Current Diagnosis of Venous Thromboembolism in Primary Care: A Clinical Practice Guideline from the American Academy of Family Physicians and the American College of Physicians

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ABSTRACT

This guideline summarizes the current approaches for the diagnosis of venous thromboembolism. The importance of early diagnosis to prevent mortality and morbidity associated with venous thromboembolism cannot be overstressed. This field is highly dynamic, however, and new evidence is emerging periodically that may change the recommendations. The purpose of this guideline is to present recommendations based on current evidence to clinicians to aid in the diagnosis of lower extremity deep venous thrombosis and pulmonary embolism.

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RECOMMENDATIONS

Recommendation 1

Validated clinical prediction rules should be used to estimate pretest probability of venous thromboembolism (VTE), both deep venous thrombosis (DVT) and pulmonary embolism, and for the basis of interpretation of subsequent tests.

Good quality evidence supports the use of clinical prediction rules to establish pretest probability of disease. The Wells prediction rules for DVT and for pulmonary embolism (Tables 1 and 2) have been validated and are frequently used to estimate the probability of VTE before performing more definitive testing on patients. The Wells prediction rule performs better in younger patients without comorbidities or a history of VTE than it does in other patients. Physicians should use their clinical judgment in cases where a patient is older or presents with comorbidities.

Recommendation 2

In appropriately selected patients with low pretest probability of DVT or pulmonary embolism, obtaining a high-sensitivity D-dimer is a reasonable option, and if negative,

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indicates a low likelihood of VTE.

In selected patients who have a low pretest probability of VTE as defined by the Well prediction rules, a negative high-sensitivity D-dimer assay for VTE has sufficiently high negative predictive value to reduce the need for further imaging studies. Currently, enzyme-linked immunosorbent assay (ELISA), quantitative rapid ELISA, and advanced turbidimetric D-dimer determinations are highly sensitive assays (sensitivity 96% to 100%) and their use is practical in diagnosis of VTE. D-dimer testing has the highest negative predictive value when used to exclude VTE in younger patients without associated comorbidity or history of VTE and with short duration of symptoms, because the Wells criteria more accurately predict a low pretest probability of VTE in such patients. In older patients, those with associated comorbidity, and long duration of symptoms, a D-dimer alone may not be sufficient to rule out VTE.

Recommendation 3

Ultrasound is recommended for patients with intermediate to high pretest probability of DVT in the lower extremities.

Use of ultrasound in diagnosing symptomatic thrombosis in the proximal veins of the lower limb is recommended for patients whose pretest probability of disease falls in the category of intermediate to high risk of DVT under the Wells prediction rule. Ultrasound is less sensitive in patients who have DVT limited to the calf; therefore, a negative ultrasound does not rule out DVT in these patients. Repeat ultrasound or venography may be required for patients who have suspected calf-vein DVT and a negative ultrasound and for patients who have suspected proximal DVT and an ultrasound that is technically inadequate or equivocal. Contrast venography is still considered the definitive test to rule out the diagnosis of DVT.

Recommendation 4

Patients with intermediate or high pretest probability of pulmonary embolism require diagnostic imaging studies.

For patients who have intermediate or high pretest probability of pulmonary embolism, imaging is essential. Possible tests include ventilation-perfusion (V/Q)

Table 1. Wells Prediction Rule for Diagnosing Deep Venous Thrombosis: Clinical Evaluation Table for Predicting Pretest Probability of Deep Vein Thrombosis

Clinical Characteristic	Score
Active cancer (treatment ongoing, within previous 6 months, or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden >3 days or major surgery within 12 weeks requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling 3 cm larger than asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Alternative diagnosis at least as likely as deep venous thrombosis	-2

Note: Clinical probability: low ≤0; intermediate 1-2; high ≥3. In patients with symptoms in both legs, the more symptomatic leg is used.

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Table 2. Wells Prediction Rule for Diagnosing Pulmonary Embolism: Clinical Evaluation Table for Predicting Pretest Probability of Pulmonary Embolism

Clinical Characteristic	Score
Previous pulmonary embolism or deep vein thrombosis	+1.5
Heart rate >100 beats per minute	+1.5
Recent surgery or immobilization	+1.5
Clinical signs of deep vein thrombosis	+3
Alternative diagnosis less likely than pulmonary embolism	+3
Hemoptysis	+1
Cancer	+1

Note: Clinical probability of pulmonary embolism: low 0-1; intermediate 2-6; high ≥7.

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scan, multidetector helical computed axial tomography (CT), and pulmonary angiography. Recent systematic reviews indicate that CT alone may not be sufficiently sensitive to exclude pulmonary embolism in patients who have a high pretest probability of pulmonary embolism.

INTRODUCTION

VTE comprises pulmonary embolism and DVT. Most deep vein thromboses are in the lower extremity. Those that involve the deep veins proximal to the knee are associated with an increased risk of pulmonary embolism. Those that involve only the calf veins are not associated with an increased risk of pulmonary embolism, but are associated with development of postthrombotic syndrome. Upper extremity

deep vein thromboses are uncommon and are outside the scope of this guideline. The annual incidence of VTE in the United States is 600,000 cases[1] and is increasing with the aging of the population. Twenty-six percent of undiagnosed and untreated patients with pulmonary embolism will have a subsequent fatal embolic event, whereas another 26% will have a nonfatal recurrent embolic event that can eventually be fatal.[2] Thus, the importance of early diagnosis to prevent mortality and morbidity associated with VTE cannot be overemphasized.

This guideline aims to present evidence-based recommendations for the diagnosis of lower extremity DVT and pulmonary embolism. The target audience for this guideline is all primary care physicians. The target patient population is all adults who have a probability of developing DVT or pulmonary embolism, including pregnant individuals.

METHODS

The guideline is based on a systematic review of the evidence as detailed in a comprehensive evidence report published in 2003[3] and updated in the accompanying background paper by members of the Johns Hopkins University Evidence-based Practice Center that prepared the original report.[4,5] Those papers contain substantial additional detail about the evidence for each of the recommendations in this guideline. The American Academy of Family Physicians (AAFP) nominated this topic to the Agency for Healthcare Research and Quality Evidence-based Practice Centers (EPC) program, and the American College of Physicians (ACP) supported the nomination. This document covers diagnosis and is the first of 2 guidelines, the second by Snow et al addresses management.[6]

This guideline's recommendations are based on the EPC review, which addressed the following questions on diagnosis formulated by the AAFP and ACP:

1. Are clinical prediction rules valuable for diagnosing DVT or pulmonary embolism, and does addition of the D-dimer assay improve the test characteristics of clinical prediction rules?

2. What are the test characteristics of D-dimer measurement alone when used for diagnosis or exclusion of lower extremity DVT or pulmonary embolism, and how does choice of assay affect the test characteristics?

3. What are the test characteristics of ultrasonography for diagnosis of DVT, including calf vein DVT?

4. What are the test characteristics of computed axial tomography (CT) for diagnosis of pulmonary embolism?

CLINICAL PREDICTION RULES ALONE AND IN COMBINATION WITH D-DIMER ASSAY FOR DIAGNOSIS OF VTE

A clinical prediction rule is used to calculate the pretest probability of VTE based on a clinical assessment of risk factors and physical findings. Of the various available prediction rules, the Wells prediction rules for DVT and pulmonary embolism[7,8] were most frequently evaluated (17 of 19 studies for DVT[7,9-24] and 3 of 8 for pulmonary embolism[25-27]). Individual clinical features are poorly predictive when not combined in a formal prediction rule.[28]

Eleven studies combined the Wells prediction rule with a D-dimer assay.* A systematic review concluded that patients with a low pretest probability and a negative D-dimer test had a 3-month incidence of DVT of 0.5%, whereas those with a negative D-dimer test and moderate or high pretest probability had incidences of 3.5% and 21.4%, respectively.[30] A recent study of the Wells rule in primary care raised doubts about its negative predictive value, but the study included patients with recurrent DVT, and its implications are not yet clear.[31]

In summary, the evidence supports the use of a clinical prediction rule for establishing pretest probability of VTE. Combination of a D-dimer assay with a clinical prediction rule provides sufficient negative predictive value to reduce the need for further imaging studies in appropriately selected patients with low pretest probability of disease.

TEST CHARACTERISTICS OF D-DIMER ASSAYS ALONE FOR DIAGNOSIS OF VTE

Four systematic reviews[4] evaluated the use of D-dimer testing alone (ie, without concomitant use of a clinical prediction rule) for diagnosis or exclusion of VTE. Two of these studies examined the use of D-dimer testing for excluding pulmonary embolism. These studies showed that both enzyme-linked immunosorbent assays (ELISA) and latex turbidimetric assays had a high sensitivity and a high negative predictive value for pulmonary embolism in patients with a low to moderate clinical probability of the disease (using a D-dimer cutoff of 500 ng/mL).[32,33] Specificity decreased, however, for patients with associated comorbidity, older age, and longer duration of symptoms. Stein et al's meta-analysis of D-dimer assays for diagnosis of DVT or pulmonary embolism using ELISA found pooled specificities ranged from 40% to 50%.[34]

In summary, the evidence suggests that a negative highly sensitive D-dimer test can help exclude the diagnosis of proximal DVT and pulmonary embolism

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* *References 9, 14, 15 17-19 ,22 ,23 ,26, 27, 29.*

in relatively healthy younger patients with short duration of symptoms who have a low pretest probability of VTE. There is variation in the sensitivity of D-dimer assays, however, and clinicians should be informed about the type of D-dimer assay used in their clinical setting relative to the population being tested and type of assay being used.

TEST CHARACTERISTICS OF ULTRASONOGRAPHY FOR DIAGNOSIS OF DVT

The EPC review found sensitivities of 89% to 96% and specificities of 94% to 99% for ultrasonography in the diagnosis of symptomatic thrombosis in the proximal veins of the lower extremity.[12,35-41] Sensitivity was lower (47% and 62%) for diagnosis of thrombi in proximal veins in asymptomatic patients.[12,38] There was also variation in sensitivity (73% to 93%) in symptomatic patients with DVT in the calf.[37-39] For asymptomatic patients, however, sensitivities for detecting DVT limited to the calf were approximately 50%. All of the reviews used contrast venography as the reference standard point for inclusion criterion.

Hence, ultrasonography has high sensitivity and specificity for diagnosing proximal DVT of the lower extremity in symptomatic patients. Though specificity is maintained, sensitivity is diminished in patients who are asymptomatic or who have DVT in the calf.

TEST CHARACTERISTICS OF HELICAL COMPUTED AXIAL TOMOGRAPHY FOR DIAGNOSIS OF PULMONARY EMBOLISM

The systematic reviews for use of helical CT in diagnosis of pulmonary embolism reported a wide range of summary sensitivities (66% to 93%) but a narrow range of summary specificities (89% to 98%).[42] Inclusion criteria and reference standards varied across the different reviews, and heterogeneity was high across individual studies. Segal and colleagues performed their own systematic review including only prospective studies and those that uniformly applied pulmonary arteriography as the reference standard, and they confirmed the finding of wide variation in sensitivity (45% to 100%) and specificity (78% to 100%).[4]

Interpretation of this evidence is controversial because of such factors as substantial referral bias associated with the published evidence. More importantly, the literature has lagged behind rapid recent advances in CT technology. The authors of the EPC report estimate that for diagnosis of pulmonary embolism, helical CT has at best a sensitivity of 90% and specificity of 95% compared with conventional pulmonary arteriog-

raphy. Data published after the EPC review was completed suggest that current-generation multidetector CT technology may offer significantly higher sensitivity and similar specificity to the technology assessed in the EPC review.[43] Even so, 2 recent systematic reviews conclude that helical CT alone may not be sufficiently sensitive to exclude pulmonary embolism in patients who have relatively high pretest probability.[44,45] Further imaging studies are likely needed in patients who have a high pretest probability of pulmonary embolism and a negative CT scan; options include single or sequential ultrasound assessment of the lower extremities or pulmonary angiography.

SUMMARY

Strong evidence supports the use of clinical prediction rules to establish pretest probability of VTE before further testing. Use of a high-sensitivity D-dimer assay in patients who have a low pretest probability of VTE has a high negative predictive value; it is highest for younger patients with low pretest probability, no associated comorbidity or previous DVT, and a short duration of symptoms. There is strong evidence supporting the use of ultrasonography for diagnosing proximal DVT in symptomatic patients; sensitivity is much lower in asymptomatic patients and for detecting calf vein DVT. Recent results suggest that newer CT technology for diagnosis of pulmonary embolism might have a higher sensitivity and specificity than seen in previous studies. In addition, it is likely that accuracy of CTs will improve with time as the technology evolves further.

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