Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department With Suspected Pulmonary Embolism

From the American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department With Suspected Pulmonary Embolism:

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ABSTRACT

This clinical policy from the American College of Emergency Physicians is the revision of a 2003 clinical policy on the evaluation and management of adult patients presenting with suspected pulmonary embolism (PE).[1] A writing subcommittee reviewed the literature to derive evidence-based recommendations to help clinicians answer the following critical questions: (1) Do objective criteria provide improved risk stratification over gestalt clinical assessment in the evaluation of patients with possible PE? (2) What is the utility of the Pulmonary Embolism Rule-out Criteria (PERC) in the evaluation of patients with suspected PE? (3)What is the role of quantitative D-dimer testing in the exclusion of PE? (4) What is the role of computed tomography pulmonary angiogram of the chest as the sole diagnostic test in the exclusion of PE? (5) What is the role of venous imaging in the evaluation of patients with suspected PE? (6) What are the indications for thrombolytic therapy in patients with PE? Evidence was graded and recommendations were given based on the strength of the available data in the medical literature.

INTRODUCTION

It is estimated that 650,000 to 900,000 individuals each year have fatal or nonfatal acute pulmonary embolism (PE)[2] and that as many as 200,000 people in the United States die each year from PE.[3] Untreated PE can be rapidly fatal, with the majority of deaths occurring in the first hour.[3,4] Furthermore, survivors of undiagnosed PE can experience disabling morbidity from pulmonary hypertension[5] and/or postthrombotic syndrome.[6-8] Because there is a strong association between deep venous thrombosis (DVT) and PE, it is difficult to discuss the diagnostic evaluation of one entity without discussing the other.[7] Approximately 50% of patients with documented DVT have perfusion defects on nuclear lung scanning and asymptomatic venous thrombosis is found in approximately 40% of patients with confirmed PE.[6,9,10]

During the past decade, there has been an explosion of published research and development of new diagnostic modalities and therapies relating to patients with suspected PE and DVT, with greater than 1,000 publications appearing in the medical literature per year. This current policy represents a revision of the 2003 American College of Emergency Physicians (ACEP) clinical policy on critical issues in the evaluation and management of adult patients with suspected PE.[1] The 2003 policy focused on 4 major areas of interest and/or controversy that existed when the policy was formulated: (1) Can a negative D-dimer result exclude PE?; (2) When can ventilation-perfusion (VQ) scan alone or in combination with venous ultrasonography and/or D-dimer assay exclude PE?; (3) Can spiral computed tomography (CT) replace VQ scanning in the diagnostic evaluation of PE?; and (4) What are the indications for thrombolytic therapy in patients with PE? This current policy focuses on 6 areas of interest and/or controversy that have developed or still exist since the 2003 policy was formulated: (1) Do objective criteria provide improved risk stratification over general clinical assessment in the evaluation of patients with possible PE?; (2) What is the utility of the Pulmonary Embolism Rule-out Criteria (PERC) in the evaluation of patients with suspected PE? (3)What is the role of quantitative D-dimer testing in the exclusion of PE?; (4) What is the role of CT pulmonary angiogram of the chest as the sole diagnostic test in the exclusion of PE?; (5) What is the role of venous imaging in the exclusion of PE?; and (6) What are the indications for thrombolytic therapy in patients with PE?

This policy does not discuss VQ scanning in the evaluation of patients with suspected PE. The authors do recognize that VQ scanning is used in the evaluation of patients with suspected PE in whom CT scan may be contraindicated.[11-13] Also, with increasing awareness of potential long-term effects of ionizing radiation exposure from repetitive CT scans, there may be additional subgroups of patients for whom a VQ scan may be preferred as the initial imaging modality because of decreased exposure to radiation compared with CT scan.[13-17] Future updates of this policy may directly address these issues.

METHODOLOGY

This clinical policy was created after careful review and critical analysis of the medical literature. Multiple searches of MEDLINE and the Cochrane Library were performed. To update the 2003 ACEP clinical policy, all searches were limited to English-language sources and human studies. Specific key words/phrases and years used in the searches are identified under each critical question. In addition, relevant articles from the bibliographies of included studies and more recent articles identified by committee members and peer reviewers are included.

The reasons for developing clinical policies in emergency medicine and the approaches used in their development have been enumerated.[18] This policy is a product of the ACEP clinical policy development process, including expert review, and is based on the existing literature; when literature was not available, consensus of emergency physicians was used. Expert review comments were received from individual emergency physicians and cardiologists and from individual members of the American College of Chest Physicians, American College of Radiology, ACEP's Emergency Ultrasound Section, and ACEP's Quality and Performance Committee. Their responses were used to further refine and enhance this policy; however, their responses do not imply endorsement of this clinical policy. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology or the practice environment changes significantly. ACEP is the funding source for this clinical policy.

All articles used in the formulation of this clinical policy were graded by at least 2 subcommittee members for strength of evidence and classified by the subcommittee members into 3 classes of evidence on the basis of the design of the study, with design 1 representing the strongest evidence and design 3 representing the weakest evidence for therapeutic, diagnostic, and prognostic clinical reports, respectively (Appendix A). Articles 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 (reliability and validity), biases (eg, selection, detection, transfer), external validity (ie, generalizability), and sufficient sample size. Articles received a final grade (Class I, II, III) on the basis of a predetermined formula, taking into account design and quality of study (Appendix B). Articles with fatal flaws were given an "X" grade and not used in formulating recommendations in this policy. Evidence grading was done with respect to the specific data being extracted and the specific critical question being reviewed. Thus, the level of evidence for any one study may vary according to the question, and it is possible for a single article to receive different levels of grading as different critical questions are answered. Question-specific level of evidence grading may be found in the Evidentiary Table included online (available at: http://www.annemergmed.com).

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 of 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 Class III studies, or in the absence of any adequate 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, and publication bias, among others, might lead to such a downgrading of recommendations.

When possible, clinically oriented statistics (eg, likelihood ratios [LRs], number needed to treat) will be presented to help the reader better understand how the results can be applied to the individual patient. For a definition of these statistical concepts, see Appendix C.

This policy is not intended to be a complete manual on the evaluation and management of patients with suspected PE but rather a focused examination of critical issues that have particular relevance to the current practice of emergency medicine.

It is the goal of the Clinical Policies Committee to provide an evidence-based recommendation when the medical literature provides enough quality information to answer a critical question. When the medical literature does not contain enough quality information to answer a critical question, the members of the Clinical Policies Committee believe that it is equally important to alert emergency physicians to this fact.

Recommendations offered in this policy are not intended to represent the only diagnostic and management options that the emergency physician should consider. ACEP clearly recognizes the importance of the individual physician's judgment. Rather, this guideline defines for the physician those strategies for which medical literature exists to provide support for answers to the crucial questions addressed in this policy.

Scope of Application. This guideline is intended for physicians working in hospital-based emergency departments (EDs) or ED-based observation centers.

Inclusion Criteria. This guideline is intended for adult patients presenting to the ED with suspected PE.

Exclusion Criteria. This guideline is not intended to address the care of patients with PE in the presence of cardiac arrest or pregnancy, patients with absence of symptoms suggestive of PE, or pediatric patients.

CRITICAL QUESTIONS

1. Do objective criteria provide improved risk stratification over gestalt clinical assessment in the evaluation of patients with possible PE?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Either objective criteria or gestalt clinical assessment can be used to risk stratify patients with suspected PE. There is insufficient evidence to support the preferential use of one method over another.

Level C recommendations. None specified.

Key words/phrases for literature searches: risk stratification, pulmonary embolism, ED, emergency service, risk assessment, diagnostic strategies, Wells criteria, Wicki criteria, Kline criteria, Geneva score, revised Geneva score, PISA model, and variations and combinations of the key words/phrases; years 2000 through December 2009.

This critical question focuses on pretest probability assessment. Estimation of pretest probability is imperative for the proper application of any diagnostic test. This general principle becomes even more important for PE because it is a common but potentially lethal disease when left undiagnosed and untreated. Unfortunately, the classic presentation of PE is rare, and physicians must make some sort of assessment about whether to evaluate patients for PE when they present with symptoms such as unexplained dyspnea, chest pain, hemoptysis, palpitations, syncope, back pain, and other commonplace symptoms that have been associated with PE. Pretest probability assessment in PE can be estimated in 2 general ways: objective criteria (clinical decision rules) or gestalt clinical assessment (implicit approach).

Objective Criteria (Clinical Decision Rules)

Clinical decision rules are a form of objective criteria that are intended to provide more accurate and reproducible measure of pretest probability assessment than the overall gestalt clinical

impression that depends on the physician's expertise and clinical experience. Such rules can be derived and validated. They also can be compared to each other and refined over time. Several clinical decision rules have been developed for use in patients with suspected PE. The most commonly used methods are: (1) Geneva score;[19-21] (2) Wells (Canadian) score;[22] (3) Kline (Charlotte) criteria;[23] and (4) Pisa model.[24,25]

Geneva Score

The original Geneva score as described by Wicki et al[19] in 2001 is a Class II study that was performed at a single hospital in Switzerland and consists of a clinical score ranging from 0 to 16 points, derived from 8 parameters relating to risk factors, clinical signs, blood gas analysis, and chest radiograph. Probability of PE in patients defined as low- (0 to 4 points), intermediate- (5 to 8 points), and high- (≥9 points) risk was 10%, 38%, and 81%, respectively. Multiple Class III studies have since validated the usefulness of the Geneva score in risk stratification of patients with suspected PE.[26-31]

Because of the reliance of the original Geneva score on room air blood gas analysis and chest radiograph interpretation, Le Gal et al,[20] in a Class II study, retrospectively analyzed data from 2 previous multicenter clinical investigations to develop a score independent of diagnostic testing. The subsequent *revised* Geneva score ranged from 0 to 25 points and was derived from 8 parameters relating to risk factors, symptoms, and clinical signs (Table 1). In the validations set, probability of PE in low- (score 0 to 3), intermediate- (score 4 to 10), and high-risk (score ≥11) patients was 8%, 29%, and 74%, respectively. To date, only one Class II investigation has validated the revised Geneva score.[32]

One of the difficulties of the revised Geneva score is that different elements have different weights, making it potentially more difficult to apply in the clinical setting (Table 1). As a result, Klok et al,[21] in a Class II study, reanalyzed the same population and developed the *simplified* revised Geneva score that uses the identical 8 parameters of the *revised* Geneva score (Table 1). One point is assigned to each parameter, except for pulse rate greater than or equal to 95 beats/min, which results in an additional point. Probability of PE in patients defined as low- (0 to 1 point), intermediate- (2 to 4 points), and high- (5 to 7 points) risk was 8%, 29%, and 64%, respectively. The investigators also divided the patients into the dichotomous group of PE unlikely (0 to 2 points; probability of PE 11.5%) and PE likely (3 to 7 points; probability of PE 35.1%) to select a patient population safe for use of D-dimer testing for exclusion of PE. Of the 330 patients with a PE unlikely score and a negative D-dimer result, no patient was diagnosed as having venous thromboembolic disease on presentation or on 3-month follow-up. Receiver operating characteristic (ROC) curve analysis revealed no differences in diagnostic performance of the revised Geneva score (area under ROC curve 0.75; 95% confidence interval [CI] 0.71 to 0.78) compared with the simplified revised Geneva score (area under ROC curve 0.74; 95% CI 0.70 to 0.77).

Table 1. Revised Geneva score as described by Le Gal et al[20] and the simplified revised Geneva score as described by Klok et al[21] for assessment of pretest probability of PE. Reprinted with permission. Copyright © American College of Physicians, Publisher. Le Gal G, Righini M, Roy P-M, et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. *Ann Intern Med*. 2006;144:165-171. Copyright © 2008 American Medical Association. All rights reserved. Klok FA, Mos IC, Nijkeuter M, et al. Simplification of the revised Geneva score for assessing clinical probability of pulmonary embolism. *Arch Intern Med*. 2008;168:2131-2136.

	Points	
Variable	**Revised Geneva**	**Simplified Revised Geneva**
Risk factors		
Age ≥65 y	1	1
Previous DVT/PE	3	1
Recent surgery/fracture (4 wk)	2	1
Active malignancy	2	1
Symptoms		
Unilateral lower-limb pain	3	1
Hemoptysis	2	1
Clinical signs		
Heart rate		
75–94 beats/min	3	1
≥95 beats/min	5	2*
Pain on lower-limb deep venous palpation and unilateral edema	4	1

Score Range	**Probability of PE, % (95% CI)**	**Patients With This Score, %**	**Interpretation of Risk**
Revised Geneva Score[20]			
0–3	7.9 (5.0–12.1)	37.0	Low
4–10	28.5 (24.6–32.8)	57.4	Moderate
11–25	73.7 (61.0–83.4)	5.5	High
Simplified Revised Geneva Score[21]			
Traditional interpretation			
0–1	7.7 (5.2–10.8)	36.0	Low
2–4	29.4 (25.9–33.1)	60	Moderate
5–7	64.3 (48.0–78.5)	4.0	High
Alternative interpretation			
0–2	12.9 (10.5–15.7)	64.9	PE unlikely
3–7	41.6 (36.5–46.8)	35.1	PE likely

*The original table from Klok et al[21] lists 1 point for heart rate ≥95 beats/min, but the assessment of score states, "[b]ecause of the weight of heart rate in the original score, we attributed 1 point to a heart rate between 75 and 94 beats/min and an additional point for a heart rate of 95 beats/min or more." Thus, a patient with a heart rate of 100 beats/min would receive a total of 2 points (personal communication, F. A. Klok, MD, PhD, Department of General Internal Medicine, Leiden University Medical Center/Bronovo Hospital Den Haag, May 2010).

Wells Score

The original Wells study was a Class III investigation in use of a clinical model to risk stratify 1,239 patients in low-, moderate-, and high-risk groups.[33] The investigators used evidence from the published literature to establish a risk-stratification model by consensus. The risk model initially assessed patients based on signs and symptoms as "typical" for PE, "atypical" for PE, or "severe." Physicians then made an assessment about whether an "alternative diagnosis that was as

Table 2. Wells Canadian Score for assessment of pretest probability for PE.[22] Reprinted with permission. Copyright © Schattauer, Publisher. Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost*. 2000; 83:416-420.

Criteria	Points
Suspected DVT	3.0
An alternative diagnosis is less likely than PE	3.0
Heart rate >100 beats/minute	1.5
Immobilization or surgery in the previous 4 weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1.0
Malignancy (on treatment, treated in the last 6 months, or palliative)	1.0

Score Range, Points	Probability of PE (%)	% With This Score	Interpretation of Risk
Traditional interpretation			
0–1	3.6 (2.0–5.9)	40.3	Low
2–6	20.5 (17.0–24.1)	52.6	Moderate
>6	66.7 (54.3–77.6)	7.1	High
Alternate interpretation			
0–4	7.8 (5.9–10.1)	71.5	PE unlikely
>4	40.7 (34.9–46.5)	28.5	PE likely

likely as or more likely than PE" to further subdivide the patients into 10 possible outcomes. These outcomes were then divided into low-, moderate-, and high-risk groups. Rates of PE in patients with low, moderate, and high risk were 3.4%, 27.8%, and 78.4%, respectively. Although this model performed well, the algorithmic approach was not suitable to be used as an objective risk-stratification tool.

Wells et al[22] subsequently performed a retrospective analysis of the data used in the original study to develop a simple scoring system that could be used in conjunction with D-dimer for the evaluation of patients with suspected PE (Table 2). Using regression techniques, a risk-stratification model consisting of 7 variables was created that classified patients as having low, moderate, and high probability of PE. In addition, an alternative interpretation system was developed in which the patients were classified into the dichotomist groups "PE unlikely" and "PE likely" to identify a group of patients for whom a negative D-dimer test would result in a PE rate of 2%. If the D-dimer result was negative, the rate of PE in patients designated PE unlikely (score 0 to 4) was 2.2% in the derivation set and 1.7% in the validation set.

This model was subsequently prospectively validated in a Class II investigation in a cohort of 4 EDs at tertiary care hospitals in Canada.[34] The initial pretest probabilities were determined by the clinical model to be low in 57% of patients, moderate in 36% of patients, and high in 7% of patients. Including follow-up events, PE was diagnosed in 1.3% of patients with low pretest probability (95% CI 0.5% to 2.7%), 16.2% of patients with moderate pretest probability (95% CI 12.5% to 20.6%), and in 40.6% of patients with high pretest probability (95% CI 28.7% to 53.7%). Of the 437 patients with a negative D-dimer result and low clinical probability, only 1 developed PE during follow-up, giving a negative predictive value for the use of the clinical model with D-dimer testing of 99.5% (95% CI 99.1% to 100%). No information is given in this investigation about performance of the alternative scoring system of "PE unlikely" and "PE likely."

A Class II investigation by the Christopher Study Investigators validated the utility of the dichotomized alternative scoring system of "PE unlikely" versus "PE likely."[35] This study was a multicenter prospective cohort of 3,306 patients. A total of 2,206 (66.7%) patients were classified as PE unlikely. Of these, 1,057 patients also had a negative D-dimer result and PE was considered to have been excluded. On 3-month follow-up, 5 (0.5%) patients received a diagnosis of venous thromboembolic disease, with no deaths. In the PE likely subgroup, PE was diagnosed on CT scan in 674 patients (20.4%).

Multiple Class II[36,37] and Class III studies[28-31,38-43] have validated the usefulness of the Wells score in risk stratification. However, a major criticism of the Wells score is that it is not truly an objective criterion because it contains the subjective variable "an alternative diagnosis is less likely than PE." This variable in essence represents physician judgment override of the objective components of the score because it is worth 3 points and thus places the patient in the intermediate-risk group.[19,32,44,45]

Kline Rule

Kline et al,[23] in a Class II study, derived a decision rule to create a binary partition of ED patients with suspected PE to select patients for whom a negative D-dimer result reliably excluded the presence of PE (Figure). Nine-hundred thirty-four patients were studied at 7 urban EDs in the United States. The history and physical process occurred prospectively, before standard imaging, to look for recognized symptoms, signs, and risk factors associated with PE. Selected variables were analyzed with multivariate logistic analysis to determine factors associated with PE. A decision rule was then constructed to categorize approximately 80% of ED patients as being able to safely undergo D-dimer testing. Six variables were used to construct the decision rule. Unsafe patients had either a shock index (pulse rate/systolic blood pressure more than 1.0) or age greater than 50 years, together with any of the following: unexplained hypoxemia (arterial blood oxygen saturation [SaO_2] <95%, no previous lung disease), unilateral leg swelling, recent major surgery, or hemoptysis. These criteria were met by 197 (21%) of 934 patients. Of these 197 patients, 83 had PE (42.1%; 95% CI 35.5% to 49.6%). When these 197 "unsafe" patients were excluded, the probability of PE was significantly decreased in the remaining 737 (79%) "safe" patients to 13.3% (95% CI 10.9% to 15.9%). Assuming use of an Enzyme-Linked Immunosorbent Assay (ELISA) D-dimer assay with a negative LR of 0.07, the use of the Kline rule in conjunction with D-dimer testing would decrease the posttest probability of PE to

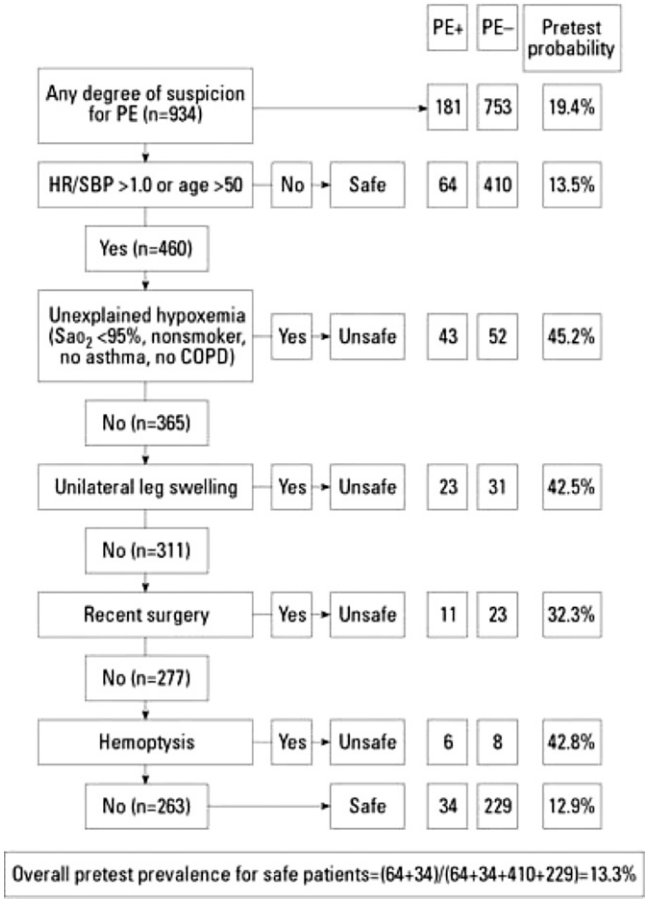

Figure. Kline decision rule for excluding PE.[23] Reprinted from *Annals of Emergency Medicine*, 39, Kline JA, Nelson RD, Jackson RE, et al. Criteria for the safe use of D-dimer testing in emergency department patients with suspected pulmonary embolism: a multicenter US study, 144-152, 2002, Copyright from the American College of Emergency Physicians, [2002].

Flow diagram demonstrating the Kline decision rule in selecting patients in whom D-dimer assay less than 500 ng/ml can reliably rule out PE. This decision rule splits the patients into 2 groups, four fifths of whom are eligible for D-dimer testing ("safe" patients with pretest probability of PE of 13.3%) and one fifth of whom are ineligible for D-dimer testing ("unsafe" patients with pretest probability of 42.1%).

approximately 1%. The authors concluded that these criteria can permit safe D-dimer testing in the majority of ED patients with suspected PE.

There are no prospective outcome studies validating the use of the Kline rule in conjunction with D-dimer, but 1 Class III study demonstrated a 21% decrease in CT scanning when they instituted this protocol.[46]

Pisa Model

The original Pisa investigation is a Class II study consisting of 1,100 consecutive patients with suspected PE who were evaluated at a single hospital in Pisa, Italy.[24] All patients underwent a detailed clinical history, physical examination, rigorous interpretation of ECG and chest radiograph, and blood gas measurements. Using logistic regression techniques, a mathematical model for predicting probability of PE was developed. Probability was categorized as low (≤10% probability of PE), intermediate (>10% to 50% probability), moderately high (>50% to 90% probability), and high (>90% probability). Ten characteristics were associated with an increased risk of PE: male sex, older age, history of DVT, acute onset dyspnea, chest pain, hemoptysis, ECG signs of right ventricular overload, radiographic signs of oligemia, amputation of the hilar artery, and pulmonary consolidations suggestive of infarction. Five characteristics were associated with a decreased risk: previous cardiovascular or pulmonary disease, fever, pulmonary consolidation other than infarction, and pulmonary edema. With this model, 432 patients (39%) were rated as having low probability (4% PE), 283 (26%) as intermediate (22% PE), 72 (7%) as moderately high probability (74% PE), and 313 (28%) as high probability (98% PE).

In the original Pisa model, the highest regression coefficients were for the chest radiograph findings (oligemia 3.86; amputation of hilar artery 3.92, and pulmonary infarction 3.55). Because of the heavy reliance of the original Pisa model on advanced chest radiograph interpretation skills beyond the skill level of the average physician, Miniati et al[25] refined the Pisa model in the same patient population after excluding chest radiograph from the final equation (Table 3). In the validation set of this Class II investigation, the prevalence of PE was 2% when the predicted clinical probability was low (0% to 10%), 28% when moderate (11% to 50%), 67% when substantial (51% to 80%), and 94% when high (81% to 100%).

Comparative Studies of Objective Criteria

There are two Class II[32,47] and 3 Class III[28,30,31] studies that have evaluated performance of the various objective criteria. In comparing the Geneva score to the Wells score, 3 studies found no significant differences in performance though the study by Chagnon et al[28] suggested that the Geneva score overridden by physician judgment may be more accurate.[28,31,32]

Miniati et al[30] compared the Geneva score, Wells score, and Pisa model in 215 patients with suspected PE and found statistically significant differences in performance of the 3 pretest probability assessment tools. Areas under the ROC curve were 0.54, 0.75, and 0.94 for the Geneva score, Wells score, and Pisa model, respectively. However, findings in this study are limited because of small sample size and the PE rate in this patient population was extremely high (43%), indicating significant patient selection bias.

Runyon et al[47] compared the Wells score with the Kline criteria in 2,603 patients with a PE prevalence of 5.8%. The Wells score identified 73% of patients as low risk (score <2), and the Kline criteria identified 88% of patients as low risk. The PE rates in these low-risk patients were 3.0% and 4.2% for the Wells and Kline criteria, respectively.

Table 3. Regression coefficients and odds ratio for the Pisa model as described by Miniati et al[25] for estimating probability of pulmonary embolism according to clinical and ECG findings. Calculation of the clinical probability of pulmonary embolism is performed as follows: (1) Add all the coefficients that apply to a given patient and the constant –3.43 to obtain a sum score; (2) the probability of pulmonary embolism equals $[1+\exp(-\text{sum})]^{-1}$. Reprinted with permission of the American Thoracic Society. Copyright © American Thoracic Society. Miniati M, Bottal M, Monti S, et al. Simple and accurate prediction of the clinical probability of pulmonary embolism. *American Journal of Respiratory and Critical Care Medicine*. 2008;178:290-294. Official journal of the American Thoracic Society, Diane Gern, Publisher.

Predictor	Coefficient	Odds Ratio	95% CI
Age, y			
57–67	0.80	2.23	1.37–3.63
68–74	0.87	2.38	1.41–4.01
≥75	1.14	3.11	1.82–5.32
Male sex	0.60	1.82	1.27–2.61
Risk factors			
Immobilization	0.42	1.53	1.08–2.15
Deep venous thrombosis (ever)	0.64	1.90	1.23–2.95
Preexisting diseases			
Cardiovascular	–0.51	0.60	0.41–0.88
Pulmonary	–0.89	0.41	0.24–0.72
Symptoms			
Dyspnea (sudden onset)	2.00	7.38	5.18–10.51
Orthopnea	–1.51	0.22	0.05–0.93
Chest pain	1.01	2.74	1.93–3.88
Fainting or syncope	0.66	1.93	1.25–2.98
Hemoptysis	0.93	2.52	1.19–5.35
Signs			
Leg swelling (unilateral)	0.80	2.23	1.35–3.70
Fever >38°C (>100.4°F)	–1.47	0.23	0.13–0.40
Wheezes	–1.20	0.30	0.14–0.66
Crackles	–0.61	0.54	0.35–0.83
Electrocardiogram			
Acute cor pulmonale*	1.96	7.11	4.66–10.87
Constant	–3.43		

*One or more of the following ECG abnormalities: $S_1Q_3T_3$, $S_1S_2S_3$, negative T waves in right precordial leads, transient right bundle branch block, pseudoinfarction.

Gestalt Clinical Assessment

Gestalt clinical assessment is an unstructured (nonruled based) estimate of the pretest probability of disease. It is based on the clinician's training, clinical experience, and judgment. This approach has also been described as implicit in nature. The clinician using this approach surmises an overall impression of the pretest probability of PE and applies that impression to the decision about whether to pursue the diagnosis through objective testing.

The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study was a prospective multi-institution investigation designed to evaluate various conventional methods for diagnosing PE.[48] The PIOPED study is the first major study reporting gestalt assessment. As one element of the study, the clinician's assessment of the likelihood of PE from 0% to 100% was recorded for 887 patients and was compared with PE status as determined by angiogram and follow-up information. For data analysis, low risk was considered pretest probability of 0% to 19%, intermediate risk 20% to 79%, and high risk 80% to 100%. PE subsequently was diagnosed in 9.2%, 29.9%, and 67.8% of patients in the low-, intermediate-, and high-risk groups, respectively. Since the PIOPED study, multiple Class III studies have validated the usefulness of gestalt assessment of pretest probability in evaluating patients with suspected PE.[49-53]

There have been several comparative studies of gestalt versus objective criteria. In a Class II study investigating potential impact of adjusting the D-dimer threshold, Kabrhel et al[37] prospectively performed pretest probability assessment, using gestalt versus the Wells score in 7,940 patients from 10 academic centers. By gestalt pretest probability assessment, 68% of patients were low risk (<15% pretest probability PE), 26% intermediate risk (15% to 40%), and 6% high risk (>40%). Rates of PE in these 3 subgroups were 3%, 10%, and 33%, respectively. By the Wells score, 69% of patients were low risk (Wells score <2), 28% intermediate (Wells score 2 to 6), and 3% high risk (Wells score >6). Rates of PE in these 3 subgroups were 3%, 13%, and 36%, respectively.

Sanson et al,[41] in a Class III study, investigated pretest probability assessment of gestalt versus the Wells score in 517 patients with a 31% PE rate. By gestalt pretest probability assessment, 14% of patients were low risk (<20% pretest probability PE), 67% intermediate risk (20% to 80%), and 19% high risk (>80% to 100%). Rates of PE in these 3 subgroups were 19%, 29%, and 46%, respectively. By the Wells score, 36% of patients were low risk (Wells score <2), 63% intermediate (Wells score 2 to 6), and 2% high risk (Wells score >6). Rates of PE in these 3 subgroups were 28%, 30%, and 38%, respectively. The authors conclude that both methods "although comparable, perform disappointingly in categorizing the pretest probability in patients with suspected PE." The high rate of patients categorized as having intermediate risk and the low rate of patients categorized as having low risk in this study compared with other studies suggest significant patient selection bias that may account for the poor performance in pretest probability assessment by these 2 methods.

Runyon et al,[47] in a Class II study, compared gestalt pretest probability assessment with the Wells criteria and the Kline rule. In the low-risk group, rate of PE was 2.6%, 3.0%, and 4.2% for gestalt, Wells, and Kline rule, respectively. Gestalt and Wells score also were equivalent in pretest probability assessment for intermediate- and high-risk patients.

Limitations

Several issues concerning performance of clinical decision rules and gestalt assessment have been raised in the literature:

(1) Interrater reliability: Nordenholtz et al[54] compared third-year emergency medicine resident and attending emergency physician interrater reliability for 271 patients with suspected PE. Specific elements of the Wells and Kline risk-stratification tools were studied. Interrater agreement was concluded to be

moderate for DVT symptoms (κ=0.54), immobilization (κ=0.41), unexplained hypoxia (κ=0.58), and PE more likely than alternative diagnosis (κ=0.5); good for hemoptysis (κ=0.76); and very good for previous DVT (κ=0.90), malignancy (κ=0.87), and tachycardia (κ=0.94). Runyon et al,[47] in a large single hospital study involving a subset of 154 patients, found only moderate interrater agreement for gestalt clinical assessment of low probability (κ=0.6) and Wells score less than 2 (κ=0.47) and very good for Kline rule "safe" (κ=0.85).

(2) Clinical experience as a factor in the determination of pretest probability of PE: Accurate determination of the pretest probability of PE appeared to trend with clinical experience. However, the authors concluded that difference in accuracy between the inexperienced and experienced physicians is not sufficiently large to distinguish between the 2 when determining whether clinical gestalt or a clinical prediction rule should be used to determine the pretest probability of PE.[55]

Iles et al[44] performed a survey to investigate whether number of years since graduation from medical school affected pretest probability score for the Geneva, Wells, and gestalt pretest probability assessment. The Geneva score was found to be the most consistent method of determining pretest probability. Gestalt assessment was inversely proportional to clinical experience, suggesting that as physicians gain experience, they recognize the difficulties in ruling out PE and are reluctant to exclude it on clinical grounds.

(3) Knowledge and use of the rules: Runyon et al[56] surveyed emergency medicine clinicians and found that only half of all clinicians reporting familiarity with the rules use them in more than 50% of applicable cases. Spontaneous recall of the rules was low to moderate.

Conclusion

Both objective criteria and gestalt assessment appear to perform equally well for patients with suspected PE. With the advent of electronic charting, future studies need to be performed investigating the use of computer support aids in facilitating pretest probability assessment. Studies also need to be performed investigating use of pretest probability assessment to guide subsequent diagnostic testing. Finally, studies need to be performed to clarify the definitions of low-, intermediate-, and high-risk groups, especially for gestalt assessment in which studies have used pretest probabilities ranging from 20% to 80% as definition for intermediate probability.

2. What is the utility of the PERC in the evaluation of patients with suspected PE?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. In patients with a low pretest probability for suspected PE, consider using the PERC to exclude the diagnosis based on historical and physical examination data alone.

Level C recommendations. None specified.

Key words/phrases for literature searches: PERC, pulmonary embolism rule-out criteria, block rule, pulmonary embolism, and variations and combinations of the key words/phrases; years 2000 through December 2009.

In 2004, Kline et al[57] published a Class II prospective study deriving clinical criteria to prevent unnecessary diagnostic testing in ED patients with suspected PE. In this multicenter study with 3,148 patients in a derivation cohort, 21 descriptive variables relevant to the diagnosis of PE were collected. The primary outcome variable was the ED diagnosis of PE using a composite criterion standard, including 90-day follow-up. The overall prevalence of venous thromboembolism (VTE) was 11%. Logistic regression analysis with stepwise backwards elimination of variables was used to identify criteria that could predict a patient population estimated to have a prevalence of disease of 1.8%. At or below this low pretest probability of disease, the authors proposed that no further laboratory or radiographic testing would be needed to exclude the diagnosis of PE, although this threshold, which was based on a previously published method for calculating testing thresholds,[58] has subsequently been more accurately estimated to be 1.4% by a more recent decision analytic model balancing the benefits and costs of using the PERC.[59] After their analysis, 8 variables were identified: age younger than 50 years, pulse rate less than 100 beats/min, SaO_2 greater than 94% (at sea level), no unilateral leg swelling, no hemoptysis, no recent trauma or surgery, no previous PE or DVT, and no hormone use. These criteria have since become known as the PERC. When all criteria are met, a patient is considered to be PERC negative.

In this same study, the authors went on to internally validate the criteria in a separate patient cohort.[57] When applied to 1,427 patients considered to be low risk for PE by gestalt assessment, 25% of patients were PERC negative. The criteria, when considered to be a diagnostic test, had 96% sensitivity and 27% specificity, yielding a LR- of 0.15 and a 1.4% false-negative rate.

In 2008, Kline et al[60] published a Class II validation study of the PERC (Table 4). This multicenter, prospective study enrolled 8,138 patients. Although limited by the number of eligible patients who were not enrolled, the authors made attempts to address this. The outcome measures were similar to those of the original study, except for follow-up occurring at 45 days as opposed to 90 days, and the overall prevalence of VTE being 6.9%. Sixty-seven percent of patients were classified as low risk by clinical gestalt, and of these, 30.7% were PERC negative. This equated to 20.4% of enrolled patients. The sensitivity, specificity, and LR- for the PERC in the low-risk cohort were 94.7%, 21.9%, and 0.12, respectively. Of note, 3.5% of enrolled patients were PERC negative but not considered to be low risk by clinical gestalt. This subgroup had a 3.1% prevalence of VTE. Although outcomes on this specific subgroup were not reported, not all PERC negative patients are low risk, and the rule's applicability in these patients is unknown. The authors concluded that the PERC could be used in combination

Table 4. The Pulmonary Embolism Rule Out Criteria (PERC).

The PERC criteria negative (PERC–) require the clinician to answer no to the 8 questions below.[60] If a patient is low risk by gestalt impression and PERC–, the posttest probability of venous thromboembolism is <2%. Reprinted with permission. Copyright © John Wiley & Sons Ltd, Publisher. Kline JA, Courtney DM, Kabrhel C, et al. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. *J Thromb Haemost*. 2008;6:772-780.

1. Is the patient older than 49 years of age?
2. Is the pulse rate greater than 99 beats/min^{-1}?
3. Is the pulse oximetry reading <95% while the patient breathes room air?
4. Is there a present history of hemoptysis?
5. Is the patient receiving exogenous estrogen?
6. Does the patient have a prior diagnosis of venous thromboembolism (VTE)?
7. Has the patient had recent surgery or trauma (requiring endotracheal intubation or hospitalization in the previous 4 weeks)?
8. Does the patient have unilateral leg swelling (visual observation of asymmetry of the calves)?

with a low pretest probability to identify very low-risk patients for whom the diagnosis of PE can be reliably excluded based on historical and physical examination data alone.

In 2008, Wolf et al[61] published a small Class III external validation of the PERC. This study was a post hoc analysis of prospectively collected data on 120 consecutive ED patients with a suspicion of PE. The original database contained all PERC variables. Outcome measures used were similar to those of the original study, yielding a 12% prevalence of PE. When their entire patient population is considered, regardless of pretest probability, the sensitivity and specificity were 100% and 16%, respectively. When only the patients with low pretest probability, as defined by Wells Criteria, are considered, the specificity increased to 22%. The authors concluded that the PERC may identify a cohort of patients with suspected PE for whom diagnostic testing, beyond history and physical examination, is not indicated.

In each of the above 3 clinical studies, even though patient data were collected prospectively, the application of the PERC rule was performed retrospectively. As such, there is no prospective outcome study of the use of the PERC rule for clinical decisionmaking. This limits the strength of recommendations that can be made based on the available evidence. Future research should focus on the clinical application of the PERC rule with measurement of accepted outcomes.

3. What is the role of quantitative D-dimer testing in the exclusion of PE?

Patient Management Recommendations

Level A recommendations. In patients with a low pretest probability for PE, a negative quantitative D-dimer assay* result can be used to exclude PE.

*High sensitivity (eg, turbidimetric, ELISA).

Level B recommendations. None specified.

Level C recommendations. In patients with an intermediate pretest probability for PE, a negative quantitative D-dimer assay* result may be used to exclude PE.

Key words/phrases for literature searches: pulmonary embolism, fibrin fragment D, sensitivity, specificity, D-dimer, differential diagnosis, and variations and combinations of the key words/phrases; years 2001 through December 2009.

This revision to the 2003 clinical policy[1] focuses on quantitative D-dimer tests that have become available to most hospital laboratories across the United States. The Clinical Policies Subcommittee on PE elected not to assess the evidence for qualitative D-dimer tests (often used in point-of-care panels) because of problems with variability in interpretation and lower sensitivity reported in multiple studies.[62-65] However, the only randomized clinical trial directly assessing the impact of a D-dimer strategy used a qualitative whole-blood agglutination test (SimpliRED; Agen Biomedical Ltd., Brisbane, Australia).[66] In this trial, potential subjects suspected of having PE were first stratified according to the Wells criteria, and those with a low clinical probability and negative D-dimer test result were randomized to either no additional testing or VQ scanning. Although interpretation of results is limited due to early study closure, the incidence of VTE during 6 months was similar among the 2 groups (0/182 versus 1/185). Given that we were unable to identify any other randomized controlled trials specifically designed to test the impact of a D-dimer strategy, our recommendations are based on data from cohort studies and high-quality systematic reviews that have been published since the original ACEP clinical policy.[1] To avoid duplication, cohort studies that were included in at least 1 of the systematic reviews are not reported in the Evidentiary Table.

Class I systematic reviews assessing the test characteristics of quantitative D-dimer tests in outpatient settings conclude that D-dimer has excellent sensitivity (pooled sensitivity=0.93 to 0.96) but only moderate specificity (pooled specificity=0.39 to 0.51).[65,67,68] Class I[35,42] and II [37,69-75]cohort studies that were not included in these systematic reviews report similar results. In patients with a low pretest probability (10%), a negative ELISA or turbidimetric D-dimer (LR-=0.1) test result would be expected to decrease the probability of PE to approximately 1%. These assumptions based on the application of Bayes' Theorem are supported by Class I,[35] Class II,[69,73-75] and Class III[38,39,46,76-79] studies that have consistently reported negative predictive values of approximately 99% when D-dimer testing is applied to low-risk or "PE unlikely" patient populations. The American College of Physicians guidelines on PE also support using D-dimer testing among low-risk patients suspected of having PE.[80,81]

Despite consensus guidelines that recommend using D-dimer testing on patients with an intermediate pretest probability for PE,[82] strong evidence supporting this approach is lacking. A retrospective analysis of 2 studies by Righini et al[83] reported zero VTE events at 3-month follow-up for both low- and intermediate-risk groups; however, the upper limit for the 95% CI was 1% for the low-probability group but extended up to

5% for the intermediate-probability group. Subsequent studies that have included intermediate pretest probability patients within their D-dimer strategy have either not reported results separately[73,75,84] or have had too few patients in this subgroup to draw any firm conclusions.[77,78,85]

Given the relatively poor specificity of D-dimer testing, various strategies have been suggested to limit the number of false-positive tests that may lead to further unnecessary diagnostic testing. Retrospective subgroup analyses suggest that D-dimer sensitivity remains fairly constant among various subpopulations but specificity decreases with certain comorbid conditions and advanced age.[67,86,87] Two prospective studies assessing the performance of D-dimer testing among cancer patients suspected of having PE reported very low specificities (specificity=0.18 to 0.21).[88,89] Pregnancy is also associated with increasing concentrations of D-dimer, particularly in women beyond the first trimester.[90] A restrictive approach to D-dimer testing whereby the elderly are excluded improves test specificity[86,91]; however, this approach is unlikely to decrease resource utilization since these patients would be expected to go directly to some form of advanced imaging. Adjusting the D-dimer test threshold based on the patient's pretest probability or other variables (eg, age) has been suggested as an alternative approach to improve the performance of D-dimer testing.[37,87,92-94] Although raising the D-dimer test threshold would be expected to increase test specificity, the associated decrease in sensitivity may be unacceptable to most clinicians and has not been prospectively studied.[95]

Potential benefits of using a highly sensitive D-dimer as a screening test include decreased cost and radiation exposure; however, if the test is ordered indiscriminately on patients with very little or no risk for PE, false-positive D-dimer results may increase the harms associated with unnecessary advanced imaging. A formal decision analysis concluded that using D-dimer was not cost-effective if CT is readily available.[96] Although the authors' assumptions about the sensitivity and specificity of quantitative D-dimer tests were consistent with the studies included in the Evidentiary Table, the authors state that their analysis was based on a patient suspected of having PE without other competing diagnoses.[96] It is rare in the ED setting to have such a straightforward clinical presentation in which only 1 diagnosis is considered.

Future research is needed for patients with an intermediate pretest probability of PE, and to assess whether changing the D-dimer cutoff for different patient subgroups could improve specificity without a clinically significant decrease in sensitivity.

4. What is the role of the CT pulmonary angiogram of the chest as the sole diagnostic test in the exclusion of PE?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. For patients with a low or PE unlikely (Wells score ≤4) pretest probability for PE who require additional diagnostic testing (eg, positive D-dimer result, or highly sensitive D-dimer test not available), a negative, multidetector CT pulmonary angiogram alone can be used to exclude PE.

Level C recommendations. (1) For patients with an intermediate pretest probability for PE and a negative CT pulmonary angiogram result in whom a clinical concern for PE still exists and CT venogram has not already been performed, consider additional diagnostic testing (eg, D-dimer,* lower extremity imaging, VQ scanning, traditional pulmonary arteriography) prior to exclusion of VTE disease.

(2) For patients with a high pretest probability for PE and a negative CT angiogram result, and CT venogram has not already been performed, perform additional diagnostic testing (eg, D-dimer,* lower extremity imaging, VQ scanning, traditional pulmonary arteriography) prior to exclusion of VTE disease.

*A negative, highly sensitive, quantitative D-dimer result in combination with a negative multidetector CT pulmonary angiogram result theoretically provides a posttest probability of VTE less than 1%.

Key words/phrases for literature searches: x-ray computed tomography, CT, spiral computed tomography, pulmonary embolism, sensitivity, specificity, probability, likelihood, pulmonary angiogram, angiography, thromboembolism, outcome, follow-up, recurrent, morbidity, mortality, false negative, false positive, prognosis, treatment outcome, and variations and combinations of the key words/phrases; years 2001 through December 2009.

The use of the spiral CT angiogram for the visualization of the pulmonary vasculature and the evaluation of PE was first described in 1992.[97] A single detector rotated in a spiral fashion at fixed intervals, collecting data to generate vascular images during a single breath hold.

Since that time, the technology of this diagnostic modality has advanced dramatically. Multidetector CT scanners now use between 4, 64, or more channels (detectors) and rotate at much faster gantry speeds (0.4 seconds versus 1 second per rotation). Thus an older-generation single-detector CT with a 1-second gantry speed captures 1 slice per second, whereas a 16-channel multidetector CT scanner rotating at a gantry speed of 0.4 seconds captures 40 slices per second.[98] This, in addition to thinner collimation, allows for faster image acquisition, less motion artifact, and ultimately higher-resolution images. Improved image acquisition protocols and resolution are believed to result in improved diagnostic performance.

In 1992, Remy-Jardin et al,[97] in a Class III investigation, reported sensitivities and specificities of 100% and 96%, respectively, for a single-detector CT for detection of PE. This finding led to eager acceptance of the spiral CT angiogram into diagnostic algorithms in the hope of simplifying the complicated diagnostic workup of PE. Since this initial study, multiple accuracy and outcomes studies, in addition to meta-analyses and systematic reviews, have been published on the performance of the CT pulmonary angiogram. Unfortunately,

data are lacking about the performance of the most current CT pulmonary angiogram technology (eg, 128-channel multidetector CTs).

Since 2001, 2 Class II[99,100] and 4 Class III[101-104] accuracy studies on the prospective diagnostic performance of single detector CT have shown variable results, with sensitivities ranging from 57% to 91% and specificities ranging from 84% to 100%. Likewise, 4 Class III systematic reviews solely evaluating single-detector CT technology demonstrated sensitivities between 37% and 100% and specificities between 78% and 100%.[98,105-107] The sensitivity for the detection of emboli to the subsegmental level (37% to 93%) was lower than that for the segmental and lobar level (53% to 100%). Because these findings demonstrate suboptimal LR- (0.09 to 0.46), most of the authors recommend caution when using single detector CT as the sole diagnostic test in the exclusion of PE.

One Class II study[108] and 2 Class III[109,110] prospective accuracy studies on multidetector CT have also been published since 2001. These studies show better performance compared with single-detector CT, with sensitivities ranging from 83% to 100% and specificities between 89% and 98%. A Class III meta-analysis[98] and one Class III systematic review[106] evaluating multidetector CT performance found the sensitivities and specificities were reported as 83% to 90% and 94% to 100%, respectively. These data are consistent with those from multiple other reviews evaluating multidetector CT in combination with single-detector CT.[111-114] As such, given the continued potential for false-negative CT results due to LRs- between 0.02 and 0.41, many of these authors still recommend caution when using multidetector CT as the sole diagnostic test in the exclusion of PE.

Negative CT Pulmonary Angiogram Outcome Studies

Although CT pulmonary angiogram alone detects the majority of pulmonary emboli, it seems that it may be falsely negative in approximately 15% of cases.[108] It has been hypothesized that the pulmonary emboli currently missed by CT pulmonary angiogram alone may be small and clinically insignificant,[115] which may justify the discharging home of ED patients, without anticoagulation. Studies reporting the outcome of patients with clinically suspected PE for whom anticoagulation was withheld following a negative CT pulmonary angiogram alone were reviewed to evaluate this hypothesis. In general, these studies enrolled patients who were clinically suspected of having a PE. The patients then received CT pulmonary angiogram imaging for the evaluation of PE. When PE was identified on imaging, they were treated with anticoagulation. If CT imaging was negative, they were discharged with no anticoagulation and followed clinically for evidence of subsequent VTE.

Some studies incorporated the pretest risk stratification of patients prior to CT in their evaluation algorithms. Patients may have had additional negative testing results (eg, D-dimer, venous imaging, VQ scanning, pulmonary arteriography) prior to discharge off anticoagulation. As general consensus in the international medical community, patients clinically suspected of experiencing a PE are presumed to have PE if lower extremity imaging reveals DVT, even if the patient has a negative CT pulmonary angiogram result.

A total of 16 articles were identified, ranging in year of publication from 2000 to 2008, that investigated outcome after a negative CT scan result (Table 5). Two studies were retrospective,[116,117] 13 studies were prospective,[11,26,35,50,84,108,115,118-123] and there was 1 meta-analysis.[111] In these studies, the evaluation of the conclusions was often confounded by one or more of the following:

(1) variability in the types of CTs and CT imaging protocols between studies
(2) variability in the definition of recurrent PE between studies
(3) failure to separate ED patients from inpatients and other outpatients
(4) lack of standardized PE screening protocols or protocols that were poorly adhered to
(5) failure to differentiate patients by their pretest probability of disease (eg, low risk, intermediate risk, or high risk)
(6) differing inclusion or exclusion criteria between studies
(7) excluding of patients who received testing other than CT pulmonary angiogram that was positive
(8) including of patients who received testing other than CT pulmonary angiogram that was negative
(9) variability in training of the interpreting radiologists between studies (eg, radiologists subspecialized in thoracic radiology versus general radiologists)
(10) differing durations of follow-up after discharge between studies
(11) loss of a significant proportion of the study sample to follow-up
(12) low rates of autopsy among patients who died

The two Class III retrospective studies used a single-detector CT scan and reported rates of subsequent PE in patients with a negative CT pulmonary angiogram result of approximately 0% to 2%.[116,117] In addition to being retrospective, these studies were also limited by smaller sample sizes, the loss of a significant proportion of patients to follow-up, the exclusion of patients who received anticoagulation before or after CT pulmonary angiogram due to a higher perceived pretest probability of PE, or the exclusion of patients who received testing, other than CT pulmonary angiogram, that was positive.

Of the 13 prospective studies between 2000 and 2008, 3 were Class I level of evidence,[35,50,84] 4 were Class II level of evidence,[11,26,108,118] and the remaining 6 studies were Class III level of evidence.[115,119-123] Of the 7 Class I and II level of evidence studies, 5 studies incorporated data from multidetector CTs[11,26,35,84,108] and 2 did not.[50,118]

One of the Class I studies[35] found a low incidence of subsequent VTE during follow-up after a negative CT pulmonary angiogram result similar to that found in the retrospective studies. In this 2006 study,[35] the Christopher

Table 5. Negative CT pulmonary angiogram outcome study table.

Author	Year	Design	Detector Type	Collimation, mm	Sample Size (CT Negative)	Patient Type	Duration of Follow-up, mo
Goodman et al[115]	2000	Prospective	Single	3	285	Inpatient/outpatient/ED	1 and 3
Musset et al[50]	2002	Prospective	Single	2–3	601	Inpatient/outpatient/ED	1, 2, and 3
Swensen et al[116]	2002	Retrospective	Single	3	993	Inpatient/outpatient/ED	3
Donato et al[117]	2003	Retrospective	Multiple	3	243	Inpatient/outpatient	3
van Strijen et al[118]	2003	Prospective	Single	5	248	Inpatient/outpatient/ED	3
Perrier et al[26]	2004	Prospective	Single/multiple	3	458	ED	3
Friera et al[119]	2004	Prospective	Single	3	132	Not specified	3
Kavanagh et al[120]	2004	Prospective	Multiple	1.25	85	Not specified	4 to 13
Moores et al[111]	2004	Meta-analysis, prospective/ retrospective	Single/multiple	1.25–5	4,657	Inpatient/outpatient/ED	3 or more
Prologo et al[121]	2005	Prospective	Single/multiple	3	221	Not specified	3 and 6
van Belle et al[35]	2006	Prospective	Single/multiple	1.25–3	1,436	Inpatient/outpatient/ED	3
Stein et al[108]	2006	Prospective	Multiple (4–16)	Not specified	773	Inpatient/outpatient/ED	6
Vigo et al[122]	2006	Prospective	Multiple	2.5	257 negative D-dimer; 279 positive D-dimer	Inpatient/outpatient	6
Anderson et al[11]	2007	Prospective	Single/multiple	1	694 positive D-dimer or at higher risk	Inpatient/outpatient/ED	3
Subramaniam et al[123]	2007	Prospective	Single	3	483	Inpatient/ED	3
Righini et al[84]	2008	Prospective	Multiple	1.25	673	ED	3

CT, Computed tomography; *ED*, emergency department; *mo*, month.

Study Investigators reported 3-month follow-up of a prospective, consecutive sample of 1,436 patients who had anticoagulation withheld following a negative CT pulmonary angiogram for the workup of clinically suspected PE. Patients were initially risk stratified as either PE "unlikely" (ie, Wells score ≤4) or PE "likely" (Wells score >4). Patients for whom the diagnosis of PE was judged "unlikely" received highly sensitive D-dimer testing. PE unlikely patients with a positive D-dimer result, and patients with a likely clinical probability of PE received further testing with CT pulmonary angiogram alone. Of the 1,436 patients with a negative CT pulmonary angiogram result who did not receive anticoagulation, 18 (1.3%; 95% CI 0.7% to 2%) were found to develop VTE during the 3-month follow-up. Seven (39%) of the patients found to have VTE in follow-up died. This mortality rate among patients with missed PE is similar to that reported in other studies.[84,116] Only 1 patient had incomplete follow-up. The results of this study were very similar to those of another, dichotomously risk-stratified, Class II study by Anderson et al[11] that reported the incidence of subsequent VTE after a combined negative CT pulmonary angiogram result and bilateral ultrasound of 1.7%. In another prospective Class II study, van Strijen et al[118] found a 2% incidence of subsequent VTE among patients with a negative single-detector CT result who were followed for 3 months. In contrast to these studies, other prospective studies have raised concerns that CT pulmonary angiogram may not reliably exclude subsequent VTE, especially among patients risk stratified as having higher clinical pretest probability for PE.[50,84,108,122]

In a 2002 Class I prospective single-detector CT study with 98.8% follow-up at 3 months, Musset et al[50] reported on the outcome of consecutive, risk-stratified patients who had anticoagulation withheld following a negative single-detector CT pulmonary angiogram result that was combined with bilateral lower extremity ultrasound. The incidence of subsequent VTE in this study during a 3-month follow-up period was 1.8% (95% CI 0.8% to 3.3%) among 507 patients with a low and intermediate pretest probability of PE. Ten low and intermediate pretest probability patients were lost to follow-up. Among the low- and intermediate-risk patient group, inpatients had a higher incidence of disease in follow-up (4.8%; 95% CI 1.8% to 10.1%) than outpatients (0.8%; 95% CI 0.2% to 2.3%). Seventy-five of 76 high pretest probability patients had VQ imaging, traditional arteriography, or both at the time of their initial evaluation. Four of the 75 (5.3%; 95% CI 1.5% to 13.1%) high-risk patients proved to have PE on subsequent imaging after a negative CT pulmonary angiogram and bilateral lower extremity ultrasound. This study combined lower extremity ultrasound imaging with CT in the evaluation process and still found a modest proportion of patients, especially inpatients and those assessed as high risk, who developed PE in follow-up. This study shows the importance of risk stratification before CT pulmonary angiogram and calls into question the reports of lower incidences of subsequent VTE among nonrisk-stratified patients.

Results from additional studies have also raised questions about the previously reported low rate of VTE after a negative CT pulmonary angiogram alone result for patients with

Table 6. Positive and negative predictive values of CTA compared with previous clinical assessment.*[108] Reprinted with permission. Copyright © Massachusetts Medical Society, Publisher. Stein PD, Fowler SE, Goodman LR, et al, for the PIOPED II Investigators. Multidetector computed tomography for acute pulmonary embolism. *N Engl J Med*. 2006;354:2317-2327.

	High Clinical Probability		Intermediate Clinical Probability		Low Clinical Probability	
Variable	**No./Total No.**	**Value (95% CI)**	**No./Total No.**	**Value (95% CI)**	**No./Total No.**	**Value (95% CI)**
Positive predictive value of CTA	22/23	96 (78–99)	93/101	92 (84–96)	22/38	58 (40–73)
Positive predictive value of CTA or CTV	27/28	96 (81–99)	100/111	90 (82–94)	24/42	57 (40–72)
Negative predictive value of CTA	9/15	60 (32–83)	121/136	89 (82–93)	158/164†	96 (92–98)
Negative predictive value of both CTA and CTV	9/11	82 (48–97)	114/124	92 (85–96)	146/151†	97 (92–98)

CI, confidence interval; *CTA*, computed tomography angiogram; *CTV*, computed tomography venogram.
*The clinical probability of pulmonary embolism was based on the Wells score: less than 2.0, low probability; 2.0 to 6.0, moderate probability; and more than 6.0, high probability.
†To avoid bias for the calculation of the negative predictive value in patients deemed to have a low probability of pulmonary embolism on previous clinical assessment, only patients with a reference test diagnosis by ventilation perfusion scanning or conventional pulmonary digital subtraction angiogram were included.

clinically suspected PE. In 2006, the PIOPED II investigators, in a Class II, prospective study of 1,090 risk-stratified inpatients and outpatients with suspected PE, reported patient outcomes of the use of CT pulmonary angiogram in conjunction with delayed CT venogram.[108] Of these 1,090 patients, 28 were excluded for not undergoing CT, 238 were excluded for not having a reference test diagnosis, and 51 were excluded for having a noninterpretable CT scan. There were 592 patients with an interpretable CT for whom PE was ruled out on initial presentation. The overall incidence of subsequent VTE on 6-month follow-up in this subgroup was 17% (95% CI 8% to 24%) after a negative CT pulmonary angiogram alone result, and 10% (95% CI 7% to 16%) after a negative CT pulmonary angiogram with CT venogram. The rate of false-negative CT studies was higher among the subjects risk stratified as "high clinical probability" and lower among the "low clinical probability" group (Table 6).

Conversely, the false positive rate was highest among the low clinical probability patients and lowest among those risk stratified as high clinical probability. This study was limited by the high exclusion rate (29%) and by the fact that patients uniformly received additional testing after their negative CT pulmonary angiogram with or without CT venogram prior to discharge; therefore, the study did not directly assess the prognostic value of a negative CT pulmonary angiogram alone result to predict outcome among patients not receiving anticoagulation.

In a 2006 Class III study with 6-month follow-up that combined the result of a highly sensitive quantitative D-dimer after a negative multidetector CT pulmonary angiogram result among 279 consecutive patients with clinically suspected PE, Vigo et al[122] found that the incidence of PE after a negative CT pulmonary angiogram and positive D-dimer result was 19.7% (55/279). The incidence of PE after a negative CT pulmonary angiogram and negative D-dimer result was 1.17% (3/257; 95% CI 0.24% to 3.38%). This study was limited by the fact that patients with a positive D-dimer result had immediate evaluation with VQ scanning prior to discharge home and the decision to prescribe anticoagulation. Additionally, there was no autopsy rate reported among the 15 patients who died in the group that had both a negative CT pulmonary angiogram and D-dimer test result. This study adds concern to the ability of CT pulmonary angiogram to reliably exclude PE among higher-risk patients.

In a 2008 Class I study, Righini et al[84] investigated the 3-month outcome of 1,819 consecutive, risk-stratified patients suspected of having PE, randomized into 2 diagnostic evaluation strategies: D-dimer combined with CT pulmonary angiogram versus D-dimer combined with venous ultrasound and CT pulmonary angiogram. The 3-month VTE risk in patients with a negative workup in these 2 subgroups was 0.3% (95% CI 0.1 to 1.2) and 0.3% (95% CI 0.1 to 1.1), respectively.

The false-negative rate of CT pulmonary angiogram alone in patients clinically deemed high risk for PE ranges in studies from 5.3% to 40%.[50,84,108] Although data are more limited about those specific high-risk patients for PE, outcome studies support the use of additional testing (eg, D-dimer, lower extremity venous imaging, VQ scanning, traditional arteriography) after a negative CT pulmonary angiogram alone result before definitively ruling out VTE in this subset of patients.

Until more perfect diagnostic testing evolves for diagnosing PE, future studies of CT should include the reproducible, pretest clinical risk stratification of patients, in addition to well-adhered-to, standardized PE screening protocols. Additionally, as screening and confirmatory tests for PE become increasingly sensitive, it will be crucial to better define the incidence, cost, and risk associated with false-positive testing. These risks may include unnecessary long-term anticoagulation, as well as uninsurability for medical financial coverage.

5. What is the role of venous imaging in the evaluation of patients with suspected PE?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. When a decision is made to perform venous ultrasound as the initial imaging modality, *a positive finding in a patient with symptoms consistent with PE can be considered evidence for diagnosis of VTE disease and may preclude the need for additional diagnostic imaging in the ED.

*Examples of situations in which a venous ultrasound may be considered as initial imaging may include patients with obvious signs of DVT for whom venous ultrasound is readily available, patients with relative contraindications for CT scan (eg, borderline renal insufficiency, CT contrast agent allergy), and pregnant patients.

Level C recommendations. (1) For patients with an intermediate pretest probability for PE and a negative CT angiogram result, for whom a clinical concern for PE still exists and CT venogram has not already been performed, consider lower extremity venous ultrasound as an additional test to exclude VTE disease (see question 4).

(2) In patients with a high pretest probability for PE and a negative CT angiogram result, and CT venogram has not already been performed, perform additional testing to exclude VTE disease (see question 4). As one of these additional tests, consider lower extremity venous ultrasound to exclude VTE disease (see question 4).

Key words/phrases for literature searches: pulmonary embolism, venous ultrasonography, sensitivity, specificity, probability, likelihood, and variations and combinations of the key words/phrases; years 2002 through December 2009.

Various strategies are currently used in the ED evaluation of patients with suspected PE. Most involve a combination of pretest probability assessment, D-dimer measurement, VQ scanning, CT angiogram and pulmonary arterial angiogram. Venous imaging, CT venous imaging (obtained in conjunction with CT pulmonary angiogram), and venous ultrasound may play useful roles in the management of these patients.

The use of venous imaging for PE assessment has been reported in 3 Class I,[36,50,84] 3 Class II,[108,124,125] and 5 Class III studies.[126-130] CT venous imaging is performed in sequence directly after CT angiogram. This technique uses the opacification of the venous system that follows rapid infusion of contrast medium that is involved with the performance of CT angiogram but also results in additional radiation exposure. Images are obtained of the veins of the legs, pelvis, and abdomen. When CT angiogram is used in the assessment of patients with suspected PE, the time to acquire these additional images is minimal. Although venous ultrasound of bilateral lower extremities does not involve additional radiation exposure, this test does not allow for evaluation of the abdominal and pelvic venous systems and typically requires more time because different technicians and departments are involved.

Previous reports of the use of venous imaging typically involve either the performance of venous ultrasound before or after CT angiogram or the use of CT venous imaging in conjunction with CT angiogram to increase the diagnostic yield for the diagnosis of thromboembolic disease.

In the assessment of ED patients with suspected PE, the performance of venous ultrasound with the finding of a significant DVT is diagnostic of VTE and may preclude the need for further diagnostic testing.[84,108,131,132] In these patients, the use of venous ultrasound before CT angiogram is for the purposes of limiting radiation exposure and, in some situations in which venous ultrasound is more available or more rapidly performed, decreasing time for evaluation. This strategy should be considered for patients with obvious signs of DVT, for patients with relative contraindications for CT scan (eg, renal insufficiency, CT contrast agent allergy), and pregnant patients. Only 1 Class I study[84] evaluated outcomes with this strategy for the use of venous ultrasound for ED patients with suspected PE before CT angiogram. This study randomized 2 different strategies for the ED workup of these patients: pretest probability assessment, D-dimer measurement, and CT angiogram with 3-month follow-up versus the same regimen except the addition of venous ultrasound testing before CT angiogram, if indicated. If the venous ultrasound revealed a significant DVT, no further testing was performed and treatment for venous thromboembolic disease was initiated. This study found that both treatment algorithms were equally safe at 3-month follow-up, and about 10% of the patients who had venous ultrasound were diagnosed with a significant DVT and did not need CT angiogram to be performed. However, the addition of venous ultrasound required 11 patients to have this additional test to identify 1 patient with DVT.

The remaining clinical trials involved the use of venous imaging after the performance of CT angiogram in order to improve the sensitivity for the diagnosis of PE. Most of these studies report on venous ultrasound after CT angiogram with no Class I studies available for CT angiogram followed by CT venous imaging.

Anderson et al,[36] in a Class I study, performed a prospective multicenter study assessing a treatment algorithm for ED patients with suspected PE that incorporated venous ultrasound after CT angiogram. This protocol involved pretest probability assessment, D-dimer measurement, CT angiogram, and venous ultrasound with 3-month follow-up. All patients who had CT angiogram testing also had venous ultrasound. This study enrolled 858 patients, of whom 9.6% (95% CI 7.7% to 11.8%) were diagnosed with PE. Of these patients, 369 had low pretest probability with a negative D-dimer result. These patients did not undergo further testing. The remaining 489 patients underwent CT angiogram and venous ultrasound testing. Of these 489 patients, 67 (13.7%; 95% CI 10.8% to 17.1%) had PE diagnosed by CT angiogram. Of the remaining 422, 13 patients had a DVT diagnosed by venous ultrasound. The addition of venous ultrasound to CT angiogram in this study identified an additional 3.1% (95% CI 1.7% to 5.2%) of patients who were treated for venous thrombotic disease. A

Class I study by Musset et al[50] used a similar protocol and found that the addition of venous ultrasound after CT angiogram identified 6.0% (95% CI 4.5% to 7.7%) of patients with significant DVTs. Of the remaining studies involving venous ultrasound testing after CT angiogram, there were 1 Class II and 2 Class III studies that revealed similar findings: Le Gal et al,[125] finding 0.9% (95% CI 0.2% to 2.6%), Au et al,[126] finding 2.6% (95% CI 0.1% to 13.8%), and Coche et al,[127] finding 2.3% (95% CI 0.1% to 12.3%) of additional patients identified with venous ultrasound testing after CT angiogram.

One Class II[108] and 5 Class III[126-130] studies assessed the utility of CT venous imaging after CT angiogram. Five of the 6 studies enrolled both inpatients and outpatients, with 4 of these studies including predominantly inpatients referred to radiology for CT angiogram for suspected PE. Additionally, none of these studies assessed 3-month follow-up in patients with negative CT angiogram results. The PIOPED II trial[108] was a Class II multicenter prospective study that enrolled adults (≥18 years) with clinically suspected PE from the inpatient or outpatient setting. All patients who met inclusion/exclusion criteria underwent pretest probability assessment and then CT angiogram, followed by CT venous imaging. CT was conducted in 824 patients, with 51 patients having inconclusive testing due to poor CT image quality. PE was diagnosed in 192 (23%; 95% CI 20.4% to 26.3%) patients, with 2.1% (95% CI 1.1% to 3.5%) being identified with the addition of CT venogram. The 5 Class III studies reported similar findings.[126-130] The addition of CT venous imaging to CT angiogram identified an additional 7.9% (95% CI 1.7% to 21.4%) of patients in the Au et al[126] study, 4.7% (95% CI 0.6% to 15.8%) in the Coche et al[127] study, 0% (95% CI 0% to 16.1%) in the Begemann et al[128] study, 0.3% (95% CI 0.01% to 1.4%) in the Johnson et al[129] study, and 5.5% (95% CI 3.8% to 7.7%) in the Loud et al[130] study.

Based on these studies, it appears that venous ultrasound and CT venous imaging after negative CT angiogram result are equally useful. There are 1 Class II and 2 Class III studies in which CT venous imaging and venous ultrasound were performed after CT angiograms in patients with suspected PE.[126,127,133] Goodman et al,[133] in a Class II study, performed a substudy analysis of the PIOPED II[108] data. There were 711 patients who underwent CT angiogram and had both CT venogram and venous ultrasound performed. Both CT venogram and venous ultrasound were positive in 81 of 711 (11%) patients. CT venogram was positive and venous ultrasound negative in 17 (2%) patients, and CT venogram was negative and venous ultrasound was positive in 15 (2%) patients. Coche et al[127] performed CT angiogram, CT venous imaging, and venous ultrasound in a prospective study of inpatients and outpatients with suspected PE (only 7 of 65 patients were from the ED). Venous ultrasound was performed within 24 hours of CT scanning. PE was diagnosed by CT angiogram alone. DVT was diagnosed if a patient had concordant DVT on CT venous imaging and venous ultrasound. For 5 patients for whom there were discordant results for CT venous imaging and venous ultrasound, standard venogram was performed in 2 patients and 3 patients had repeated focalized venous ultrasound to arrive at final diagnosis. VTE was diagnosed in 38 (58.5%) patients and consisted of 22 (33.8%) patients with isolated PE, 13 (20%) with co-existent PE and DVT, and 3 (4.6%) with DVT. In the 16 patients with DVT, CT venous imaging had a sensitivity/specificity for DVT of 93.8%/98%, respectively, compared with 87.5%/98% for venous ultrasound. CT venous imaging identified an additional 2 patients with VTE (5.3% of total patients with VTE) compared with CT angiogram, whereas venous ultrasound identified an additional 1 (2.6%) patient. The study by Au et al[126] reported similar results. Given the available data, venous ultrasound and CT venous imaging after CT angiogram both appear to be equally effective in the evaluation of VTE in patients with suspected PE.[84,126,127,130]

In summary, venous imaging may be a useful adjunct in the diagnostic algorithm of ED patients suspected of having PE. The use of venous ultrasound as the initial diagnostic test may establish the diagnosis of VTE in approximately 10% of patients and preclude the need for CT angiogram. This strategy may be particularly useful in patients who have obvious clinical signs of DVT, contraindications for contrast dye administration (eg, renal dysfunction, CT contrast agent allergy), or when limitation of radiation exposure is extremely important (eg, pregnancy). However, for most patients (~90%), this strategy will involve a negative venous ultrasound test and the increased time and expense of this additional test. The use of venous imaging (venous ultrasound or CT venous imaging) identifies DVT in approximately 0% to 6% of patients with a negative CT angiogram.

A limitation of the presently available studies is that most of the data come from research using older single-detector CTs. Theoretically, higher-resolution multidetector CTs will have greater sensitivity for detecting PE, and future studies need to address whether venous imaging is warranted for patients with a negative CT angiogram result when obtained with the newest generation of CT scanners. Future studies also need to identify which patients would most benefit from adding venous imaging to CT angiogram. An additional area of future research is identification of subgroups of patients with suspected PE who would most benefit from a protocol of venous ultrasound as the initial diagnostic test before CT angiogram.

6. What are the indications for thrombolytic therapy in patients with PE?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Administer thrombolytic therapy in hemodynamically unstable patients with confirmed PE for whom the benefits of treatment outweigh the risks of life-threatening bleeding complications.*

*In centers with the capability for surgical or mechanical thrombectomy, procedural intervention may be used as an alternative therapy.

Level C recommendations. (1) Consider thrombolytic therapy in hemodynamically unstable patients with a high clinical suspicion for PE for whom the diagnosis of PE cannot be confirmed in a timely manner.

(2) At this time, there is insufficient evidence to make any recommendations regarding use of thrombolytics in any subgroup of hemodynamically stable patients. Thrombolytics have been demonstrated to result in faster improvements in right ventricular function and pulmonary perfusion, but these benefits have not translated to improvements in mortality.

Key words/phrases for literature searches: pulmonary embolism, thrombolytic therapy, massive pulmonary embolism, and variations and combinations of the key words/phrases; years 2000 through December 2009.

Despite proven benefit of thrombolytic therapy in patients with ST-segment elevation acute myocardial infarction (STEMI)[134] and select patients with acute cerebral vascular accidents,[135,136] indications for use of thrombolytic therapy in patients with PE remain controversial despite more than 40 years of experience.[1,82,137-142] It is well established that treatment of PE with thrombolytic therapy[†] results in more rapid resolution of arterial emboli, decreased pulmonary artery pressure, and improvements in cardiac output and pulmonary circulation.[143-151] However, none of these clinical benefits have been demonstrated to result in improvement in mortality or recurrent PE in unselected patients with PE.

Treatment benefit for acute myocardial infarction and cerebral vascular accident is directly related to time from symptom onset until administration of thrombolytic therapy (ie, door-to-needle time). For acute myocardial infarction, benefit has been demonstrated during the first 12 hours of symptom onset.[134] For cerebral vascular accident, the National Institute of Neurologic Disorders and Stroke (NINDS) Study Group[135] demonstrated benefit of treatment with alteplase during the first 3 hours, and Hacke et al[136] subsequently demonstrated a benefit in the 3- to 4.5-hour time window. Theoretically, similar time-dependent treatment benefits should exist for thrombolytic therapy in PE. To date, no randomized trial has investigated potential time-dependent benefits during the initial hours of symptom onset.

Clinical Investigations of Thrombolytics in PE

There are 11 randomized studies investigating utility of thrombolytics in PE that have appeared in subsequent meta-analyses.[146-156] Four of these 7 articles were given a grade of X by this subcommittee.[153-156] Table 7 summarizes some of the important features of these 11 randomized studies (see Evidentiary Table for more detailed information).

[†]The 2 thrombolytic drugs available in the United States that are approved for use by the Food and Drug Administration are streptokinase (250,000-unit bolus, followed by 100,000 units/hour for 24 hours) and recombinant tissue plasminogen activator (rt-PA) (100 mg infused over 2 hours).

The shortest inclusion criterion from time of symptom onset until presentation was 96 hours in the study by Konstantinides et al.[152] Two studies did not provide time eligibility information,[153,156] and the remaining studies used 5 days,[149,151] 7 days,[150,155] 10 days,[146] and 14 days.[147,148,154] None of these studies reported time-dependent treatment benefits, and thus it is impossible to perform any valid meta-analysis on this topic.

A significant limitation of the 11 studies investigating PE is that only 2 studies had mortality as a primary outcome measure.[152,154] The primary endpoint of the remaining 9 studies related to pulmonary perfusion parameters or hemodynamic parameters.[146-151,153,155,156] Seven studies excluded hypotensive patients.[146-150,152,155] Other significant limitations relate to the multitude of differing thrombolytic agents, differing doses and routes of administration, differing inclusion/exclusion criteria, and differing clinical endpoints.

The 3 largest studies to date are the Class II study by Goldhaber et al[147] and the Class III studies by the Urokinase Pulmonary Embolism Trial (UPET) Study Group[151] and by Konstantinides et al.[152] The Goldhaber et al[147] study was a single-center, nonblinded, randomized controlled trial in 101 patients whose primary outcomes were right ventricular hemodynamics and pulmonary perfusion by nuclear lung scanning. The study demonstrated improvements in right ventricular wall motion (39% versus 17%; $P<0.05$) and in degree of 24-hour pulmonary perfusion (14.6% versus 1.5%; $P<0.05$) in patients treated with thrombolytics. No recurrent PE was observed in the alteplase group as opposed to 5 patients in the heparin group ($P=0.06$). A significant limitation of this study was the inclusion of late presenters as these patients had already survived the initial phase of their disease and thus were at extremely low risk of adverse outcome (approximately 30% of study patients presented >5 days after symptom onset).

The UPET Class III study was a multicenter, randomized, placebo-controlled trial in 160 patients whose primary outcomes were pulmonary angiogram scores, hemodynamic measurements via right heart catheterization, and pulmonary perfusion scanning.[151] Significant improvements in the thrombolytic group were observed in pulmonary angiogram scores (53% versus 9% with moderate or greater improvement, *P* values and CI not provided), mean hemodynamic abnormalities, and 24-hour lung scanning (22.1% versus 8.1%, *P* values and CI not provided).

The Class III study by Konstantinides et al[152] was a multicenter, double-blinded, randomized, placebo-controlled trial in 256 patients presenting within 96 hours of symptom onset. The primary endpoint was defined as inhospital death or clinical deterioration that required an escalation of treatment (secondary thrombolysis, catecholamines, cardiopulmonary resuscitation, and surgical embolectomy). The primary endpoint occurred in 11.0% of alteplase versus 24.6% of heparin patients ($P<0.05$). However, analysis of the data reveals that there were no differences in the individual outcomes of the composite endpoint among those patients who received alteplase versus

Table 7. Important features of the 11 randomized clinical trials of thrombolytic therapy in PE that were used in subsequent meta-analyses.

Study	Class	Thrombolytic Regimen	Primary Endpoints	Symptom Onset Inclusion Criteria	Excluded Hypotensive Patients
Dalla-Volta et al[146]	III	Alteplase 10-mg bolus plus 90 mg during 100 min plus heparin	Angiogram score	10 days	Yes
Goldhaber et al[147]	II	Alteplase 100 mg during 2 h plus heparin	Right ventricular function; pulmonary perfusion; mortality	14 days	Yes
Levine et al[148]	III	Alteplase 0.6 mg/kg during 2 min plus heparin	Pulmonary perfusion	14 days	Yes
Ly et al[149]	III	Streptokinase 250,000 IU load; then 100,000/h during 72 h	Angiogram score	5 days	No
PIOPED Investigators[150]	III	Alteplase 40 to 80 mg infused at 1 mg/min plus heparin	Angiogram score; pulmonary perfusion	7 days	Yes
UPET Study Group[151]	III	Urokinase 2,000 IU/pound/h load; then 2,000 IU/pound during 12 h, followed by heparin	Angiogram score; hemodynamics	5 days	No
Konstantinides et al[152]	III	Alteplase 10-mg bolus plus 90 mg during 120 min plus heparin	Mortality; escalation of treatment	96 h	Yes
Dotter et al[153]	X	Streptokinase 250,000 load during 20 to 30 min; then 100,000 IU/h for 18 to 72 h, followed by heparin	Angiogram score	Not stated*	No
Jerjes-Sanches et al[154]	X	Streptokinase 1,500,000 IU during 1 h, followed by heparin	Mortality	14 days	No
Marini et al[155]	X	Urokinase 2,400,000 IU during 3 days (10 patients); urokinase 3,300,00 IU during 12 h (10 patients)	Pulmonary perfusion	7 days	Yes
Tibbutt et al[156]	X	Streptokinase 600,000 IU load; then 100,000/h during 72 h by pulmonary artery catheter	Angiogram score	Not stated	No

h, Hour; *IU*, unit; *kg*, kilogram; *mg*, milligram; *min*, minute.
*Eighty percent of patients presented within 96 h of symptom onset.

heparin for death (3.4% versus 2.2%; $P=0.71$), catecholamine infusion (2.5% versus 5.8%; $P=0.33$), intubation (2.5% versus 2.2%; $P=0.85$), cardiopulmonary resuscitation (0% versus 1%; $P=1$), and embolectomy (0% versus 1%; $P=1$).The only outcome that had a statistically significant difference was secondary thrombolysis (7.6% versus 23.2%); however, the study had a serious flaw in that the study protocol allowed breaking of the randomization code if consideration was being given for escalation of treatment. Given this unblinding of group allocation, it is likely that patients who had already failed thrombolytic therapy were less likely to undergo secondary thrombolysis. In conclusion, the findings of this study provide evidence that thrombolytics do not decrease mortality in hemodynamically stable patients with PE.

A recent Class III study by Becattini et al[157] that is not included in the meta-analyses was a multicenter, double-blinded, randomized controlled trial comparing tenecteplase to placebo in patients presenting within 10 days of symptom onset. Primary outcome was right ventricular dysfunction as assessed by echocardiography at 24 hours. The study was prematurely terminated after enrollment of 58 patients because of startup of the Pulmonary Embolism Thrombolysis Study (PEITHO).[158] Although this study demonstrated improvements in the primary outcome of right ventricular dysfunction in patients treated with tenecteplase, it was underpowered to detect any differences in secondary efficacy or safety outcomes.

Meta-analyses of Thrombolytics in PE

There have been 4 meta-analyses of randomized studies comparing thrombolytic therapy versus heparin therapy in patients with PE.[159-162] The study by Agnelli et al[159] was given an X for serious flaws in methodology, discussed in the Evidentiary Table. Of the remaining 3 meta-analyses, the study by Dong et al[162] was a Class II study, and those by Thabut et al[160] and Wan et al[161] were Class III studies. Table 8 is a summary of the individual studies included in each meta-analysis.

All 3 meta-analyses found no decrease in either mortality or recurrent PE in unselected patients treated with thrombolytics. Wan et al[161] performed subgroup analysis of studies that did not exclude patients with hemodynamic instability. This subgroup analysis consisting of 5 trials revealed a significant reduction in the combined endpoint of death or recurrent PE in patients treated with thrombolytics (9.4% versus 19%; odds ratio [OR] 0.45, CI 0.22 to 0.92). The findings of this subgroup analysis are highly suspect because 3 of the 5 studies that did not exclude hemodynamically unstable patients were

Table 8. Summary of randomized trials of thrombolytic therapy in PE used in the meta-analysis by Thabut et al,[160] Wan et al,[161] and Dong et al.[162]

	Class	Thabut, 2002[160] (III) (n=461)	Wan, 2004[161] (III) (N=748)	Dong, 2006[162] (II) (n=679)
Dalla-Volta et al[146] (N=36)	III	Yes	Yes	Yes
Goldhaber et al[147] (N=101)	II	Yes	Yes	Yes
Levine et al[148] (N=58)	III	Yes	Yes	Yes
Ly et al[149] (N=25)	III	Yes	Yes	Yes
PIOPED Investigators[150] (N=13)	III	Yes	Yes	Yes
UPET Study Group[151] (N=160)	III	Yes	Yes	Yes
Konstantinides et al[152] (N=256)	III	NA	Yes	Yes
Dotter et al[153] (N=31)*	X	No	Yes*	No
Jerjes-Sanches et al[154] (N=8)	X	Yes*	Yes*	No
Marini et al[155] (N=30)	X	Yes*	Yes*	No
Tibbutt et al[156] (N=30)	X	Yes*	Yes*	Yes*

NA, Study not available for inclusion in the meta-analysis.
*Studies graded as an X that were included in the meta-analysis.

given an X by this subcommittee for serious methodologic flaws. After exclusion of data from these 3 studies, mortality occurred in 7 of 96 (7.3%) patients treated with thrombolytics compared with 9 of 89 (10.1%) patients in the heparin group.

Thrombolytic Administration in Select Subgroups of Patients

A controversial issue is whether or not hemodynamically stable patients with right ventricular dysfunction as demonstrated on echocardiography (often referred to as submassive PE) should be considered a criterion for thrombolytic therapy.[1,142,163-166] Although it is well established that patients with right ventricular dysfunction on echocardiography have more rapid return of right ventricular function and restoration of pulmonary perfusion when treated with thrombolytics, these improvements have not translated to decreases in mortality.[143,144,146-151]

In an unstable patient with strong clinical suspicion of PE, it has been advocated that one should consider thrombolytic therapy in a patient in whom the diagnosis of PE is unable to be confirmed (eg, patient instability, unavailability of testing, contraindications for testing).[1,137,138,142,167] In this subgroup of patients, the finding of right ventricular dysfunction on bedside echocardiography may be used as indirect evidence for presence of PE although this technology or skill level is unavailable in most EDs.[1,142,163,164,166,168]

Another subgroup of patients who theoretically may benefit from thrombolytics are patients with PE and right heart thrombus on echocardiography because these patients are at higher risk for recurrent PE and death.[169,170] Torbicki et al[170] analyzed data from the International Cooperative Pulmonary Embolism Registry (ICOPER). Of the 2,454 patients in the ICOPER registry, 1,113 had baseline echocardiography as part of the evaluation. In this subgroup, 42 patients were identified as having right heart thrombus. The mortality rate was 21% in patients with right heart thrombus as compared to 11% without right heart thrombus ($P<0.05$). There were no differences in mortality between patients treated with and without thrombolytics (20.8% versus 23.5%). However, patients selected for treatment with thrombolytics had more significant hemodynamic compromise that may have biased these findings. Rose et al[171] retrospectively analyzed 177 patients with PE and right heart thrombus. The authors looked at patients with no treatment, heparin alone, thrombolytic therapy, and embolectomy. The mortality in these 4 subgroups was 100%, 28.6%, 23.8%, and 11.3%, respectively. On multivariate analysis, only thrombolytic therapy was associated with a decreased mortality. The findings of this article are limited by significant selection bias because the patient population is derived from 95 case reports or case series.

Risk Benefit Assessment of Patients With PE

When one considers thrombolytic therapy in PE, just as in the treatment of patients with STEMI or acute cerebral ischemia, one must conduct a risk-benefit assessment. Presumably patients at higher risk of death from PE have greater potential for benefit from thrombolytic therapy. The ICOPER found overall 3-month mortality from PE to be 17.4%.[172] Factors that have been associated with higher mortality from PE include age greater than 70 years, congestive heart failure, chronic obstructive lung disease, presence of one lung, cancer, hypotension, tachypnea, hypoxia, tachycardia, altered mental status, right ventricular hypokinesis, syncope, chronic renal failure, previous cerebral vascular accident, elevated troponin level, elevated brain-type natriuretic peptide level, and right heart thrombus.[170,172-180]

The Pulmonary Embolism Severity Index (PESI) is a score that may assist the physician in determining the risk of mortality in a patient with PE (Table 9).[181-183] The score was initially developed using logistic regression in 15,531 inpatients with a discharge diagnosis of PE.[181] The prediction rule is based on 11 patient characteristics that were independently associated with mortality and stratifies patients into 5 severity classes with increasing risk.[181] The score is easily calculated and has been

Table 9. The Pulmonary Embolism Severity Index (PESI) and mortality by total point score.[181] Reprinted with permission of the American Thoracic Society. Copyright © American Thoracic Society. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. *American Journal of Respiratory and Critical Care Medicine*. 2005;172:1041-1046. Official journal of the American Thoracic Society, Diane Gern, Publisher.

Prognostic Variables	Points Assigned
Demographics	
Age	Age, in y
Male sex	+10
Comorbid conditions	
Cancer	+30
Heart failure	+10
Chronic lung disease	+10
Clinical findings	
Pulse ≥110 beats/min	+20
Systolic blood pressure <100 mm Hg	+30
Respiratory rate ≥30 breaths/min	+20
Temperature <36°C (<96.8°F)	+20
Altered mental status	+60
Arterial oxygen saturation <90%	+20

Risk Class	30-Day Mortality* (95% CI)	Total Point Score†
I	1.6% (0.9–2.6)	≤65
II	3.5% (2.5–4.7)	66–85
III	7.1% (5.7–8.7)	86–105
IV	11.4% (9.3–13.8)	106–125
V	23.9% (21.4–26.5)	>125

*Mortality by class reported for the 5,177-patient internal validation sample.
†A total point score for a given patient is obtained by summing the patient's age in years and the points for each applicable prognostic variable.

validated in subsequent clinical investigations.[182,183] Although the PESI score was originally developed as a decision aid to identify patients suitable for outpatient treatment, it appears to reliably predict mortality and thus has the potential to assist physicians in making risk-benefit decisions when considering administration of thrombolytics.

Risk-benefit assessment must also take into account the risk of serious bleeding complications with thrombolytic therapy. A meta-analysis of 5 studies on thrombolytic therapy in PE found an intracranial hemorrhage rate of 2%, with a mortality rate of 0.5%.[184] Diastolic hypertension was the principal risk factor in predicting development of intracranial hemorrhage. The meta-analysis by Dong et al[162] found no differences on pooled analysis in risk of major hemorrhagic events (OR 1.6; 95% CI 0.91 to 2.86) or in minor hemorrhagic events (OR 1.98; 95% CI 0.68 to 5.75) in the thrombolytic group compared with the heparin group.

Data from the ICOPER registry found that intracranial bleeding in thrombolytic-treated patients occurred in 3.0% and major bleeding occurred in 21.7% versus 0.3% ($P<0.05$) and 8.8% ($P<0.05$), respectively, in patients not receiving thrombolytics.[172] Factors that are associated with increased bleeding complications are increasing age, uncontrolled hypertension, recent stroke or surgery, and bleeding diathesis.[185]

Conclusion

In conclusion, there is little evidence to guide the emergency physician in the administration of thrombolytic therapy. Overwhelming consensus opinion, based on Class III reports and published clinical guidelines, is to treat hemodynamically unstable patients with confirmed PE when the benefits of treatment outweigh the risks. Also, based on available evidence, thrombolytic therapy does not reduce mortality in the majority of hemodynamically stable patients. Because it is doubtful that any randomized study in the treatment of the hemodynamically unstable patients will ever receive Institutional Review Board approval, future studies need to focus on the treatment of hemodynamically stable patients at higher risk for adverse outcomes who present during the initial hours of symptom onset, as well as determining whether outcomes other than mortality and recurrent PE should be used. The PEITHO trial is in progress and is a multicenter, double-blinded, randomized, controlled trial comparing tenecteplase with placebo in PE patients with right ventricular dysfunction and an elevated troponin level.[158] Primary outcome is 7-day mortality or hemodynamic collapse, with an enrollment goal of 1,000 patients. It is hoped that this study will provide evidence to support recommendations for thrombolytic therapy in this subgroup of patients at higher risk for adverse outcome.

Relevant industry relationships: There were no relevant industry relationships disclosed by the subcommittee or committee members.

Relevant industry relationships are those relationships with companies associated with products or services that significantly impact the specific aspect of disease addressed in the critical question.

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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 or meta-analysis of prospective studies	Population prospective cohort or meta-analysis of prospective studies
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 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

Appendix C. Likelihood ratios and number needed to treat.*

LR (+)	LR (−)	
1.0	1.0	Useless
1–5	0.5–1	Rarely of value, only minimally changes pretest probability
10	0.1	Worthwhile test, may be diagnostic if the result is concordant with pretest probability
20	0.05	Strong test, usually diagnostic
100	0.01	Very accurate test, almost always diagnostic even in the setting of low or high pretest probability

*Number needed to treat (NNT): number of patients who need to be treated to achieve 1 additional good outcome; NNT=1/absolute risk reduction×100, where absolute risk reduction is the risk difference between 2 event rates (ie, experimental and control groups).