Agency for Healthcare Research and Quality

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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.

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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.

- 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

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.

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