree relatives with history of DVT)
Minor Points

History of recent trauma (≥60 days) to the symptomatic leg
Pitting oedema; symptomatic leg only
Dilated superficial veins (non-varicose) in symptomatic leg only
Hospitalization within previous 6 months
Erythema
Clinical Probability
<u>High</u>
≥3 major points and no alternative diagnosis
≥2 major points and ≥2 minor points + no alternative diagnosis
<u>Low</u>
1 major point + ≥2 minor points + has an alternate diagnosis

1 major point + ≥1 minor point + no alternative diagnosis	
0 major points + ≥3 minor points + has an alternative diagnosis	
0 major points + ≥2 minor points + no alternative diagnosis	
<u>Moderate</u>	
All other combinations	
Active cancer did not include non-melanomatous skin cancer; deep-vein tenderness had to be elicited either in the calf or thigh in the anatomical distribution of the deep venous system.	

Table 2: Comparison of imaging modalities used in the diagnosis of PE

Characteristic	V/Q Scintigraphy	Pulmonary Arteriography	Helical CT	MRI
Noninvasive?	Yes	No	Yes	Yes
Does not require iodinated contrast?	Yes	No	No	Yes
Available in many emergency departments?	No	No	Yes	No

Quick examination (<15 minutes)?	No	No	Yes	No
Minimal patient discomfort?	Yes	No	Yes	No
Relatively inexpensive (<500 USD)?	Yes	No	Yes	No

Chapter 4: Conclusions

Key Findings

Q1. What are the efficacy and safety of LMWH compared with UFH for the treatment of DVT?
Q2. What are the efficacy and safety of LMWH compared to UFH for treatment of PE?

! Fourteen systematic reviews of this topic have been published.
! The quality of these reviews was high enough to allow conclusions to be drawn for patients with DVT (with or without concomitant PE). Evidence from systematic reviews about the use of LMWH for patients with PE (with or without concomitant DVT) was more limited.
! The evidence suggested that for treatment of DVT, LMWH is more efficacious than UFH for reducing the rate of VTE recurrence, thrombus extension, and death, and LMWH causes less major bleeding than UFH (Evidence Grade: A).
! The evidence suggested that for treatment of PE, LMWH was likely to be as effective and safe as UFH (Evidence Grade: B).

Q3a. What are the efficacy and safety of outpatient versus inpatient treatment of DVT with LMWH or UFH?
Q3b. What is the cost-effectiveness of outpatient versus inpatient treatment of DVT with LMWH or UFH?

! The studies that evaluated LMWH as an outpatient treatment, or as treatment for patients with early hospital discharge, did not demonstrate a difference in adverse outcomes compared to UFH, and showed a major reduction in duration of hospitalization and associated costs.
! The studies comparing LMWH treatment in the hospital to LMWH treatment at home revealed no difference in outcomes, but a major savings in hospitalization costs.
! These studies primarily enrolled patients who were selected as being appropriate for outpatient therapy, and the results may not be applicable to all patients presenting with VTE.
! Thus, the evidence indicated that outpatient treatment of DVT with LMWH is likely to be efficacious and safe (Evidence Grade: B).
! The cost-effectiveness studies were consistent in suggesting that LMWH is either cost-saving or cost-effective compared with UFH, regardless of whether this drug is administered in the hospital or at home (Evidence Grade: B). The cost savings would be greater if hospitalization can be avoided.

Q4. What is the optimal duration of treatment for DVT and PE in patients without known thrombophilic disorders and in patients with thrombophilic disorders?

! For a first episode of idiopathic DVT, outcomes were best if warfarin was given for three to six months.

! For symptomatic calf vein thrombosis, outcomes were best if warfarin was given for six weeks.

! No randomized studies focused exclusively on duration of treatment for patients with PE.

! For patients with any first VTE, which included some patients with PE, six months of therapy was superior to six weeks.

! For patients with VTE and transient risk factors, three months of therapy may be sufficient.

! Indefinite treatment was most efficacious for patients with a second episode of VTE or patients with a thrombophilic condition, although the evidence was sparse.

! Thus, the evidence regarding duration of therapy for patients with idiopathic DVT or DVT with only temporary risks was relatively consistent (Evidence grade: B); for patients with VTE and a thrombophilic condition or a second DVT, the evidence was sparse (Evidence Grade: I). Little evidence was found on treatment duration for patients with PE (Evidence grade: I).

Q5. How accurate are clinical prediction rules used for the diagnosis of DVT or PE?

! Nineteen studies addressed this topic

! The most frequently tested clinical prediction rule for diagnosing DVT was the one developed by Wells et al. in 1995.

! Studies were relatively consistent in showing that the Wells model is useful for identifying patients that have no more than a ten percent chance of having a DVT, and is useful for identifying patients with a high enough risk of DVT to warrant additional testing (Evidence Grade: B).

! The model was not sufficiently specific to rule in the diagnosis of DVT without further radiological testing.

! The model performed better if the DVT was in a proximal vein rather than in a distal vein.

! Addition of the D-dimer assay to the model improved the diagnostic performance.

! The clinical prediction rules for detecting PE were tested less thoroughly and were less accurate than those used for detecting DVT (Evidence Grade: C).

Q6a. What are the test characteristics of ultrasonography for diagnosis of DVT?
Q6b. Are calf vein thromboses adequately identified with ultrasound?

! The evidence was consistent in showing that ultrasonography has relatively high sensitivity and specificity for diagnosis of proximal lower extremity DVT in symptomatic patients (Evidence Grade: A).
! For diagnosis of VTE in asymptomatic patients, ultrasonography retains its high specificity but its sensitivity was markedly reduced.
! Ultrasound had low sensitivity and specificity for diagnosing upper extremity DVT, although recent studies suggested that its efficacy may be higher than previously thought (Evidence Grade: C).
! Ultrasound had poor sensitivity for the diagnosis of calf vein thrombosis (Evidence Grade: B).

Q7a. What are the test characteristics of helical CT for diagnosis of PE relative to V/Q scanning and/or standard angiography?
Q7b. What are the test characteristics of MRI and MRA for diagnosis of PE relative to V/Q scanning and/or standard angiography?

! Examination of systematic reviews and primary studies revealed moderate variation in the reported sensitivity of helical CT for the diagnosis of PE, ranging from 45 to 100 percent, while the reported specificity ranged from 78 to 100 percent (Evidence Grade: B).
! The source of the variability in sensitivity was unclear and was not completely explained by differences in study design or smallest arterial level interpreted.
! The evidence from a few small studies suggested that MRA is sensitive and specific in detecting acute PE of the lobar and segmental branches of pulmonary arteries in patients whose clinical presentation suggests PE (Evidence Grade: B).
! The accuracy of detecting smaller emboli with MRI was reduced substantially for emboli distal to the lobar segment of the arteries.

Q8. What are the test characteristics of D-dimer for diagnosis of VTE?

! The evidence on the use of D-dimer assays gave a relatively wide range of estimates on the sensitivity and specificity of this test (Evidence Grade: C).
! D-dimer tests generally had greater specificity than sensitivity for diagnosing VTE.

Limitations

Q1. What are the efficacy and safety of LMWH compared with UFH for the treatment of DVT?
Q2. What are the efficacy and safety of LMWH compared to UFH for treatment of PE?

! Published systematic reviews on this topic differed markedly in trial inclusion criteria, but the consistency of the estimates suggested generalizability of the results for the treatment of DVT.

! Only three clinical trials (two of them pilot studies) evaluated the efficacy and safety of LMWH for patients with PE (with or without concomitant DVT). Inferences from systematic reviews for the treatment of PE therefore are limited.

Q3a. What are the efficacy and safety of outpatient versus inpatient treatment of DVT with LMWH or UFH?
Q3b. What is the cost-effectiveness of outpatient versus inpatient treatment of DVT with LMWH or UFH?

! Most of these studies were small with infrequent adverse events and thus were underpowered to look at the designated outcomes.

! The cost studies often did not include all relevant costs (e.g., time lost from work, cost of outpatient visits).

! The trials had stringent criteria for patients to be considered for outpatient therapy; consequently, results may not apply to all patients seen in usual clinical practice.

! The cost-effectiveness studies used different methods and measures, thus making it difficult to compare one with another.

! These studies varied in several aspects of study quality.

Q4. What is the optimal duration of treatment for DVT and PE in patients without known thrombophilic disorders and in patients with thrombophilic disorders?

! Randomized studies excluded important subpopulations of patients with VTE such as patients with malignancies and thrombophilic disorders.

! The literature provided little evidence on the efficacy and safety of treatments for children with VTE.

! Randomized studies focusing exclusively on the duration of treatment for patients with PE were lacking.

Q5. How accurate are clinical prediction rules used for the diagnosis of DVT or PE?

! Referral bias was a possibility in all of these studies because most of the studied patients were referred for a diagnostic evaluation and therefore had a high pretest probability of VTE.

! The results of this evidence cannot be extrapolated to patients with suspected DVT in whom there is a known malignancy, family history of DVT, a previous episode of VTE, or

concomitant PE.

! Most of the clinical prediction rules were not estimated by two independent blinded observers, thus allowing the possibility of misclassification.

! The Wells clinical prediction rule has not been validated in a large sample in the United States, although there is little reason to think that it would perform differently in the United States than in Canada.

Q6a. What are the test characteristics of ultrasonography for diagnosis of DVT?
Q6b. Are calf vein thromboses adequately identified with ultrasound?

! Not all of the published systematic reviews required that trials specify whether consecutive patients were approached for enrollment. The absence of this information made it difficult to estimate the possibility of referral bias.

! The systematic reviews provided little data about the participants in the included trials so the results are difficult to generalize.

! There is no uniformly accepted way to combine results from diagnostic studies, and so the aggregate sensitivities and specificities should be interpreted with caution.

! Ultrasonography is highly operator-dependent and results may not be generalizable to all clinical settings.

Q7. What are the test characteristics of helical CT, MRI and MRA for diagnosis of PE relative to V/Q scanning or standard angiography?

! Nearly all of the evidence concerning helical CT diagnosis of PE was based on individuals who had been referred for imaging; it excluded individuals in whom PE was suspected but who were not referred for imaging. Therefore, potential selection bias existed in nearly all studies.

! The techniques of MRI/MRA of the chest have not been standardized (e.g., MRA studies used greatly varying amounts of contrast).

! Most of the studies had few patients.

! The practical issues of MRI/MRA use may make it less useful than anticipated (e.g., patients on ventilators cannot use MRI/MRA without specialized equipment; access to patients is more hindered by magnetic resonance machines than CT machines; magnetic resonance images also take longer than CT, and possibly even conventional angiography, to acquire and synthesize; and the necessity of breath holding and non-fast heart rates may make MRI/MRA impractical in ill patients).

Q8. What are the test characteristics of D-dimer for diagnosis of VTE?

! The lack of standardization of the D-dimer assays, variable cut-off levels, and

specimen-type variation (whole blood or plasma) contributed to the difficulty in summarizing this literature.

! Previous systematic reviews on this topic had more limitations than we expected.

! Another group of investigators has finished an updated systematic review of the use of D-dimer for diagnosis of VTE, but at the time of this writing, their complete results were not available for our review.[144,145]

Overall Limitations

! We included only English language literature; it is unclear whether this may have biased our results.

! Our literature search strategy relied heavily on specific electronic databases and may have missed a small amount of published literature. However, we found very few additional articles when we searched the references in key articles, scanned the table of contents of key journals, and queried our core experts.

Implications

Q1. What are the efficacy and safety of LMWH compared to UFH for the treatment of DVT?
Q2. What are the efficacy and safety of LMWH compared with UFH for treatment of PE?

! Clinicians may consider the strong evidence on the efficacy and safety of LMWH compared with UFH when making decisions about treatment of DVT or PE.

Q3a. What are the efficacy and safety of outpatient versus inpatient treatment of DVT with LMWH or UFH?
Q3b. What is the cost-effectiveness of outpatient versus inpatient treatment of DVT with LMWH or UFH?

! Clinicians may consider the evidence presented here when making decisions about inpatient versus outpatient treatment of DVT for selected patients. Protocols may be needed to guide clinicians in selecting patients appropriate for outpatient management.

Q4. What is the optimal duration of treatment for DVT and PE?

! A reasonable, but not definitive body of evidence exists to guide clinicians when making decisions about the duration of treatment for DVT.

! Very little evidence exists to guide such decisions about the duration of treatment for PE and for recurrent VTE.

Q5. How accurate are clinical prediction rules used for the diagnosis of DVT or PE?

! The most tested clinical prediction rule, the Wells model, has utility in diagnosis of DVT and its incorporation into guidelines may be appropriate for guiding the ordering of radiological tests.

6a. What are the test characteristics of ultrasonography for diagnosis of DVT?
6b. Are calf vein thromboses adequately identified with ultrasound?

! A strong body of evidence exists to guide clinicians when making decisions about use of ultrasonography for diagnosis of proximal DVT in symptomatic patients.

Q7. What are the test characteristics of helical CT, MRI, and MRA for diagnosis of PE relative to V/Q scanning and/or standard angiography?

! The evidence on the accuracy of helical CT for diagnosing PE has limitations that clinicians should be aware of when deciding on the tests needed to definitively rule out a PE.

! MRA has great potential for clinical use as the evidence suggests that it is almost equivalent to conventional angiography for detecting large central segmental emboli, although practical issues need to be solved.

Q8. What are the test characteristics of D-dimer for diagnosis of VTE?

! The widely varying estimates of the sensitivity and specificity of the D-dimer test make it difficult to define the optimal role of this test in the evaluation of patients suspected of having VTE.

Chapter 5. Future Research

Q1. What are the efficacy and safety of LMWH compared with UFH for the treatment of DVT?
Q2. What are the efficacy and safety of LMWH compared with UFH for treatment of PE?

! Studies need to address the relative risks and benefits of the different LMWH preparations that are available to determine whether they are interchangeable.
! Studies need to determine the optimal dosing regimens for LMWH (e.g., once/day vs. twice/day).
! Studies need to include evaluation of LMWH in subpopulations of patients with VTE (e.g., PE with or without concomitant DVT, patients with massive PE after initial stabilization, patients with thrombophilic conditions).

Q3a. What are the efficacy and safety of outpatient versus inpatient treatment of DVT with LMWH or UFH?
Q3b. What is the cost-effectiveness of outpatient versus inpatient treatment of DVT with LMWH or UFH?

! High quality trials are needed that are designed as equivalency studies to confirm that LMWH as an outpatient is as efficacious and safe as UFH in the hospital.
! Additional studies need to evaluate the use of outpatient treatment among a less restricted group of patients, or specifically in subgroups such as patients with malignancies or hereditary thrombophilias.
! Studies should examine the efficacy and safety of LMWH as an outpatient for stable patients with PE.
! Studies should evaluate the efficacy and safety of LMWH as an outpatient for treatment of symptomatic calf vein thrombosis.

Q4. What is the optimal duration of treatment for DVT and PE?

! Randomized studies are needed to determine the optimal duration of therapy for PE.
! Randomized studies of VTE treatment duration are needed in patients with malignancies, in patients with thrombophilia, and in children.
! Studies should evaluate the use of low-dose warfarin for long duration prophylaxis, to see if safety may be improved without sacrificing efficacy.

Q5. How accurate are clinical prediction rules used for the diagnosis of DVT or PE?

> ❗ Studies need to further refine the clinical prediction rules to optimize their performance characteristics.

❗ Studies should test the addition of laboratory testing to clinical prediction rules. This addition should also be evaluated with cost-effectiveness analyses.

❗ Further research is needed to identify the optimal role for clinical prediction rules. Are they to be used to aid in interpretation of radiological tests or can they supplant further testing?

❗ Further research needs to look at the most effective way to apply these prediction rules in general practice.

Q6a. What are the test characteristics of ultrasonography for diagnosis of DVT?
Q6b. Are calf vein thromboses adequately identified with ultrasound?

> ❗ Studies are needed to clarify the role of ultrasonography for diagnosis of upper extremity DVT; identification of one successful high quality study suggests that this topic needs further study.
> ❗ Studies need to incorporate discussion whether calf vein thromboses even need to be identified, when evaluating the sensitivity and specificity of testing modalities.

Q7. What are the test characteristics of helical CT, MRI, and MRA for diagnosis of PE relative to V/Q scanning and/or standard angiography?

> ❗ This question would benefit from more prospective studies of high quality in which helical CT is directly compared with pulmonary arteriography for detecting PE.
> ❗ Future studies of MRI/MRA need to be standardized in terms of speed, image acquisition (number and time), number of breath holds, presence or absence of cardiac gating and dose of contrast to yield more precise estimates of test characteristics.
> ❗ The feasibility of MRI/MRA in patients with symptomatic PE (with tachypnea and tachycardia) needs to be studied.
> ❗ Results of studies of these testing modalities should be reported with positive and negative predictive values stratified by location of the thrombus (lobar, segmental, subsegmental).

❗ Beyond determination of sensitivity and specificity, further studies are needed that examine the role of CT and MRI/MRA within existing clinical diagnostic strategies.

Q8. What are the test characteristics of D-dimer for diagnosis of VTE?

! Because many of the available D-dimer assays yield continuous rather than dichotomous results, studies of this test need to report the results with ROC curves. This will allow clinicians to appreciate how the choice of an optimal cutoff depends on how the test is to be employed, and will more easily allow comparisons of different assays and comparisons across populations of patients.

! Research is needed to address the issue that D-dimer levels may be abnormal in patients with calf vein thrombosis for whom the clinical significance is uncertain.

! The role of D-dimer measurement as a screening tool in asymptomatic post-operative patients is unknown.

! Studies are needed to determine the usefulness of D-dimer measurement in patients with comorbid illnesses.

! A systematic review is currently being completed by a group of investigators at the University of Virginia School of Medicine. At the time of this writing, complete results were not available for our review.

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Evidence Table 1: Description of systematic reviews of low molecular weight heparin compared to unfractionated heparin for treatment of venous thromboembolism

Author, Year	Study aim	# trials	Most recent study	# pts	LMWH used in trials [a]	Systematic review quality scores					
						Overall [b]	Search [c]	Eligibility [d]	Study Quality [e]	Combining Results [f]	Aims & Conclusions [g]
Green, 1994	To compare IV or SQ LMWH to IV or SQ UFH for tx of DVT	9	1993	1308	1, 2, 3, 4, 5	22	0	33	0	0	75
Hirsh, 1995	To compare IV or SQ LMWH to IV or SQ UFH for first episode of VTE	13	1993	1723	1, 2, 3, 4, 5	77	50	83	75	75	100
Lensing, 1995	To compare IV or SQ LMWH to IV or SQ UFH for tx of DVT	10	1994	1512	1, 2, 3, 4, 6	67	67	67	0	100	100
Leizorovicz, 1996	To compare IV or SQ LMWH to IV or SQ UFH for tx of DVT	20	1996	3333	2, 5, 7, 8, 9, 10, 11	37	17	17	0	75	75
Howard, 1997	To compare IV or SQ dalteparin to IV or SQ UFH for tx of VTE	8	1995	863	7	42	50	33	0	25	100
Brewer, 1998 [h]	To compare LMWH to UFH for tx of adults with DVT	6	1997	2986	5, 7, 10, 11, 12	53	50	67	0	50	100
Hettiarachchi, 1998	To compare SQ LMWH to UFH for tx of VTE	13	1998	4509 [i]	2, 5, 7, 10, 11, 12	65	67	83	0	75	100
Hunt, 1998	To compare LMWH to UFH for tx of VTE	10	1997		5, 7, 10, 11, 12	22	33	0	0	0	75
Martineau, 1998	To compare IV or SQ LMWH to IV or SQ UFH for tx of DVT	13	1996	2825	5, 7, 10, 11	43	33	83	0	0	100
Gould, 1999	To compare SQ fixed-dose LMWH to adjusted dose UFH for tx of acute DVT	11	1997	3674	5, 7, 10, 11, 12	92	83	100	75	100	100
Dolovich, 2000	To compare SQ LMWH to IV UFH for initial tx of VTE	13	1997	4447	5, 7, 10, 11, 12	77	67	67	50	100	100
Rocha, 2000	To compare IV or different dosages of SQ LMWH to IV or SQ UFH for tx of VTE	21	1997	4472	2, 4, 5, 7, 9, 10, 12, 13	62	50	83	0	100	75

Evidence Table 1: Description of systematic reviews of low molecular weight heparin compared to unfractionated heparin for treatment of venous thromboembolism (continued)

Author, Year	Study aim	# trials	Most recent study	# pts	LMWH used in trials [a]	Systematic review quality scores					
						Overall [b]	Search [c]	Eligibility [d]	Study Quality [e]	Combining Results [f]	Aims & Conclusions [g]
van den Belt, 2000	To compare SQ LMWH to SQ or IV UFH for tx of VTE	14	1997	4754	2, 5, 7, 10, 11, 12	92	83	100	75	100	100
van der Heijden, 2000	To compare SQ LMWH to IV or SQ UFH for VTE	16	2000	6055	2, 5, 7, 9, 10, 11, 12	60	33	67	0	100	100

[a]   LMWH: 1=fragmin, 2=CY222, 3=fraxiparin, 4=logiparin, 5=enoxaparin, 6=clexane, 7=dalteparin, 8=parnaparin, 9=certoparin, 10=nadroparin, 11=tinzaparin, 12=reviparin, 13=OP2123

[b]   **Overall Quality Score:** The mean of the percentage scores from the categories: Search Methods, Inclusion & Description, Quality Assessment, Methods of Combination, and Aims/Conclusions (see below).

[c]   **Search Methods:** Percentage score based on a total maximum score of 6 points. This included description of search methods (2 points), comprehensiveness of search methods (2 points), and reproducibility of review methods (2 points).

[d]   **Eligibility and Description:** Percentage score based on a total maximum score of 6 points. This included description of study inclusion criteria (2 points), appropriateness of study inclusion criteria (2 points), and discussion of variation in the original literature based on differences in study design (2 points).

[e]   **Study Quality Assessment:** Percentage score based on a total maximum score of 4 points. This included description of quality assessment (2 points), and appropriateness of quality assessment (2 points).

[f]   **Combining Results:** Percentage score based on a total maximum score of 4 points. This included description of methods used to combine study results (2 points), and appropriateness of methods used to combine study results (2 points).

[g]   **Aims & Conclusions:** Percentage score based on a total maximum score of 4 points. This included whether the question to be addressed by the review was clearly stated (2 points), and whether the conclusions reached by the review were supported by data and/or analyses (2 points).

[h]   Review examined 3 meta-analyses and 6 RCTs. Only the data from RCTs is presented here.

[i]   Not reported. Review also included 1 study (Simmoneau, 1997) that examined LMWH vs. UFH for PE.

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Evidence Table 2: Results of systematic reviews of low molecular weight heparin compared to unfractionated heparin for treatment of venous thromboembolism

Author, Year	Pt populations in RCTs	Recurrence of symptomatic VTE (LMWH vs UFH)	Thrombus extension (LMWH vs UFH)	Major bleeding during tx (LMWH vs UFH)	All deaths (LMWH vs UFH)	Other outcomes/comments (LMWH vs UFH)
Green, 1994	Pts w/DVT	During mos 3 to 6: incidence 2.7 vs 7.4%; RRR 63% [CI 30-80%], 8 trials	64 vs 50% had thrombus size reduction, 6 vs 12% had increase in size, p<0.001; 8 trials	0.9 vs 3.2%; RRR 71% [CI 33-88%]; 8 trials		
Hirsh, 1995	Pts w/first episode of VTE	Day 1-15: incidence 0.8 vs 2.4%; RRR 68%; p=0.02; 6 trials		2.2 vs 4.7%; RRR 66%, p=0.04; 10 trials	0.6 vs 1%; days 1-15: RRR 39%, p=0.3; 12 trials.	No difference in minor bleeding; 10 trials. Fatal PE, 0.4 vs 0.7%, p=0.4.
		Day 16-90: incidence 1.6 vs 2% RRR 26%; p=0.8; 6 trials			2.5 vs 4.5%; days 16-90: RRR 52%, p=0.03; 12 trials.	Pts w/ca: mortality 13.5 vs. 28.4%; RRR 67%, p=0.01; pts w/o ca: 1.9 vs 2.6%, p=0.40; 4 trials.
		Day 1-90: incidence 2.4 vs 4.5%; RRR 50%, p=0.02; 6 trials			3.3 vs 5.9%; days 1-90: RRR 49%, p=0.01; 12 trials.	Level 1 studies[a] (3 trials): VTE recurrence, Day 1-15: RR 0.24 [CI 0.06-0.8]; Day 16-90: RR 0.60 [CI 0.2-1.5]; RR 0.39 [CI 0.3-0.8]; Major bleeding: RR 0.42 [CI 0.2-0.9].
Lensing, 1995	Pts w/DVT	Incidence 3.1 vs 6.6%; RRR 53% [CI 18-73%]; 5 trials	63 vs 52% had reduction in thrombus size; 6 vs 12% had increase in thrombus size; p<0.001; 9 trials.	0.9 vs 3.2%; RRR 68% [CI 31-85%]; 10 trials.	3.9 vs 7.1%; RRR 47% [CI 10-69%]; 5 trials.	Subgroup of pts w/ca: all deaths 12 vs 28%; RRR 56% [CI 17-77%].

Evidence Table 2: Results of systematic reviews of low molecular weight heparin compared to unfractionated heparin for treatment of venous thromboembolism (continued)

Author, Year	Pt populations in RCTs	Recurrence of symptomatic VTE (LMWH vs UFH)	Thrombus extension (LMWH vs UFH)	Major bleeding during tx (LMWH vs UFH)	All deaths (LMWH vs UFH)	Other outcomes/comments (LMWH vs UFH)
Leizorovicz, 1996	Pts w/DVT	Incidence 3.8 vs 5.2%; OR 0.77 [CI 0.55-1.08]; 20 trials	6.0 vs 9.5%; OR 0.65 [CI 0.44-0.96]; 12 trials	1.5 vs 3.1%; OR 0.59 [CI 0.35-0.98]; 20 trials	3.7 vs 5.4%; OR 0.70 [CI 0.50-0.98]; 20 trials.	Results similar for safety and efficacy for LMWH daily or bid.

LMWH reduced VTE recurrence and mortality when provided at home (UFH in-hospital; 2 trials) or in-hospital (UFH in-hospital, 18 trials). |
| Howard, 1997 | Pts w/VTE | | | | | Descriptive study.[b] Authors concluded that dalteparin may be as effective as UFH in tx for DVT and PE; more data needed. |
| Brewer, 1998 | Adults w/VTE | | | | | Descriptive study.[b] Authors concluded that LMWH as effective and safe as UFH. Thrombocytopenia less frequent w/ LMWH. Osteoporosis may be less common w/LMWH. |
| Hettiarachchi, 1998 | Pts w/VTE | Incidence 3.8 vs 4.8%; OR 0.77[CI 0.56-1.04]; 10 trials | | 1.3 vs 2.2%; OR 0.60 [CI 0.38-0.95]; 13 trials. | 4.8 vs 6.5%; OR 0.72 [CI 0.55-0.96]; 9 trials. | Results similar w/ or w/o ca.

Pts w/PE: VTE recurrence OR 0.91 [CI 0.42-1.97]; 2 trials. |
| Hunt, 1998 | Pts w/VTE | | | | | Descriptive study.[b] Authors concluded that LMWH cheaper, better tolerated, potentially more effective than UFH for DVT. Insufficient data regarding PE. |
| Martineau, 1998 | Pts w/first episode of DVT | | | | | Descriptive study.[b] Authors concluded LMWH as safe and effective as UFH. |

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Evidence Table 2: Results of systematic reviews of low molecular weight heparin compared to unfractionated heparin for treatment of venous thromboembolism (continued)

Author, Year	Pt populations in RCTs	Recurrence of symptomatic VTE (LMWH vs UFH)	Thrombus extension (LMWH vs UFH)	Major bleeding during tx (LMWH vs UFH)	All deaths (LMWH vs UFH)	Other outcomes/comments (LMWH vs UFH)
Gould, 1999	Pts w/acute DVT	Incidence 4.6 vs 5.4%; OR 0.85 [CI 0.63 to 1.14]; ARR 0.88% [CI -0.48-2.24%], NNT 114; 11 trials		Random-effects model: OR 0.71 [CI 0.40 to 1.27]; 11 trials 1.1 vs 1.9%; fixed-effects model OR 0.57 [CI 0.33 to 0.99]; ARR 0.61% [CI -0.04% to 1.26%], NNT 164; 11 trials	5.0 vs 6.8%; OR 0.71 [CI 0.53-0.94]; ARR 1.65% [CI 0.36-2.94], NNT 61; 11 trials	Minor bleeding: OR 0.98 [CI 0.63 to 1.51]. Thrombocytopenia: OR 0.74 [CI 0.37-1.48]. PE during tx: OR 0.84 [CI 0.51-0.36]. DVT during tx: OR 0.85 [CI 0.59-1.23]. Pts w/ca: Mortality 16.7 vs 25.9%; OR 0.57 [CI 0.31 to 1.03]; ARR 9.75% [CI 0.34% to 19.2%], NNT 10. Reduced mortality benefit in more recent studies. Dalteparin, tizaparin, and nadroparin favored LMWH whereas studies using enoxaparin or reviparin favored UFH. Benefit of LMWH noted if all pts received inpt LMWH, but not if LMWH was permitted as outpt.
Dolovich, 2000	Pts w/VTE	Incidence 4.3 vs 5.1%; RR 0.85 [CI 0.65-1.12]; 13 trials		1.5 vs 2.6%; RR 0.63 [CI 0.37-1.05]; 13 trials	4.9 vs 6.5%; RR 0.76 [CI 0.59-0.98]; 10 trials.	PE: 1.9 vs 1.8%; RR 1.02 [CI 0.64-1.62]; 12 trials. Minor bleeding: 5.6 vs 4.7%; RR 1.18 [CI 0.87-1.61]; 12 trials. Thrombocytopenia: 1.0 vs 1.3%; RR 0.85 [CI 0.45-1.62]; 11 trials. Results similar whether LMWH daily or bid.

Evidence Table 2: Results of systematic reviews of low molecular weight heparin compared to unfractionated heparin for treatment of venous thromboembolism (continued)

Author, Year	Pt populations in RCTs	Recurrence of symptomatic VTE (LMWH vs UFH)	Thrombus extension (LMWH vs UFH)	Major bleeding during tx (LMWH vs UFH)	All deaths (LMWH vs UFH)	Other outcomes/comments (LMWH vs UFH)
Rocha, 2000	Pts w/VTE	OR 0.78 [CI 0.59-1.04]; 13 trials	OR for extension 0.73 [CI 0.59-0.90]; 12 trials	OR 0.65 [CI 0.43-0.98]; 8 trials	OR 0.68 [CI 0.50-0.91]; 9 trials.	Bid LMWH formulations more effective than UFH to prevent thrombus extension (p=0.004). Daily less likely than UFH to cause major bleeding (p=0.025). NSD between once daily and bid for VTE recurrence or mortality.
van den Belt, 2000	Pts w/VTE	Initial tx: incidence 1.8 vs 2.6%; OR 0.70 [CI 0.46-1.06]; 11 trials. 3 months f/u: incidence 3.8 vs 5.1%; OR 0.75 [CI 0.46-1.01], 9 trials 6 months f/u: OR 0.76 [CI 0.44-1.30]; 3 trials End of f/u: incidence 4.3 vs 5.6%; OR 0.76 [CI 0.57-1.01]; 11 trials	60 vs 54% had reduction in thrombus size; OR 0.77 [CI 0.61-0.97] for better venographic outcome; 8 trials	1.3 vs 2.1%; OR 0.60 [CI 0.39 to 0.93]; 14 trials	6.4 vs 8.0%; OR 0.78 [CI 0.62-0.99]; 11 trials.	Pts w/PE: VTE recurrence OR 0.91 [CI 0.42-1.97]. Pts w/ca: Mortality OR 0.53 [CI 0.33-0.85]; pts w/o ca: OR 0.97 [CI 0.61-1.56]; 6 trials. Pts w/proximal DVT: VTE recurrence, major hemorrhage and mortality all significantly lower w/LMWH. Studies that reported concealed allocation (7 studies): similar results as all studies but ORs were not significant.
van der Heijden, 2000	Pts w/VTE	OR 0.66 [CI 0.51-0.86]; 13 trials		OR 0.56 [CI 0.38-0.83]; 16 trials	OR 0.68 [CI 0.53-0.88]; 12 trials.	Greater benefit from LMWH in studies w/ higher rates of VTE recurrence in UFH group. LMWH benefit unrelated to incidence of outcomes for major hemorrhage or mortality.

[a] Blind assessment
[b] No quantitative pooling of data.

Evidence Table 3: Description of studies comparing outpatient to inpatient treatment of venous thromboembolism

Author, Year	Location	Study aims	Design	Recruit dates	Mean f/u (mos)	Surveillance	VTE character	Exclusions	
								General criteria	Risk factors
LMWH at home compared to UFH in the hospital									
Koopman, 1996	Europe & Australia	To demonstrate equivalence in efficacy and safety and evaluate use of resources.	RCT		6	N	No PE	Preg/childbirth; unlikely to comply; LE < 6 mos; tx w/ heparin for 24 hrs; age < 18yrs	Previous VTE; known thrombophilia; known malignancy
Levine, 1996	Canada	To compare use of UFH in the hospital with LMWH at home for acute DVT tx.	RCT	1992-95	3	Y	No: calf vein only, PE	Unlikely to comply; hereditary bleeding; contraindication to AC	VTE in preceding 6 months
Belcaro, 1999	Europe	To compare IV heparin or SQ heparin w/LMWH either at home or in hospital, with oral anticoagulant for tx of proximal DVT.	RCT	1992-95	3	Y	No: PE, thrombcytopenia	Preg/childbirth; unlikely to comply; hereditary bleeding	
Pearson, 1999	United States	To present short-term outcomes of pts treated as outpt and to compare associated costs before and after implementation.	CohR	1996-97	0.5	N	No PE		
Grau, 2001	Europe	To compare incidence of recurrent VTE in UFH inpts and LMWH outpts.	CohR	1986-99		N	No PE	Inclusion: Preg/childbirth; OCPs/HRT; recent fracture/cast	Known thrombophilia
Vinson, 2001	United States	To evaluate effectiveness & safety of outpt care pathway for tx of DVT with LMWH.	CohP	1994-99	0.5	N	No: UE, calf vein only, PE, CVA, anemia	Preg/childbirth; allergy; unlikely to comply; hereditary bleeding; contraindication to AC, age <18	

Evidence Table 3: Description of studies of comparing outpatient to inpatient treatment of venous thromboembolism (continued)

Author, Year	Location	Study aims	Design	Recruit dates	Mean f/u (mos)	Surveillance	VTE character	Exclusions General criteria	Risk factors
Huse, 2002	United States	To quantify the economic benefits of early discharge of pts treated for DVT with LMWH using data from managed health care plans.	CohR			N		Unlikely to comply	Known thrombophilia; recent surgery; previous VTE; positive family history
Smith, 2002	Australia	To perform a cost minimization analysis in pts receiving LMWH managed w/o hospitalization. To evaluate costs and satisfaction with at-home tx of DVT using enoxaparin vs. inpt care w/UFH.		1999-99		N	No PE	Preg/childbirth; LE < 2 yrs; allergy; unlikely to comply; hereditary bleeding; contraindication to AC	Known thrombophilia; known malignancy; recent fracture/cast; previous VTE
LWMH at home compared to LMWH in the hospital									
Boccalon, 2000	Europe	To compare LMWH inpts versus outpts for efficacy and cost.	RCT	1993-97	6	Y	No: calf vein only, PE	Preg/childbirth; unlikely to comply; contraindication to AC, age <18 or age >85	Previous VTE
Kovacs, 2000	Canada	To evaluate the use of dalteparin in outpts w/PE.	CohP	1996-98	3	N	PE	Unlikely to comply, age <18	Unstable (O_2 requirements; hemodynamic instability; pain)

Evidence Table 4: Quality of studies comparing outpatient to inpatient treatment of venous thromboembolism

Author, Year	Overall [a]	Representativeness of study population [b]	Bias & confounding [c]	Description of treatment [d]	Outcomes & f/u [e]	Statistical quality & interpretation [f]
LMWH at home compared to UFH in the hospital						
Koopman, 1996	79	88	88	50	85	83
Levine, 1996	78	100	81	50	75	83
Belcaro, 1999	67	100	75	50	60	50
Pearson, 1999	38	88	31	25	10	38
Grau, 2001	47	88	31	25	30	63
Vinson, 2001	57	100	38	50	30	67
Huse, 2002	41	50	13	0	65	75
Smith, 2002	41	75	31	25	10	63
LMWH at home compared to LMWH in the hospital						
Boccalon, 2000	64	63	63	75	80	38
Kovacs, 2000	54	75	44	50	70	33

[a] **Overall:** The mean of the percentage scores from categories: Representativeness of Study Population, Bias and Confounding, Description of Treatment, Outcomes and Followup, and Statistical Quality and Interpretation (see below).

[b] **Representativeness of Study Population:** Percentage score based on a total maximum score of 8 points. This included description of study setting and population (2 points), description of inclusion/exclusion criteria (2 points), information on excluded or non-participating patients (2 points), and description of key patient characteristics (2 points).

[c] **Bias and Confounding:** Percentage score based on a total maximum score of 6 points. This included random assignment of patients to study groups (2 points), differences between study groups in key patient characteristics (2 points), and blinding of clinicians, patients, and outcome assessors (2 points).

[d] **Description of Treatment:** Percentage score based on a total maximum score of 4 points. This included description of the details of the treatment regimen (2 points), and description of other treatments given to each study group (2 points).

[e] **Outcomes and Followup:** Percentage score based on a total maximum score of 10 points. This included description of the criteria used for determining outcomes (2 points), description of adverse events experienced by patients (2 points), reporting on numbers and reasons for withdrawals or patients lost to followup (2 points), proportion of patients who withdrew or were lost to followup (2 points), and adequacy of the planned length of followup (2 points).

[f] **Statistical Quality and Interpretation:** Percentage score based on a total maximum score of 8 points. This included reporting on the magnitude of differences between groups with an index of variability (2 points), clear identification of all statistical analyses (2 points), use of multivariate or stratified analyses to adjust for potential confounders (2 points), and appropriate handling of withdrawals, crossovers, and loss to followup (2 points).

Evidence Table 5: Characteristics of patients in studies comparing outpatient to inpatient treatment of venous thromboembolism

Author, Year	Intervention	LMWH	Therapy duration (days)	Adjuvant therapy during f/u	Clinical characteristics(%)			
					Mean age (yrs)	Male (%)	Prior VTE (%) / Family hx (%) / Thrombophilia (%)	Recent surgery/ TRF (%)
LMWH at home compared to UFH in the hospital								
Koopman, 1996	LMWH in/outpt[a], 250 IU/kg bid	Nadroparin	6	Warfarin or other AC	59	53	20 / NR / NR	49 / 69
	UFH, 5000 u then 1250 u/hr		6	"	62	48	19 / NR / NR	52 / 68
Levine, 1996	LMWH in/outpt, 1 mg/kg bid	Enoxaparin	5	Warfarin	57	62	21 / NR / 0	29 / 100
	UFH, 5000 u then 1280 u/hr		5	"	59	58	14 / NR / 0	28 / 100
Belcaro, 1999	LMWH in/outpt, 100 IU/kg bid	Nadroparin	14	Warfarin	54	55	7 / NR / 0	20 / 100
	UFH, 5000 u then 1300 u/hr			"	53	59	7 / NR / 0	22 / 100
	UFH, 12500 IU bid		90	None	54	53	9 / NR / 0	22 / 100
Pearson, 1999	LMWH in/outpt, 1 mg/kg bid	Enoxaparin	5	Warfarin	57	42	NR / NR / NR	NR / NR
	UFH			"	56	43	NR / NR / NR	NR / NR
Grau, 2001	LMWH outpt, 175 u/kg bid	Nadroparin	5	Acencoumarol	68	58	2.3 / NR / NR	30 / 81
	UFH		5	"	59	58	3.4 / NR / NR	37 / 79
Vinson, 2001	LMWH outpt, 1 mg/kg bid	Enoxaparin	7	Warfarin, Comp stockings	63	56	14 / NR / 0	25 / 100
	UFH			Warfarin	63	46	20 / NR / 0	32 / 100
Huse, 2002	LMWH in/outpt	Enoxaparin		Warfarin	48	46	NR / NR / NR	NR / NR
	UFH			"	54	44	NR / NR / NR	NR / NR
Smith, 2002	LMWH outpt, 1 mg/kg bid	Enoxaparin	5	Warfarin	57	61	0 / NR / NR	NR / NR
	UFH		5	"	57	61	0 / NR / NR	NR / NR

Evidence Table 5: Characteristics of patients in studies comparing outpatient to inpatient treatment of venous thromboembolism (continued)

Author, Year	Intervention	LMWH	Therapy duration (days)	Adjuvant therapy during f/u	Clinical characteristics(%)			
					Mean age (yrs)	Male (%)	Prior VTE (%) / Family hx (%) / Thrombophilia (%)	Recent surgery/ TRF (%)
LMWH at home compared to LMWH in the hospital								
Boccalon, 2000	LMWH outpt	Dalateparin or enoxaparin or nadroparin		Comp stockings, vitamin K antagonist, or fluindione	65	54	NR / NR / NR	NR / NR
	LMWH inpt			"	63	59	NR / NR / NR	NR / NR
Kovacs, 2000	LMWH outpt, 200 u/kg qd	Dalteparin	5	Warfarin		56	NR / NR / 12	NR / NR
	LMWH in/outpt, 200 u/kg qd		5	"		59	NR / NR / 7	NR / NR

a   Outpatient treatment after a brief inpatient stay

Evidence Table 6: Results of studies comparing outpatient to inpatient treatment of venous thromboembolism

Author, Year	Group	# pts	F/u (mos)	Outcomes n (%) DVT	PE	Major bleeding	Minor bleeding	Deaths	Inpt days	Costs /pt	Costs included in tabulation
LMWH at home compared to UFH in the hospital											
Koopman, 1996	Outpt	202		10 (5)	4 (2)	1 (0.5)	27 (13)	14 (7)	2.7		
	Inpt	190		12 (6)	5 (3)	4 (2)	15 (8)	16 (8)	8.1		
Levine, 1996	Outpt	247	3	11 (4)	2 (1)	5 (2)	6 (2)	11 (4)	1.1		
	Inpt	253	3	15 (6)	2 (1)	3 (1)	6 (2)	17 (7)	6.5		
Belcaro, 1999	Outpt	98		6 (6)	0 (0)	0 (0)	3 (3)		5.1	773 USD	Hospital, tx and monitoring costs.
	Inpt	97		6 (6)	0 (0)	0 (0)	4 (4)		5.4	2,760 USD	
	Outpt	99		7 (7)	0 (0)	0 (0)	1 (1)		0	220 USD	
Pearson, 1999	Outpt	40	0.5	1 (2.5)	0 (0)	0 (0)		0 (0)		3,719 USD [a]	Hospital, drug, home care, and outpt visit costs.
	Inpt	67								5,465 USD [a]	
Grau, 2001	Outpt	130	21.6	5 (4)	1 (1)	3 (2)	1 (1)	11 (8)			
	Inpt	149	35	13 (9)	9 (6)	1 (1)	4 (3)	17 (11)			
Vinson, 2001	Outpt	178	0.5	0 (0)	1 (1)	0 (0)	2 (1)	0 (0)	0.03		
	Inpt	96	0.5	0 (0)	1 (1)	1 (1)	1 (1)	0 (0)	4		
Huse, 2002	Outpt	164	12	11 (7) [a]		1 (1)			4.2	1,886 USD	Outpt costs only.
	Inpt	1696	12	153 (9)[a]		14 (1)			6.8	986 USD	
Smith, 2002	Outpt	28								756 USD	U/S, doctors, nurse visits, drug, monitoring, office staff, discharge planning costs.
	Inpt	28								2,208 USD	

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Evidence Table 6: Results of studies comparing outpatient to inpatient treatment of venous thromboembolism (continued)

| Author, Year | Group | # pts | F/u (mos) | Outcomes n (%) | | | | | Inpt days | Costs /pt | Costs included in tabulation |
				DVT	PE	Major bleeding	Minor bleeding	Deaths			
LMWH at home compared to LMWH in the hospital											
Boccalon, 2000	Outpt	99		1 (1)		2 (2)	17 (17)	0 (0)	1	9,230 FRF [a]	U/S, doctors, nurse visits, monitoring, hospital costs, drug costs.
	Inpt	102		2 (2)		2 (2)	11 (11)	2 (2)	9.6	20,932 FRF [a]	
Kovacs, 2000	Outpt	81		0 (0)	5 (6)	1 (1)	3 (4)	4 (5)			
	Inpt	27		1 (4)	0 (0)	1 (4)	2 (7)	0 (0)			

[a] p < 0.05 for difference

Evidence Table 7: Description of modeled analysis of the costs of using low molecular weight heparin compared to unfractionated heparin for treatment of venous thromboembolism

Author, year	Aims	Total quality score (%) [a]
Hull, 1997	To perform an economic evaluation comparing tinzaparin to UFH for inpt tx of prox DVT.	100
Rodger, 1998	To assess the cost-effectiveness of LMWH and UFH using data from a meta-analysis and patient-specific case-costing data.	83
Gould, 1999	To evaluate the costs and health effects of a LMWH compared to UFH for inpt tx of acute DVT.	100
Estrada, 2000	To perform an economic evaluation comparing LMWH to UFH for treating a DVT in inpts and outpts.	89
Lloyd, 1997	To evaluate the inpt cost of treating a DVT with nadroparin compared to UFH.	83
van den Belt, 1998	To assess the cost consequences of outpt management in the treatment of DVT.	89
O'Brien, 1999	To evaluate the overall cost of treating a prox DVT with enoxoparin as outpt vs UFH as inpt.	78
deLissovoy, 2000	To evaluate the overall inpt cost of treating an acute VTE with enoxoparin vs UFH.	94
Tillman, 2000	To evaluate the clinical and economic outcomes associated with implementation of outpt DVT tx w/ LMWH.	67

[a] Total quality score: Percentage score based on a total maximum score of 18 points (See Appendix H, items 1-9).

Evidence Table 8: Designs of the modeled analyses of the costs of using low molecular weight heparin compared to unfractionated heparin for treatment of venous thromboembolism

Author, Year	Design	Perspective	Time-horizon	Comparisons	Sources of cost estimates[a]	Sources of estimates of event rates	Units of benefits	Sensitivity analyses
Hull, 1997	CE	Payor	3 mos.	a) Inpt tinzaparin (175 IU/kg qd). b) Inpt UFH.	Direct medical costs in pts enrolled (1992 CAD and USD).	Observed in trial.	Deaths averted, recurrences averted.	Varied across range of observed data in centers.
Rodger, 1998	CE	Payor	3 mos.	a) Outpt LMWH if eligible or inpt LMWH. b) Outpt LMWH if eligible or inpt UFH. c) Inpt LMWH. d) Inpt UFH.	Case-costing using an online resource-utilization-based patient-specific cost accounting system (1995 CAD).	Systematic literature review.	Deaths averted.	Ran model using "worst case scenario", biased against LMWH.
Gould, 1999	CE	Society	Death or age 99 yrs.	a) Inpt enoxaparin (1mg/kg bid). b) Inpt UFH (includes 2° analysis of outpt enoxaparin).	ME reimbursement rates, rx costs, wholesale prices (1997 USD), (analysis included 3%/yr discounting).	From the literature, also used US life table to construct survival curves.	Quality-adjusted and unadjusted LY.	Varied across 95% CI of base case estimates.
Estrada, 2000	CE	Payor	3 mos.	a) LMWH: outpt if eligible or inpt LMWH. b) LMWH: outpt if eligible or inpt UFH. c) Inpt UFH.	Direct medical costs taken from literature review, institutional accounting, and costs to ME (1996 USD).	Literature.	Deaths averted, recurrences averted.	Based on literature.

Evidence Table 8: Designs of the modeled analyses of the costs of using low molecular weight heparin compared to unfractionated heparin for treatment of venous thromboembolism (continued)

Author, Year	Design	Perspective	Time-horizon	Comparisons	Sources of cost estimates[a]	Sources of estimates of event rates	Units of benefits	Sensitivity analyses
Lloyd, 1997	Cost-minimization	Payor	5 days.	a) Inpt nadroparin (weight-based bid). b) Inpt UFH (two routes: SQ or IV).	Direct costs measured as hospital charges to payor (Swiss sickness fund), public list prices of drugs. (1994 USD)	Assumed equivalent in all arms.	USD.	Did not vary the costs.
van den Belt, 1998	Cost-minimization	Payor	6 mos.	a) Outpt fraxaparine (weight adjusted). b) Inpt UFH.	Direct medical costs measured in 1 of 9 settings participating in clinical trial (1993 NLG).	Rates observed in all trial sites, considered equivalent in both groups.	NLG.	Monte Carlo simulations and one-way analyses; ranges.
O'Brien, 1999	Cost-minimization	Society	3 mos.	a) Outpt enoxaparin (1mg/kg bid). b) Inpt UFH.	Canadian national data-systems, local labor and rx costs (1997 CAD).	Observed in trial, measured health related quality of life.	Health related quality of life.	
deLissovoy, 2000	Cost-minimization	Payor	3 mos.	a) Inpt enoxaparin (1.5 mg/kg qd or 1.0 mg/kg bid). b) Inpt UFH.	Direct medical costs from 33 US sites participating in a multicenter trial (1997 USD).	Observed in the 33 US trial sites.	USD.	Varied cost data from 50 to 150% of base case.
Tillman, 2000	Decision-model	Payor	3 mos.	a) Outpt enoxaparin (1 mg/kg bid). b) Inpt UFH.	Direct medical costs measured in 391 pts treated as outpts in group-model HMO; source of inpt costs is unclear (1998 USD).	Measured in outpts.	USD.	Varied cost data from 50 to 300% of base case estimates.

[a] See Acronyms and Abbreviations list for international currencies

Evidence Table 9: Results of the modeled analyses of the costs of using low molecular weight heparin compared to unfractionated heparin for treatment of venous thromboembolism

Author, Year	Least costly strategy	Strategy with greatest benefits	Incremental cost-effectiveness	Cost-savings	Sensitivity analysis	Comments
Hull, 1997	Inpt tinzaparin	Inpt tinzaparin.	Tinzaparin dominates.	401 USD per person w/ tinzaparin, (11% savings).	Robust to all one-way analyses, when cost of tinzaparin is 5.8 times base cost per case it is not cost-saving.	If 37% treated as outpt, cost saving 913 USD per person.
Rodger, 1998	LMWH outpt if eligible/ LMWH inpt	Either LMWH all inpt or LMWH outpts if eligible/LMWH inpts.	LMWH outpts dominate if eligible.	767 USD per person w/ LMWH outpts/ inpts relative to UFH, (23% savings).	Even using "worst case" estimates, cost effectiveness of inpt LMWH relative to inpt UFH is 25,667 USD per life saved at 3 mos.	If equivalent efficacy and safety in all arms is assumed, LMWH is cheaper to deliver in any tx setting and dominates model.
Gould, 1999	Inpt UFH	Inpt enoxaparin.	6,910 USD per LY or 7,820 USD per QALY w/ enoxaparin.		Cost-saving when 8% of enoxaparin pts receive tx as outpts, or when 13% have an early discharge. Model sensitive to frequency of late complications, robust to other analyses.	Robustly cost-effective; becomes cost-saving if treated as outpts w/LMWH.
Estrada, 2000	LMWH in outpts/UFH in inpts	LMWH in outpts and inpts.	9,667 USD per recurrence averted or 80,685 USD per death averted w/ LWMH in outpt/inpt relative to LWMH outpt/UFH inpts.	310 USD per person for LWMH outpts/ inpts relative to UFH (10% savings).	Results sensitive to the % of pts eligible for outpt tx: if fewer than 14% eligible then UFH is less costly than LMWH outpt/inpt. Model sensitive to costs of UFH.	Lower costs primarily due to inpt savings.
Lloyd, 1997	Inpt nadroparin	NA: assumed to be equivalent for model.		153 USD per person with nadroparin 57%.	Robust even to all one-way analyses; savings if nadroparin pts have daily PTT measurement.	

Evidence Table 9: Results of the modeled analyses of the costs of using low molecular weight heparin compared to unfractionated heparin for treatment of venous thrombolembolism (continued)

Author, Year	Least costly strategy	Strategy with greatest benefits	Incremental cost-effectiveness	Cost-savings	Sensitivity analysis	Comments
van den Belt, 1998	Outpt fraxaparine	NA: assumed to be equivalent for model.		5,528 NLG per person with fraxaparine (64% savings).	Fraxaparine cost saving w/50% home care visits, cost saving w/ 50% requiring inpt care.	
O'Brien, 1999	Outpt enoxaparin	Higher social functioning on SF 36 in the enoxaparin group, otherwise NSD in health-related QOL or events.		3,045 USD per person w/ enoxaparin (57% savings).	Robust to all one-way analyses.	
deLissovoy, 2000	NSD	Inpt enoxaparin bid. Fewest readmissions for recurrent DVT and for all causes.		None.	Robust to all one-way analyses.	Protocol blood testing and costs of medication offset by fewer readmissions with enoxaprin.
Tillman, 2000	Outpt enoxaparin	Unknown.		2,828 USD per person w/enoxaparin (60% savings).	Enoxaparin not cost saving if drug cost increase 750% or if hospitalization costs decrease 77%.	Rates of events in the UFH arm not explicitly stated.

Evidence Table 10: Description of the studies evaluating optimal duration of therapy with warfarin after venous thromboembolism

Author, Year	Location	Design	Aims	Recruitment yrs	Planned f/u (mos)	Recurrence surveillance	Inclusion/exclusion criteria	
							Inclusion criteria (Participants-%)	Exclusion criteria
O'Sullivan, 1972	Australia	Single site RCT	To determine: 1) the number of recurrent VTE & bleeding episodes after 6 wks vs 6 mos of warfarin, 2) whether a gradual decrease or abrupt discontinuation of warfarin results in more thrombotic complications.		> 12	None	DVT ± PE (DVT alone-63%, DVT+PE-20%, PE-16%)	Depends on attending MD preference.
Holmgren, 1985	Europe	Multicenter RCT	To study VTE recurrence rate among patients with a 1st DVT treated for 1 vs 6 mos w/warfarin.	1979 - 81	12	IPG or thermography in 48%	1st DVT, calf or proximal (Proximal-83%, Calf-17%)	Contraindication to AC.
Lagerstedt, 1985	Europe	Single site RCT	To assess the need for oral AC after calf DVT.	1981 - 84	12	99m Tc-plasmin isotope scans	Calf vein DVT	Unlikely to comply; requires LT AC; sx of PE; predisposition to recurrence or malignancy.
Schulman, 1985	Europe	Single site RCT	To evaluate whether a shorter course of warfarin can be given w/o risks to pts with a 1st DVT & a TRF, 1st DVT and a PRF or 2nd DVT.		> 15	IPG	Proximal DVT	Preg; low compliance.
Petitti, 1986	United States	Retro-spective Multicenter CohR	To determine the risk of thrombosis & bleeding with warfarin in retrospective review of patients treated in Kaiser-Permanente clinics in Northern CA.	1970 - 80		None	DVT ± PE	Preg/childbirth; systemic disease associated with thrombophilia; malignancy; recent surgery or trauma (w/i 6 wks); death w/i 1 wk of admission; missing chart.

Evidence Table 10: Description of the studies evaluating optimal duration of therapy with warfarin after venous thromboembolism (continued)

Author, Year	Location	Design	Aims	Recruitment yrs	Planned f/u (mos)	Recurrence surveillance	Inclusion/exclusion criteria	
							Inclusion criteria (Participants-%)	Exclusion criteria
Fennerty, 1987	Europe	Single site RCT	To compare outcomes w/ 3 wks vs 6 wks of AC after DVT/PE.		12	None	DVT ± PE	Preg; malignancy; prolonged immobility; previous VTE w/in 5 yrs.
British Thoracic Society (BTS), 1992	Europe	Multicenter RCT	To compare efficacy of 4 wks vs 3 mos of AC for VTE.	1988 - 90	12	None	DVT± PE. (DVT-51%, DVT+PE-19%, PE-31%)	Preg/childbirth; requires LT AC; thrombolytic therapy; pulmonary embolectomy; malignancy; prolonged immobility; previous VTE in last 3 yrs.
Levine, 1995	Canada & Europe	Multicenter RCT	To test whether 1) normal IPG after 4 wks of warfarin for a proximal DVT identifies a group whose warfarin can be d/c 2) normal IPG at 4 wks predicts a lower risk of recurrence than an abnormal IPG 3) continuing risk factors are associated w/ recurrence.	1987 - 92	11	IPG	Proximal DVT	Preg; major psychiatric disorder; life expectancy < 3 mos; unlikely to f/u; requires LT AC; familial bleeding disorder; active bleeding; peptic ulcer; thrombophilia; ≥2 previous VTE.
Schulman, 1995	Europe	Multicenter RCT	To compare 6 wks with 6 mos of AC for a 1st VTE.	1988 - 91	24	None	1st VTE, DVT ±PE (DVT-88%, PE-12%)	Preg; allergy; requires LT AC; unable to f/u; arterial insufficiency; venous ulcerations precluding compression stockings; age < 14 yrs; thrombophilia; malignancy; previous VTE; total limb paresis.

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Evidence Table 10: Description of the studies evaluating optimal duration of therapy with warfarin after venous thromboembolism (continued)

Author, Year	Location	Design	Aims	Recruitment yrs	Planned f/u (mos)	Recurrence surveillance	Inclusion/exclusion criteria	
							Inclusion criteria (Participants-%)	Exclusion criteria
Schulman, 1997	Europe	Multicenter RCT	To compare 6 mos vs indefinite oral AC for a 2nd VTE.	1988 - 91	48	None	2nd VTE, DVT ± PE (DVT-85%, PE - 15%)	Preg; allergy to warfarin/ dicoumarol; requires LT AC; unable to f/u; arterial insufficiency; venous ulcerations precluding comp stockings; age <14 yrs; thrombophilia; malignancy; or total limb paresis.
Kearon, 1999	United States & Canada	Multicenter RCT	To determine whether 24 additional mos of warfarin is more effective than 3 mos for 1st idiopathic VTE.	1994 - 97	24	None	1st idiopathic VTE, DVT±PE (DVT-75%, PE - 25%)	Preg; major psychiatric disorder; life expectancy <2 yrs; requires LT therapy w/ASA/NSAIDs or AC; allergy; unlikely to comply; familial bleeding disorder; contraindication to AC; or tx w/unlicenced LMWH preparation; thrombophilia; malignancy within last 5 yrs; immobilization for > 3 days; recent fracture or cast of lower limb; recent general anesthesia.

Evidence Table 10: Description of the studies evaluating optimal duration of therapy with warfarin after venous thromboembolism (continued)

Author, Year	Location	Design	Aims	Recruitment yrs	Planned f/u (mos)	Recurrence surveillance	Inclusion criteria (Participants-%)	Exclusion criteria
							Inclusion/exclusion criteria	
Agnelli, 2001	Europe	Multicenter RCT	To evaluate LT benefit of extending AC from 3 mos to 1 yrs after a 1st idiopathic DVT in terms of symptomatic recurrence, bleeding, & death.	1995 - 98	24	None	1st idiopathic proximal DVT	Preg/childbirth; major psychiatric disorder; life expectancy < 2 yrs; unlikely to f/u; requires LT AC; age <15 or >85 yrs; thrombophilia or malignancy; recent surgery or trauma (w/in 3 mos); immobilization >7 days; OCPs.
Pinede, 2001	Europe	Multicenter RCT	To determine optimal duration of oral AC for a 1st proximal or calf DVT or PE.	1993 - 98	15	None	1st DVT, calf or proximal, or PE (Proximal DVT-43%, Proximal DVT+PE-18%, Calf DVT-27%, Calf DVT+PE - 7%)	Preg; BF; requires LT AC; thrombolytic therapy; surgical thrombectomy; free-floating IVC clot; liver disease; severe PE; age < 18 yrs; thrombophilia; malignancy; previous DVT; vena caval filter.

Evidence Table 11: Quality of the studies evaluating optimal duration of therapy with warfarin after venous thromboembolism

Author, Year	Overall [a]	Representativeness of study population [b]	Bias & confounding [c]	Description of tx [d]	Outcomes & f/u [e]	Statistical quality & interpretation [f]
O'Sullivan, 1972	15	0	25	25	25	0
Holmgren, 1985	46	75	50	50	55	0
Lagerstedt, 1985	73	50	63	100	70	83
Schulman, 1985	63	50	69	50	80	67
Petitti, 1986	46	75	0	0	80	75
Fennerty, 1987	31	25	25	25	45	33
BTS, 1992	53	50	63	25	60	67
Levine, 1995	83	100	88	50	75	100
Schulman, 1995	90	88	81	100	80	100
Schulman, 1997	86	88	88	75	80	100
Kearon, 1999	82	75	100	50	85	100
Agnelli, 2001	87	100	88	50	95	100
Pinede, 2001	82	75	88	75	70	100

[a] **Overall** The mean of the percentage scores from categories: Representativeness of Study Population, Bias and Confounding, Description of Treatment, Outcomes and Followup, and Statistical Quality and Interpretation (see below).

[b] **Representativeness of Study Population:** Percentage score based on a total maximum score of 8 points. This included description of study setting and population (2 points), description of inclusion/exclusion criteria (2 points), information on excluded or non-participating patients (2 points), and description of key patient characteristics (2 points).

[c] **Bias and Confounding:** Percentage score based on a total maximum score of 6 points. This included random assignment of patients to study groups (2 points), differences between study groups in key patient characteristics (2 points), and blinding of clinicians, patients, and outcome assessors (2 points).

[d] **Description of Treatment:** Percentage score based on a total maximum score of 4 points. This included description of the details of the treatment regimen (2 points), and description of other treatments given to each study group (2 points).

[e] **Outcomes and Followup:** Percentage score based on a total maximum score of 10 points. This included description of the criteria used for determining outcomes (2 points), description of adverse events experienced by patients (2 points), reporting on numbers and reasons for withdrawals or patients lost to followup (2 points), proportion of patients who withdrew or were lost to followup (2 points), and adequacy of the planned length of followup (2 points).

[f] **Statistical Quality and Interpretation:** Percentage score based on a total maximum score of 8 points. This included reporting on the magnitude of differences between groups with an index of variability (2 points), clear identification of all statistical analyses (2 points), use of multivariate or stratified analyses to adjust for potential confounders (2 points), and appropriate handling of withdrawals, crossovers, and loss to followup (2 points).

Evidence Table 12: Characteristics of patients in studies evaluating optimal duration of therapy with warfarin after venous thromboembolism

Author, year	Group[a]	Intervention Drug	Intervention Duration (days)	Type of VTE	Mean age (yrs)	Male (%)	% Prior VTE/ % Family hx/ % Thrombophilia	TRF/ Proximal DVT (%)
O'Sullivan, 1972	I	Warfarin	42				NR / NR / NR	NR / NR
	III	"	180				NR / NR / NR	NR / NR
Holmgren, 1985	I	Warfarin	30	Comp stockings	62	59	NR / NR / NR	NR / 87
	III	"	180	"	62	64	NR / NR / NR	NR / 79
Lagerstedt, 1985	NA	No warfarin		Comp stockings	61	54	21 / NR / NR	NR / NR
	II	Warfarin	90	"	65	61	13 / NR / NR	NR / NR
Schulman, 1985	I	Warfarin	45		56	50	NR / NR / NR	100 / NR
	II	"	90		60	50	NR / NR / NR	100 / NR
	II[b]	"	90		58	60	NR / NR / NR	NR / NR
	III[b]	"	180		66	75	NR / NR / NR	NR / NR
	III	"	180		64	40	100 / NR / NR	NR / NR
	IV	"	360		66	40	100/ NR / NR	NR / NR
Petitti, 1986	I	Warfarin	7-42				NR / NR / NR	NR / NR
	I/II/III	"	49-182				NR / NR / NR	NR / NR
	IV	"	>182				NR / NR / NR	NR / NR
Fennerty, 1987	I	Warfarin	21		56	51	NR / NR / NR	NR / NR
	I	"	42		57	61	NR / NR / NR	NR / NR
BTS, 1992	I	Warfarin	28		58	56	NR / NR / NR	NR / NR
	II	"	90		58	51	NR / NR / NR	NR / NR

Evidence Table 12: Characteristics of patients in studies evaluating optimal duration of therapy with warfarin after venous thromboembolism (continued)

Author, year	Group[a]	Intervention Drug	Intervention Duration (days)	Type of VTE	Mean age (yrs)	Male (%)	% Prior VTE/ % Family hx/ % Thrombophilia	TRF/ Proximal DVT (%)
Levine, 1995	I/I	Warfarin/ warfarin	28/56		63	48	10 / NR / NR	40 / NR
	I/I	Warfarin/ placebo	28/56		63	54	8 / NR / NR	36 / NR
	II	Warfarin	90		62	59	9 / NR / NR	24 / NR
Schulman, 1995	I	Warfarin or dicumarol	42	Comp stockings	61	56	NR / 16 / NR	NR / 55
	III	"	180	"	61	57	NR / 14 / NR	NR / 58
Schulman, 1997	III	Warfarin or dicumarol	180	"	65	63	NR / 22 / NR	20 / 72
	IV	"	1460	"	64	59	NR / 19 / NR	18 / 66
Kearon, 1999	II/IV	Warfarin/ placebo	90/720		58	53	4 / NR / NR	NR / NR
	II/IV	Warfarin/ warfarin	90/720		59	68	6 / NR / NR	NR / NR
Agnelli, 2001	II	Warfarin/ acenocoumarol	90		68	61	NR / NR / NR	NR / 100
	IV	"	360		67	55	NR / NR / NR	NR / 100
Pinede, 2001[c]	I	Fluindione	42				NR / 19.2 / NR	68.3 / NR
	I	"	84				NR / 25.8 / NR	69.7 / NR
	I	"	84				NR / 15.5 / NR	45.8 / NR
	III	"	168				NR / 15.2 / NR	46 / NR

[a] I: Less than 3 months (1 - 89 days); II: 3 to 4 months (90 - 149 days); III: 5 to 6 months (150 - 180 days); IV: Greater than 6 months (181+ days); NA: not applicable

[b] All had first DVT with a permanent risk factor

Evidence Table 12: Characteristics of patients in studies evaluating optimal duration of therapy with warfarin after venous thromboembolism (continued)

c   The first two subject groups consist of patients with calf vein DVT (comparing 42 and 84 days of therapy) while the third and fourth groups consist of patients with proximal DVT/PE (84 and 168 days of therapy)

Evidence Table 13: Results of studies evaluating optimal duration of therapy with warfarin after venous thromboembolism

Author, Year	Group[a]	# of pts	Mean f/u (mos)	Intensity of therapy	VTE Recurrence All VTE n (%)	DVT n (%)	PE n (%)	Adverse Events Major bleeding n (%)	Minor bleeding n (%)	Deaths n (%)
O'Sullivan, 1972	I	94				6 (6)	2 (2)			
	III	92				9 (9)	3 (3)			
Holmgren, 1985	I	69				7 (10)	5 (7)			6 (9)
	III	66				5 (8)	5 (8)			4 (6)
Lagerstedt, 1985	NA	28			9 (32) [b]					
	II	23			1 (4) [b]					
Schulman, 1985	I	10	24	[c]		1 (10)	0 (0)			0 (0)
	II	10	20			2 (20)	0 (0)			0 (0)
	II	20	22			3 (15)	1 (5)			3 (15)
	III	20	21			2 (10)	0 (0)			2 (10)
	III	10	33			0 (0)	1 (10)			1 (10)
	IV	10	28			3 (30)	0 (0)			1 (10)
Petitti, 1986	I				[d]					
	I/II/III				[d]					
	IV				[d]					
Fennerty, 1987	I	49			2 (4) [e]					1 (2)
	I	51			2 (4) [e]					5 (10)
BTS, 1992	I	358		86% [f]	14 (4) [e]			5 (1)	10 (3)	26 (7)
	II	354		80% [f]	7 (2) [e]			4 (1)	18 (5)	28 (8)
Levine, 1995	I/I	109		2.3 (±0.4) [g]	7 (7)	7 (7)	0 (0)	1 (1)		9 (9)
	I/I	105			12 (12) [h]	9 (9)	3 (3)	0 (0)		9 (9)
	II				19 (13)					

Evidence Table 13: Results of studies evaluating optimal duration of therapy with warfarin after venous thromboembolism (continued)

Author, Year	Group[a]	# of pts	Mean f/u (mos)	Intensity of therapy	VTE Recurrence			Adverse Events		Deaths n (%)
					All VTE n (%)	DVT n (%)	PE n (%)	Major bleeding n (%)	Minor bleeding n (%)	
Schulman, 1995	I	443		65% [i]	80 (18) [b]			1(0.2)		22 (5)
	III	454		59% [i]	43 (10) [b]			5 (1)		17 (4)
Schulman, 1997	III	111			23 (21) [b]			3 (3)		16 (14)
	IV	116		62% [j]	3 (3) [b]			10 (9)		10 (9)
Kearon, 1999	II/IV	83	9			11 (13)	6 (7)	0 (0)	1 (1)	3 (4)
	II/IV	79	12	2.5 ($\pm$1.0)[h]		0 (0)	1 (1)	3 (4)	6 (8)	1 (1)
Agnelli, 2001	II	133	37.2			18 (14)	3 (2)	2 (2)		7 (5)
	IV	134	37.8	81% [j, k] [l]		16 (12)	5 (4)	4 (3)		7 (5)
Pinede, 2001	I	105				2 (2)	0 (0)	1 (1)	12 (12)	
	I	92				2 (2)	1 (1)	3 (3)	16 (18)	
	I	270				18 (7)	6 (2)	5 (2)	38 (14)	
	III	269				15 (6)	6 (2)	7 (3)	38 (14)	

[a] I: Less than 3 months (1 - 89 days); II: 3 to 4 months (90 - 149 days); III: 5 to 6 months (150 - 180 days); IV: Greater than 6 months (181+ days) NA: Not applicable
[b] p<0.05 for the difference between groups
[c] Effective anticoagulation [Thrombotest ® (Nyegaard, Norway) < 13%] achieved in 68% and 67% respectively of the reduced duration and regular duration subjects.
[d] Relative risk of recurrence: Group A (1-6 weeks of therapy) vs Group C (>26 weeks)= 1.1; Group B (7-26 weeks) vs Group C (>26 weeks)= 0.7.
[e] Only objectively confirmed events included.
[f] In therapeutic range 67% of time in 86% of participants in Group A and 80% of participants in Group B. Test and therapeutic range not specified.
[g] Mean INR (± standard deviation (SD))
[h] VTE at 2 mos. f/u: Group A= 1 (1%), Group B= 9 (9%), p<0.009
[i] % w/ effective AC (INR 2.0 for 75% or more of PTT).
[j] % of pts in target range (INR 2.0-2.85).
[k] INR was 2.0-3.0 in 81% of tests during additional 9 mos. of therapy.
[l] Median INR 2.0 in 96% of subjects, distribution similar between arms.

Evidence Table 14: Description of studies evaluating clinical prediction rules used in diagnosis of venous thromboembolism

Author, Year	Location	Study aims	Recruitment dates	Study test	Reference standard	Inclusions	Exclusions
Deep Venous Thrombosis							
Nypaver, 1993	United States	To define clinical criteria that might predict the diagnostic value of VDS.		Clinical model		Suspected DVT in inpts	PE.
Wells, 1995	Canada	To assess the ability of a clinical model to stratify symptomatic outpatients with suspected DVT into groups with high, moderate, and low probability of DVT and to evaluate this model in combination with U/S.	1992 - 93	Wells model	Venogram	Referral for suspected DVT in outpts	Preg/childbirth; contrast dye allergy; renal failure; suspected PE; below the knee amputation.
Wells, 1997	Canada		1994 - 96	Wells model	Venogram U/S	Referral for suspected DVT in outpts	Age < 18 yrs; previous VTE; requires LT AC; PE; imminent death.
Anderson, 1999	Canada	To determine the accuracy of a clinical model, and determine if the model is safe and feasible.	1997	Wells model	U/S	Suspected DVT in ED	Age < 18 yrs; Preg/childbirth; previous VTE; short life expectancy; unlikely to be compliant; hereditary bleeding; contraindication to AC; thrombolytic therapy; PE.
Aschwanden, 1999	Europe		1997	Wells model Wells model + D-dimer	U/S	Referral for suspected idiopathic DVT	

Evidence Table 14: Description of studies evaluating clinical prediction rules used in diagnosis of venous thromboembolism (continued)

Author, Year	Location	Study aims	Recruitment dates	Study test	Reference standard	Inclusions	Exclusions
Lennox, 1999	Europe	To determine the actual value of the D-dimer test and its combination with clinically derived risk stratification in the diagnostic work up of patients with suspected DVT.		Risk assessment score for DVT (RAS) RAS + D-dimer	U/S	Suspected DVT in inpts/outpts	Previous VTE; chronic DVT on US; symptoms > 1 mos; AC > 48 hours; PE.
Wells, 1999	Canada	To evaluate the accuracy of D-dimer in hospitalized patients.	1994 - 96	Wells Model Wells Model + D-dimer	U/S, thigh/popliteal	Referral for suspected DVT in inpts	Age < 18 yrs; previous VTE; short life expectancy; unlikely to be compliant; requires LT AC; PE; screening.
Anderson, 2000	Canada	To determine the accuracy of D-dimer and to determine the potential of combining the D-dimer with the Wells model.		Wells Model Wells Model + D-Dimer	U/S	Suspected DVT in ED	Age < 18 yrs; hereditary bleeding; contraindication to AC; thrombolytic therapy; PE.
Constans, 2001	Europe	To determine whether one or two of these scores maintained the same level of performance in various hands.	1999 - 99	Kahn model Wells model Sant-Andre hospital model	U/S, thigh/popliteal		Previous VTE
Dryjski, 2001	United States	To evaluate the efficacy and cost effectiveness of a DVT screening protocol consisting of global PTP, selective D-dimer, and selective venous Doppler imaging.	2000 - 01	Wells model Wells + D-dimer + PTP	U/S, thigh/popliteal	Suspected DVT in ED	

Evidence Table 14: Description of studies evaluating clinical prediction rules used in diagnosis of venous thromboembolism (continued)

Author, Year	Location	Study aims	Recruitment dates	Study test	Reference standard	Inclusions	Exclusions
Funfsinn, 2001	Europe	To determine the reliability of several rapid D-dimer tests in combination with a simple clinical model to predict the pretest probability.		Wells model	Venogram, central, thigh/popliteal, calf; U/S, thigh/ popliteal	Referral for suspected DVT	Preg/childbirth; hospitalization; AC for 24 hours.
Kearon, 2001	Canada	Test if U/S can be withheld from pts w/ low probability scores.	1995 - 97	Wells model Wells model + D-dimer	U/S	Referral for suspected DVT	
Cornuz, 2002	Europe	To compare clinical assessment and the Wells score, in isolation and in combination with rapid quantitative D-dimer.		Wells model Wells model + D-dimer	Venogram, thigh/popliteal; U/S	Referral for suspicion of DVT	Preg/childbirth; PE.
Kraaijenhagen, 2002	Europe	To study if combination of normal results of compression ultrasonography and rapid whole blood bedside D-dimer assay at referral can safely exclude the presence of thrombosis.	1995 - 99	Wells model	U/S		<18 yrs, previous VTE PE, AC >48 hrs, geographic inaccessibility.

Pulmonary Embolism

Author, Year	Location	Study aims	Recruitment dates	Study test	Reference standard	Inclusions	Exclusions
Wells, 1998	Canada	To find a clinical model for safe management of patients with suspected PE.	1993 - 96	Wells PE model	V/Q	PE, suspected PE in inpts/ outpts	UE VTE; Preg/childbirth; short life expectancy; contrast dye allergy; recent AC use.

Evidence Table 14: Description of studies evaluating clinical prediction rules used in diagnosis of venous thromboembolism (continued)

Author, Year	Location	Study aims	Recruitment dates	Study test	Reference standard	Inclusions	Exclusions
Sanson, 2000	Europe	To compare the accuracy and variability of the clinical probability estimate between the PIOPED and the two clinical models by Wells.	1997 - 98	PIOPED study model Wells simplified model Wells extended model for PE	V/Q, SPECT (tomographic) Helical CT, PA	Unsuspected DVT in inpts/outpts	Age < 18 yrs; Preg/childbirth; undergone testing for PE; inability to complete protocol.
Stollberger, 2000	Europe	To derive and validate a prediction rule based on clinical and easily obtained instrumental findings by which PE can be diagnosed.		Clinical model	V/Q	High suspicion for PE (enough to start heparin)	Contraindication for PE evaluation.
Wells, 2000	Canada	Simplify the clinical model and examine the potential safety and clinical utility of combining the new model with D-dimer results to enable exclusion of PE.		Wells PE model Wells PE model + D-dimer	V/Q	Suspected PE	
Wells, 2001	Canada	Demonstrate the safety of excluding the diagnosis of pulmonary embolus in an emergency department using diagnostic algorithms that were based on pretest probability and D-dimer assay results.	1998 - 99	Wells PE model	V/Q	Acute dyspnea or chest pain less than 30 days.	Suspected DVT of the upper extremity, AC >24 hrs, and short LE contraindication to contrast media, Preg, geographic inaccessibility, age <18 yrs.

Evidence Table 15: Quality of studies evaluating clinical prediction rules used in diagnosis of venous thromboembolism

Author, year	Overall [a]	Representativeness of study population [b]	Bias & confounding [c]	Description of prediction rule [d]	Test interpretation [e]	Statistical quality & interpretation [f]
Deep Venous Thrombosis						
Nypaver, 1993	64	38	30	83	67	100
Wells, 1995	84	75	60	83	100	100
Wells, 1997	82	100	25	100	83	100
Anderson, 1999	78	100	25	83	83	100
Aschwanden, 1999	70	38	60	100	100	50
Lennox, 1999	63	63	35	100	67	50
Wells, 1999	78	100	25	83	83	100
Anderson, 2000	85	100	40	83	100	100
Constans, 2001	66	75	40	100	67	50
Dryjski, 2001	74	88	30	100	100	50
Funfsinn, 2001	71	75	30	67	83	100
Kearon, 2001	75	88	20	83	83	100
Cornuz, 2002	88	88	50	100	100	100
Kraaijenhagen, 2002	93	100	80	100	100	100
Pulmonary Embolism						
Wells, 1998	61	75	45	83	100	0
Sanson, 2000	90	100	50	100	100	100
Stollberger, 2000	51	50	20	67	67	50
Wells, 2000	49	38	25	83	100	0
Wells, 2001	84	88	60	100	100	100

[a] **Overall:** The mean of the percentage scores from the categories: Representativeness of Study Population, Bias and Confounding, Description of Test Protocols, Test Interpretation, and Statistical Quality and Interpretation (see below).

Evidence Table 15: Quality of studies evaluating clinical prediction rules used in diagnosis of venous thromboembolism (continued)

[b] **Representativeness of Study Population:** Percentage score based on a total maximum score of 8 points. This included description of study setting and population (2 points), description of inclusion/exclusion criteria (2 points), information on excluded or non-participating patients (2 points), and description of key patient characteristics (2 points).

[c] **Bias and Confounding:** Percentage score based on a total maximum score of 10 points. This included use of the reference test on all subjects receiving the study test (2 points), use of the study test in the decision to obtain the reference test (2 points), blinding of test interpretation and clinical data (2 points), interpretation of the study test by two or more independent observers (2 points), and interpretation of the reference test by two or more independent observers (2 points).

[d] **Description of Prediction Rule:** Percentage score based on a total maximum score of 6 points. This included description of the clinical model being tested (2 points), description of the reference test protocol (2 points), and reporting on the methods used in the development of the clinical model being tested (2 points).

[e] **Test Interpretation:** Percentage score based on a total maximum score of 6 points. This included description of the criteria for a positive interpretation of the study test (2 points), description of the criteria for a positive interpretation of the reference test (2 points), and reporting on numbers and reasons for withdrawals or patients lost to followup (2 points).

[f] **Statistical Quality and Interpretation:** Percentage score based on a total maximum score of 4 points. This included reporting of a summary index of test performance and of an index of variability (2 points), and use of multivariate or stratified analyses to adjust for potential confounders (2 points).

Evidence Table 16: Characteristics of patients in studies evaluating clinical prediction rules used in diagnosis of venous thromboembolism

Author, Year	N	Age (yrs)		Male (%)	Prior VTE (%)	Family history (%)	TRF (%)	Malignancy (%)
		Mean	Range/SD					
Deep Venous Thrombosis								
Nypaver, 1993	68							
Wells, 1995	605							
Wells, 1997	593	57.1		41			22	13
Anderson, 1999	344	53.8		45			19	5
Aschwanden, 1999	343	61 [a]	17 - 94 [b]					
Lennox, 1999	200	58	18 - 91 [b]	37				
Wells, 1999	150	63.8		49			49	
Anderson, 2000	214	54.8		45			19	6
Constans, 2001	273	68	17 [c]	38	20	7		17
Dryjski, 2001	66	63	19 - 92 [b]	25				
Funfsinn, 2001	106	56.3	16 - 88 [b]	49				
Kearon, 2001	445							
Cornuz, 2002	278	60	19 [c]	62	18		10	10
Kraaijenhagen, 2002	1726	60	18 - 96 [b]	37			15	13
Pulmonary Embolism								
Wells, 1998	1401							
Sanson, 2000	517	51		42	14	20		10
Stollberger, 2000	168	64	21 - 86 [b]	47				
Wells, 2000	295							
Wells, 2001	903	50.5	16 - 93 [b]	37			16	7.2

[a] Median   [b] Range   [c] Standard deviation

Evidence Table 17: Results of studies evaluating clinical prediction rules used in diagnosis of venous thromboembolism

Author, Year	Study test	Clinical prediction probability [a]	# pts w/VTE (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	ROC curve area
Deep Venous Thrombosis								
Nypaver, 1993	Clinical model			91	51	26	97	
Wells, 1995	Wells model	High	69 (81%)	61	97	81	91	0.90
		Moderate	34 (24%)	91	70	45	97	
		Low	10 (3%)	–	–	–	--	
Wells, 1997	Wells model	High	53 (75%)	53	96	75	91	0.87
		Moderate	35 (18%)	88	64	33	96	
		Low	12 (4%)	--	--	--	--	
Anderson, 1999	Wells model	High	24 (49%)	53	92	49	93	0.79
		Moderate	15 (14%)	87	62	25	97	
		Low	6 (3%)	--	--	--	--	
Aschwanden, 1999	Wells model	High		84	56	26	95	
	Wells model + D-dimer	High		96	46	32	98	
Lennox, 1999	Risk assessment score for DVT (RAS)	High	30 (67%)	65	90	67	90	0.87
		Moderate	12 (18%)	91	54	38	95	
		Low	4 (5%)	--	--	--	--	
	RAS + D-dimer							0.91
Wells, 1999	Wells model	High	22 (76%)	54	94	76	84	0.81
		Moderate	14 (20%)	88	41	36	90	
		Low	5 (10%)	--	--	--	--	
	Wells model + D-dimer	High				79	33	
		Moderate				28	89	
		Low				20	96	

Evidence Table 17: Results of studies evaluating clinical prediction rules used in diagnosis of venous thromboembolism (continued)

Author, Year	Study test	Clinical prediction probability [a]	# pts w/VTE (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	ROC curve area
Anderson, 2000	Wells model	High	15 (50%)	54	92	50	93	0.83
		Moderate	9 (14%)	86	61	25	97	
		Low	4 (3%)	--	--	--	--	
	Wells model + D-Dimer							0.87
Constans, 2001	Wells model	High	33 (51%)	50	85	52	84	0.74
		Moderate	26 (19%)	89	32	31	90	
		Low	7 (10%)	--	--	--	--	
	Kahn model	High	2 (100%)	3	100	100	75	0.59
		Moderate	47 (28%)	74	43	29	81	
		Low	17 (19%)	--	--	--	--	
	Sant-Andre hospital model	High	13 (76%)	20	98	76	79	0.77
		Moderate	38 (33%)	77	61	39	89	
		Low	15 (11%)	--	--	--	--	
Dryjski, 2001	Wells model	High	6 (17%)	100	50	17	100	0.75
		Moderate	0 (0%)	100	12	10	100	
		Low	0 (0%)	--	--	--	--	
	Wells model + D-dimer + PTP			100	25	12	100	
Funfsinn, 2001	Clinical Model (Well's DVT)[b]	High	30 (71%)	75	77	71	80	0.77
		Moderate	10 (28%)	100	27	51	100	
		Low	0 (0%)	--	--	--	--	
Kearon, 2001	Wells model	High	35 (69%)	55	96	69	93	0.87
		Moderate	24 (13%)	92	53	25	98	
		Low	5 (2%)	--	--	--	--	
	Wells model + D-dimer	Low					99	

Evidence Table 17: Results of studies evaluating clinical prediction rules used in diagnosis of venous thromboembolism (continued)

Author, Year	Study test	Clinical prediction probability [a]	# pts w/VTE (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	ROC curve area
Cornuz, 2002	Wells model	High	32 (67%)	39	92	67	78	0.75
		Moderate	36 (30%)	83	48	40	87	
		Low	14 (13%)	--	--	--	--	
	Wells model + D-dimer	High				73	100	
		Moderate				38	90	
		Low				16	100	
Kraaijemhagen, 2002	Wells model	High	228 (66%)	53	91	66	91	0.87
		Moderate	135 (27%)	85	63	43	63	
		Low	62 (8%)	--	--	--	--	
Pulmonary Embolism								
Wells, 1998	Wells PE model	High	80 (78%)	37	98	78	88	0.88
		Moderate	112 (28%)	88	69	38	97	
		Low	25 (3%)	--	--	--	--	
Sanson, 2000	PIOPED study model	High	35 (45%)	28	85	45	73	0.61
		Moderate	80 (29%)	91	16	33	81	
		Low	11 (19%)	--	--	--	--	
	Wells simplified model	High	3 (38%)	2	98	38	71	0.52
		Moderate	78 (30%)	66	36	30	72	
		Low	41 (28%)	--	--	--	--	
	Wells extended model for PE pulmonary angiogram	High	18 (46%)	20	86	46	64	0.58
		Moderate	54 (39%)	81	29	41	72	
		Low	17 (28%)	--	--	--	--	

Evidence Table 17: Results of studies evaluating clinical prediction rules used in diagnosis of venous thromboembolism (continued)

Author, Year	Study test	Clinical prediction probability [a]	# pts w/VTE (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	ROC curve area
Stollberger, 2000	Clinical model	> 0.65		55	100			
		> 0.35		98	82			
		> 0.02		100	5	35	100	
Wells, 2000	Wells PE model	High	10 (50%)	28	95	50	89	0.82
		Moderate	24 (19%)	94	46	23	98	
		Low	2 (2%)	--	--	--	--	
	Wells PE model +							0.85
Wells, 2001	Wells PE model	High	24 (41%)	27	95	36	95	0.85
		Moderate	55 (16%)	92	62	20	98	
		Low	7 (1.3%)	--	--	--	--	

[a] High probability≥ 3, moderate probability=1 or 2, low probability<1.

b Models with D-dimer testing also presented in paper.

Table 18: Summary of systematic reviews on ultrasound in the diagnosis of deep venous thrombosis

Author, Year	Study aim	Most recent study	Systematic review quality scores					
			Overall [a]	Search [b]	Eligibility [c]	Study quality [d]	Combining results [e]	Aims & Conclusions [f]
White, 1989	To assess accuracy of duplex U/S for the dx of prox DVT in symptomatic pts.	1988	65	33	67	75	75	75
Becker, 1989	To review the evidence for the use of real-time U/S in dx of suspected DVT.	1988	73	33	83	100	100	100
Cogo, 1995	To assess accuracy of non-invasive dx of 1st episode of suspected DVT.	1992	38	17	50	0	75	75
Wells, 1995	To evaluate accuracy of screening U/S for dx of DVT in post-operative orthopedic pts.	1993	82	50	83	75	100	100
Kearon, 1998	To review non-invasive methods of dx for a 1st DVT.	1997	83	83	100	50	100	100
Gottlieb, 1999	To determine the accuracy of U/S for detection of isolated calf DVT.	1996	58	50	67	0	100	100
Mustafa, 2002	To determine sensitivity and specificity of U/S for dx of upper extremity DVT.	1997	63	50	67	75	100	100

a   **Overall Quality Score:** The mean of the percentage scores from the categories, Search Methods, Inclusion & Description, Quality Assessment, Methods of Combination, and Aims/Conclusions (see below).

b   **Search Methods:** Percentage score based on a total maximum score of 6 points. This included description of search methods (2 points), comprehensiveness of search methods (2 points), and reproducibility of review methods (2 points).

c   **Eligibility and Description:** Percentage score based on a total maximum score of 6 points. This included description of study inclusion criteria (2 points), appropriateness of study inclusion criteria (2 points), and discussion of variation in the original literature based on differences in study design (2 points).

d   **Study Quality Assessment:** Percentage score based on a total maximum score of 4 points. This included description of quality assessment (2 points), and appropriateness of quality assessment (2 points).

e   **Combining Results:** Percentage score based on a total maximum score of 4 points. This included description of methods used to combine study results (2 points), and appropriateness of methods used to combine study results (2 points).

f   **Aims & Conclusions:** Percentage score based on a total maximum score of 4 points. This included whether the question to be addressed by the review was clearly stated (2 points), and whether the conclusions reached by the review were supported by data and/or analyses (2 points).

Table 19: Results of systematic reviews on ultrasound in the diagnosis of deep venous thrombosis

Author, Year	Design of trials [a]	# of trials	Total pts	% DVT	Patient population [b]	Ultrasonography	Mean sensitivity (95% CI), %	Mean specificity (95% CI), %	Comments
White, 1989	Prosp/ consec	4	266	46	Symp/prox DVT/level 1	Compression	93 (88-97)	98 (96-100)	Level 1 studies had both tests w/i 24 hrs of each other; blinded.
		9	424	61	Symp/prox DVT/level 2	Compression	98 (96-100)	96 (93-99)	
Becker, 1989		15	1578	50	Symp/lower extremity DVT	Compression +/- Doppler	96 (92-100) [c]	99 (96-100) [c]	Only 3 studies looked for calf DVT.
Cogo, 1995	Prosp/ consec	9	989	43	Symp/1st prox DVT	Compression	96	98	Consistency in results despite different qualities of studies. Duplex + color Doppler offered no advantage over compression; low sens for calf DVT.
		4	247	42	Symp/1st prox DVT	Compression +/- Doppler	95	93	
		4	340	37	Symp/1st prox DVT	Compression +/- color Doppler	97	97	
		4			Symp/1st calf DVT	All types	75 (56-88)	N/A	
Wells, 1995	Prosp/ consec	11	1616	9	Asymp/post-op prox DVT/level 1	Compression +/- Doppler	62	97	Only moderate sens for detecting DVT in asymp patients; sens lower among studies that minimize potential for bias.
		5	385	17	Symp/post-op prox DVT/level 2	Compression +/- Doppler	95	97	
		2			Symp/post-op calf DVT/level 1	Compression +/- Doppler	48 (29-67)	100	
Kearon, 1998	Prosp/ consec	18	2763	40	Symp/1st prox DVT	Compression +/- Doppler	89 (85-92)	94 (90-98)	Sens dependent on presence of symptoms; low sens for calf DVT.
		11 [d]	1316 [d]		Calf DVT [d]		73 (54-93)	N/A	
		16	2035	16	Symp/1st prox DVT	Compression +/- Doppler	47 (37-57)	94 (91-98)	
		12 [d]	1681 [d]	N/A	Calf DVT [d]		53 (32-74)	N/A	
Gottlieb, 1998		5	212 [e]	25	Symp/calf vein DVT	Compression	93 (82-98)	99 (96-99)	High frequency of indeterminate studies.

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Table 19: Results of reviews on ultrasound in the diagnosis of deep venous thrombosis (continued)

Author, Year	Design of trials [a]	# of trials	Total pts	% DVT	Patient population [b]	Ultrasonography	Mean sensitivity (95% CI), %	Mean specificity (95% CI), %	Comments
Mustafa, 2002	Prosp	6	170	73	Symp/upper extremity DVT	Doppler +/- compression	(56-100) [c]	(77-100) [c]	Highest quality study used compression and color Doppler; sens 100 and spec 93.

[a] Prosp=prospective design, consec=consecutively enrolled patients
[b] Level 1=higher quality trial, level 2= lower quality trials, post-op=evaluated post-operatively

[c] Mean and range, or just range

[d] Subset of studies

[e] Number of legs screened

Evidence Table 20: Description of the systematic reviews on the use of computed tomography for the diagnosis of pulmonary embolism

Author, Year	Main Inclusion Criteria	Date of most recent study	# studies	Total pts	Systematic review quality scores					
					Overall [a]	Search [b]	Eligibility [c]	Study quality [d]	Combining results [e]	Aims & Conclusions [f]
Harvey, 2000	Prospective and retrospective studies with pulmonary arteriography as reference standard.	1998	11	931	77	50	83	75	75	100
Mullins, 2000	Diagnosis established by pulmonary arteriography or a clinical reference standard.	1998	11	714	75	33	67	75	100	100
Rathburn, 2000	Prospective studies evaluating the use of CT for diagnosis of PE using any reference standard.	1999	15	1330	78	50	67	75	100	100
Cueto, 2001	Prospective studies with positive and negative CT results; pulmonary arteriography reference standard.	1998	7	268	72	50	83	75	50	100
van Beek, 2001	Prospective studies reporting sensitivity and specificity of CT relative to arteriography or V/Q scan.	1999	12	1171	55	33	67	50	50	75
Safriel, 2002	Diagnosis established by pulmonary arteriography or high-probability V/Q scan; not limited to acute PE.	1999	12	1250	55	50	83	0	50	75

[a] **Overall Quality Score:** The mean of the percentage scores from the categories, Search Methods, Inclusion & Description, Quality Assessment, Methods of Combination, and Aims/Conclusions (see below).

[b] **Search Methods:** Percentage score based on a total maximum score of 6 points. This included description of search methods (2 points), comprehensiveness of search methods (2 points), and reproducibility of review methods (2 points).

[c] **Eligibility and Description:** Percentage score based on a total maximum score of 6 points. This included description of study inclusion criteria (2 points), appropriateness of study inclusion criteria (2 points), and discussion of variation in the original literature based on differences in study design (2 points).

[d] **Study Quality Assessment:** Percentage score based on a total maximum score of 4 points. This included description of quality assessment (2 points), and appropriateness of quality assessment (2 points).

[e] **Combining Results:** Percentage score based on a total maximum score of 4 points. This included description of methods used to combine study results (2 points), and appropriateness of methods used to combine study results (2 points).

[f] **Aims & Conclusions:** Percentage score based on a total maximum score of 4 points. This included whether the question to be addressed by the review was clearly stated (2 points), and whether the conclusions reached by the review were supported by data and/or analyses (2 points).

Evidence Table 21: Results of the systematic reviews on the use of computed tomography in the diagnosis of pulmonary embolism

Author, Year	Subgroup	Total pts	Overall prevalence of PE (%)	Combined sensitivity % (range) or [95% CI]	Combined specificity % (range) or [95% CI]	Conclusions
Harvey, 2000	Studies in which all participants had arteriography as reference standard; segmental PE data.	190	46	82 (53-100)	91 (78-100)	CT may be less accurate in diagnosis of PE than previously reported
	Studies in which some or all participants had arteriography reference standard; segmental PE data.	813	34	79 (47-100)	89 (75-100)	
	Studies that included data on diagnosis of segmental and subsegmental PE.	358	44	66 (45-91)	91 (78-100)	
Mullins, 2000	Studies that compared CT with arteriography for segmental PE diagnosis.	367	35	93 (50-100)	97 (92-100)	CT may have role as "rule-in" test for large central emboli, but additional research is required to establish its place in clinical practice
Rathburn, 2000	All studies.	1330		(53-100)	(81-100)	Use of CT in diagnosis of PE has not been adequately evaluated; all studies satisfied few criteria for methodological quality
Cueto, 2001	All studies.	268		80 [73-86]	94 [91-98]	CT may be an appropriate study in clinical evaluation of suspected PE
	Studies reporting segmental PE data.	166		77 [67-88]	91 [86-97]	
	Studies reporting combined segmental and subsegmental PE data.	169		81 [72-90]	98 [95-100]	
van Beek, 2001	All studies.	1171	39	88 [83-91]	92 [89-94]	Exact role of CT in management of suspected PE needs to be determined in prospective studies
Safriel, 2002	All studies.	1250		74 [57-100]	90 [68-100]	CT has acceptable sensitivity and specificity.

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Evidence Table 22: Study design and characteristics of patients in studies evaluating computed tomography or magnetic resonance imaging for diagnosis of pulmonary embolism

Author, Year	Location	Aims	Test evaluated	Reference standard	Source of participants	N	Mean age in yrs (range)	Male (%)
Computed tomography								
Remy-Jardin, 1992	Europe	To compare quality and effectiveness of helical CT with results of pulmonary arteriography in dx of central PE.	HCT	PA	Referral with clinically suspected PE or unexplained chest radiograph abnormality.	42	34 (21-65)	71
Blum, 1994	Europe	To compare helical CT versus pulmonary arteriography in diagnosis of acute massive PE.	HCT	PA	Clinical suspicion of massive PE.	10	43 (18-76)	40
Goodman, 1995	United States	To prospectively compare helical CT with pulmonary arteriography for detecting PE in patients with unresolved clinical and V/Q scan dx.	HCT	PA	Non-diagnostic V/Q scan.	20	53 (25-84)	60
Remy-Jardin, 1996	Europe	To evaluate accuracy of helical CT in dx of PE.	HCT	PA	Referral for pulmonary arteriography.	75	59 (22-83)	43
Christiansen, 1997		To test diagnostic validity of CT compared to pulmonary arteriography in acute PE.	HCT	PA	High clinical suspicion of PE.	70	67 (22-87)	48
Drucker, 1998	United States	To determine sensitivity and specificity of helical CT for the dx of acute PE.	HCT	PA	Referral for pulmonary arteriography.	47	57 (22-89)	47
Qanadli, 2000	Europe	To evaluate the accuracy of dual-section helical CT in acute PE dx.	HCT (dual section)	PA	Referral to radiology department.	157	58 (14)[a]	46
Velmahos, 2001	United States	To evaluate sensitivity and specificity of helical CT for dx of PE in critically ill surgical patients.	HCT	PA	Surgical ICU patients with explicitly defined clinical findings associated with PE.	22	38 (20-75)	73
Magnetic Resonance Imaging								
Grist, 1993	United States	To study the accuracy of MRA in pts w/PE	MR (fast GRE)	PA	Pts referred for PA.	14	(35-82)	50
Erdman, 1994	United States	To assess accuracy of MRI in the evaluation of patients with suspected PE.	MRI of clot (SE, GRE)	PA or V/Q	Suspected PE referred for PA or V/Q.	64	(18-73)	47

Evidence Table 22: Study design and characteristics of patients in studies evaluating computed tomography or magnetic resonance imaging for diagnosis of pulmonary embolism (continued)

Author, Year	Location	Aims	Test evaluated	Reference standard	Source of participants	N	Mean age in yrs (range)	Male (%)
Loubeyre, 1994	Europe	To evaluate contrast-enhanced MRA in the diagnosis of thrombi in both the proximal and peripheral portions of the pulmonary arteries	MRA (fast GRE + Gd)	PA	Suspected PE.	23	50 (20-66)	52
Meaney, 1997	United States	To compare MRA with PA in for diagnosing PE in patients referred for PA.	MRA (fast GRE + Gd)	PA	Suspected PE referred for PA.	30	52 (22-83)	50
Berthezene, 1999	Europe	To assess accuracy of MR perfusion imaging compared with perfusion scintigraphy in patients with suspected lung perfusion defects (due to PE or emphysema).	Perfusion MRI (fast GRE + Gd)	V/Q	Suspected PE referred for V/Q.	48	(34-83)	63
Gupta, 1999	Australia	To prospectively evaluate MRA to dx pts w/ suspected PE in whom V/Q scans are of intermediate probability or clinical suspicion is high, and who are referred for PA.	MRA (fast GRE + Gd)	PA	Suspected PE referred for PA .	36	59 (28-84)	47
Oudkerk, 2001	Europe	To assess accuracy of MRA for diagnosis of PE in non-selected patients with suspected PE and an abnormal V/Q scan.	MRA (fast GRE + Gd)	PA	Suspected PE with abnormal V/Q referred for PA.	115	53 (16-87)	43

[a] Standard deviation

Evidence Table 23: Quality of studies evaluating computed tomography or magnetic resonance imaging for diagnosis of pulmonary embolism

Author, year	Overall [a]	Representativeness of study population [b]	Bias & confounding [c]	Description of test protocols [d]	Test interpretation [e]	Statistical quality & interpretation [f]
Computed tomography						
Remy-Jardin, 1992	82	88	70	100	100	50
Blum, 1994	44	25	70	50	25	50
Goodman, 1995	74	88	80	100	100	0
Remy-Jardin, 1996	77	75	60	100	100	50
Christiansen, 1997	61	0	30	75	100	100
Drucker, 1998	81	75	80	100	100	50
Qanadli, 2000	84	88	80	100	100	50
Velmahos, 2001	83	100	90	75	100	50
Magnetic Resonance Imaging						
Grist, 1993	75	38	70	75	100	50
Erdman 1994	67	63	20	100	100	50
Loubeyre	68	25	60	100	100	50
Meaney 1997	77	75	10	100	100	100
Berthezene 1999	60	13	10	100	75	100
Gupta 1999	77	75	10	100	100	100
Oudkerk 2001	76	75	5	100	100	100

[a] **Overall:** The mean of the percentage scores from the categories: Representativeness of Study Population, Bias and Confounding, Description of Test Protocols, Test Interpretation, and Statistical Quality and Interpretation (see below).

[b] **Representativeness of Study Population:** Percentage score based on a total maximum score of 8 points. This included description of study setting and population (2 points), description of inclusion/exclusion criteria (2 points), information on excluded or non-participating patients (2 points), and description of key patient characteristics (2 points).

[c] **Bias and Confounding:** Percentage score based on a total maximum score of 10 points. This included use of the reference test on all subjects receiving the study test (2 points), use of the study test in the decision to obtain the reference test (2 points), blinding of test interpretation and clinical data (2 points), interpretation of the study test by two or more independent observers (2 points), and interpretation of the reference test by two or more independent observers (2 points).

[d] **Description of Test Protocols:** Percentage score based on a total maximum score of 4 points. This included description of the study test protocol (2 points), and description of the reference test protocol (2 points).

[e] **Test Interpretation:** Percentage score based on a total maximum score of 6 points. This included description of the criteria for a positive interpretation of the study test (2 points), description of the criteria for a positive interpretation of the reference test (2 points), and reporting on numbers and reasons for withdrawals or patients lost to followup (2 points).

[f] **Statistical Quality and Interpretation:** Percentage score based on a total maximum score of 4 points. This included reporting of a summary index of test performance and of an index of variability (2 points), and use of multivariate or stratified analyses to adjust for potential confounders (2 points).

Evidence Table 24: Results of studies evaluating computed tomography or magnetic resonance imaging for diagnosis of pulmonary embolism

Author, Year	Most distal arterial level interpreted	Subgroup	N	TP[a]	FP[b]	TN[c]	FN[d]	Sensitivity % [95% CI]	Specificity % [95% CI]	Accuracy % [95% CI]	PPV % [95% CI]	NPV % [95% CI]	Prevalence %
Computed tomography													
Remy-Jardin, 1992	Segmental		42	18	1	23	0	100 [81-100]	96 [79-100]	98 [87-100]	95 [74-100]	100 [85-100]	43
Blum, 1994	Segmental		10	7	0	3	0	100 [59-100]	100 [29-100]	100 [69-100]	100 [59-100]	100 [29-100]	70
Goodman, 1995	Segmental		20	6	1	12	1	86 [42-100]	92 [64-100]	90 [68-99]	86 [42-100]	92 [64-100]	35
	Subsegmental		20	7	1	8	4	64 [31-89]	89 [52-100]	75 [51-91]	88 [47-100]	67 [35-90]	55
Remy-Jardin, 1996	Segmental	All cases	75	39	7	25	4	91 [78-97]	78 [60-91]	85 [75-92]	85 [71-94]	86 [68-96]	57
		Excluding inconclusive cases	65	39	0	25	1	98 [87-100]	100 [86-100]	98 [92-100]	100 [91-100]	96 [80-100]	62
Christiansen, 1997	Segmental		70	17	2	49	2	89 [67-99]	96 [87-100]	94 [86-98]	89 [67-99]	96 [87-100]	27
Drucker, 1998	Segmental	Inexperienced readers	47	9	6	26	6	60 [32-84]	81 [64-93]	74 [60-86]	60 [32-84]	81 [64-93]	32
		Experienced readers	47	8	1	31	7	53 [27-79]	97 [84-100]	83 [69-92]	89 [52-100]	82 [66-92]	32
Qanadli, 2000	Subsegmental	All cases	157	56	6	89	6	90 [80-96]	94 [87-98]	92 [87-96]	90 [80-96]	94 [87-98]	39
		Excluding inconclusive cases	151	56	3	89	3	95 [86-99]	97 [91-99]	96 [92-99]	95 [86-99]	97 [91-99]	39

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Evidence Table 24: Results of studies evaluating computed tomography or magnetic resonance imaging for diagnosis of pulmonary embolism (continued)

Author, Year	Most distal arterial level interpreted	Subgroup	N	TP[a]	FP[b]	TN[c]	FN[d]	Sensitivity % [95% CI]	Specificity % [95% CI]	Accuracy % [95% CI]	PPV % [95% CI]	NPV % [95% CI]	Prevalence %
Velmahos, 2001	Subsegmental		22	5	2	9	6	45 [17-77]	82 [48-98]	64 [41-83]	71 [29-96]	60 [32-84]	50
Magnetic Resonance Imaging													
Grist, 1993	All cases	Referred for PA	14	6	3	5	0	100	62	79	67	100	43
Erdman, 1994	Segmental	All cases	63	31	3	26	4	88	90	90	91	87	55
Loubeyre, 1994	Segmental	All cases	23	10	0	11	2	83	100	91	100	85	52
Meaney, 1997	Segmental	All cases	30	8	1	21	0	100	95	97	89	100	27
Berthezene, 1999	Segmental	All cases	24					69	91				
Gupta, 1999	Segmental	All cases	36	11	2	22	1	85	96	92	85	96	36
Oudkerk, 2001	Segmental	All cases	118	27	2	81	8	77	98	92	93	91	30

[a] TP=true positive   [b] FP=false positive   [c] TN=true negative   [d] FN=false negative

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Appendix A. Core Technical Experts and Peer Reviewers

Core Technical Experts		
Expert Area and Organization	**Name**	**Location**
Partner Organization		
American Academy of Family Physicians	Lee Green MD	University of Michigan, Ann Arbor, MI
Cochrane Collaboration		
Dutch Cochrane Center	Jeroen van der Heijden MD	Academic Medical Centre, Amsterdam, the Netherlands
Diagnostic Testing Expert		
	Steven W. Heim MD	University of Virginia, Charlottesville, VA
Payor		
Center for Medicare and Medicaid Services	Steve Phurrough MD, MPA	Baltimore, MD
Primary Care Organizations		
American College of Physicians–American Society of Internal Medicine	Rodney E. Hornbake MD	Gentiva Health Services, Melville, NY
	Patricia Barry MD	Merck Institute of Aging and Health, Washington, DC
Society of General Internal Medicine	Richard White MD	University of California at Davis, CA
Professional Organizations		
American College of Chest Physicians	Gordan Guyatt MD	McMaster University, Hamilton, Ontario
	Jack Hirsch MD	Hamilton Civic Hospitals Research Centre, Hamilton, Ontario
	Agnes YY Lee MD	McMaster University, Hamilton, Ontario
	Phillip Wells MD	Ottawa Hospital, Ottawa, Ontario
American Association of Health Plans		Washington DC
American College of Radiology	Michael A. Bettmann MD	Dartmouth University, Hanover, NH
Funding Organization		
Agency for Healthcare Research and Quality (AHRQ)	David Atkins MD	Rockville, MD

Appendix B. Priority Journals for Hand Searching*

Priority Journal Titles
American Journal of Respiratory and Clinical Care Medicine
American Journal of Roentgenology (AJR)
Annals of Internal Medicine
Arteriosclerosis, Thrombosis, and Vascular Biology
Blood
British Journal of Haematology
British Medical Journal
Chest
Circulation
Circulation Research
JAMA
Journal of Computer Assisted Tomography
Journal of Nuclear Medicine
Lancet
Magnetic Resonance Medicine
New England Journal of Medicine
Radiology
Seminars in Nuclear Medicine
Thorax
Thrombosis and Haemostasis

* Tables of Contents reviewed from 1 October 2001 to 31 March 2002.

Appendix C. Literature Search Strategies

Question 1 and Question 2 — Low molecular weight heparin for deep venous thrombosis and pulmonary embolism (systematic reviews)

Medline
(quantitative* OR methodolog* OR systematic* OR meta-analysis OR "metaanalysis" OR " meta analysis" OR "meta-analyses" OR " metaanalyses" OR "meta analyses" OR (MEDLINE AND review[pt]) OR "clinical conference"[pt] OR "consensus development conference"[pt] OR "guideline"[pt] OR "meta analysis"[pt] OR "practice guideline"[pt] OR (review [pt] AND systematic*)) AND (deep venous thrombosis OR venous thromboembolism OR pulmonary embolism) AND (low molecular weight heparin OR lmwh OR enoxoparin OR Lovenox OR logiparin OR Innohep OR nadroparin OR fraxoparine OR dalteparin OR Fragmin OR reviparin OR clivarin OR CY222 OR tinzaparin OR innohep OR logiparin OR certoparin OR sandoparin OR embolex OR parnaparin OR fluxum OR clexane OR tedelparin OR Tedral)

Cochrane
((LOW and (MOLECULAR and (WEIGHT and HEPARIN))) AND ((DVT or PE) OR (VENOUS AND THROMBOSIS)))

Question 3a. Inpatient versus outpatient (primary literature)
(inpatients OR hospital) AND (ambulatory care OR ambulatory care facility OR outpatient) AND (deep venous thrombosis OR venous thromboembolism OR pulmonary embolism) AND (low molecular weight heparin OR lmwh OR enoxoparin OR Lovenox OR logiparin OR Innohep OR nadroparin OR fraxoparine OR dalteparin OR Fragmin OR reviparin OR clivarin OR CY222 OR tinzaparin OR innohep OR logiparin OR certoparin OR sandoparin OR embolex OR parnaparin OR fluxum OR clexane OR tedelparin OR Tedral)

Question 3b. Low molecular weight heparin costs (primary literature)
(cost OR charge) AND (low molecular weight heparin OR lmwh OR enoxoparin OR Lovenox OR logiparin OR Innohep OR nadroparin OR fraxoparine OR dalteparin OR Fragmin OR reviparin OR clivarin OR CY222 OR tinzaparin OR innohep OR logiparin OR certoparin OR sandoparin OR embolex OR parnaparin OR fluxum OR clexane OR tedelparin OR Tedral) AND (deep venous thrombosis OR pulmonary embolism OR venous thromboembolism)

Question 4. Duration of treatment (primary literature)
duration of treatment OR ("time factors/adverse effects" [MESH] OR "time factors/standards"[MESH]) AND (deep vein thrombosis OR pulmonary embolism or venous thromboembolism) AND (warfarin OR coumadin OR low molecular weight heparin)

Question 5. Clinical prediction rules
(sensitivity AND specificity) AND (deep venous thrombosis or pulmonary embolism and venous thromboembolism) AND clinical

Question 6. Ultrasound (systematic reviews)
(quantitative* OR methodolog* OR systematic* OR meta-analysis OR "metaanalysis" OR " meta analysis" OR "meta-analyses" OR " metaanalyses" OR "meta analyses" OR (MEDLINE AND review[pt]) OR "clinical conference"[pt] OR "consensus development conference"[pt] OR "guideline"[pt] OR "meta analysis"[pt] OR "practice guideline"[pt] OR (review [pt] AND systematic*)) AND (deep vein thrombosis OR venous thromboembolism) AND (ultrasonography OR ultrasound OR Doppler)

Question 7. Computerized tomography or magnetic resonance imaging (systematic reviews)
(quantitative* OR methodolog* OR systematic* OR meta-analysis OR "metaanalysis" OR " meta analysis" OR "meta-analyses" OR " metaanalyses" OR "meta analyses" OR (MEDLINE AND review[pt]) OR "clinical conference"[pt] OR "consensus development conference"[pt] OR "guideline"[pt] OR "meta analysis"[pt] OR "practice guideline"[pt] OR (review [pt] AND systematic*)) AND (pulmonary embolism) AND (computed tomography OR magnetic resonance imaging)

(Primary literature)
evaluation AND pulmonary embolism AND (computed tomography OR magnetic resonance imaging)

Question 8. D-dimer (systematic reviews)
(quantitative* OR methodolog* OR systematic* OR meta-analysis OR "metaanalysis" OR " meta analysis" OR "meta-analyses" OR " metaanalyses" OR "meta analyses" OR (MEDLINE AND review[pt]) OR "clinical conference"[pt] OR "consensus development conference"[pt] OR "guideline"[pt] OR "meta analysis"[pt] OR "practice guideline"[pt] OR (review [pt] AND systematic*)) AND d-dimer AND (deep venous thrombosis OR pulmonary embolism OR venous thromboembolism)

Appendix D. Abstract Review Form for Primary Literature

Record Number: **EPC Venous Thromboembolism Project**   **Reviewer:** __< >____

Abstract review Form   **Data Entry:** _____

Title:

☐ **Article for reference only**

Article relates to Key Questions (check **all** that apply**):**   ☐ LMWH for DVT   (**Q1**)   ☐ LMWH for PE   (**Q2**)   ☐ efficacy and cost-effectiveness of outpatient treatment with LMWH or UFH for DVT (**Q3**)   ☐ duration of therapy   (**Q4**)   ☐ use of clinical prediction rules   (**Q5**)   ☐ ultrasonography for DVT diagnosis   (**Q6**)   ☐ helical CT or MRI/MRA scan for PE diagnosis (**Q7**)   ☐ d-dimer for thromboembolism diagnosis (**Q8**)   ☐ does not apply to any question
Do not review article, because article ... (check 1 or more**):**   ☐ is not in English   ☐ has no original data   ☐ does not include human data   ☐ is a case report (single patient)   ☐ is a meeting abstract (no full article for review)   ☐ other _____   ☐ involves *only* prevention
If Question 3:   **If Question 4:**   **Do not review article, because ...**   **Do not review article, because...**   ☐ does not involve a comparison group (in an RCT or observational study) **or** is not a cost-effectiveness analysis   ☐ does not involve a comparison group (in an RCT or observational study
If Question 5:   **If Question 7:**   **Do not review article, because ...** (check 1 or more)   **Do not review article, because ...** (check 1 or more)   ☐ does *not* include 2 of 3 (history, physical exam, laboratory testing)   ☐ does not report test characteristics of CT **or** MRI for diagnosis of PE   ☐ does not specify a reference standard (gold standard)   ☐ does not use angiography **or** VQ scan as reference

Appendix E. Abstract Review Form for Systematic Reviews

Record Number: **EPC Venous Thromboembolism Project**   **Reviewer:** __< >____

First Abstract Review: **Abstract review Form**   **Data Entry: _____**

Title:

Do not review article, because article … (check 1 or more):	**Article relates to Key Questions** (check all that apply)
☐ is not in English ☐ does not include human data ☐ is a meeting abstract (no full article for review) ☐ does *not* include a systematic review, meta-analysis, or cost-effectiveness analysis ☐ reports primary data, not a review article ☐ focuses on *prevention* of venous thromboembolism ☐ does not apply to a key question ☐ other: (specify)_____ ☐ Uncertain; retrieve article to decide **Do not continue if any item above is checked. Otherwise, continue to next column and check *at least one box***	☐ LMWH for DVT (Q1a) ☐ LMWH for PE (Q1b) ☐ outpatient treatment of DVT (Q2a) ☐ cost-effectiveness of LMWH/ outpatient treatment (Q2b) ☐ duration of therapy (Q3) ☐ use of clinical prediction rules (Q4) ☐ ultrasonography for DVT diagnosis (Q5) ☐ helical CT scan for PE diagnosis (Q6a) ☐ MRI/MRA for PE diagnosis (Q6b) ☐ d-dimer for thromboembolism diagnosis (Q7) ☐ does not apply to any question

☐   **Article for reference only**

Appendix F. Quality Review Form for Key Questions 3 and 4

Johns Hopkins Evidence-based Practice Center
DVT Project - Quality Review Form, Primary Literature
Q3 and 4 (Treatment Studies)

Article ID _____   First Author _____   1st reviewer (initials) _____   2nd reviewer (initials) _____

Primary reasons for exclusion: (Check all that apply)	
□ Not in English	□ Does not involve a comparison group in a(n) RCT or observational study
□ Does not include human data	□ Involves 5 or fewer patients
□ Does not apply to out key question	□ All data reported in a subsequent publication
□ Focuses only on prevention of VTE	□ Other: (specify)_____

If ANY of the above items is CHECKED - STOP: Do Not Continue: return article and form to Mollie

REPRESENTATIVENESS OF STUDY POPULATION

1. Did the study team describe the setting and population from which the study sample was drawn, and the dates of the study?

	a. Adequate	(Setting AND population described AND start and end date specified)	2
	b. Fair	(One or more of these NOT reported OR poor description)	1
	c. Inadequate	(Not Specified)	0

2. Were detailed inclusion/exclusion criteria provided?

	a. Adequate	(Detailed description of specific inclusion and exclusion criteria OR statement that all eligible patients enrolled)	2
	b. Fair	(Some description, but would be difficult to replicate based on information provided)	1
	c. Inadequate	(Minimal description or none at all)	0

3. Was information provided on excluded or not participating patients?

	a. Adequate	(All reasons for exclusion AND number excluded OR no exclusions)	2
	b. Fair	(Only one of above criteria specified or information not sufficient to allow replication)	1
	c. Inadequate	(Non of the above criteria specified)	0

4. Does the study describe key patient characteristics at enrollment?

Demographics: age, gender

VTE Features: **Type:** DVT, PE   **Event Number:** first VTE, recurrent VTE   **Cause:** idiopathic VTE, malignancy-associated temporary risk factor

	a. Adequate	(Demographic AND VTE features well described)	2
	b. Fair	(Demographics AND only one VTE feature described; OR no demographics described but VTE features well described)	1
	c. Inadequate	(No key patient characteristics well described)	0

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BIAS AND CONFOUNDING

5. Was assignment of patients to study group randomized?			
	a. Adequate	(Investigators could not predict assignment)	2
	b. Partial	(Date of birth, admission date, hospital record number, or other non-random scheme for assignment OR did not state)	1
	c. Not randomized		0
	d. Unclear		0

6. Did the patient groups have any important differences on key patient characteristics?	
Demographics: age, gender	
VTE Features: **Type:** DVT, PE **Event Number:** first VTE, recurrent VTE **Cause:** idiopathic VTE, malignancy-associated temporary risk factor	

	a. Groups equivalent in all factors examined	2
	b. Groups have minor difference in 1 or 2 factors	1.5
	c. Groups have an important difference in one or more factors OR minor difference in more than two factors	1
	d. Analysis not done	0

7. Was there blinding of clinician, patients, and outcome assessors?			
	a. Excellent	(All three blinded, including all treatment arms)	2
	b. Good	(Only 2 of the 3 blinded, or some but not all of the arms)	1.5
	c. Fair	(Only 1 of the 3 blinded)	1
	d. Poor	(No blinding or not stated)	0

DESCRIPTION OF THERAPY/MANAGEMENT

8. Did the study describe details of the treatment regimen?			
	a. Adequate	(Drug, dose intensity, duration and time in therapeutic range)	2
	b. Fair	(One of the above NOT described)	1
	c. Inadequate	(More than one of above NOT described)	0

* time in therapeutic range data not required for LMWH treated patients

9.Was there a description of other treatments given to each study group?

Treatments: compression stockings, aspirin, NSAIDs, oxygen

	a. Adequate	(Other treatment fully described)	2
	b. Fair	(Some description, but information not sufficient to allow replication)	1
	c. Inadequate	(Not described)	0

OUTCOMES AND FOLLOWUP

10. Was there a description of the criteria for determining outcomes?

Recurrence Measures: duplex ultrasonography, venography, MRV, V/Q scan, spiral CT scan, MRA

Bleeding Measures: Major bleeding and minor bleeding defined

	a. Adequate	(Clear definitions of each outcome AND exact techniques to assess the outcome)	2
	b. Fair	(Some description, but information not sufficient to allow replication)	1
	c. Inadequate	(No information provided)	0

11. Did the study describe adverse effects experienced by patients?

Treatment: Bleeding, thrombocytopenia, osteoporosis, other

	a. Adequate	(Bleeding and at least one other adverse effects described fully)	2
	b. Fair	(Only bleeding mentioned OR other adverse effects mentioned, but NOT described fully)	1
	c. Inadequate	(Bleeding NOT mentioned)	0

12. Did the study report the numbers of and reasons for withdrawals from the study protocol or patients otherwise lost to follow-up?

	a. Numbers and reasons reported (or no withdrawals)	2
	b. Only numbers OR reasons reported	1
	c. Neither given	0

13. What was the greatest percentage of patients in a treatment group that withdrew from the study protocol or were lost to follow-up?

	a. None	2
	b. < 10%	1.5
	c. 10 - 20%	1
	d. > 20%	0
	e. Not stated	0

14. What was the planned length of follow-up?

	a. > 2 years	2
	b. 1 - 2 years	1.5
	c. 6 - 11 months	1
	d. 0 - 5 months	0

STATISTICAL QUALITY AND INTERPRETATION

15. For primary endpoints, did the study report the magnitude of difference between groups (or magnitude of association between key variables) AND an index of variability (e.g., test statistic, p value, standard error, confidence intervals)?

	a. Adequate	(Both reported, with standard error or confidence intervals as index or variability)	2
	b. Fair	(Both reported, with only test statistic or p value as index of variability)	1
	c. Inadequate	(No information given)	0

16. Was the statistical test of all analyses clearly identified?

	a. Adequate	(Identified for all analyses)	2
	b. Fair	(Identified for some of the analyses)	1
	c. Inadequate	(Not identified)	0

17. If groups were not comparable at study onset, was there adjustment for protocol confounders with multi-variate or stratified analyses AND were confounders coded in a way to make such control adequate?

	a. Adequate	(Adjustment AND confounders appropriately coded)	2
	b. Fair	(Adjustment BUT confounders not coded appropriately OR coding unclear)	1
	c. Inadequate	(No adjustment OR not mentioned)	0
	d. Not applicable		N/A

18. Were withdrawals, crossovers, and loss to follow-up handled appropriately in analysis?

	a. No loss to follow-up, withdrawals, or crossovers	2
	b. Sensitivity analysis	2
	c. By intention to treat/screen	2
	d. By 'intervention received' analysis only	1
	e. By none of the above	0
	f. Unknown	0

CONFLICTS OF INTEREST

19. Did the study report identify the sources of funding and the type and degree of involvement of the funding agency?

	a. Adequate	(Source AND type or degree of involvement OR no funding)	2
	b. Fair	(Source only)	1
	c. Inadequate	(Neither)	0

**THANK YOU for your time and attention to completing this work.
Please return completed form to Mollie.**

Appendix G. Quality Review Form for Key Questions 5 and 7

Johns Hopkins Evidence-Based Practice Center
VTE Project - Quality Review Form, Primary Literature - *Diagnosis (Q5 and Q7)*

Article ID _____ First author _____ 1st Reviewer _____ 2nd Reviewer _____

Primary reasons for exclusion: (Check all that apply)	
☐ Not in English	☐ Reports only basic science
☐ Does not include human data	☐ Meeting abstract (no full article for review)
☐ Does not apply to key question	☐ All data reported in a subsequent publication
☐ Focuses on prevention of VTE	☐ Other: (specify) _____
☐ No original data or results reported	

Additional exclusions per Key Question refinements: (Check all that apply)

Question 5:

☐ DVT diagnosis not confirmed with imaging (US, contrast venography)

☐ PE diagnosis not confirmed with study (high prob V/Q, pulmonary arteriography, spiral CT, autopsy)

☐ No clinical model presented: does not include 2 of 3 (history, exam, laboratory testing) evaluated in combination

☐ Total study population < 30

Question 7:

☐ Does not report test characteristics of CT or MRI for diagnosis of PE (e.g., sensitivity, specificity, ROC)

☐ Does not use VQ scan or pulmonary arteriography as reference ("gold") standard

☐ Is a case report

If ANY of the above items is CHECKED - STOP: Do Not Continue; return article and form to Mollie

REPRESENTATIVENESS OF STUDY POPULATION

1. Did the study describe the setting and population from which the study sample was drawn, and the dates of the study?			
	a. Adequate	(Setting AND population described AND start and end date specified)	2
	b. Fair	(One or more of these NOT reported OR poor description)	1
	c. Inadequate	(Not specified)	0

2. Were detailed inclusion/exclusion criteria provided?			
	a. Adequate	(Detailed description of specific inclusion and exclusion criteria OR statement that all eligible patients enrolled)	2
	b. Fair	(Some description, but would be difficult to replicate based on information provided)	1
	c. Inadequate	(Minimal description or none at all)	0

3. Was information provided on excluded or non-participating patients?			
	a. Adequate	(All reasons for exclusion AND number excluded OR no exclusions)	2
	b. Fair	(Only one of above criteria specified or information not sufficient to allow replication)	1
	c. Inadequate	(None of the above criteria specified)	0

4. Does the study describe key patient characteristics at enrollment? *Demographics*: age, gender *DVT/PE Risk Factors (if any)*: recent surgery, medications, prior DVT/PE, malignancy, recurrence			
	a. Adequate	(Demographic and risk factors well described)	2
	b. Fair	(Only demographics well described)	1
	c. Inadequate	(No key patient characteristics well described)	0

BIAS AND CONFOUNDING

5. Did all individuals receiving the study test also receive the reference test?			
	a. All	(All received both tests)	2
	b. Some	(Some received both tests)	1
	c. None	(No one received both tests)	0

For Q6 we want to understand the extent to which testing decisions were independent of each other. There are two ways for testing to be *dependent*: 1) the decision to perform the 2nd test can be dependent on the *results* of the 1st test 2) the decision to include a patient in the study can be based on a *referral* for testing.

6. Was the decision to obtain the reference test affected in any way by the result of the study test, or vice versa?			
	a. No	(Decision to test **not** affected by *either* 1) above *or* 2) above)	2
	b. No (implied)	(Decision to test **is** affected by *either* 1) above *or* 2) above)	1
	c. Yes	(Decision to test was affected by other test's results)	0

7. Was there blinding of study test interpretation, reference test interpretation, and clinical data? (Note: This question concerns *blinding*, not independence, of interpretations.)			
	a. Excellent	(All three blinded, including both test interpretations with each other)	2
	b. Good	(Test interpretations blinded to each other but not to clinical data)	1
	c. Fair	(Test interpretations blinded to clinical data but not to each other)	0.5
	d. Poor	(No blinding or not stated)	0

8. Was interpretation of the study test performed by two or more independent observers?			
	a. Adequate	(Multiple observers AND independent)	2
	b. Fair	(Multiple observers but NOT independent)	1
	c. Inadequate	(Neither or not stated)	0

9. Was interpretation of the reference test performed by two or more independent observers?			
	a. Adequate	(Multiple observers AND independent)	2
	b. Fair	(Multiple observers but NOT independent)	1
	c. Inadequate	(Neither or not stated)	0

DESCRIPTION OF TEST PROTOCOLS

10. Did the study describe details of the study test protocol?			
	a. Adequate	(Enough description to replicate)	2
	b. Fair	(Some description, but not enough to replicate)	1
	c. Inadequate	(No description)	0

11. Did the study describe details of the reference test protocol?			
	a. Adequate	(Enough description to replicate)	2
	b. Fair	(Some description, but not enough to replicate)	1
	c. Inadequate	(No description)	0

12. (Q5 ONLY) Does the study report the methods used to develop the clinical model being tested (e.g., pilot testing, literature-based, collective experience)?			
	a. Adequate	(3 characteristics)	2
	b. Fair	(1-2 characteristics)	1
	c. Inadequate	(None)	0
	d. Not applicable	(Does not concern Q5)	N/A

TEST INTERPRETATION

13. Were the interpretation criteria of a positive test described for the study test?			
	a. Adequate	(Enough description to replicate)	2
	b. Fair	(Some description, but not enough to replicate)	1
	c. Inadequate	(No description)	0

14. Were the interpretation criteria of a positive test described for the reference test?			
	a. Adequate	(Enough description to replicate)	2
	b. Fair	(Some description, but not enough to replicate)	1
	c. Inadequate	(No description)	0

15. Did the study report the numbers of and reasons for withdrawals from the study protocol or patients otherwise lost to follow-up?

	a. Adequate	(Both numbers AND reasons reported, or no withdrawals)	2
	b. Fair	(Only numbers OR reasons reported)	1
	c. Inadequate	(Neither given)	0
	d. Not applicable	(No longitudinal follow-up was performed)	N/A

STATISTICAL QUALITY AND INTERPRETATION

16. Was a summary index of test performance (e.g., sensitivity/specificity, area under ROC curve) reported for the study test AND an indicator of variability (standard error, confidence interval)?

	a. Adequate	(Both reported)	2
	b. Fair	(Test performance but no index of variability)	1
	c. Inadequate	(No information given)	0

17. If groups were not comparable at study onset, was there adjustment for potential confounders with multivariate or stratified analyses AND were confounders coded in a way to make such control adequate?

	a. Adequate	(Adjustment AND confounders appropriately coded)	2
	b. Fair	(Adjustment BUT confounders not coded appropriately OR coding unclear)	1
	c. Inadequate	(No adjustment OR not mentioned)	0
	d. Not applicable	(Only one group being studied)	N/A

CONFLICT OF INTEREST

18. Did the study report identify the source of funding and the type and degree of involvement of the funding agency?

	a. Adequate	(Source AND type or degree of involvement if conflict of interest possible OR no funding)	2
	b. Fair	(Source only)	1
	c. Inadequate	(Neither)	0
	d. Not applicable		N/A

THANK YOU for your time and attention to completing this work.

Appendix H. Quality Review Form for Key Questions 3b - costs

Johns Hopkins Evidence-Based Practice Center
VTE Project - Quality Review Form, Primary Literature - *Costs (Q3b)*

Article ID _____   First author _____   1st Reviewer _____   2nd Reviewer _____

Primary reasons for exclusion: (Check all that apply)

☐ Not in English   ☐ No original data or results reported

☐ Does not include human data   ☐ Is a case report (single patient)

☐ Meeting abstract (no full article for review)   ☐ Other: (note if applies to another key question) _____

☐ Involves *only* prevention   ☐ Does not involve a comparison group (in an RCT or
                                                     observational study) or is not a cost-effectiveness analysis
☐ Does not apply to key question

If ANY of the above items is CHECKED - STOP: Do Not Continue; return article and form to Mollie

1. Is the research question and its economic importance clearly stated?			
	a. Adequate	(States research question and the economic importance of the question)	2
	b. Fair	(States one or the other but not both)	1
	c. Inadequate	(Does not address)	0

2. Do the authors state the perspective of the analysis? (e.g. payor, physician, patient, society)			
	a. Adequate	(Perspective clearly defined)	2
	b. Fair	(Perspective could be inferred)	1
	c. Inadequate	(Perspective unclear)	0

3. Are the comparison strategies clearly described?			
	a. Adequate	(Includes the most relevant strategies, and justified if others were excluded)	2
	b. Fair	(Includes some of the relevant strategies)	1
	c. Inadequate	(Does not clearly describe)	0

4. Is the structure of the economic analysis clear? (e.g. cost-benefit, cost-effectiveness, cost-utility, cost minimization)			
	a. Adequate	(Structure is clear, replicable, and appropriate for the posed question)	2
	b. Fair	(Analysis could not be replicated due to insufficient details or is inappropriate for the question)	1
	c. Inadequate	(Does not use an acceptable form of economic analysis)	0

5. Are the costs and outcomes appropriately valued?			
	a. Adequate	(Comprehensive systematic search for data on costs and rates of outcomes OR collection of primary data to generate this information)	2
	b. Fair	(Mostly used data on costs and outcomes from the literature but did not search systematically for this data, or primary data collection was inadequate)	1
	c. Inadequate	(Majority of data on costs and outcomes was estimated)	0

6. Were allowances made for uncertainties in the analysis?

	a. Adequate	(Included a sensitivity analysis in which estimates were varied over an appropriate range; and range was chosen based on literature review)	2
	b. Fair	(Included a sensitivity analysis in which estimates were varied over an arbitrary range of values)	1
	c. Inadequate	(No sensitivity analysis)	0

7. Is it clear to what patient population the results will be applicable?			
	a. Adequate	(Clearly states what the base case is for the analyses, or defines the population in whom costs were measured)	2
	b. Fair	(Base case estimates or population is described but is inappropriate for the question or insufficiently described)	1
	c. Inadequate	(Does not)	0

8. Are the appropriate costs and benefits of each strategy presented?			
Cost-effectiveness: incremental costs per a unit measure of benefit **Cost-minimization:** all costs in all strategies **Cost-benefit:** costs of strategies and costs of outcomes in monetary units			
	a. Adequate	(Appropriately reports the results with a correct measure for the study design)	2
	b. Fair	(Describes optimal strategy but without presenting data)	1
	c. Inadequate	(Does not address optimal strategy)	0

9. Results of sensitivity analyses are appropriately interpreted and presented?			
	a. Adequate	(Authors state results and under what conditions the optimal strategies differ)	2
	b. Fair	(State the results with no comments about sub-populations or the results if parameters change)	1
	c. Inadequate	(Do not clearly state results)	0

CONFLICT OF INTEREST

10. Did the study report identify the source of funding and the type and degree of involvement of the funding			
	a. Adequate	(Source AND type or degree of involvement OR no funding)	2
	b. Fair	(Source only)	1
	c. Inadequate	(Neither)	0
	d. Not applicable		N/A

THANK YOU for your time and attention to completing this work.

Appendix I. Quality Review Form for Systematic Reviews

Quality Assessment Form for Systematic Literature Reviews
Johns Hopkins University Evidence-based Practice Center
Deep Venous Thrombosis Project

Ref #: _____   Key Question: _____   Reviewer: _____

1. Did the authors clearly state the question addressed by the overview at the beginning of the article?		
a.	Yes. The authors stated a focused clinical question about tests or treatment, AND specified a target population	2
b.	Partially.	1
c.	No	0

2. Did the authors describe the search methods used to find evidence (original research) on the primary question(s)?		
a.	Yes. Enough information was reported to permit replication	2
b	Partially.	1
c	No.	0

3. Was the search for evidence reasonably comprehensive?		
a.	Yes. Search included MEDLINE (or other electronic database), hand-searching of select journals or reference lists, AND query of 1 or more experts.	2
b	Partially. Search included MEDLINE (or other electronic database), but did not include hand-searching of journals or reference lists AND/OR did not include a query of experts.	1
c	No. Search did not include an electronic database of journals.	0
d	Can't tell.	0

4. Did the authors report on the criteria they used for deciding which studies to include in the systematic review?		
a.	Yes. Criteria were specified clearly enough to permit replication.	2
b	Partially. Criteria specified, but without enough detail to permit replication.	1
c	No. Criteria not specified.	0

5. Were the inclusion criteria appropriate (aimed at avoiding bias in the included studies)?		
a.	Yes. Inclusion criteria are likely to capture all relevant studies (e.g., included languages other than English).	2
b	Partially.	1
c	No. Inclusion criteria likely to lead to biased sampling of studies.	0
d	Cannot tell. Inclusion criteria described inadequately.	0

6. Did the authors assess study quality?		
a.	Yes. Criteria to assess study quality were specified with adequate detail to permit replication.	2
b	Partially. Criteria to assess study quality not adequately described.	1
c	No.	0

7. Was the quality assessment done appropriately?		
a.	Yes. Quality assessment was done using a validated instrument (with citation) or the authors demonstrated validity of their methods.	2
b	Partially. Authors used their own quality assessment instrument without validation, or another instrument with unknown measurement properties.	1
c	No.	0
d	Cannot tell. There was no quality assessment reported.	0

8. Did the authors demonstrate that their methodology was reproducible?		
a.	Yes. The investigators mostly (>50% of the time) agreed on selection of articles, on quality assessment, AND on the data that was extracted.	2
b	Partially. Disagreement occurred the majority of the time either on the selection of articles, quality assessment, or data extraction (but not all 3).	1
c	No. Disagreement occurred the majority of the time on the selection of articles, quality assessment, AND data extraction.	0
d	Can't tell. Authors didn't comment on reproducibility.	0

9. Did the authors discuss whether the variation in the results of the original research may be due to differences in study design or population?		
a.	Yes. Text or tables provide comparative information on most of following: study design, populations, exposures or interventions, and outcome measures	2
b	Partially.	1
c	No.	0

10. Did the authors describe the methods they used to combine the results of the relevant studies (to reach a conclusion)?		
a.	Yes. Methods were reported clearly enough to allow replication.	2
b	Partially.	1
c	No.	0

11. Were the results of the relevant studies combined appropriately relative to the primary question?		
a.	Yes. The overview included some assessment of the qualitative and quantitative heterogeneity of study results AND used an accepted pooling method (i.e., more than simple addition)	2
b	Partially.	1
c	No.	0
d	Cannot tell. No description of the methods used for combining studies.	0

12. Were the conclusions of the authors supported by the data and/or analysis reported in the overview?		
a.	Yes.	2
b	Partially.	1
c	No.	0

THANK YOU for your time and attention to completing this work.
Please return completed form to Mollie.

Appendix J: Acronyms and Abbreviations

Abbreviation	Term
AC	anticoagulants
ARR	absolute risk reduction
ASA	aspirin
asymp	asymptomatic
BF	breastfeeding
bid	twice a day
ca	cancer
CA	California
CAD	Canadian dollars
CE	cost effectiveness
CI	confidence interval
CohP	cohort prospective
CohR	cohort retrospective
comp	compression
consec	consecutive
CT	computized tomography
CVA	cerebrovascular accident
d/c	discontinuation
DVT	deep venous thrombosis
dx	diagnosis
ED	emergency department
ELISA	enzyme-linked immunosorbent assay
FN	false negative
FP	false positive
FRF	French francs
f/u	followup
Gd	Gadolinium
GRE	gradient echo
hr	hour
HRT	hormone replacement therapy
ICU	intensive care unit
inpt	inpatient
INR	international normalized ratio
IPG	impedance plesthymography
IU	international units
IV	intravenous
IVC	inferior vena cava
LE	life expectancy
LMWH	low molecular weight heparin
LT	long term
LY	life year(s)
MD	physician
ME	Medicare
mo	month(s)
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
N/A	not applicable
NLG	Netherlands guilders
NNT	number needed to treat

NPV	negative predictive value
NR	non-response
NSAID	nonsteroidal anti-inflammatory drug
NSD	no significant difference
OCP	oral contraceptive pill
OR	odds ratio
outpt	outpatient
PA	pulmonary angiogram
PE	pulmonary embolism
Preg	pregnancy
PIOPED	Prospective investigation of pulmonary embolism diagnosis
postop	postoperative
PPV	positive predictive value
PRF	permanent risk factor
prosp	prospective
prox DVT	proximal deep vein thrombosis
PTP	pretest probability
pts	patients
PTT	partial thromboplastin time
QALY	quality adjusted life years
qd	every day
QOL	quality of life
RAS	risk assessment score
RCT	randomized controlled trial
ROC	receiver operating characteristic
RR	risk ratio
RRR	relative risk reduction
rx	prescription
sens	sensitivity
spec	specificity
SPECT	single-photon emission computerized tomography
SQ	subcutaneous
sx	symptom(s)
symp	symptomatic
tid	three times a day
tiw	three times per week
TN	true negative
TP	true positive
TRF	temporary risk factor
tx	treatment
u	units
UFH	unfractionated heparin
UE	upper extremity
U/S	ultrasound
USD	United States dollars
VDS	venous duplex sonography
V/Q	ventilation perfusion
vs	versus
VTE	venous thromboembolism
w/	with
w/i	within

w/o	without
wk	week(s)
yr	year(s)

Not listed above:
hx

Appendix K. Acknowledgments