Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients Presenting With Suspected Lower-Extremity Deep Venous Thrombosis

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This clinical policy was developed by the ACEP Clinical Policies Committee and the Clinical Policies Subcommittee on Suspected Lower-Extremity Deep Venous Thrombosis. For a complete listing of subcommittee and committee members, please see page 131.

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This clinical policy focuses on critical issues in the evaluation and management of patients with signs or symptoms of lower-extremity deep venous thrombosis (DVT). A MEDLINE search for clinical trials published from January 1995 through April 2001 was performed using the key words deep venous thrombosis with limits of clinical investigations and clinical policies. Subcommittee members also supplied articles with direct bearing on the policy. This policy focuses on 3 major areas of current interest and/or controversy: (1) utility of D-dimer testing in the diagnostic evaluation of lower-extremity DVT, (2) utility of venous Doppler ultrasonography in the diagnostic evaluation of lower-extremity DVT, and (3) indications for fibrinolytic therapy in DVT.

Recommendations for patient management are provided for each one of these topics on the basis of strength of evidence (Level A, B, or C). *Level A recommendations* represent patient management principles that reflect a high degree of clinical certainty; *Level B recommendations* represent patient management principles that reflect moderate clinical certainty; and *Level C recommendations* represent other patient management strategies that are based on preliminary, inconclusive, or conflicting evidence, or panel consensus. This guideline is intended for physicians working in hospital-based emergency departments.

INTRODUCTION

Approximately 2 million patients are diagnosed with deep venous thrombosis (DVT) each year, and another 600,000 are diagnosed with pulmonary embolism (PE).[1] Even in the absence of PE, DVT may cause significant morbidity resulting from chronic swelling, ulceration, debilitating pain, and future risk of recurrent DVT and PE.[1-3] Approximately 50% of patients with documented DVT have perfusion defects on nuclear lung scanning, and coexistent venous thrombosis is found in approximately 70% of patients with confirmed PE.[1,4] Because of the strong association between DVT and PE, it is difficult to discuss one entity without the other. The American College of Emergency Physicians (ACEP) has addressed PE in a separate clinical policy.[5] This current policy is meant to complement and supplement the PE policy specifically as it relates to the diagnosis and treatment of lower-extremity DVT.

Over the past decade, there has been an explosion of published research and development of new diagnostic modalities and therapies relating to patients with suspected DVT, with more than 1,000 publications appearing in the medical literature per year. The 1995 ACEP "Clinical Policy for the Initial Approach to Adults Presenting With a Chief Complaint of Chest Pain, With No History of Trauma," indirectly addressed DVT as it relates to subsequent development of chest pain secondary to PE.[6] In 1999, a decision was made to develop a revised chest pain policy that focused initially on critical issues in evaluation and management of patients with suspected acute coronary syndrome[7] to be followed by a policy focusing on patients with suspected PE.[5] Although this policy focuses exclusively on lower-extremity DVT, it is important to realize that the increased use of indwelling catheters in the subclavian vein (eg, in chemotherapy patients and dialysis patients), may result in an increased frequency of upper-extremity DVT in the emergency department. Preliminary evidence suggests that PE resulting from upper-extremity DVT occurs at approximately the same frequency as PE resulting from lower-extremity DVT.[8,9] There currently is insufficient evidence in the literature for any evidence-based discussion on upper-extremity DVT. It is hoped that future revisions of this policy will be able to address this issue.

METHODOLOGY

This clinical policy was created after careful review and critical analysis of the peer-reviewed literature. All papers were graded by at least 2 subcommittee members for strength of evidence. An initial MEDLINE search for articles published from January 1995 through April 2001 was performed using the key words deep venous thrombosis and yielded 6,727 hits. The search was therefore limited to clinical trials and clinical policies, which reduced the hits to 675. The abstracts from these articles were reviewed by subcommittee members, who then met to select areas of critical importance on which to focus this policy. Pertinent practice guidelines reviewed in the development of this document included the 1996 American Heart Association "Management of Deep Vein Thrombosis and Pulmonary Embolism,"[1] the 1998 American College of Chest Physicians consensus statement "Opinions Regarding the Diagnosis and Management of Venous Thromboembolic Disease,"[10] 2000 recommendations on antithrombotic therapy from the American College of Chest Physicians Sixth ACCP Consensus Conference on Antithrombotic Therapy,[11] and the 1999 American Thoracic Society "The Diagnostic Approach to Acute Venous Thromboembolism."[12] Subcommittee members also supplied references with direct bearing on the policy by reviewing bibliographies of initially selected papers or from their own knowledge base. After review of the initial literature, the committee determined that emphasis should be placed on the following topics: (1) utility of D-dimer testing in the diagnostic evaluation of lower-extremity DVT, (2) utility of venous Doppler ultrasonography in the diagnostic evaluation of lower-extremity DVT, and (3) indications for fibrinolytic therapy in DVT.

This policy is not intended to be a complete manual on the initial evaluation and management of patients with DVT, but rather a focused look at critical issues that have particular relevance to the practice of emergency medicine. Detailed discussion of risk factors, etiology, pathophysiology, physical examination findings, and anticoagulation therapy can be found in any standard textbook of emergency medicine or internal medicine. Some areas considered for discussion but not included in this policy were utilization of low-molecular-weight heparin,[13-16] effectiveness of aspirin in DVT prophylaxis,[17] indications for vena cava filter placement,[18] risk factors for predicting reoccurrence,[19] computed tomography (CT) and magnetic resonance imaging (MRI) venography,[20-23] nuclear venography,[24-26] impedance plethysmography,[27-30] and strain gauge plethysmography.[31-33] This policy is also nondirective on proposed management algorithms for the evaluation and treatment of patients with suspected DVT, as well as on how to deal with conflicting test results.[34] These areas represent topics that ACEP may address in future updates of this current policy.

The reasons for developing clinical policies in emergency medicine and the approaches used in their development have been enumerated.[35] This policy is a product of the ACEP clinical policy development process, including expert review, and is based on the existing literature; where literature was not available, consensus of emergency physicians was used. Expert review comments were received from individual emergency physicians; members of the ACEP Section of Emergency Ultrasound; physicians from other specialties, such as cardiologists; and specialty societies, including individual members of the American Academy of Family Physicians, American College of Cardiology, American College of Chest Physicians, American College of Radiology, and the Society of Critical Care Medicine. Their responses were used to further refine and enhance this policy. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology or the practice environment changes significantly.

This policy presents evidence for answering important questions about these critical diagnostic and management issues. Recommendations in this policy are not intended to represent the only diagnostic and management options that emergency physicians can consider. ACEP clearly recognizes the importance of the individual clinician's judgment. Rather, they define for the clinician those strategies for which medical literature exists to provide strong support for answers to the critical questions addressed in this policy.

During the review process, all papers used in the formulation of the recommendations in this policy were classified by the subcommittee members into 3 classes based on design of study, with design 1 representing strongest evidence and design 3 representing weakest evidence for therapeutic, diagnostic, and prognostic clinical reports respectively (Appendix A). Reports were then graded on 6 dimensions thought to be most relevant to the development of a clinical guideline: blinded versus nonblinded outcome assessment, blinded or randomized allocation, direct or indirect outcome measures, biases (eg, selection, detection, transfer), external validity (ie, generalizability), and sufficient sample size.[36-38] Articles received a final grade (I, II, III) on the basis of a predetermined formula taking into account design and grade of study (Appendix B). Articles with fatal flaws were given an "X" grade and not used in the creation of this policy.

Clinical findings and strength of recommendations regarding patient management were then made according to the following criteria:

Level A recommendations. Generally accepted principles for patient management that reflect a high degree of clinical certainty (ie, based on "strength of evidence class I" or overwhelming evidence from "strength of evidence class II" studies that directly address all the issues).

Level B recommendations. Recommendations for patient management that may identify a particular strategy or range of management strategies that reflect moderate clinical certainty (ie, based on "strength of evidence class II" studies that directly address the issue, decision analysis that directly addresses the issue, or strong consensus of "strength of evidence class III" studies).

Level C recommendations. Other strategies for patient management that are based on preliminary, inconclusive, or conflicting evidence, or in the absence of any published literature, based on panel consensus.

There are certain circumstances in which the recommendations stemming from a body of evidence should not be rated as highly as the individual studies on which they are based. Factors such as heterogeneity of results, uncertainty about effect magnitude and consequences, strength of prior beliefs, and publication bias, among others, might lead to such a downgrading of recommendations.

Scope of Application. This guideline is intended for physicians working in hospital-based EDs.

Inclusion Criteria. This guideline is intended to apply to adult patients presenting with signs or symptoms of lower-extremity DVT.

Exclusion Criteria. Patients lacking signs or symptoms of lower-extremity DVT.

CRITICAL ISSUES IN LOWER-EXTREMITY DVT

Lower-extremity DVT can present with a wide spectrum of signs and symptoms. Most commonly, symptomatic patients will complain of swelling or pain in the calf.[1,39] Some patients with DVT may only experience a mild cramping sensation. Although symptom onset is usually gradual, some patients with DVT report that the symptoms begin rather suddenly. Physical examination findings can range from no findings to swelling and induration of the entire leg. In its most extreme manifestation, DVT can occlude the entire iliofemoral venous system, producing a painful, blue leg, a condition referred to as phlegmasia cerulea dolens, which can produce venous gangrene and even lead to amputation. Because DVT presents with such a wide spectrum of signs and symptoms, it is difficult to describe in narrative form how to perform a quantitative pretest probability assessment for DVT. However, the proper application of any diagnostic modality to screen for DVT requires a pretest probability assessment for utilization of the likelihood ratio to calculate posttest probability. The reader is referred to other sources for the specific method of computing posttest probability.[40,41]

To help provide a more objective and reproducible method of quantifying the pretest probability of DVT, Wells et al[42] devised a scoring system that is based largely on objective criteria to assess the risk of DVT (Table). The Wells et al criteria have been examined in other ED populations and appear to provide reliable risk stratification information at the 2 ends of clinical probability.[43] First, in the subgroup deemed low risk, the Wells et al model appears to reliably estimate the pretest probability below 10%. Second, the model appears to reliably predict the probability of DVT to at least 50% when the score exceeds 3 points. In contrast to the use of the standardized scoring system described previously, 1 study has found that empiric patient assessment can produce more accurate pretest probability estimation for DVT than the Wells et al scoring system.[43] Regardless of whether empiric assessment or a structured score is used, patients deemed low risk have a lower than 10% probability of DVT, and patients deemed high risk have a higher than 65% probability of DVT.

Bilateral contrast venography remains the criterion standard for ruling out the presence of DVT.[1] Contrast venography offers precise detail of the venous anatomy and the ability to reliably exclude thrombosis in the calf. A venogram can help distinguish whether a clot is acute or chronic and can demonstrate the presence of collateral circulation indicative of chronic deep venous occlusive disease. The main drawback to contrast venography is that many radiologists are now uncomfortable, or unwilling, to perform this procedure. The procedure does require injection of contrast and can produce chemical phlebitis. On the basis of the frequency of venography reported in published studies, venography appears to be still used more frequently in Canada than the United States, but for the most part, has been supplanted by venous ultrasonography in both countries.[44]

Table.
Wells et al[42] clinical model for predicting pretest probability for DVT. Reprinted with permission from Elsevier Science. Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management.* Lancet. *1997;350:1795-1798.*

Clinical Feature	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 for >3 days or major surgery within 4 weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling >3 cm when compared with the asymptomatic leg (measured 10 cm below tibial tuberosity)	1
Pitting edema (greater in the symptomatic leg)	1
Collateral superficial veins (nonvaricose)	1
Alternative diagnosis as likely as or greater than that of DVT	–2

*In patients with symptoms in both legs, the more symptomatic leg should be used. High pretest probability ≥3 points; moderate pretest probability=1–2 points; low pretest probability=zero or negative points.

CRITICAL QUESTIONS

I. Can lower-extremity DVT be excluded by a negative D-dimer?

A large volume of evidence has been forwarded that demonstrates the D-dimer to be a relatively sensitive test to screen for DVT.[45-50] D-Dimer is a fibrin degradation product that is usually increased in the presence of thromboembolic disease. D-Dimer also is increased after surgery or major trauma, in inflammatory arthritis, cancer, and infection.[51-53] D-Dimer levels also increase with advancing age, thus limiting the usefulness of this test in patients older than 70 years.[54] The diagnostic performance of the D-dimer depends on the assay type. In general, the tests with the highest sensitivity are the quantitative D-dimer assays. A reasonable body of evidence has been forwarded to suggest that a normal (<500 mg/L) D-dimer concentration, as measured by the turbidimetric,[55-58] or enzyme-linked immunosorbent assay (ELISA) technique (either standard or rapid),[46-48,59-66] in a patient with a low-risk pretest probability has less than a 1% posttest probability of DVT. Additionally, considerable evidence has been forwarded to indicate that the whole-blood qualitative D-dimer assay, if properly performed,[67] has approximately a 90% sensitivity and 70% specificity for proximal DVT.[68-70] Multiple studies have also demonstrated that a negative whole-blood qualitative D-dimer in conjunction with a low-risk patient as assessed by the Wells et al criteria reliably excludes the diagnosis of DVT by identifying a subgroup of patients with a less than 1% likelihood of DVT.[71-74] The sensitivity for all D-dimer assays is lower for calf DVT compared with proximal DVT.[48,69] The D-dimer should not be used to rule out DVT in patients who have a moderate or high pretest probability of DVT.[40,41,75-77] Published evidence does not support the use of a latex D-dimer to rule out DVT in any subgroup.[46,47,61,62,65] Because the positive likelihood ratio of positive D-dimer assay results for DVT is approximately 1.8 (specificity approximately 50%), a positive result indicates that further testing is required to confirm or exclude the diagnosis of DVT. The immunofiltration D-dimer test also holds promise for ED use because these assays can be used at the bedside and provide tests results within 10 minutes. Preliminary studies show that these rapid tests have a sensitivity comparable to the qualitative ELISA assay.[77,78] A list of US Food and Drug Administration (FDA)–approved D-dimer assays can be accessed on the FDA Web site at http://www.fda.gov/search/databases.html.

Patient Management Recommendations: Can lower-extremity DVT be excluded by a negative D-dimer?

Level A recommendations. None specified.

Level B recommendations. In patients with low clinical probability for lower-extremity DVT, the following test results can be used to exclude DVT:

1. A negative quantitative D-dimer assay result (turbidimetric or ELISA) for exclusion of proximal* and distal† lower-extremity DVT.
2. A negative whole blood D-dimer assay result in conjunction with the Wells et al scoring system for exclusion of proximal* and distal† DVT.
3. A negative whole blood D-dimer assay result for exclusion of proximal* lower-extremity DVT.

Patients with a moderate-to-high risk of lower-extremity DVT cannot have DVT excluded by a single negative D-dimer test.

Level C recommendations. None specified.

II. Can lower-extremity DVT be excluded by normal findings on a venous ultrasonographic scan?

Real-time venous ultrasonography provides a relatively painless, noninvasive method to image the venous system that has been extensively validated and is widely available.[79] In general, lower-extremity venous ultrasonography includes compressibility of the veins, together with color Doppler examination for the quality of venous flow. By evaluating for the absence of vein compressibility and reduced venous flow, the qualified observer can detect the presence of venous thrombosis in the proximal venous system. The main drawbacks to

**Proximal lower-extremity DVT is defined as DVT from the knee to the inguinal ligament.*

†Distal lower-extremity DVT is defined as DVT isolated to calf.

venous ultrasonography are that it is unreliable in the diagnosis of thrombosis in the calf veins, does not identify venous thrombosis in pelvic veins or the vena cava, and cannot reliably distinguish acute DVT from chronic DVT.[80,81]

In a comprehensive class I meta-analysis, Kearon et al[79] demonstrated that the sensitivity for venous ultrasonography varies significantly with the location of the thrombosis (proximal versus distal) and with the presence or absence of classic symptoms of DVT. The sensitivity of a single venous ultrasonographic test in symptomatic proximal venous thrombosis was 97% (95% confidence interval [CI] 96% to 98%), compared with a sensitivity of 73% in symptomatic patients with distal DVT (95% CI 54% to 93%). In patients with no symptoms of DVT (who were mainly composed of postoperative orthopedic patients), the sensitivity of a single lower-extremity ultrasonographic scan for proximal DVT was 62%, and sensitivity for distal DVT was 53%. These data underscore the fact that the sensitivity of the ultrasonographic scan is subject to spectrum bias: the venous ultrasonographic scan is more sensitive in patients who have large obstructing proximal clots compared with patients who have asymptomatic distal clots. The fact that the diagnostic accuracy of the venous ultrasonographic scan decreases as the severity of signs and symptoms become more vague reflects the fact that patients with minimal DVT symptoms are more likely to have DVT isolated to the calf. Among patients with minimal symptoms of DVT, more than one half have isolated calf vein DVT, whereas only 15% of patients with classic symptoms of DVT have clots isolated to the calf veins.[82] This fact should be considered in ED practice. If a venous ultrasonographic scan is ordered to rule out DVT in a patient with classic symptoms or signs, the test is reasonably sensitive. On the other hand, if the venous ultrasonographic scan is ordered to help decrease the probability of DVT in a patient with no symptoms or signs of DVT, as is often the case when PE is suspected, the diagnostic performance of the venous ultrasonography decreases significantly.[83] Despite the data that indicate a low rate of serious complications from calf vein thrombosis,[84-87] abundant evidence suggests that approximately 10% to 20% of distal calf DVTs propagate to proximal DVT, which often embolizes to the lungs.[88-91] If propagation and embolization do not occur, calf vein thrombosis may produce postthrombotic syndrome in one quarter of cases, although few have serious disease.[85-87] The American College of Chest Physicians advocates anticoagulant treatment in patients with symptomatic calf vein thrombosis for at least 6 to 12 weeks.[11] However, the subcommittee preparing this document was unable to find any randomized studies comparing anticoagulation therapy versus treatment with compression therapy plus aspirin in patients with isolated calf vein thrombosis.

One small nonrandomized cohort study demonstrated a progression rate of 25% in 32 patients without anticoagulation (compression therapy only) compared with 0% in 52 patients receiving low-molecular-weight heparin.[92] No symptomatic PE occurred in either group. Furthermore, a survey of emergency physicians on the Clinical Policies Committee revealed a broad range of management options that take into account multiple factors, including the location of calf vein thrombosis, extent of thrombosis, severity of symptoms, history of previous DVT, and presence of risk factors and other comorbid conditions. If a decision is made not to treat isolated calf thrombosis with full anticoagulation, studies have demonstrated that propagation as demonstrated on serial ultrasonography predicts those patients at highest risk for thromboembolic complications.[90] In patients treated with anticoagulation, a 6-week course is as effective as a 12-week course.[93-96]

The specificity of lower-extremity venous ultrasonography has generally been demonstrated to be excellent, with a positive predictive value of 94% to 97% in the symptomatic patient.[79] Thus, anticoagulation therapy can be initiated on the basis of a positive test result. In patients with symptoms or signs of DVT who are categorized as low risk (ie, <10% pretest probability using either the Wells et al score or by empirical assessment by an experienced clinician), the negative likelihood ratio for a single normal lower-extremity

venous ultrasonographic scan will be approximately 0.03. Thus, the posttest probability for DVT will be approximately 0.5%.[79] In a patient deemed to have moderate risk of DVT (30% pretest probability), the posttest probability will be 1.3%. Thus, in a patient with a low pretest probability, negative results on a single lower-extremity venous ultrasonographic scan are sufficient to rule out clinically significant DVT, but in patients with a moderate or higher risk, serial examinations are necessary to exclude the diagnosis.[96] Multiple serial ultrasonography protocols are reported in the literature.[79,96-98] Heijboer et al[97] report on a protocol of repeat ultrasonographic examinations at day 2 and day 8 in 491 patients with suspected DVT. DVT was identified in a total of 84 patients. Of these, 93% were identified on day 1 (baseline), 3.5% on day 2, and 3.5% on day 8. Birdwell et al[98] performed testing on day 1 (baseline) and days 5 to 7 in 405 outpatients with suspected DVT. Sixty-three patients had abnormal results on baseline venous ultrasonography, and an additional 7 patients were identified on a second ultrasonographic scan at days 5 to 7. Although only a minority of the patients with abnormal scan results had confirmatory venogram, no patient with negative ultrasonography results at baseline and days 5 to 7 developed PE at 3-month follow-up. Wells et al[42] performed repeat ultrasonography on day 7 in 193 patients with a moderate pretest probability of DVT (Wells score of 1 to 2; Table). A total of 32 (17%) patients were diagnosed as having DVT on 3-month follow-up. Of these, 27 (84%) were diagnosed on initial ultrasonographic scan, and an additional 3 (9%) patients were diagnosed on day 7. There is insufficient evidence to advocate one serial testing protocol over another. Whether to perform both early (1 to 2 days) and late testing (5 to 7 days) or late testing only must take into account factors such as patient presenting characteristics, risk factors for propagation, and availability of institutional resources.

Patient Management Recommendations: Can lower-extremity DVT be excluded by normal findings of a venous ultrasonographic scan?

Level A recommendations. None specified.

Level B recommendations. In patients with low clinical probability for lower-extremity DVT, negative findings on a single venous ultrasonographic scan in symptomatic patients excludes proximal* lower-extremity DVT and clinically significant distal† lower-extremity DVT. In patients with moderate to high pretest probability of lower-extremity DVT, serial‡ ultrasonographic examinations need to be performed. Patients with high suspicion of pelvic or inferior vena cava thrombosis may require additional imaging technique.

Level C recommendations. None specified.

III. What are the indications for fibrinolytic therapy in lower-extremity DVT?

As in the treatment of patients with acute coronary syndromes, one must make a risk-benefit decision when considering fibrinolytic treatment in patients with lower-extremity DVT. No information is known at this time regarding serious bleeding complications in patients treated with isolated lower-extremity DVT with fibrinolytic treatment, but theoretically these patients should have similar rates to patients with PE. A meta-analysis of 5 studies on fibrinolytic therapy in PE found an intracranial hemorrhage rate of 2%, with a mortality rate of 0.5%.[99] Diastolic hypertension was the principal risk factor in predicting development of intracranial hemorrhage. Meta-analysis of early studies comparing heparin alone to heparin plus streptokinase reveals an increased rate of intracranial hemorrhage of approximately 1% and increased rate of other serious bleeding complications of 3%.[100] Indications for fibrinolytic therapy in patients with isolated lower-extremity DVT are unclear. Evidence does suggest a lower incidence of postthrombotic syndrome in patients treated with fibrinolytic agents.[1,11,101,102] Goldhaber et al[103] report a meta-analysis of 6 randomized trials compar-

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†Distal DVT is defined as DVT isolated to calf.

‡Serial venous ultrasonographic examinations refers to scheduling a patient for follow-up ultrasonographic examination within 5 to 7 days or referral of the patient to a primary care physician for follow-up management.

ing streptokinase versus heparin for treating acute proximal DVT. Thrombolysis was achieved 3.7 times more often in the streptokinase group as assessed by venography. However, major bleeding complications were 2.9 times greater. In the largest study to date, Schweizer et al[101] randomized 250 patients into 3 major groups: heparin, heparin plus locoregional fibrinolytic agents, and heparin plus systemic fibrinolytic agents. Patients receiving fibrinolytic agents had higher rates of serious bleeding complications. Nine patients receiving fibrinolytic agents experienced PE versus no patients in the heparin-only group. The authors conclude that fibrinolytic agents should be used selectively in limb-threatening thrombotic situations. Decision analysis suggests that treatment with anticoagulants is the best choice for the vast majority of patients with DVT.[100] Current recommendations from the American College of Chest Physicians are to reserve fibrinolytic therapy for younger patients with massive iliofemoral thrombosis.[11] Treatment usually is administered locally via catheter[104-106] but may be effective when used systemically.[107,108]

Patient Management Recommendations: Indications for fibrinolytic treatment in patients with lower-extremity DVT

Level A recommendations: None specified.

Level B recommendations: None specified.

Level C recommendations: Consider fibrinolytic therapy in patients with limb-threatening thrombosis of the iliofemoral system in whom the benefits of treatment outweigh the risks of serious bleeding complications.

This clinical policy was developed by the ACEP Clinical Policies Committee and the Clinical Policies Subcommittee on Suspected Lower-Extremity Deep Venous Thrombosis.

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APPENDIX A.

Literature classification schema.[*]

Design/ Class	Therapy[†]	Diagnosis[‡]	Prognosis[§]
1	Randomized, controlled trial or meta-analyses of randomized trials	Prospective cohort using a criterion standard	Population prospective cohort
2	Nonrandomized trial	Retrospective observational	Retrospective cohort Case control
3	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)

[*]Some designs (eg, surveys) will not fit this schema and should be assessed individually.
[†]Objective is to measure therapeutic efficacy comparing ≥2 interventions.
[‡]Objective is to determine the sensitivity and specificity of diagnostic tests.
[§]Objective is to predict outcome including mortality and morbidity.

APPENDIX B.

Approach to downgrading strength of evidence.

	Design/Class		
Downgrading	**1**	**2**	**3**
None	I	II	III
1 level	II	III	X
2 levels	III	X	X
Fatally flawed	X	X	X