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:

Francis M. Fesmire, MD (Subcommittee Chair; Committee Co-Chair)
Michael D. Brown, MD, MSc
James A. Espinosa, MD
Richard D. Shih, MD
Scott M. Silvers, MD
Stephen J. Wolf, MD
Wyatt W. Decker, MD (Committee Co-Chair)

Approved by the ACEP Board of Directors, January 13, 2011
Suppported by the Emergency Nurses Association, March 17, 2011

0196-0644/$-see front matter

doi:10.1016/j.annemergmed.2011.01.020

[Ann Emerg Med. 2011;57:628-652.]

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

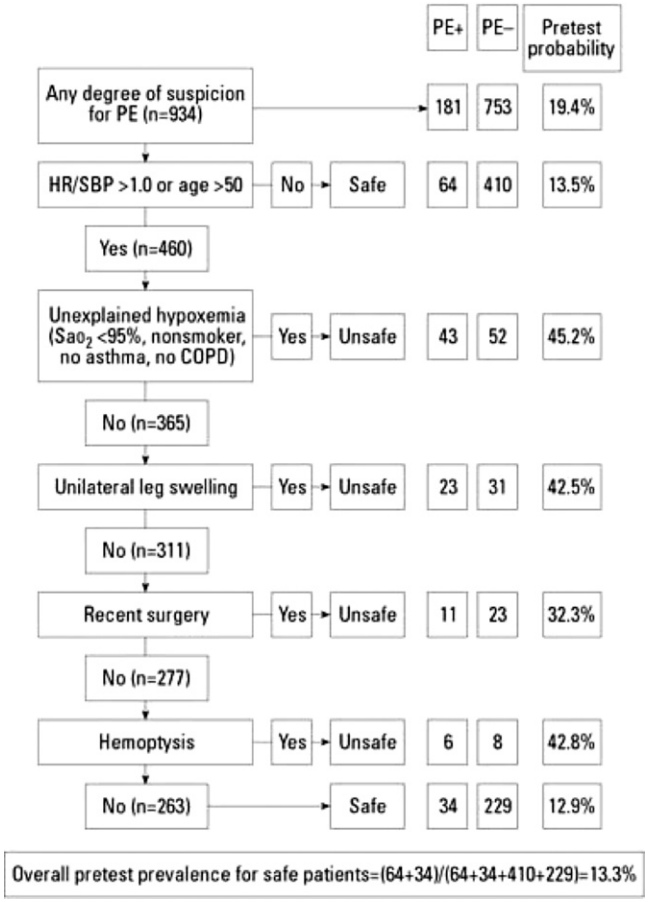

Figure. Kline decision rule for excluding PE.[23] Reprinted from *Annals of Emergency Medicine*, 39, Kline JA, Nelson RD, Jackson RE, et al. Criteria for the safe use of D-dimer testing in emergency department patients with suspected pulmonary embolism: a multicenter US study, 144-152, 2002, Copyright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

REFERENCES

1. American College of Emergency Physicians. Clinical policy: critical issues in the evaluation and management of patients presenting with suspected pulmonary embolism. *Ann Emerg Med*. 2003;41:257-270.
2. Sutherland SF. Pulmonary embolism. Emedicine 2009: May 8. Available at: http://www.medscate.com/viewarticle/552618. Accessed October 20, 2009.
3. Wood KE. Major pulmonary embolism: review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. *Chest*. 2002;121:877-905.
4. Moser KM. Fatal pulmonary embolism: old pitfalls, new challenges. *Mayo Clin Proc*. 1995;70:501-502.
5. Menzel T, Wagner S, Kramm T, et al. Pathophysiology of impaired right and left ventricular function in chronic embolic pulmonary hypertension: changes after pulmonary thromboendarterectomy. *Chest*. 2000;118:897-903.
6. Hirsh J, Hoak J. Council on Thrombosis (in consultation with the Council on Cardiovascular Radiology), American Heart Association. Management of deep vein thrombosis and pulmonary embolism. A statement for healthcare professionals. *Circulation*. 1996;93:2212-2245.
7. Bell WR, Simon TL. Current status of pulmonary thromboembolic disease: pathophysiology, diagnosis, prevention, and treatment. *Am Heart J*. 1982;103:239-262.

8. Schulman S, Lindmarker P, Holmstrom M, et al. Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months. *J Thromb Haemost*. 2006;4:734-742.
9. Moser KM, Fedullo PF, LitteJohn JK, et al. Frequent asymptomatic pulmonary embolism in patients with deep venous thrombosis. *JAMA*. 1994;271:223-225.
10. van Rossum AB, van Houwelingen HC, Kieft GJ, et al. Prevalence of deep vein thrombosis in suspected and proven pulmonary embolism: a meta-analysis. *Br J Radiol*. 1998;71:1260-1265.
11. Anderson DR, Kahn SR, Rodger MA, et al. Computed tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients with suspected pulmonary embolism. A randomized controlled trial. *JAMA*. 2007;298:2743-2753.
12. Sostman HD, Stein PD, Gottschalk A, et al. Acute pulmonary embolism: sensitivity and specificity of ventilation-perfusion scintigraphy in PIOPED II study. *Radiology*. 2008;246:941-946.
13. Anderson DR, Barnes DC. Computerized tomographic pulmonary angiography versus ventilation perfusion lung scanning for the diagnosis of pulmonary embolism. *Curr Opin Pulm Med*. 2009; 15:425-429.
14. Brenner DJ, Hall EJ, Phil D. Computed tomography—an increasing source of radiation exposure. *N Engl J Med*. 2007; 357:2277-2284.
15. Fazel R, Krumholz HM, Wang Y, et al. Exposure to low-dose ionizing radiation from medical imaging procedures. *N Engl J Med*. 2009;361:849-857.
16. Stein EG, Haramati LB, Bellin E, et al. Radiation exposure from medical imaging in patients with chronic and recurrent conditions. *J Am Coll Radiol*. 2010;7:351-359.
17. Stein EG, Haramati LB, Chamarthy M, et al. Success of a safe and simple algorithm to reduce use of CT pulmonary angiography in the emergency department. *AJR Am J Roentgenol*. 2010;194:392-397.
18. Schriger DL, Cantrill SV, Greene CS. The origins, benefits, harms, and implications of emergency medicine clinical policies. *Ann Emerg Med*. 1993;22:597-602.
19. Wicki J, Perneger TV, Junod AF, et al. Assessing clinical probability of pulmonary embolism in the emergency ward. *Arch Intern Med*. 2001;161:92-97.
20. 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.
21. 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.
22. 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.
23. 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. *Ann Emerg Med*. 2002;39:144-152.
24. Miniati M, Monti S, Bottai M. A structured clinical model for predicting the probability of pulmonary embolism. *Am J Med*. 2003;114:173-179.
25. Miniati M, Bottal M, Monti S, et al. Simple and accurate prediction of the clinical probability of pulmonary embolism. *Am J Respir Crit Care Med*. 2008;178:290-294.
26. Perrier A, Roy P-M, Aujesky D, et al. Diagnosing pulmonary embolism in outpatients with clinical assessment, D-dimer measurement, venous ultrasound, and helical computed tomography: a multicenter management study. *Am J Med*. 2004;116:291-299.
27. Tillie-Leblond I, Marquette C-H, Perez T, et al. Pulmonary embolism in patients with unexplained exacerbation of chronic obstructive pulmonary disease: prevalence and risk factors. *Ann Intern Med*. 2006;144:390-396.
28. Chagnon I, Bounameaux H, Aujesky D, et al. Comparison of two clinical prediction rules and implicit assessment among patients with suspected pulmonary embolism. *Am J Med*. 2002;113:269-275.
29. Moores LK, Collen JF, Woods KM, et al. Practical utility of clinical prediction rules for suspected acute pulmonary embolism in a large academic institution. *Thromb Res*. 2004;113:1-6.
30. Miniati M, Bottai M, Monti S. Comparison of 3 clinical models for predicting the probability of pulmonary embolism. *Medicine*. 2005;84:107-114.
31. Ollenberger GP, Worsley DF. Effect of patient location on the performance of clinical models to predict pulmonary embolism. *Thromb Res*. 2006;118:685-690.
32. Klok FA, Kruisman E, Spaan J, et al. Comparison of the revised Geneva score with the Wells rule for assessing clinical probability of pulmonary embolism. *J Thromb Haemost*. 2008;6:40-44.
33. Wells PS, Ginsberg JS, Anderson DR, et al. Use of a clinical model for safe management of patients with suspected pulmonary embolism. *Ann Intern Med*. 1998;129:997-1005.
34. Wells PS, Anderson DR, Rodger M, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and D-dimer. *Ann Intern Med*. 2001;135:98-107.
35. van Belle A, Buller HR, Huisman MV, et al. Writing Group for the Christopher Study Investigators. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. *JAMA*. 2006;295:172-179.
36. Anderson DR, Kovacs MJ, Dennie C, et al. Use of spiral computed tomography contrast angiography and ultrasonography to exclude the diagnosis of pulmonary embolism in the emergency department. *J Emerg Med*. 2005;29:399-404.
37. Kabrhel C, Courtney DM, Camargo CA Jr, et al. Potential impact of adjusting the threshold of the quantitative D-dimer based on pretest probability of acute pulmonary embolism. *Acad Emerg Med*. 2009;16:325-332.
38. Goekoop RJ, Steeghs N, Niessen RW, et al. Simple and safe exclusion of pulmonary embolism in outpatients using quantitative D-dimer and Wells' simplified decision rule. *Thromb Haemost*. 2007;97:146-150.
39. Hogg K, Dawson D, Mackway-Jones K. Outpatient diagnosis of pulmonary embolism: the MIOPED (Manchester Investigation of Pulmonary Embolism Diagnosis) study. *Emerg Med J*. 2006;23: 123-127.
40. Kruip MJ, Slob MJ, Schijen JH, et al. Use of a clinical decision rule in combination with D-dimer concentration in diagnostic workup of patients with suspected pulmonary embolism: a prospective management study. *Arch Intern Med*. 2002;162: 1631-1635.
41. Sanson B-J, Lijmer JG, Mac Gillavry MR, et al. ANTELOPE-Study Group. Comparison of a clinical probability estimate and two clinical models in patients with suspected pulmonary embolism. *Thromb Haemost*. 2000;83:199-203.
42. Wolf SJ, McCubbin TR, Feldhaus KM, et al. Prospective validation of Wells criteria in the evaluation of patients with suspected pulmonary embolism. *Ann Emerg Med*. 2004;44:503-510.
43. Yap KS, Kalff V, Turlakow A, et al. A prospective reassessment of the utility of the Wells score in identifying pulmonary embolism. *Med J Aust*. 2007;187:333-336.

44. Iles S, Hodges AM, Darley JR, et al. Clinical experience and pre-test probability scores in the diagnosis of pulmonary embolism. *Q J Med*. 2003;96:211-215.
45. Testuz A, Le Gal G, Righini M, et al. Influence of specific alternative diagnoses on the probability of pulmonary embolism. *Thromb Haemost*. 2006;95:958-962.
46. Goergen SK, Chan T, de Campo JF, et al. Reducing the use of diagnostic imaging in patients with suspected pulmonary embolism: validation of a risk assessment strategy. *Emerg Med Australas*. 2005;17:16-23.
47. Runyon MS, Webb WB, Jones AE, et al. Comparison of the unstructured clinician estimate of pretest probability for pulmonary embolism to the Canadian score and the Charlotte rule: a prospective observational study. *Acad Emerg Med*. 2005; 12:587-593.
48. PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism diagnosis. Results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED). *JAMA*. 1990;263:2753-2759.
49. Barghouth G, Yersin B, Boubaker A, et al. Combination of clinical and V/Q scan assessment for the diagnosis of pulmonary embolism: a 2-year outcome prospective study. *Eur J Nucl Med*. 2000;27:1280-1285.
50. Musset D, Parent F, Meyer G, et al. Diagnostic strategy for patients with suspected pulmonary embolism: a prospective multicentre outcome study. *Lancet*. 2002;360:1914-1920.
51. Nilsson T, Mare K, Carlsson A. Value of structured clinical and scintigraphic protocols in acute pulmonary embolism. *J Intern Med*. 2001;250:213-218.
52. Perrier A, Bounameaux H, Morabia A, et al. Diagnosis of pulmonary embolism by a decision analysis-based strategy including clinical probability, D-dimer levels, and ultrasonography: a management study. *Arch Intern Med*. 1996; 156:531-536.
53. Perrier A, Miron M-J, Desmarais S, et al. Using clinical evaluation and lung scan to rule out suspected pulmonary embolism. Is it a valid option in patients with normal results of lower-limb venous compression ultrasonography? *Arch Intern Med*. 2000;160:512-516.
54. Nordenholz KE, Naviaux NW, Stegelmeier K, et al. Pulmonary embolism risk assessment screening tools: the interrater reliability of their criteria. *Am J Emerg Med*. 2007;25:285-290.
55. Kabrhel C, Camargo CA Jr, Goldhaber SZ. Clinical gestalt and the diagnosis of pulmonary embolism. Does experience matter? *Chest*. 2005;127:1627-1630.
56. Runyon MS, Richman PB, Kline JA. Pulmonary Embolism Research Consortium Study Group. Emergency medicine practitioner knowledge and use of decision rules for the evaluation of patients with suspected pulmonary embolism: variations by practice setting and training level. *Acad Emerg Med*. 2007;14:53-57.
57. Kline JA, Mitchell AM, Kabrhel C, et al. Clinical criteria to prevent unnecessary diagnostic testing in emergency department patients with suspected pulmonary embolism. *J Thromb Haemost*. 2004;2:1247-1255.
58. Pauker SG, Kassirer JP. The threshold approach to clinical decision making. *N Engl J Med*. 1980;302:1109-1117.
59. Lessler AL, Isserman JA, Agarwal R, et al. Testing low-risk patients for suspected pulmonary embolism: a decision analysis. *Ann Emerg Med*. 2010;55:316-326.
60. 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.
61. Wolf SJ, McCubbin TR, Nordenholz KE, et al. Assessment of the pulmonary embolism rule-out criteria rule for evaluation of suspected pulmonary embolism in the emergency department. *Am J Emerg Med*. 2008;26:181-185.
62. Geersing GJ, Janssen KJM, Oudega R, et al. Excluding venous thromboembolism using point of care D-dimer tests in outpatients: a diagnostic meta-analysis. *BMJ*. 2009;339:b2990.
63. Kline JA, Runyon MS, Webb WB, et al. Prospective study of the diagnostic accuracy of the simplify D-dimer assay for pulmonary embolism in emergency department patients. *Chest*. 2006;129: 1417-1423.
64. Stein PD, Hull RD, Patel KC, et al. D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism. A systematic review. *Ann Intern Med*. 2004;140:589-602.
65. Di Nisio M, Squizzato A, Rutjes AW, et al. Diagnostic accuracy of D-dimer test for exclusion of venous thromboembolism: a systematic review. *J Thromb Haemost*. 2007;5:296-304.
66. Kearon C, Ginsberg JS, Douketis J, et al. An evaluation of D-dimer in the diagnosis of pulmonary embolism. A randomized trial. *Ann Intern Med*. 2006;144:812-821.
67. Brown MD, Rowe BH, Reeves MJ, et al. The accuracy of the enzyme-linked immunosorbent assay D-dimer test in the diagnosis of pulmonary embolism: a meta-analysis. *Ann Emerg Med*. 2002;40:133-144.
68. Brown MD, Lau J, Nelson RD, et al. Turbidimetric D-dimer test in the diagnosis of pulmonary embolism: a metaanalysis. *Clin Chem*. 2003;49:1846-1853.
69. Courtney DM, Steinberg JM, McCormick JC. Prospective diagnostic accuracy assessment of the HemosIL HS D-dimer to exclude pulmonary embolism in emergency department patients. *Thromb Res*. 2010;125:79-83.
70. Ghanima W, Almaas V, Aballi S, et al. Management of suspected pulmonary embolism (PE) by D-dimer and multi-slice computed tomography in outpatients: an outcome study. *J Thromb Haemost*. 2005;3:1926-1932.
71. Mitchell AM, Nordenholz KE, Kline JA. Tandem measurement of D-dimer and myeloperoxidase or C-reactive protein to effectively screen for pulmonary embolism in the emergency department. *Acad Emerg Med*. 2008;15:800-805.
72. Parent F, Maitre S, Meyer G, et al. Diagnostic value of D-dimer in patients with suspected pulmonary embolism: results from a multicentre outcome study. *Thromb Res*. 2007;120:195-200.
73. Perrier A, Roy P-M, Sanchez O, et al. Multidetector-row computed tomography in suspected pulmonary embolism. *N Engl J Med*. 2005;352:1760-1768.
74. Steeghs N, Goekoop RJ, Niessen RW, et al. C-reactive protein and D-dimer with clinical probability score in the exclusion of pulmonary embolism. *Br J Haematol*. 2005;130:614-619.
75. Than MP, Helm J, Calder K, et al. Comparison of high specificity with standard versions of a quantitative latex D-dimer test in the assessment of community pulmonary embolism HaemosIL D-dimer and pulmonary embolism. *Thromb Res*. 2009;124:230-235.
76. Carrier M, Righini M, Djurabi RK, et al. VIDAS D-dimer in combination with clinical pre-test probability to rule out pulmonary embolism. A systematic review of management outcome studies. *Thromb Haemost*. 2009;101:886-892.
77. Legnani C, Cini M, Scarvelis D, et al. Multicenter evaluation of a new quantitative highly sensitive D-dimer assay, the Hemosil® D-dimer HS 500, in patients with clinically suspected venous thromboembolism. *Thromb Res*. 2010;125:398-401.
78. Runyon MS, Beam DM, King MC, et al. Comparison of the Simplify D-dimer assay performed at the bedside with a laboratory-based quantitative D-dimer assay for the diagnosis of pulmonary embolism in a low prevalence emergency department population. *Emerg Med J*. 2008;25:70-75.

79. Ten Wolde M, Hagen PJ, Macgillavry MR, et al. Non-invasive diagnostic work-up of patients with clinically suspected pulmonary embolism; results of a management study. *J Thromb Haemost*. 2004;2:1110-1117.
80. Qaseem A, Snow V, Barry P, et al. Current diagnosis of venous thromboembolism in primary care: a clinical practice guideline from the American Academy of Family Physicians and the American College of Physicians. *Ann Fam Med*. 2007;5:57-62.
81. Segal JB, Eng J, Tamariz LJ, et al. Review of the evidence on diagnosis of deep venous thrombosis and pulmonary embolism. *Ann Fam Med*. 2007;5:63-73.
82. Torbicki A, Perrier A, Konstantinides S, et al. The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2008;29:2276-2315.
83. Righini M, Aujesky D, Roy P-M, et al. Clinical usefulness of D-dimer depending on clinical probability and cutoff value in outpatients with suspected pulmonary embolism. *Arch Intern Med*. 2004;164:2483-2487.
84. Righini M, Le Gal G, Aujesky D, et al. Diagnosis of pulmonary embolism by multidetector CT alone or combined with venous ultrasonography of the leg: a randomized non-inferiority trial. *Lancet*. 2008;371:1343-1352.
85. Kabrhel C. Outcomes of high pretest probability patients undergoing D-dimer testing for pulmonary embolism: a pilot study. *J Emerg Med*. 2008;35:373-377.
86. Sohne M, Kamphuisen PW, van Mierlo PJ, et al. Diagnostic strategy using a modified clinical decision rule and D-dimer test to rule out pulmonary embolism in elderly in- and outpatients. *Thromb Haemost*. 2005;94:206-210.
87. Righini M, Le Gal G, De Lucia S, et al. Clinical usefulness of D-dimer testing in cancer patients with suspected pulmonary embolism. *Thromb Haemost*. 2006;95:715-719.
88. Di Nisio M, Sohne M, Kamphuisen PW, et al. D-dimer test in cancer patients with suspected acute pulmonary embolism. *J Thromb Haemost*. 2005;3:1239-1242.
89. King V, Vaze AA, Moskowitz CS, et al. D-dimer assay to exclude pulmonary embolism in high-risk oncologic population: correlation with CT pulmonary angiography in an urgent care setting. *Radiology*. 2008;247:854-861.
90. Kline JA, Williams GW, Hernandez-Nino J. D-dimer concentrations in normal pregnancy: new diagnostic thresholds are needed. *Clin Chem*. 2005;51:825-829.
91. Brown MA, Vance SJ, Kline JA. An emergency department guideline for the diagnosis of pulmonary embolism: an outcome study. *Acad Emerg Med*. 2005;12:20-25.
92. Linkins L-A, Bates SM, Ginsberg JS, et al. Use of different D-dimer levels to exclude venous thromboembolism depending on clinical pretest probability. *J Thromb Haemost*. 2004;2:1256-1260.
93. Douma RA, le Gal G, Sohne M, et al. Potential of an age adjusted D-dimer cut-off value to improve the exclusion of pulmonary embolism in older patients: a retrospective analysis of three large cohorts. *BMJ*. 2010;340:c1475.
94. Duriseti RS, Brandeau ML. Cost-effectiveness of strategies for diagnosing pulmonary embolism among emergency department patients presenting with undifferentiated symptoms. *Ann Emerg Med*. 2010;56:321-332.
95. Le Gal G, Righini M, Roy P-M, et al. Value of D-dimer testing for the exclusion of pulmonary embolism in patients with previous venous thromboembolism. *Arch Intern Med*. 2006;166:176-180.
96. Duriseti RS, Shachter RD, Brandeau ML. Value of quantitative D-dimer assays in identifying pulmonary embolism: implication from a sequential decision model. *Acad Emerg Med*. 2006;13:755-766.
97. Remy-Jardin M, Remy J, Wattinne L, et al. Central pulmonary thromboembolism: diagnosis with spiral volumetric CT with the single-breath-hold technique—comparison with pulmonary angiography. *Radiology*. 1992;185:381-387.
98. Russo V, Piva T, Lovato L, et al. Multidetector CT: a new gold standard in the diagnosis of pulmonary embolism? State of the art and diagnostic algorithms. *Radiol Med*. 2005;109:49-63.
99. Perrier A, Howarth N, Didier D, et al. Performance of helical computed tomography in unselected outpatients with suspected pulmonary embolism. *Ann Intern Med*. 2001;135:88-97.
100. Ost D, Rozenshtein A, Saffran L, et al. The negative predictive value of spiral computed tomography for the diagnosis of pulmonary embolism in patients with nondiagnostic ventilation-perfusion scans. *Am J Med*. 2001;110:16-21.
101. Nilsson T, Soderberg M, Lundqvist G, et al. A comparison of spiral computed tomography and latex agglutination D-dimer assay in acute pulmonary embolism using pulmonary arteriography as gold standard. *Scand Cardiovasc J*. 2002;36:373-377.
102. Ruiz Y, Caballero P, Caniego JL, et al. Prospective comparison of helical CT with angiography in pulmonary embolism: global and selective vascular territory analysis. Interobserver agreement. *Eur Radiol*. 2003;13:823-829.
103. Stone E, Roach P, Bernard E, et al. Use of computed tomography pulmonary angiography in the diagnosis of pulmonary embolism in patients with an intermediate probability ventilation/perfusion scan. *Intern Med J*. 2003;33:74-78.
104. van Strijen MJ, De Monye W, Kieft GJ, et al. Accuracy of single-detector spiral CT in the diagnosis of pulmonary embolism: a prospective multicenter cohort study of consecutive patients with abnormal perfusion scintigraphy. *J Thromb Haemost*. 2005;3:17-25.
105. Eng J, Krishnan JA, Segal JB, et al. Accuracy of CT in the diagnosis of pulmonary embolism: a systematic literature review. *AJR Am J Roentgenol*. 2004;183:1819-1827.
106. Stein PD, Kayali F, Hull RD. Spiral computed tomography for the diagnosis of acute pulmonary embolism. *Thromb Haemost*. 2007;98:713-720.
107. Cueto SM, Cavanaugh SH, Benenson RS, et al. Computed tomography scan versus ventilation-perfusion lung scan in the detection of pulmonary embolism. *J Emerg Med*. 2001;21:155-164.
108. 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.
109. Winer-Muram HT, Rydberg J, Johnson MS, et al. Suspected acute pulmonary embolism: evaluation with multidetector row CT versus digital subtraction pulmonary arteriography. *Radiology*. 2004;233:806-815.
110. Coche E, Verschuren F, Keyeux A, et al. Diagnosis of acute pulmonary embolism in outpatients: comparison of thin-collimation multidetector row spiral CT and planar ventilation-perfusion scintigraphy. *Radiology*. 2003;229:757-765.
111. Moores LK, Jackson WL Jr, Shorr AF, et al. Meta-analysis: outcomes in patients with suspected pulmonary embolism managed with computed tomographic pulmonary angiography. *Ann Intern Med*. 2004;141:866-874.
112. Hayashino Y, Goto M, Noguchi Y, et al. Ventilation-perfusion scanning and helical CT in suspected pulmonary embolism: meta-analysis of diagnostic performance. *Radiology*. 2005;234:740-748.
113. Hogg K, Brown G, Dunning J, et al. Diagnosis of pulmonary embolism with CT pulmonary angiography: a systematic review. *Emerg Med J*. 2006;23:172-178.

114. Roy PM, Colombet I, Durieux P, et al. Systematic review and meta-analysis of strategies for the diagnosis of suspected pulmonary embolism. *BMJ*. 2005;331:259.
115. Goodman LR, Lipchik RJ, Kuzo RS, et al. Subsequent pulmonary embolism: risk after a negative helical CT pulmonary angiogram—prospective comparison with scintigraphy. *Radiology*. 2000;215:535-542.
116. Swensen SJ, Sheedy PF II, Ryu JH, et al. Outcomes after withholding anticoagulation from patients with suspected acute pulmonary embolism and negative computed tomographic findings: a cohort study. *Mayo Clin Proc*. 2002;77:130-138.
117. Donato AA, Scheirer JJ, Atwell MS, et al. Clinical outcomes in patients with suspected acute pulmonary embolism and negative helical computed tomographic results in whom anticoagulation was withheld. *Arch Intern Med*. 2003;163:2033-2038.
118. van Strijen MJ, de Monye W, Schiereck J, et al. Single-detector helical computed tomography as the primary diagnostic test in suspected pulmonary embolism: a multicenter clinical management study of 510 patients. *Ann Intern Med*. 2003;138:307-314.
119. Friera A, Olivera MJ, Suarez C, et al. Clinical validity of negative helical computed tomography for clinical suspicion of pulmonary embolism. *Respiration*. 2004;71:30-36.
120. Kavanagh EC, O'Hare A, Hargaden G, et al. Risk of pulmonary embolism after negative MDCT pulmonary angiography findings. *AJR Am J Roentgenol*. 2004;182:499-504.
121. Prologo JD, Gilkeson RC, Diaz M, et al. The effect of single-detector CT versus MDCT on clinical outcomes in patients with suspected acute pulmonary embolism and negative results on CT pulmonary angiography. *AJR Am J Roentgenol*. 2005;184:1231-1235.
122. Vigo M, Pesavento R, Bova C, et al. The value of four-detector row spiral computed tomography for the diagnosis of pulmonary embolism. *Semin Thromb Hemost*. 2006;32:831-837.
123. Subramaniam RM, Blair D, Gilbert K, et al. Withholding anticoagulation after a negative computed tomography pulmonary angiogram as a stand-alone imaging investigation: a prospective management study. *Int Med J*. 2007;37:624-630.
124. Elias A, Colombier D, Victor G, et al. Diagnostic performance of complete lower limb venous ultrasound in patients with clinically suspected acute pulmonary embolism. *Thromb Haemost*. 2004;91:187-195.
125. Le Gal G, Righini M, Sanchez O, et al. A positive compression ultrasonography of the lower limb veins is highly predictive of pulmonary embolism on computed tomography in suspected patients. *Thromb Haemost*. 2006;95:963-966.
126. Au VW, Walsh G, Fon G. Computed tomography pulmonary angiography with pelvic venography in the evaluation of thrombo-embolic disease. *Australas Radiol*. 2001;45:141-145.
127. Coche EE, Hamoir XL, Hammer FD, et al. Using dual-detector helical CT angiography to detect deep venous thrombosis in patients with suspicion of pulmonary embolism: diagnostic value and additional findings. *AJR Am J Roentgenol*. 2001;176:1035-1039.
128. Begemann PG, Bonacker M, Kemper J, et al. Evaluation of the deep venous system in patients with suspected pulmonary embolism with multi-detector CT: a prospective study in comparison to Doppler sonography. *J Comput Assist Tomogr*. 2003;27:399-409.
129. Johnson JC, Brown MD, McCullough N, et al. CT lower extremity venography in suspected pulmonary embolism in the ED. *Emerg Radiol*. 2006;12:160-163.
130. Loud PA, Katz DS, Bruce DA, et al. Deep venous thrombosis with suspected pulmonary embolism: detection with combined CT venography and pulmonary angiography. *Radiology*. 2001;219:498-502.
131. Perrier A, Bounameaux H. Accuracy or outcome in suspected pulmonary embolism. *N Engl J Med*. 2006;354:22.
132. Tapson VF. Acute pulmonary embolism. *N Engl J Med*. 2008;358:1037-1052.
133. Goodman LR, Stein PD, Matta F, et al. CT venography and compression sonography are diagnostically equivalent: data from PIOPED II. *AJR Am J Roentgenol*. 2007;189:1071-1076.
134. FibrinolyticTherapyTrialists (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet*. 1994;343:311-322.
135. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:1581-1587.
136. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359:1317-1329.
137. British Thoracic Society Standards of Care Committee Pulmonary Embolism Guideline Development Group. British Thoracic Society guidelines for the management of suspected acute pulmonary embolism. *Thorax*. 2003;58:470-483.
138. Buller HR, Agnelli G, Hull RD, et al. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126:401S-428S.
139. Dalen JE, Alpert JS, Hirsh J. Thrombolytic therapy for pulmonary embolism. Is it effective? Is it safe? When is it indicated? *Arch Intern Med*. 1997;157:2550-2556.
140. Dalen JE. Thrombolysis in submassive PE? No. *J Thromb Haemost*. 2003;1:1130-1132.
141. Konstantinides S. Thrombolysis in submassive pulmonary embolism? Yes. *J Thromb Haemost*. 2003;1:1127-1129.
142. Harris T, Meek S. When should we thrombolyse patients with pulmonary embolism? A systematic review of literature. *Emerg Med J*. 2005;22:766-771.
143. Anderson DR, Levine MN. Thrombolytic therapy for the treatment of acute pulmonary embolism. *CMAJ*. 1992;146:1317-1324.
144. Konstantinides S, Tiede N, Geibel A, et al. Comparison of alteplase versus heparin for resolution of major pulmonary embolism. *Am J Cardiol*. 1998;82:966-970.
145. Nass N, McConnell MV, Goldhaber SZ, et al. Recovery of regional right ventricular function after thrombolysis for pulmonary embolism. *Am J Cardiol*. 1999;83:804-806.
146. Dalla-Volta S, Palla A, Santolicandro A, et al. PAIMS2: alteplase combined with heparin versus heparin in the treatment of acute pulmonary embolism. Plasminogen Activator Italian Multicenter Study 2. *J Am Coll Cardiol*. 1992;20:520-526.
147. Goldhaber SZ, Haire WD, Feldstein ML, et al. Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion. *Lancet*. 1993;341:507-511.
148. Levine M, Hirsh J, Weitz J, et al. A randomized trial of a single bolus dosage regimen of recombinant tissue plasminogen activator in patients with acute pulmonary embolism. *Chest*. 1990;98:1473-1479.
149. Ly B, Arnesen H, Eie H, et al. A controlled clinical trial of streptokinase and heparin in the treatment of major pulmonary embolism. *Acta Med Scand*. 1978;203:465-470.
150. PIOPED Investigators. Tissue plasminogen activator for the treatment of acute pulmonary embolism. A collaborative study by the PIOPED Investigators. *Chest*. 1990;97:528-533.

151. Urokinase Pulmonary Embolism Trial (UPET) Study Group. Urokinase pulmonary embolism trial. Phase 1 results. A cooperative study. *JAMA*. 1970;214:2163-2172.
152. Konstantinides S, Geibel A, Heusel G, et al, for the Management Strategies and Prognosis of Pulmonary Embolism-3 Trial Investigators. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl J Med*. 2002;347:1143-1150.
153. Dotter CT, Seaman AJ, Rosch J, et al. Streptokinase and heparin in the treatment of major pulmonary embolism: a randomized comparison. *Vasc Surg*. 1979;13:42-52.
154. Jerjes-Sanchez C, Ramirez-Rivera A, de Lourdes Garcia M, et al. Streptokinase and heparin versus heparin alone in massive pulmonary embolism: a randomized controlled trial. *J Thromb Thrombolysis*. 1995;2:227-229.
155. Marini C, Di Ricco G, Rossi G, et al. Fibrinolytic effects of urokinase and heparin in acute pulmonary embolism: a randomized clinical trial. *Respiration*. 1988;54:162-173.
156. Tibbutt DA, Davies JA, Anderson JA, et al. Comparison by controlled clinical trial of streptokinase and heparin in treatment of life-threatening pulmonary embolism. *Br Med J*. 1974;1:343-347.
157. Becattini C, Agnelli G, Salvi A, et al. TIPES Study Group. Bolus tenecteplase for right ventricle dysfunction in hemodynamically stable patients with pulmonary embolism. *Thromb Res*. 2010;125:e82-e86.
158. Meyer G. PEITHO Pulmonary Embolism Thrombolysis Study. Clinical Trials.gov [Web site]. Bethesda, MD: National Library of Medicine; 2000. Available at: http://clinicaltrials.gov/ct2/show/NCT00639743?tem=nct00639743 NLM Identifier:NCT00639743. Accessed May 11, 2010.
159. Agnelli G, Becattini C, Kirschstein T. Thrombolysis vs heparin in the treatment of pulmonary embolism. A clinical outcome-based meta-analysis. *Arch Intern Med*. 2002;162:2537-2541.
160. Thabut G, Thabut D, Myers RP, et al. Thrombolytic therapy of pulmonary embolism. A meta-analysis. *J Am Coll Cardiol*. 2002;40:1660-1667.
161. Wan S, Quinlan DJ, Agnelli G, et al. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism. A meta-analysis of the randomized controlled trials. *Circulation*. 2004;110:744-749.
162. Dong B, Jirong Y, Liu G, et al. Thrombolytic therapy for pulmonary embolism. *Cochrane Database Syst Rev*. 2006;(2):CD004437. DOI: 10.1002/14651858.CD004437.pub2.
163. Goldhaber SZ. Echocardiography in the management of pulmonary embolism. *Ann Intern Med*. 2002;136:691-700.
164. Nakamura M, Nakanishi N, Yamada N, et al. Effectiveness and safety of the thrombolytic therapy for acute pulmonary thromboembolism: results of a multicenter registry in the Japanese Society of Pulmonary Embolism Research. *Int J Cardiol*. 2005;99:83-89.
165. Wolfe MW, Lee RT, Feldstein ML, et al. Prognostic significance of right ventricular hypokinesis and perfusion lung scan defects in pulmonary embolism. *Am Heart J*. 1994;127:1371-1375.
166. Wood KE. Major pulmonary embolism. Review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. *Chest*. 2002;121:877-905.
167. Kasper W, Konstantinides S, Geibel A, et al. Management strategies and determinants of outcome in acute major pulmonary embolism: results of a multicenter registry. *J Am Coll Cardiol*. 1997;30:1165-1171.
168. American Thoracic Society. The diagnostic approach to acute venous thromboembolism. Clinical practice guideline. *Am J Respir Crit Care Med*. 1999;160:1043-1066.
169. Kasper W, Konstantinides S, Geibel A, et al. Prognostic significance of right ventricular afterload stress detected by echocardiography in patients with clinically suspected pulmonary embolism. *Heart*. 1997;77:346-349.
170. Torbicki A, Gali N, Covezzoli A, et al. Right heart thrombi in pulmonary embolism. Results from the International Cooperative Pulmonary Embolism Registry. *J Am Coll Cardiol*. 2003;41:2245-2251.
171. Rose PS, Punjabi NM, Pearse DB. Treatment of right heart thromboemboli. *Chest*. 2002;121:806-814.
172. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet*. 1999;353:1386-1389.
173. Konstantinides S, Geibel A, Olschewski M, et al. Association between thrombolytic treatment and the prognosis of hemodynamically stable patients with major pulmonary embolism. Results of a multicenter registry. *Circulation*. 1997;96:882-888.
174. Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism. A meta-analysis. *Circulation*. 2007;116:427-433.
175. Kucher N, Wallmann D, Carone A, et al. Incremental prognostic value of troponin I and echocardiography in patients with acute pulmonary embolism. *Eur Heart J*. 2003;24:1651-1656.
176. Aujesky D, Obrosky S, Stone RA, et al. A prediction rule to identify low-risk patients with pulmonary embolism. *Arch Intern Med*. 2006;166:169-175.
177. Jimenez D, Uresandi F, Otero R, et al. Troponin-based risk stratification of patients with acute nonmassive pulmonary embolism. Systematic review and metaanalysis. *Chest*. 2009;136:974-982.
178. Kreit JW. The impact of right ventricular dysfunction on the prognosis and therapy of normotensive patients with pulmonary embolism. *Chest*. 2004;125:1539-1545.
179. Klok FA, Mos IC, Huisman MV. Brain-type natriuretic peptide levels in the prediction of adverse outcome in patients with pulmonary embolism. A systematic review and meta-analysis. *Am J Respir Crit Care Med*. 2008;178:425-430.
180. Stein PD, Matta F, Janjua M, et al. Outcome in stable patients with acute pulmonary embolism who had right ventricular enlargement and/or elevated levels of troponin I. *Am J Cardiol*. 2010;106:558-563.
181. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. *Am J Respir Crit Care Med*. 2005;172:1041-1046.
182. Aujesky D, Roy P-M, Le Manach CP, et al. Validation of a model to predict adverse outcomes in patients with pulmonary embolism. *Eur Heart J*. 2006;27:476-481.
183. Donze J, Le Gal G, Fine MJ, et al. Prospective validation of the Pulmonary Embolism Severity Index. A clinical prognostic model for pulmonary embolism. *Thromb Haemost*. 2008;100:943-948.
184. Kanter DS, Mikkola KM, Patel SR, et al. Thrombolytic therapy for pulmonary embolism. Frequency of intracranial hemorrhage and associated risk factors. *Chest*. 1997;111:1241-1245.
185. River-Bou WL, Cabanas JG, Villanueva SE, et al. Thrombolytic therapy. eMedicine 2008. Available at: http://emedicine.medscape.com/article/811234-overview. Accessed December 16, 2009.

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).

Evidentiary Table.

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Anderson et al[11]	2007	Prospective inpatients and outpatients	Single-detector CT and multidetector CT	3-mo follow-up for VTE	133/694 (19.2%) CT patients had PE; data available in 694 CT patients, 3-mo follow-up available in 561; 2/561 (9.4%) had VTE; 17/561 (3%) died in follow-up; 38 patients did not receive CT despite being randomized to this group; 9/531 (1.7%) of negative CT scans found to have VTE in follow-up either by initial ultrasound on the day of evaluation or during 3 mo follow-up	Unusually thin CT collimation; study of negative CT pulmonary angiogram plus bilateral lower extremity ultrasound outcome data, only D-dimer-positive patients or patients with Wells ≥4.5 were included; 19.2% incidence of PE in original high-risk sample lower than that of other study samples of patients who were not risk stratified; no report of autopsy rate among patients who died; 38 patients did not receive CT despite being randomized to this group	II
Wicki et al[19]	2001	Retrospective analysis of consecutive patients with suspected PE from 2 previous published studies	PE was diagnosed using a clinical algorithm that used clinical assessment, D-dimer, VQ scan, and venous ultrasound; logistic regression used to identify variables associated with predicting PE to develop a scoring system for prediction of PE	3-mo VTE	296 (25%) of 1,090 patients with PE; the optimal estimate of clinical probability was based on 8 variables; based on the developed scoring system, a total of 486 patients (49%) had a low clinical probability of PE (score ≤4) of which 50 (10.3%) had a proven PE; prevalence of PE was 38% in the 437 patients with an intermediate probability (score 5-8), and 81% in the 63 patients with a high probability score (≥9)	Retrospective analysis of database; did not have derivation and validation set	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Le Gal et al[20]	2006	Retrospective analysis of patient population with suspected PE from previously published study	PE was diagnosed using a clinical algorithm that used clinical assessment, D-dimer, CTA, and venous ultrasound; logistic regression analyses techniques used to develop a simplification of the scoring system used by Wicki et al[19] 2001	3-mo VTE	956 patients in derivation set and 749 patients in validation set; 8 variables generated 3 categories of risk; in the validation set, the rate of PE for low-, intermediate-, and high-risk groups was 7.9%, 28.5%, and 73.7%, respectively	Retrospective; interobserver agreement for score items was not studied	II
Klok et al[21]	2008	Retrospective analysis of consecutive patients with suspected PE from 2 previous published studies	PE was diagnosed using a clinical algorithm that used clinical assessment, D-dimer, CTA, and venous ultrasound; logistic regression analyses techniques were used to develop a simplification of the scoring system used by Le Gal et al[20] 2006	3-mo VTE	1,049 patients (23% PE); area under the ROC curve for predicting PE was 0.75 (95% CI 0.71 to 0.78) for the revised Geneva score vs 0.74 (95% CI 0.70 to 0.77) for the Simplified Revised Geneva score	Retrospective analysis; some missing data; did not have derivation and validation set	II
Wells et al[22]	2000	Retrospective analysis of previous prospective cohort study	PE was diagnosed using a clinical algorithm that used clinical assessment, D-dimer, VQ scan, and venous ultrasound; logistic regression was used to identify variables associated with predicting PE to develop a scoring system for prediction of PE	3-mo VTE	1,260 patients (80% derivation and 20% validation; a score of <2 with a negative D-dimer results in a PE rate of 1.5% (95% CI 0.4% to 3.7%) in the derivation set and 2.7% (95% CI 0.3% to 9%) in the validation set	Intrinsic to study: inpatients may not reflect ED patients, possible subjectivity of alternative diagnosis element; extrinsic: study was from 1998; VQ scan used as diagnostic test	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Kline et al[23]	2002	Retrospective analysis of prospectively collected clinical data	Logistic regression model used to develop a clinical rule from 8 continuous variables and 18 categorical variables to yield a subset of patients whose pretest probability of PE was too great to use D-dimer to exclude PE (investigators assumed a pretest probability threshold of ≥40% was unsafe for D-dimer testing)	6-mo VTE	934 patients (19.4% with PE); 6 variables found to be significant on multivariate analysis; unsafe patients had either a shock index (pulse rate/systolic blood pressure) >1 or age >50 y, together with any 1 of: unexplained hypoxemia (saturation <95%) with no previous lung disease, unilateral leg swelling, recent major surgery or hemoptysis; the rate of PE in the 197 unsafe patients was 42.1% (95% CI 35.3% to 49.6%) compared with 13.7% (95% CI 10.9% to 15.9%) in the 737 safe patients	Model derived from a relatively small dataset (181 patients with PE); diagnosis by VQ scanning predominantly	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Miniati et al[24]	2003	Retrospective analysis of prospectively acquired clinical database	Logistic regression was used to develop a model to predict PE	6-mo VTE	440 patients (40% PE); 10 characteristics were associated with an increased risk of PE (male sex, older age, history of thrombophlebitis, sudden-onset dyspnea, chest pain, hemoptysis, electrocardiographic signs of acute right ventricular overload, radiographic signs of oligemia, amputation of the hilar artery, and pulmonary consolidation suggestive of infarction); 5 characteristics were associated with a decreased risk (previous cardiovascular or pulmonary disease, high fever, pulmonary consolidation other than infarction, and pulmonary edema on the chest radiograph); 432 patients (39%) were rated a low probability; 283 (26%) were rated an intermediate probability; 72 (7%) were rated a moderately high probability; rates of PE in these 3 subgroups were 4%, 22%, and 74%, respectively	Most of the patients were hospitalized at the time of study entry	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Miniati et al[25]	2008	Retrospective	Logistic regression was used to simplify the Miniati et al[24] 2003 model by excluded chest radiograph findings	6-mo VTE	1,100 patients; 10 variables associated with PE: older age, male sex, prolonged immobilization, history of DVT, sudden-onset dyspnea, chest pain, syncope, hemoptysis, unilateral leg swelling, electrocardiographic signs of acute cor pulmonale; 6 variables negatively associated with PE: previous cardiovascular disease, pulmonary disease, orthopnea, high fever, wheezes, or crackles on chest auscultation; in the validation sample, 165 (41%) of 400 patients had PE; the prevalence of PE was 2% (0% to 10%), 28% (11% to 50%), 67% (51% to 80%), and 94% (81% to 100%) for slight, moderate, substantial, and high risk, respectively; model performed equally well in inpatients and outpatients	Most of the patients were hospitalized at the time of study entry	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Perrier et al[26]	2004	Prospective observational	PE was diagnosed using a clinical algorithm that used clinical assessment by Geneva score, D-dimer, CTA, and venous ultrasound	3-mo VTE	965 patients; VTE ruled out by negative D-dimer and low pretest probability in 280 patients (29%); 92 patients (9.5%) had positive venous ultrasound; 593 patients (61%) underwent CTA and PE found in 124 patients (12.8%); PE was considered ruled out in the 450 patients (46.6%) with a negative ultrasound and CT scan result and a low to intermediate clinical probability; 8 patients with a negative ultrasound and CT scan result with a high clinical probability underwent pulmonary angiogram (positive: 2; negative: 6); helical CT was inconclusive in 11 patients (PE: 4; no PE: 7); rate of VTE in patients classified as not having PE was 1.0% (95% CI 0.5% to 2.1%)	25% of eligible patients were excluded; there was a mix of single-detector and multidetector CT scans	III for risk stratification II for CTA

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Tillie-Leblond et al[27]	2006	Prospective cohort study, single French hospital	All patients had CTA and venous ultrasound; pretest probability assessment by Geneva score	3-mo VTE	197 patients; 49 (25%) with PE; 49/197 (25%); clinical factors associated with PE were previous VTE (risk ratio 2.43 [95% CI 1.49 to 3.94]), malignant disease (risk ratio 1.82 [95% CI 1.13 to 2.92]), and decrease in $PaCO_2$ of at least 5 mm Hg (risk ratio 2.10 [95% CI 1.23 to 3.58]); a total of 9.2% (95% CI 4.7% to 15.9%) of patients with a low probability Geneva score had PE; substituting malignant disease for recent surgery in the Geneva score improved accuracy of score in this patient population	Single-center design; limited to patients with COPD; patients with COPD requiring invasive mechanical ventilation in the intensive care unit were not included	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Chagnon et al[28]	2002	Prospective observational	PE was diagnosed using a clinical algorithm that used clinical assessment, D-dimer, VQ scan, CTA, and venous ultrasound; clinical assessment performed prospectively with Geneva score and retrospectively with Wells score	3-mo VTE	277 patients; the Geneva score, overridden by physician judgment, and Wells score performed similarly in proportion of patients having a low (53% to 58% of patients), intermediate (37% to 41% of patients), or high (4% to 10% of patients) probability of PE; and in the rate of PE (5% to 13% in the low, 38% to 40% in the intermediate, and 67% to 91% in the high clinical probability categories); ROC curve analysis showed no differences between the prediction rules, but the Geneva score overridden by physician judgment had a nonstatistically significant greater accuracy; concordance between the 2 prediction rules was fair (κ coefficient=0.43); the Geneva score was overridden by physician judgment in 21% of patients (n=57)	29% of patients were not included in the analysis because an ABG had not been performed	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Moores et al[29]	2004	Retrospective analysis	Pretest probability was calculated using Wells criteria and Geneva score	VTE on presentation	295 patients (30% PE); the prevalence of PE in the low, intermediate, and high pretest probability groups using the Wells score was 15.3% (95% CI 9.5% to 23.7%), 34.8% (95% CI 27.9% to 42.4%), and 47.2% (95% CI 32.0% to 63.0%), respectively; when compared with the low pretest probability group, the OR of the likelihood of PE was 2.95 (95% CI 1.56% to 5.59%) in the intermediate pretest probability group, and 4.95 (95% CI 2.11% to 11.64%) in the high pretest probability group; prevalence of PE in the Geneva Pure (N=79 patients) and Geneva Presumed (ABG not obtained) groups were 34.2% vs 34.7%, 53.2% vs 55.3%, and 12.6% vs 10% for patients with low, intermediate, and high pretest groups, respectively	Retrospective review; single center; may not include lowest-risk patients in whom PE was suspected but radiologic testing was not performed	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Miniati et al[30]	2005	Prospective observational	VQ scanning and pulmonary arteriogram; prospective pretest probability assessment by the Wells score and Pisa model, and retrospective calculation of Geneva score	PE on presentation	248 patients (43.3% PE); the proportion of patients categorized as having low, intermediate, or high probability were, respectively: 12%, 60%, and 28% for the Geneva model; 30%, 55%, and 15% for the Wells model; 37%, 37%, and 26% for the Pisa model; the frequencies of PE in the low, intermediate, and high probability categories were, respectively: 50%, 39%, and 49% for the Geneva model; 12%, 54%, and 64% for the Wells model; 5%, 42%, and 98% for the Pisa model	Single institution; relatively small sample; Geneva score calculated retrospectively	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Ollenberger and Worsley[31]	2006	Retrospective analysis of PIOPED database	VQ scan; pretest probability assessment by Wells and Wicki score	PE diagnosed according to the PIOPED criteria	The prevalence of PE in the 3 clinical probability categories was similar for the 2 scoring methods; both clinical models yielded the lowest diagnostic performance in patients referred from surgical wards; the AUC for both clinical prediction rules decreased significantly when applied to inpatients in comparison to outpatients	Retrospective; 361 (27%) patients from the PIOPED study had no arterial blood gas measurements and were excluded from Wicki score group	III
Klok et al[32]	2008	Retrospective analysis of subset of patients in van Belle et al (Christopher study)[35]	Wells rule (prospectively calculated) was compared with the revised Geneva score (retrospectively calculated)	3-mo VTE	300 patients (16% with PE); the performance of the revised Geneva score as measured by the AUC in a ROC analysis did not differ statistically from the Wells rule (P=0.1)	The revised Geneva score was assessed retrospectively, which could have led to selection bias	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Wells et al[33]	1998	Prospective cohort study at 5 tertiary care hospitals	Pretest clinical assessment (alternative diagnosis more or less likely than PE) and VQ scan; predefined model used to determine need for venous ultrasound, venogram, or pulmonary arteriogram	3-mo VTE	1,239 patients; pretest probability was low in 3.4%, moderate in 27.8%, and high in 78.4%; 3 of the 665 patients (0.5%) (95% CI .1% to 1.3%) with low or moderate pretest probability and a nonhigh probability scan who were considered negative for PE had VTE on 90-day follow-up; this rate did not differ from that in patients with a normal VQ scan result (0.6% CI 0.1% to 1.8%)	Model too complicated for routine clinical use; VQ scan used as diagnostic test	III
Wells et al[34]	2001	Prospective cohort study, EDs at 4 tertiary care hospitals in Canada; 930 consecutive patients with suspected PE	Pretest probability assessment and D-dimer; VQ scanning in patients with nonlow pretest probability or positive D-dimer	3-mo VTE	Pretest probability of PE was low in 1.3%, moderate in 16.2%, high in 37.5%; the VTE rate (PE or DVT) was 5/849 (0.6%) (CI 0.2% to 1.4%) patients in whom the diagnosis of PE was initially excluded; of the 437 patients with a negative D-dimer result and low clinical probability, only 1 developed VTE during follow-up; the negative prediction value for VTE of the combined strategy of clinical model with D-dimer testing was 99.5% (95% CI 99.1% to 100%)	Protocol violations in 10% of total sample; lower prevalence of PE in this study than in others	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
van Belle et al[35] (Christopher Study Investigators)	2006	Prospective cohort study of consecutive patients with clinically suspected acute PE	VIDAS® (ELISA) and Tinaquant (turbidimetric) D-dimer threshold >500 ng/mL; pretest probability by dichotomous Wells criteria	VTE during 3 mo primary outcome; clinical follow-up for patients considered "PE unlikely" per Wells criteria (score ≤4) with negative D-dimer result; CT thorax for patients considered "PE likely" per Wells criteria (score >4) or positive D-dimer result; blinded adjudication committee made final determination for presence or absence of VTE at 3 mo	12% prevalence of PE among 2,206 patients considered "unlikely" per Wells criteria: sensitivity=0.98 (95% CI 0.96 to 0.99); specificity =0.54 (95% CI 0.52 to 0.57); LR+=2.1 (95% CI 2.0 to 2.3); LR-=0.03 (95% CI 0.01 to 0.08); among the low-risk group with a negative D-dimer result, 3-mo incidence of VTE=0.5%; of 1,436 patients who did not receive anticoagulation, 18 (1.3%; 0.7% to 2%) experienced VTE during 3-mo follow-up; 11/18 were nonfatal (3 PE and 8 DVT) and 7/18 were fatal (0.5%, 0.2% to 1%), 2 by autopsy; 1 of 1,436 patients had incomplete follow-up (0.1%) — if patient had PE then incidence would be 1.3% (0.8% to 2.1%)	Authors note that a randomized controlled design would have been stronger; predominantly outpatient population (82%); potential for differential reference standard bias; approximately half had VIDAS® D-dimer (specificity=0.44) and half Tinaquant (specificity=0.51) but detailed data to complete 2x2 table for each test not reported	II for risk stratification I for D-dimer and CTA

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Anderson et al[36]	2005	Prospective multicenter observational design	Pretest probability, D-dimer, CTA, Doppler ultrasound, and 3-mo follow-up	PE diagnosed by positive CTA, positive CTV, positive Doppler ultrasound; primary outcome VTE at 3-mo follow-up	858 patients; VTE excluded in 369 patients by low pretest probability and negative D-dimer result; none of these patients developed VTE; the remaining 489 patients underwent CTA and venous ultrasound; 67 patients with PE by CTA; 15 patients with negative CTA result had proximal DVT on ultrasound for a total prevalence of VTE of 82/489 (16.8%); rate of 3-mo VTE in the 409 patients who had PE excluded in the initial evaluation phase was 0.5% (95% CI 0% to 1.8%)	Authors noted that there may have been a tendency to overinterpret the results of the spiral CT to err on the side of safety	II for risk stratification I for venous imaging

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Kabrhel et al[37]	2009	Prospective, observational multicenter study of ED patients in the United States	Multiple quantitative D-dimer tests, VIDAS® (ELISA) and Liatest (turbidimetric) were the most common (63%); the standard test threshold was used for each type of quantitative D-dimer (ie, >500 ng/mL for VIDAS®); for the sensitivity analysis using variable cutoffs based on pretest probability groups, the test threshold was twice that of standard threshold for patients with low pretest probability and half that of the standard threshold for those with high pretest probability; pretest probability by clinical gestalt and Wells criteria	VTE during 45 days primary outcome; clinical follow-up for patients with negative D-dimer result and no imaging; VQ scan, CT thorax, or pulmonary angiogram for those considered moderate/ high risk or positive D-dimer result; presence or absence of VTE at 45 days based on telephone interview or chart review	5.4% prevalence of PE among 4,357 patients; sensitivity=0.94 (95% CI 0.91 to 0.97), specificity=0.58 (95% CI 0.56 to 0.60); LR+=2.2, LR-=0.10 (95% CI .06 to 0.16); sensitivity analysis using variable cutoffs based on Wells score: sensitivity=0.85 (95% CI 0.80 to 0.89), specificity=0.75 (95% CI 0.74 to 0.77); LR+=3.4, LR-=0.20 (95% CI 0.15 to 0.27)	Various D-dimer assays were used at different participating institutions; asymptomatic patients were not tested for VTE in follow-up; ED population from 10 academic medical centers and 2 community hospitals suspected of having PE; 3,583 from original cohort who either did not have D-dimer testing or result not available were excluded from the analysis; no mention of blinded interpretation of reference standard for both imaging studies and persons conducting telephone or chart review follow-up; potential for differential reference standard bias; 95% CI not reported for LR+ results	II for risk stratification II for D-dimer

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Goekoop et al[38]	2007	Prospective cohort	VIDAS® (ELISA) D-dimer threshold ≥500 ng/mL; pretest probability by dichotomous Wells criteria	VTE during 3-mo primary outcome; clinical follow-up for patients considered "PE unlikely" per Wells criteria (score ≤4) with negative D-dimer result; VQ scan or CT thorax for "PE likely" per Wells criteria (score >4) or positive D-dimer result; investigators final determination for presence or absence of VTE at 3 mo based on office visit, telephone interview, medical record review	879 patients (12% PE); 450 patients (51.2%) had a clinical decision score ≤4.0 points and a normal D-dimer concentration; VTE rate was 2/450 (0.4%) (95% CI 0 to 1.1); 780 had D-dimer testing; 2/450 with negative D-dimer result had VTE on follow-up: NPV=99.5%	ED and outpatient clinic population suspected of having PE; 6 patients lost to follow-up in negative D-dimer group; no mention of blinded interpretation of reference standard for both imaging studies and persons conducting office or phone follow-up; potential for differential reference standard bias; data to complete 2x2 table for D-dimer not reported; includes patient population in Steeghs et al[74] 2005	III for risk stratification III for D-dimer

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Hogg et al[39]	2006	Prospective, diagnostic cohort study conducted in a large UK city ED	The aim of this study was to validate an algorithm for the diagnosis of PE in ED patients with pleuritic chest pain using Well's score, IL Test (turbidimetric) D-dimer threshold $\geq$0.278 mg/L, and imaging modalities (CTA, VQ, or pulmonary angiography)	3-mo VTE	A total of 408 patients completed the diagnostic algorithm; 86.5% (353/408) were investigated as outpatients, 5.4% (22/408) were diagnosed as having PE, and 98.8% (403/408) were followed up for 3 mo; of the 381 patients without PE who completed follow-up, the incidence of thromboembolic disease was 0.8% (95% CI 0.3% to 2.3%): 2 patients had PE and 1 had DVT	Single-center study; 5 lost to follow-up; no mention of blinded interpretation of reference standard for imaging studies; potential for differential reference standard bias; data to complete 2x2 table for D-dimer not reported	III for risk stratification III for D-dimer

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Kruip et al[40]	2002	Prospective, single center study in Netherlands	Consecutive patients with suspected PE had D-dimer testing and clinical probability assessment with the Wells criteria; patients with a low probability and a normal D-dimer concentration (<500 ng/mL) were considered not to have PE, and further diagnostic testing and anticoagulant therapy were withheld; in patients with a low probability and elevated D-dimer level or with a moderate or high probability, bilateral compression ultrasonography of the legs was performed; if DVT was detected, VTE was diagnosed; if compression ultrasonography was normal, pulmonary angiogram was performed	3-mo VTE	234 patients (22% PE); 26% had the combination of a low probability and normal D-dimer level; during the follow-up period, none of these patients died and 3 patients had recurrent complaints of PE; in these 3 patients, PE was excluded by objective testing; the 3-mo thromboembolic risk was therefore 0% (95% CI 0% to 6%)	Single hospital; relatively small patient population	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Sanson et al[41]	2000	Prospective multi-institutional study	Clinical probability assessed by gestalt and by the extended Wells criteria and simplified Wells criteria; all patients underwent VQ scanning; if VQ scan nondiagnostic or high probability, CTA performed; if patient with high-probability VQ scan and negative CTA result, pulmonary arteriogram performed	PE on presentation	517 study patients; 160 (31%) were classified as having PE; of these patients, 14% had a low probability as estimated by the treating physician, whereas 25% to 36% were categorized as having a low clinical probability with the use of 2 clinical models; the objectively confirmed prevalence of PE in these 3 low-probability categories was 19%, 28%, and 28%, respectively; the 3 methods yielded comparable predictive values for PE in the other probability categories; the authors concluded that a physician's clinical judgment alone and 2 standardized clinical models, although comparable, perform disappointingly in categorizing the pretest probability in patients with suspected PE	15% of patients excluded due to time of presentation and other factors	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Wolf et al[42]	2004	Prospective observational study	Liatest (turbidimetric) D-dimer threshold >400 ng/mL and VIDAS® (ELISA) D-dimer threshold >500 ng/mL; pretest probability by Wells criteria	VTE during 3-mo primary outcome; presence of VTE determined by pulmonary angiogram, CT thorax, VQ scan, or clinical follow-up if negative D-dimer result and no ED imaging; clinical follow-up based on combination of telephone interview and medical record review	134 patients; 16 (12%) patients were diagnosed with PE; the κ values for Wells criteria were 0.54 and 0.72 for the trichotomized and dichotomized scorings, respectively; when Wells criteria were trichotomized into low (n=59, 44%), moderate (n=61, 46%), or high pretest probability (n=14, 10%), the PE prevalence was 2%, 15%, and 43%, respectively; when Wells criteria were dichotomized into PE unlikely (n=88, 66%) or PE likely (n=46, 34%), the prevalence was 3% and 28%, respectively; for quantitative latex: sensitivity=0.94 (95% CI 0.70 to 1.0), specificity=0.36 (95% CI 0.36 to 0.54); LR+=1.7, LR-=0.1; equivalent results for ELISA D-dimer	ED population suspected of having PE; 66% of population considered "PE unlikely" (Wells ≤4); unclear whether interpretation of imaging studies persons conducting follow-up were blind to D-dimer results	III for risk stratification I for D-dimer

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Yap et al[43]	2007	Prospective, observational	Ventilation scintigraphy was performed using technetium-99m Technegas, and VQ results were interpreted in conjunction with Wells scores	Likelihood of PE for each Wells score interval; overall prevalence of PE	633 studies on 595 patients; rates of PE for scores of <2, 2 to 6, and >6 were 4%, 13%, and 67%, respectively	The reporting nuclear medicine physician was responsible for generating both the Wells score and the VQ result; the authors note that this may have influenced reporting; there was no prolonged follow-up of negative imaging studies	III
Iles et al[44]	2003	Questionnaire survey; large New Zealand hospital	Pretest determination by the Geneva and Wells pretest probability scores	Physicians were grouped by grade (mean number of y since graduation +/- semester): house officers 0.7+/-0.2, registrars 6.3+/-0.6, consultants 25+/-4, and applied pretest probability scores to actual case scenarios	The Geneva score was the most consistent method of determining pretest probability and was unaffected by clinical experience (Geneva κ=0.73, Wells κ=0.38, empirical κ=0.23, P<0.001); with empirical judgment, interrater variability was inversely proportional to clinical experience (house officers κ=0.37, registrars κ=0.24, consultants κ=0.16, P<0.05)	Survey study design, using case scenarios	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Testuz et al[45]	2006	Retrospective analysis	15 categories of alternative diagnoses evoked in patients with PE; PE diagnostic protocol consisted of combination of pretest probability assessment, D-dimer, VQ scan, venous ultrasound, CTA, and pulmonary arteriogram	VTE on presentation	913 patients (48% with PE); the presence of an alternative diagnosis as or more likely strongly reduced the probability of PE (OR 0.15, 95% CI 0.1 to 0.2, $P<0.01$); in almost every diagnostic category, the prevalence of PE was much lower than in the reference group with an OR below or near 0.2	Retrospective design; 51 patients excluded for clinician evoking more than one alternative diagnosis	III
Goergen et al[46]	2005	Prospective cohort	IL Test (turbidimetric) D-dimer threshold ≥0.2 mg/L; pretest probability by the Kline rule	VTE during 3-mo primary outcome; clinical follow-up for patients considered "low risk" per Kline rule with negative D-dimer result; VQ scan or CT thorax for considered "high risk" per Kline rule or positive D-dimer result; investigators final determination for presence or absence of VTE at 3 mo based on mail or telephone interview	9.5% prevalence of PE among 791 study patients; 780 had D-dimer testing; 1/114 low-risk patients with negative D-dimer had VTE on follow-up: NPV=99%	ED population suspected of having PE; 13% lost to follow-up, thus having no reference standard applied; only 65% had risk assessment recorded; no mention of blinded interpretation of reference standard for both imaging studies and persons conducting mail or telephone follow-up; potential for differential reference standard bias; data to complete 2x2 table for D-dimer not reported	III for risk stratification III for D-dimer

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Runyon et al[47]	2005	Prospective observational study conducted in a single urban academic ED	Clinical gestalt assessment pretest probability compared with Wells score and Kline rule; all patients evaluated for PE using a previously published protocol including D-dimer and alveolar dead space measurements and selected use of pulmonary vascular imaging	VTE during 45 days	2,603 patients (5.8% with PE; 95% CI 4.9% to 6.8%); 69% were deemed low risk by the unstructured estimate <15%, 73% by the Wells score <2, and 88% by the Kline rule "safe"; rates of PE in these low-risk groups were 2.6%, 3.0%, and 4.2%, respectively; weighted Cohen's κ values were 0.60 (95% CI 0.46 to 0.74) for the unstructured clinical estimate, 0.47 (95% CI 0.33 to 0.61) for the Wells score <2, and 0.85 (95% CI 0.69 to 1.0) for the Kline rule "safe"	Single center design	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
PIOPED Investigators[48]	1990	Prospective study, 6 clinical centers	VQ scans and pulmonary arteriogram; gestalt pretest probability	PE on presentation if patient had diagnostic pulmonary arteriogram; if arteriogram negative for PE, patients were contacted at 1, 3, 6, 12 mo for VTE events	931 patients underwent scintigraphy and 755 underwent pulmonary angiogram; 251 (33%) of 755 demonstrated PE; 102 of 116 patients with high-probability scans and definitive angiograms had PE; high-probability VQ scan had sensitivity 41% and specificity 97% for PE; 105 of 322 (33%) with intermediate-probability scans and definitive angiograms had PE; rates of PE for normal, low-probability, intermediate-probability and high-probability VQ scans were 4%, 14%, 30%, and 87%, respectively; rates of PE for pretest probability assessment of low, intermediate, or high were 9%, 30%, and 68%, respectively; rate of PE of a normal or low-probability VQ scan and a low pretest probability was 3.3%	Not all patients had both VQ scan and pulmonary arteriogram; significant interrater disagreement in detection of subsegmental PE on pulmonary arteriogram	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Barghouth et al[49]	2000	Prospective observational	Gestalt pretest probability and VQ scan; pulmonary arteriogram if indicated	PE on presentation or VTE during 2-y follow-up	134 patients (24.5% with PE); rates of PE in patients with low (<0.4), intermediate (0.4 to 0.69), and high (≥0.7) pretest probability were 11.1%, 21.9%, and 60%, respectively; rates of PE for patients with normal, low, intermediate, or high probability VQ scans were 0%, 5.2%, 41.7%, and 100%, respectively	Small sample size; pretest probability determined by 4 residents and 2 chief residents	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Musset et al[50]	2002	Prospective multicenter outcome study	Single-detector CT plus bilateral lower extremity ultrasound; gestalt pretest probability assessment	3-mo VTE	1,041 patients (34.6% with PE); N=601 negative CT and ultrasounds, 525 were low or intermediate pretest probability and 76 were high probability; 18 of 525 received anticoagulants for reasons other than PE; 9 of 507 experienced PE (1.8%; 0.8% to 3.3%); (0.8%; 0.2% to 2.3% outpatients); (4.8%; 1.8% to 10.1% inpatients); 10 of 507 had incomplete follow-up; 75 of 76 high-probability patients with negative CT and ultrasound results had VQ, arteriography, or both; 4 of 75 had PE (5.3%; 1.5% to 13.1%); of patients with PE diagnosed during the original evaluation, 3.8% died, 4.1% had major bleeding, 2.3% had recurrent PE; of 12 patients with subsegmental PE and negative ultrasound results, 3 had PE confirmed by arteriography or VQ scan; of the 9 that were negative and had anticoagulation held, none had PE in 3-mo follow-up; of 51 patients who died 9 cases were thought possibly or definitely the result of PE	D-dimer testing was not used in the strategy; study included inpatients and outpatients; single-detector CT	III for risk stratification I for CTA and venous imaging

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Nilsson et al[51]	2001	Prospective, single hospital in Sweden	Gestalt clinical probability (low, ≤25%; intermediate, 26% to 75%; and high, >75%) and VQ scanning	PE as determined by a committee of experts including 2 radiologists, 1 nuclear physician, and 3 internists who analyzed all available data (including 6-mo follow-up) during one session	170 patients; 53 patients had PE (31.2%); rates of PE for gestalt pretest probability of low, intermediate, and high were 9.4%, 35.7%, and 80.8%, respectively; rates of PE for low, intermediate, and high pretest probability VQ scans were 7.5%, 37.8%, and 93.5%, respectively	Small sample size; unusual definition of PE	III
Perrier et al[52]	1996	Prospective study, ED of the University Hospital of Geneva	Diagnostic protocol that included gestalt clinical probability assessment and VQ scan followed by sequential diagnostic tests: D-dimer, venous ultrasound, and pulmonary arteriogram; patients without PE according to the diagnostic workup did not receive anticoagulant treatment	Primary outcome: VTE on presentation (a diagnosis of PE was considered definite by a high-probability lung scan and abnormal arteriogram, or finding of DVT on ultrasound); secondary outcome: 6-mo VTE, mortality, and bleeding events	308 patients; 69 (22.4%) with PE; PE rates for the gestalt probability groups 0 to 0.2, 0.21 to 0.4, 0.41 to 0.60, 0.61 to 0.79, 0.80 to 1 were approximately (from bar graph) 15%, 25%, 50%, 70%, and 90%, respectively; PE was diagnosed by high-probability scan in 63 patients, high clinical probability and nondiagnostic scan in 7 patients, positive ultrasound result in 17 patients, positive pulmonary arteriogram result in 22 patients; PE was excluded by low clinical probability and nondiagnostic scan in 48 and a negative D-dimer result in 53 patients; on 6-mo follow-up, 2 of 199 patients without PE had VTE (1%; 95% CI 0.1 to 3.6)	VQ scan was the principal diagnostic modality; relatively small N; patients with high pretest probability and nondiagnostic scan result deemed to have PE and patients with low pretest probability and nondiagnostic scan result deemed not to have PE (incorporation bias in determining accuracy of pretest probability assessment)	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Perrier et al[53]	2000	Pooled analysis of 2 consecutive cohort management studies performed in 2 university hospitals (Geneva University Hospital, Geneva, Switzerland, and Hospital Saint-Luc, Montreal, Quebec, Canada).	Gestalt pretest clinical probability followed by a sequential diagnostic protocol of assessment, lung scan, D-dimer testing, lower-limb venous compression ultrasound, and pulmonary angiogram in case of inconclusive results of noninvasive workup	3-mo VTE	1,313 patients; the prevalence of PE was 27.6%; PE occurred in 8.2% of patients deemed to have low pretest probability of PE; 180 patients had a low clinical probability of PE and a nondiagnostic lung scan; among these patients, ultrasound showed DVT in 5; 175 patients (21.5%) had low pretest probability, a nondiagnostic VQ scan result and a normal venous ultrasound result; the 3-mo thromboembolic risk in these patients was low (1.7%) (95% CI 0.4% to 4.9%); rate of PE in patients with intermediate and high pretest probability was approximately (from bar graph) 40% and 65%, respectively	VQ scan principal diagnostic mode; incorporation bias for pretest probability assessment in that patients with high pretest probability and nondiagnostic lung scan result deemed to have PE	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Nordenholz et al[54]	2007	Prospective convenience sample	Comparison of attending emergency physician and third-y resident about agreement in selected elements of Wells and Kline scores	Looked at interrater reliability of the criteria of PE risk assessment tools (Wells and Kline)	271 patients; κ scores are as follows: previous DVT, 0.90 (0.83 to 0.97); malignancy, 0.87 (0.76 to 0.97), DVT symptoms, 0.54 (0.39 to 0.7), immobilization, 0.41 (0.26 to 0.57), and PE more likely than another diagnosis, 0.50 (0.36 to 0.64)	Relatively small sample size; no information is given about number of patients with PE; 23 patients did not have data sheets completed by both physicians; treating physician choice in patient enrollment	III
Kabrhel et al[55]	2005	Prospective observational study, single academic ED	The physician treating the patient was asked whether he or she considered PE the most likely diagnosis or whether an alternative diagnosis was most likely	VTE on presentation	583 patients with PE rate of 10%; PE was considered most likely diagnosis for 153 patients (26%) and less likely in 430 (74%); PE was diagnosed in 32 patients with PE more likely (21%) and 27 less likely (6%); there were no differences in percentage of patients for whom physicians considered PE more likely across all experience level (PGY-1, PGY-2 and -3, PGY-4+); the likelihood ratio for PE for physicians with pretest assessment of PE for the above 3 groups was 1.5 (95% CI 0.7 to 3.0), 2.3 (95% CI 1.6 to 3.5), and 3.3 (95% CI 2.2 to 5.2), respectively	Single-center design; the 3 physician groups (PGY-1, PGY-2 and -3, PGY-4+) evaluated 139, 245, and 199 patients, respectively; because the 3 groups did not evaluate all patients and because the experience level of the physician evaluating the patient was not randomized, direct comparisons between these subgroups is extremely limited	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Runyon et al[56]	2007	Survey study, 32 academic and community hospitals in the United States and the United Kingdom	Survey study methodology used to determine respondents' familiarity with, frequency of use of, and comprehension of the Wells and Kline rules; survey also queried use of gestalt assessment and why physicians choose not to use decision rules	Responses to survey	555 clinicians (80% academics, 20% community); 57% of respondents used gestalt in more than half the cases; 73% of academic physicians compared with 49% of community physicians reported familiarity with the Wells and Kline rules; respondents frequently could not identify a key component of the individual rules (43% for Wells; 23% for Kline)	Survey study; setting for response not controlled; authors noted that some clinicians could have consulted reference materials to answer the questions	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Kline et al[57]	2004	Multicenter, Prospective	Derivation: 21 PE-related predictive variables vs endpoint/outcomes variables; logistic regression analysis with stepwise backwards elimination yielded PERC low-risk validation cohort: defined by unstructured pretest probability, unknown consecutive vs convenience sample, evaluated PERC performance; very low-risk validation cohort: defined as dyspnea and PE not most likely diagnosis, convenience sample, evaluate PERC performance	Outcome=VTE diagnosis; criterion standard=composite diagnostic evaluation and 90-day follow-up	Derivation: N=3,148; overall VTE=11%; PERC: aged <50 y, pulse <100 beats per min, SaO_2 >94% (at sea level), no unilateral leg swelling, no hemoptysis, no recent trauma or surgery, no previous PE or DVT, and no hormone use; PERC(-) VTE=1.8%, low-risk validation: N=1,427, VTE=8%, 25% PERC (-); sensitivity 96%, specificity 27%, LR- 0.15, false-negative rate 1.4%; very low-risk validation: N=328, VTE=2%, 15% PERC (-); sensitivity 100%, specificity 15%, LR- 0	Ill-defined inclusion/exclusion and enrollment criteria; very low-risk cohort was a convenience sample; very low specificity	II
Lessler et al[59]	2010	Decision analysis	Decision analytic modeling to balance cost-benefit for PE testing threshold	Modeled 14 patient cohorts	Ideal average testing threshold=1.4%		III
Kline et al[60]	2008	Prospective multicenter study	Validation of PERC rule in a low and very low-risk patient population	Outcome=VTE diagnosis; criterion standard=composite diagnostic evaluation and 45-day follow-up	Eligible=12,213; enrolled=8,138, VTE=6.9%, PERC (-)=24%, low risk=67%, very low risk PERC [-] and low risk)=20%; PERC performance on entire cohort: sensitivity 95.7%, specificity 25.4%, LR- 0.17; PERC performance on low-risk cohort: sensitivity 94.7%, specificity 21.9%, LR- 0.12	Enrollment rate=66%; no follow-up=304 patients	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Wolf et al[61]	2008	Prospective	Post hoc analysis on prospectively collected data to validate PERC	Outcome=VTE diagnosis; criterion standard=composite diagnostic evaluation and 90-day follow-up	N=120, VTE=12%; PERC performance on entire cohort: sensitivity 100%, specificity 16%, LR-0; PERC performance on low-risk cohort: sensitivity 100, specificity 22%, LR- 0	Small study size; post hoc analysis	III
Stein et al[64]	2004	Systematic review	D-dimer tests, multiple assays including ELISA and quantitative latex; primary analysis based on 500 ng/mL threshold	PE or DVT	31 studies met final inclusion criteria (Tier 2) with a prevalence of PE ranging from 8% to 62%; pooled estimates for ELISA: sensitivity=0.96 (95% CI 0.88 to 1.00), specificity=0.51 (95% CI 0.44 to 0.59); LR+=2.0; LR -=0.1; for quantitative latex: sensitivity=0.89 (95% CI 0.80 to 0.99), specificity=0.47 (95% CI 0.38 to 0.57); LR+=1.7, LR- =0.2	Outpatients and inpatients including postpartum and trauma patients; Tier 2 studies met all a priori inclusion criteria, Tier 1 studies compared ELISA with 1 other D-dimer test and Tier 3 studies were of lower quality	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Di Nisio et al[65]	2007	Systematic review	D-dimer tests, multiple assays including ELISA and quantitative latex; primary analysis based on 500 ng/mL threshold	PE and DVT; measurement of outcomes adjusted for in analysis	81 PE studies with an incidence of VTE ranging from 3% to 69%; pooled estimates: microplate ELISA sensitivity=0.96 (95% CI 0.79 to 1.00), specificity=0.39 (95% CI 0.13 to 0.79); LR+=1.6, LR-=0.1; quantitative latex: sensitivity =0.96 (95% CI 0.63 to 1.00), specificity=0.43 (95% CI 0.16 to 0.88); LR+=1.7, LR-=0.1; multivariable analysis demonstrated that specificity decreased in studies that included more inpatients or older patients (mean age >60 y)	The type of patient (inpatient vs outpatient) and study design were included in the multivariable model (eg, adjusted for type of reference standard used and risk of differential reference standard bias); there was essentially no difference between the summary results of the microplate ELISA, membrane ELISA, and ELFA	I
Brown et al[67]	2002	Systematic review	ELISA D-dimer; variable thresholds ranged from 250 to 500 ng/mL (8/11 studies used 500 ng/mL)	VTE during 3-mo primary outcome; acceptable reference standard for diagnosis of PE included positive pulmonary angiogram result, CT thorax, lower extremity imaging, or high-probability VQ scan; acceptable reference standard for exclusion of VTE included negative pulmonary angiogram result, normal VQ scan result, or 3-mo clinical follow-up	11 studies (N=2,126) met final inclusion criteria, with a prevalence of PE ranging from 17% to 58%; the most valid pooled estimates based on traditional microplate ELISA methods (9 studies): sensitivity=0.94 (95% CI 0.88 to 0.97), specificity=0.45 (95% CI 0.36 to 0.55); LR+=1.9, LR-=0.1; subgroup analysis demonstrated that specificity decreased in the elderly (age >70 y) and both sensitivity and specificity decreased with prolonged duration of symptoms (≥4 days)	All studies were predominantly of outpatients (>80%) and used an appropriate reference standard; some studies had inadequate blinding of reference standard interpretation or were prone to differential reference standard bias	I

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Brown et al[68]	2003	Systematic review	Quantitative latex D-dimer (turbidimetric); variable thresholds ranged from 190 to 500 ng/mL (7/9 studies used 500 ng/mL)	VTE during 3-mo primary outcome; acceptable reference standard for diagnosis of PE included positive pulmonary angiogram result, CT thorax, lower extremity imaging, or high-probability VQ scan; acceptable reference standard for exclusion of VTE included negative pulmonary angiogram result, normal VQ scan result, or 3-mo clinical follow-up	9 studies (N=1,901) met final inclusion criteria, with a prevalence of PE ranging from 9% to 62%; pooled estimates: sensitivity=0.93 (95% CI 0.89 to 0.96), specificity=0.51 (95% CI 0.42 to 0.59); LR+=1.7, LR-=0.1	All studies were predominantly of outpatients (>80%) and used an appropriate reference standard; none of the studies were prone to differential reference standard bias and the majority were adequately blinded	I

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Courtney et al[69]	2010	Prospective cohort	HemosIL HS (turbidimetric) D-dimer threshold >243 ng/mL; pretest probability by clinical gestalt, dichotomous Wells criteria applied retrospectively for analysis	VTE during 45-day primary outcome; CT thorax, lower extremity ultrasound, or VQ scan if positive D-dimer result; clinical follow-up if low pretest probability (<15%) with negative D-dimer result based on telephone interview and medical record review	4.7% prevalence of VTE among 526 ED patients having D-dimer testing: sensitivity=0.96 (95% CI 0.80 to 1.0), specificity=0.66 (95% CI 0.61 to 0.70); LR+=2.8 (95% CI 2.4 to 3.2), LR-=0.06 (95% CI 0.01 to 0.42); among the low-risk group with a negative D-dimer, 3-mo incidence of VTE =0.3%	ED population suspected of having PE considered to be at low risk; however, 22 patients were nonlow risk by Wells criteria or physician's estimate; radiologists were not blinded to D-dimer result and blinding of persons conducting follow-up unclear; potential for differential reference standard bias	II
Ghanima et al[70]	2005	Prospective cohort, multicenter	STA Liatest (turbidimetric) D-dimer threshold >0.4 mg/L; pretest probability by clinical gestalt	VTE during 3-mo primary outcome; PE ruled out by normal CT thorax or lower extremity ultrasound result when CT result inconclusive, or normal VQ scan result; if low or intermediate pretest probability and negative D-dimer result, then outcome based on clinical follow-up; cause of death determined by independent adjudication committee	24% prevalence of VTE among 432 enrolled during 3 mo; sensitivity=1.0 (95% CI 0.96 to 1.0); specificity=0.37 (95% CI 0.32 to 0.42)	ED population suspected of having PE; blinded interpretation of reference standard uncertain for both imaging studies and persons conducting follow-up; estimates for pretest probability flawed, given that not all patients had an estimate recorded, a validated clinical prediction rule not used, and clinicians were not blinded to the D-dimer results when estimating pretest probability; potential for differential reference standard bias	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Mitchell et al[71]	2008	Prospective cohort, multicenter	Biosite D-dimer threshold ≥500 ng/mL; pretest probability estimated by clinical gestalt	VTE during 3-mo primary outcome; reference standards for diagnosis of VTE included positive CT thorax, VQ scan results; acceptable reference standard for exclusion of VTE included normal CT thorax, VQ scan results or negative 3-mo clinical follow-up by telephone or medical record review	7% prevalence of VTE among 304 ED patients suspected of having PE having D-dimer testing: sensitivity=1.00 (95% CI 0.85 to 1.0), specificity=0.59 (95% CI 0.53 to 0.65)	ED population suspected of having PE; study objective was to assess the value of adding a second biomarker for D-dimer-positive patients; excluded 45 patients with incomplete assays; persons conducting telephone follow-up and medical record review were blinded to D-dimer result; no mention of blinded interpretation of imaging studies; potential for differential reference standard bias	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Parent et al[72]	2007	Prospective cohort, multicenter	VIDAS® (ELISA) and Liatest (turbidimetric) D-dimer threshold >500 ng/mL; pretest probability estimated by clinical gestalt	VTE during 3-mo primary outcome; reference standards for diagnosis of VTE included positive pulmonary angiogram, CT thorax, high probability VQ scan, positive lower extremity imaging results; acceptable reference standard for exclusion of VTE included negative pulmonary angiogram, normal CT thorax, and lower extremity ultrasound results, or 3-mo clinical follow-up determined by adjudication committee	39% prevalence of PE among 352 patients; sensitivity=0.96 (95% CI 0.93 to 0.99), specificity=0.39 (95% CI 0.32 to 0.45); LR+=1.6 (95% CI 1.4 to 1.7); LR-=0.1 (95% CI .04 to 0.23)	Outpatient (76%) and inpatient population suspected of having PE; selection bias likely given high prevalence of PE with only 23% of population considered to have a low pretest probability;78% had quantitative latex D-dimer but results for both types of test were not reported separately; clinicians (and probably radiologists) were blind to D-dimer results; however, the methods used to conduct clinical follow-up not clearly reported	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Perrier et al[73]	2005	Prospective cohort, multicenter	VIDAS® (ELISA) D-dimer threshold >500 ng/mL; pretest probability by Geneva score	Primary outcome was the proportion of patients with proximal DVT with negative CT thorax result; secondary outcome was VTE during 3 mo; reference standards for diagnosis of VTE included positive pulmonary angiogram, CT thorax, high probability VQ scan, positive lower extremity imaging results; acceptable reference standard for exclusion of VTE included negative pulmonary angiogram, CT thorax, and lower extremity ultrasound results, or 3-mo clinical follow-up determined by adjudication committee	26% prevalence of PE among 756 patients; 674 low/intermediate risk had D-dimer testing; sensitivity=1.0 (95% CI 0.97 to 1.0); specificity=0.42 (95% CI 0.38 to 0.46); among patients with a negative D-dimer result, 0/674 were diagnosed with VTE during 3 mo	ED population suspected of having PE; D-dimer accuracy was not the primary objective but data for 2x2 table were reported; potential for differential reference standard bias	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Steeghs et al[74]	2005	Prospective cohort, multicenter	VIDAS® (ELISA) D-dimer threshold ≥500 ng/mL; C-reactive protein; pretest probability by dichotomous Wells criteria	VTE during 3-mo primary outcome; clinical follow-up for patients considered "PE unlikely" per Wells criteria (score ≤4) with negative D-dimer result; VQ scan or CT thorax for "PE likely" per Wells criteria (score >4) or positive D-dimer result; investigators' final determination for presence or absence of VTE at 3 mo based on office visit, telephone interview, and medical record review	14% prevalence of PE among 331 patients; 279 "PE unlikely" had D-dimer testing; sensitivity=0.97 (95% CI 0.90 to 1.0), specificity=0.68 (95% CI 0.62 to 0.74); among patients with low pretest probability and a negative D-dimer, 1/279 were diagnosed with VTE over 3 mo	ED and outpatient clinic population suspected of having PE; 84% considered low probability per Wells criteria; potential for differential reference standard bias; no mention of blinded interpretation of reference standard for both imaging studies and persons conducting office or telephone follow-up; reasons for the high specificity uncertain	II
Than et al[75]	2009	Prospective cohort	HemosIL HS (turbidimetric) D-dimer threshold ≥250 ng/mL; Wells criteria applied retrospectively for analysis	VTE during 3-mo primary outcome; pulmonary angiogram, CT thorax, lower extremity ultrasound, or VQ scan if positive D-dimer result; clinical follow-up if negative standard D-dimer result based on telephone interview and medical record review; cause of death adjudicated by blinded independent review	4.5% prevalence of VTE among 402 ED patients having D-dimer testing: sensitivity=1.00 (95% CI 0.82 to 1.0), specificity=0.58 (95% CI 0.53 to 0.63); NPV=100% (95% CI 98.4 to 100%)	ED population suspected of having PE; excluded 14 patients lost to follow-up from analysis; 78% low risk and 21% moderate risk per Wells criteria; potential for differential reference standard bias; no mention of blinded interpretation of imaging studies but those conducting follow-up were blinded to D-dimer results	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Carrier et al[76]	2009	Systematic review	VIDAS® (ELISA) D-dimer threshold >500 ng/mL; low to intermediate pretest probability by Wells criteria, Geneva score, or clinical gestalt	VTE during 3-mo primary outcome; acceptable reference standard for diagnosis of PE included positive pulmonary angiogram, CT thorax, or high probability VQ scan; acceptable reference standard for exclusion of VTE included negative pulmonary angiogram result, normal VQ scan result, or 3-mo clinical follow-up	7 studies (N=2,248) met final inclusion criteria (nonhigh pretest probability with negative D-dimer result); incidence of VTE at 3-mo follow-up after excluding 71 patients who received anticoagulation and 11 patients lost to follow-up was 3/2, 166: NPV=99.9%	All studies were predominantly outpatients having a low to intermediate pretest probability of PE; all studies used clinical follow-up as the reference standard and were prone to differential reference standard bias	III
Legnani et al[77]	2010	Prospective cohort; multicenter	HemosIL HS (turbidimetric) D-dimer threshold >500 ng/mL; pretest probability by Wells criteria	VTE during 3-mo primary outcome; pulmonary angiogram, CT thorax, lower extremity ultrasound or plethysmography, or VQ scan if positive D-dimer result; clinical follow-up if negative D-dimer result	15.0% prevalence of VTE among 346 ED patients suspected of having PE having D-dimer testing: sensitivity=1.00 (95% CI 0.93 to 1.0), specificity=0.48 (95% CI 0.43 to 0.54); NPV=100% (95% CI 97.4 to 100%)	Outpatient clinic and ED populations suspected of having PE or DVT; of those 346 suspected of having PE, 87 were low risk and 235 were moderate risk; methods for follow-up not reported; potential for differential reference standard bias; no mention of blinded interpretation of imaging studies or of those conducting follow-up	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Runyon et al[78]	2008	Prospective cohort	VIDAS® (ELISA) D-dimer or MDA (turbidimetric) D-dimer threshold >500 ng/mL; pretest probability by clinical gestalt	VTE during 45-day primary outcome; clinical follow-up for patients with negative D-dimer result and no imaging; VQ scan, CT thorax with or without lower extremity venogram for those considered moderate/high risk or positive D-dimer result; presence or absence of VTE at 45 days based on telephone interview or medical record review	3.5% prevalence of PE among 1,136 patients; sensitivity=0.93 (95% CI 0.80 to 0.98), specificity=0.57 (95% CI 0.54 to 0.60); LR+=2.2 (95% CI 1.9 to 2.4); LR-= 0.13 (95% CI 0.05 to 0.35) ; NPV= 99.5% (95% CI 98.6 to 99.9%)	ED population suspected of having PE; excluded 57 patients who did not have quantitative D-dimer test; 84% low risk and 14% moderate risk, sensitivity equivalent among risk groups; potential for differential reference standard bias; radiologist blinded to D-dimer result but uncertain whether those conducting follow-up were blinded	III
Ten Wolde et al[79]	2004	Prospective cohort, multicenter	Tinaquant (turbidimetric) D-dimer threshold ≥500 ng/mL; pretest probability by clinical gestalt	VTE during 3-mo primary outcome; clinical follow-up for patients considered low risk (<20% pretest probability) with negative D-dimer result; all others had VQ scan and those with a nondiagnostic result had serial lower extremity ultrasound; all outcomes adjudicated by blinded independent committee	20% prevalence of VTE among 631 patients; 519 had D-dimer testing; among the 95 patients with low pretest probability and negative D-dimer result the incidence of VTE during 3 mo=0% (95% CI 0% to 3.8%)	Outpatient (65%) and inpatient population suspected of having PE; 25% of population considered to have a low pretest probability; methods used to conduct clinical follow-up not clearly reported; data to complete 2x2 table for D-dimer not reported, however, the data were adequately reported by Di Nisio et al[88] 2005	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Righini et al[84]	2008	Prospective multicenter (6 sites), randomized design	Pretest probability, D-dimer, CTA and 3-mo follow-up vs the same regimen except the addition of Doppler ultrasound before the CTA; if the Doppler ultrasound result was positive then no further testing was performed	PE diagnosed by positive CTA, positive CT venogram, or positive Doppler ultrasound result and positive VTE result at 3-mo follow-up	1,819 patients enrolled, 461/1,819 (25.3%) (95% CI 23.4 to 27.4) were diagnosed with PE; positive Doppler ultrasound result: 53/574 (9.2%) (95% CI 7.0 to 11.9); patients left untreated in the D-dimer and CT group: 2/649 (0.3%) (95% CI 0.1 to 1.1); patients left untreated in the D-dimer, Doppler ultrasound and CT group: 2/627 (0.3%) (95% CI 0.1 to 1.2)	CT scanner: multidetector row spiral CTs (16 to 64 row detectors at the different sites); an outcome study that randomizes Doppler ultrasound in a diagnostic protocol for patients with clinically suspected PE; ED patients only; pretest probability performed and included 3-mo follow-up	I for D-dimer, CTA and venous imaging
Di Nisio et al[88]	2005	Prospective cohort stratified by presence of cancer, blinded interpretation of imaging studies	Tinaquant (turbidimetric) D-dimer threshold ≥500 ng/mL; pretest probability by clinical gestalt	VTE during 3-mo primary outcome; PE ruled out by normal pulmonary angiogram, CT thorax, lower extremity ultrasound, or VQ scan result; clinical follow-up if low pretest probability (<20%) and negative D-dimer result; cause of death adjudicated by independent committee	20% prevalence of PE among 519 patients, lower specificity among the 72 patients with cancer: sensitivity=1.0 (95% CI 0.82 to 1.0), specificity=0.21 (95% CI 0.10 to 0.32); among the 447 without cancer: sensitivity=0.93 (95% CI 0.87 to 0.98), specificity =0.53 (95% CI 0.48 to 0.58); LR+= 2.0, L -=0.14	Outpatient (67%) and inpatient population suspected of having PE; potential for differential reference standard bias; methods used to conduct clinical follow-up not clearly reported; generalizability of results on cancer subgroup questionable given that only 33 of the outpatients had cancer; same patient population as Ten Wolde et al	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
King et al[89]	2008	Prospective cohort	STA Liatest (turbidimetric) D-dimer threshold ≥0.5 mg/L	PE on CT thorax primary outcome	21.9% prevalence of PE among 201 cancer patients; sensitivity=0.98 (95% CI 0.88 to 1.0), specificity=0.18 (95% CI 0.13 to 0.25); LR+=1.2 (95% CI 1.1 to 1.3), LR -=0.12 (95% CI 0.02 to 0.88) NPV= 97% (95% CI 83% to 100%)	Outpatient oncology clinic population suspected of having PE; patients not having D-dimer or CT for various reasons were excluded; no planned system for follow-up on CT-negative patients	II
Brown et al[91]	2005	Prospective cohort	VIDAS® (ELISA) D-dimer threshold >500 ng/mL; clinical pathway based on modified Kline rule	VTE during 3-mo primary outcome; presence of VTE determined by positive CT thorax, CT venogram, VQ scan, or lower extremity ultrasound result; those without ED diagnosis of VTE had clinical follow-up at 3-mo based on combination of telephone interview, mail, and medical record review	5.8% prevalence of VTE among 1,207 patients; prevalence 4% among the low-risk subgroup of 677 patients having D-dimer testing: sensitivity=0.93 (95% CI 0.77 to 0.98), specificity=0.74 (95% CI 0.70 to 0.77); LR+=3.6, LR-= 0.09	ED population suspected of having PE; clinical pathway based on modified Kline rule recommended D-dimer testing only on low pretest probability patients <70 y of age, resulting in higher specificity; no mention of blinded interpretation of reference standard for both imaging studies and persons conducting follow-up; potential for differential reference standard bias, given different reference standard for D-dimer-negative versus D-dimer-positive patients	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Russo et al[98]	2005	Systematic review of CT literature 1995-2004	CTA by single and multidetector scanners	PE as determined by reviewed studies	Single detector CT: sensitivity/specificity= 37% to 94%/81% to 100%; multidetector CT: sensitivity/specificity= 87% to 94%/94% to 100%	Did not establish criteria for quality of evidence; says it is a meta-analysis but made no attempt to pool analysis	III
Perrier et al[99]	2001	Prospective	Observational study to determine the sensitivity, specificity, and LR- of CTA	Consecutive patients with suspected PE and positive D-dimer result; all had CTA and reference standard; reference standard=validated algorithm that included clinical assessment, lower extremity ultrasound, VQ scan, and pulmonary angiogram	N=118; VTE=39%; CTA sensitivity/specificity/ LR-=70/91/0.32	All single-detector CTs; only D-dimer-positive patients imaged	II
Ost et al[100]	2001	Prospective	Observational study to determine the NPV of CTA in patients with high pretest probability	All high pretest probability patients with intermediate or low probability VQ scan had single-detector CTA; patients with positive CTA result were considered PE positive; reference standards used were conventional pulmonary angiogram or clinical outcomes with follow-up for 6 mo	N=103; for pulmonary angiogram reference standard, CTA had a LR- of 0.8 and a NPV of 93%; for clinical outcomes reference standard CTA had a LR- of 0.12 and a NPV of 96%	All single-detector CTs	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Nilsson et al[101]	2002	Prospective	Observational study to determine the sensitivity and specificity of CT angiogram	All patients with suspected PE underwent D-dimer, CTA, and pulmonary angiogram; CTA compared with reference standard of pulmonary angiogram and 3-mo follow-up	N=90; VTE=37%; CTA sensitivity/ specificity/LR-=91%/96%/0.09	Only daytime enrollment; low enrollment rates for study duration; 49 patients excluded for not having pulmonary angiogram in stipulated time or for other protocol violation; all single-detector CTs	III
Ruiz et al[102]	2003	Prospective	Observational study to determine the sensitivity, specificity, and interobserver agreement of CTA compared with pulmonary angiogram	Consecutive patients with suspected PE underwent CTA and pulmonary angiogram; observers 1 and 2 independently interpreted the CTA	N=66; VTE=38%; observer 1: CTA sensitivity/specificity/ LR-=91%/81.5%/0.11; observer 2: CTA sensitivity/specificity/ LR-=88%/86%/0.14; interobserver agreement for final diagnosis was 80% (κ=0.65)	Low enrollment rates for study duration; inclusion criteria included request for pulmonary angiogram; all single-detector CTs; interobserver agreement decrease for subsegmental vasculature	III
Stone et al[103]	2003	Prospective	Observational study to assess performance of CTA in patients with intermediate-probability VQ scan compared with pulmonary angiogram	Convenience referral from inpatient and ED	N=25 with intermediate-probability VQ scan; VTE=28%; CTA sensitivity/specificity/ LR-=57%/94%/0.46	All single-detector CTs; concern for significant selection bias	III
van Strijen et al[104]	2005	Prospective	Observational study to assess performance of CTA in patients with intermediate probability VQ scan compared with pulmonary angiogram	Consecutive patients with abnormal VQ scan result underwent CTA; composite outcome used, including pulmonary angiogram on selected patients	N=517; abnormal VQ=282 (55%); CTA sensitivity/specificity/ LR-=69%/84%/0.4	All single-detector CTs; high exclusion rate (56%) due to timing of evaluation, protocol failure, and failure to obtain informed consent	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Eng et al[105]	2004	Systematic review; 6 systematic review articles and 8 primary studies reported sensitivity/specificity of CTA for detection of PE	CTA and pulmonary arteriogram	PE as diagnosed by individual studies	6 systematic reviews: combined sensitivity CTA 66% to 93% and combine specificity 89% to 97%; 8 primary studies: combined sensitivity CTA 45% to 100% and combined specificity 78% to 100%	Authors advise caution in interpreting pooled estimates in reported literature due to selection bias, heterogeneity, and fact that data for multidetector scanners not available	III
Stein et al[106]	2007	Meta-analysis of studies reporting sensitivity/specificity of CTA for PE and CT venogram for DVT	CTA	PE as diagnosed by individual studies	Single detector: pooled sensitivity of 73% and specificity of 87% (LR+ 5.7; LR- 0.31); 4-detector: sensitivity 83% and specificity 96% (LR+ 19.6; LR- 0.18); among patients with suspected PE evaluated with single-slice CT, 20% diagnosed as having VTE on basis of positive CT venous phase venogram compared with 14% for multislice CT; outcome studies demonstrated recurrent PE in 1.7% of patients with negative CTA result	Dates of literature search and search terms not specified; data pooled for 3 tiers of quality of individual studies; methodology poorly described	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Cueto et al[107]	2001	Systematic review of studies with CTA and pulmonary arteriogram from 1980 to 2000	CTA and pulmonary arteriogram	PE as diagnosed by individual studies	Composite sensitivity of CTA was 79.6% (95% CI 73% to 86%) and specificity was 94.3% (95% CI 91% to 98%); PIOPED found that a high- or intermediate- probability VQ scan had a sensitivity of 82.5% (95% CI 78% to 87%) and specificity of 51.9% (95% CI 47% to 56%)	Composite analysis of data from systematic review was then compared with the results of the PIOPED; as PIOPED is not part of the systematic review database, the comparison is extremely limited	III
Stein et al[108]	2006	Prospective multicenter	Multidetector CTA alone and in combination with CT venogram for detection of pulmonary embolism (PIOPED II)	PE diagnosed by a composite reference standard requiring 1 of the following: high probability VQ scan, positive pulmonary arteriogram result, or positive venous ultrasound result	1,090 patients (824 with reference diagnosis who underwent CT); sensitivity/specificity of CTA was 83%/96% (LR+ 19.6; LR- 0.18); sensitivity/specificity of CTA-CT venogram was 90%/95% (LR+ 16.5; LR- 0.11); inclusion of Wells criteria improved NPV in low clinical probability subgroup	High fallout rate: 238 did not undergo reference test diagnosis (primarily because test was inconclusive and patients or their medical team did not think it best to go on to arteriography) and a smaller proportion of these were low clinical probability; 51 patients excluded for noninterpretable CT and 28 excluded for not having CT	II for CTA II for venous imaging
Winer-Muram et al[109]	2004	Prospective	Multidetector CT vs digital substraction pulmonary angiogram for the diagnosis of PE	PE status, vessel location, and lobar location; reference standard=pulmonary angiogram	N=100; 7 protocol failures; 18/93 (19.3%) PE positive at 50 vessel levels; multidetector CT sensitivity/specificity=100%/ 89%; multidetector CT with 8/28 (30%) false-positive rate; pulmonary angiogram identified 3.8 times more subsegmental PEs; multidetector CT identified more large-order vessel involvement (OR=3.75)	Single center; multidetector CT=4; unclear eligibility: all referred for pulmonary angiogram vs all suspected of having PE; enrollment process not well defined: only 100 patients for 19 mo; only partially blinded given potential for same radiologist to do both studies; 7% protocol failure; high false-positive rate	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Coche et al[110]	2003	Prospective	Multidetector CT and VQ scanning (pulmonary arteriogram if results inconclusive)	PE on presentation	94 patients (66 with PE); CTA: sensitivity 96% (95% CI 82% to 99%), specificity 86% (95% CI 67% to 96%); VQ scan: sensitivity 98% (95% CI 92% to 99%), specificity 88% (95% CI 77% to 94%); CT scan found an alternative diagnosis in 29% of patients without PE	Low n; the high sensitivity of VQ scan for PE suggests extreme selection bias	III
Moores et al[111]	2004	Meta-analysis MEDLINE 1966-2004 and EMBASE 1974-2004; articles: rate of subsequent symptomatic VTE in patients who did not receive anticoagulation after a negative or indeterminate CTPA result		VTE within 3 mo	4,657 patients; VTE rate=1.4% (95% CI 1.1% to 1.8%); fatal PE=0.51% (95% CI 0.33% to 0.76%); 16 studies reported indeterminate CTPA result; subsequent rate of VTE=16.2%	No management strategies were identical, difference in patient selection, some outcomes determined objectively by testing and some by panel adjudication; follow-up was not complete in most studies, CTPA techniques varied, other diagnostic techniques usually applied in addition to CT	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Hayashino et al[112]	2005	Meta-analysis	Meta-analysis CT and VQ vs pulmonary angiogram reference standard from 1990 to 2003	Summary ROC present from 1990 to 2003; sensitivity analysis 1995 to 2003; posttest probability analysis; all data presented with respect thresholds for a positive VQ result; threshold 1 (T1): only high-probability positive VQ result; threshold 2 (T2): high probability and intermediate probability positive VQ; threshold 3 (T3): high probability, intermediate-probability, and low-probability VQ positive, all not VQ positive were considered VQ negative; all compared with pulmonary angiogram as reference standard	12 studies in the analysis (9 CT and 4 VQ); weighted pooled CT sensitivity/specificity/LR-: 85%/94%/0.16, respectively; weighted pooled VQ sensitivity/specificity/LR-: 39%/97%/0.62 for T1; 86%/46%/0.3 for T2; and 98%/5%/0.4 for T3; CT posttest probability analysis for a negative/positive CT result: 0.005/0.296, 0.055/0.841, and 0.347/0.980 for low (0.03), moderate (0.27), and high (0.78) pretest probabilities, respectively; probability analysis for a negative/positive VQ result: 0.019/0.296 for T1 and low probability and 0.546/0.789 for T3 and high probability	All single-detector CTs	II
Hogg et al[113]	2006	Systematic review	Diagnostic accuracy of CT pulmonary angiogram	Systematic review 1966-2005; diagnostic studies used a diagnostic reference standard; follow-up studies used 6 wk to 3-mo follow-up as reference standard	13 diagnostic studies included showing sensitivity 89%, specificity 95%; 11 follow-up heterogeneous studies included showing false-negative rates ranging from 0.9% to 10.7%		III
Roy et al[114]	2005	Systematic review, meta-analysis	Assess the likelihood ratios of diagnostic strategies for PE, including CTA	Review of the literature from 1990-2003; composite endpoints used; strategies assessed included CTA alone and CTA with lower extremity ultrasound	9 CTA-alone studies identified a pooled LR-=0.11; 3 CTA with lower extremity ultrasound studies identified a pooled LR-=0.04		I

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Goodman et al[115]	2000	Prospective inpatients and outpatients	Single detector CT	1- and 3-mo follow-up by pulmonologist	N=285 had negative CT result; 198 of 285 (69.5%) completed the 3-mo follow-up; 24 (8.4%) were lost to follow-up; 63 (22.1%) received anticoagulation; of 527, VQ results were negative or low probability; 115 (21.8%) had ultrasound, and 5 (0.9%) had angiogram; 350 of 527 patients (66.4%) completed 3-mo follow-up, 188 normal scans and 162 low-probability scans, and 73 (13.8%) were lost to follow-up; 104 of 527 (19.7%) received anticoagulation, 4 patients with low-probability VQ who had PE diagnosed by other imaging within 24 h were not included; subsequent PE in 2 (1%) of 198 patients who had negative CT result and in 5 (1.4%) of patients who had normal or low-probability VQ result; during follow-up there were more deaths in the CT group 34 (17.2%) than VQ 20 (5.7%)	Combined ultrasound in nonreproducible means; CT performed among patients with abnormal chest radiograph result who were more likely to have another cause for their symptoms; imaging was not systematically performed; only reviewed cases of diagnosed subsequent PE or DVT that resulted in treatment; could have interviewed family or referring physician as in other studies; patients lost to follow-up were dropped from the study; 5 (21%) ED patients were lost to follow-up; outcome measured with knowledge of risk factor; patients who received CT were more likely to die	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Swensen et al[116]	2002	Retrospective inpatients and outpatients	Single-detector CT	3-mo follow-up for PE	8 patients (0.5%, 0.2% to 1%) found to have DVT or PE within 3 mo after a negative CT result, 3 (37.5%) of these patients died	If patients received anticoagulation for PE but on clinical basis alone, they were not included; 17 patients who received anticoagulation despite a negative CT result were not included; patients receiving anticoagulation for a short period while awaiting completion of their studies were not included (and these were the higher-risk patients); only 34 of 118 deaths had autopsy; 19 patients lost to follow-up	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Donato et al[117]	2003	Retrospective inpatients and outpatients	Multidetector CT	3 mo or more for PE	N=243 with negative CT result and no anticoagulation; 233 (96%) had records obtained and reviewed (68% ED, 21% inpatient, 7% outpatient, 3% ICU); follow-up available for 239 (98%); 33 patients (13.8%) died, 1 of the 33 was determined to be highly suspicious for PE; 4 (1.7%; 0% to 3.2%) of 239 were found to have PE at follow-up and 3 of the 4 died	Retrospective data review limited by absence of a control group; some patients had other tests such as VQ scan that made them lower risk at discharge, 4/50 (8%) VQs had normal or near-normal VQ result or higher risk if high probability such that they received anticoagulation and were excluded (did not add 2 patients with high probability VQ scan in study because they received anticoagulation); no comment on the number of autopsies of those who died; excluding those receiving anticoagulation for other reasons may also lead to the study sample being a healthier group; relied on family members for proportion of follow-up	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
van Strijen et al[118]	2003	Prospective inpatients and outpatients	Single-detector CT; serial ultrasound on days 0, 4, and 7 if CT normal or inconclusive	3-mo follow-up for VTE	510 patients; CT revealed PE in 124 (24.3%), normal in 248 (48.6%), alternative diagnosis in 130 (25.5%), and indeterminate in 8 patients (1.6%) ; serial venous ultrasound revealed DVT, 2 in patients with normal CT on day 1 and none on day 4 and 7; on 3-mo follow-up, overall mortality in patients with normal, alternative diagnosis, and indeterminate CT scans was 4%, 21.5%, and 0%, respectively; rates of 3-mo VTE in these 3 subgroups was 0.2%, 0.2 % and 0%, respectively with VTE mortality of 0%, 0.8%, and 0%; overall VTE mortality in patients with normal or alternative CT scan was 0.3%	Informed consent obtained in 512 (83.8%) of 611 eligible study patients; single-detector CT; no patients lost to follow-up; anticoagulation withheld if patient with no objective findings of VTE; 23% of patients with normal CT did not complete serial venous ultrasound; cause of death determined by adjudication committee and not by autopsy; unknown how many of the study patients were in the ED vs inhospital	II
Friera et al[119]	2004	Prospective	Withholding anticoagulation in patients with a negative CTA result for PE	9-mo VTE, death	209 patients; 53 patients (25.5%) had PE and were excluded; during 3-mo follow-up, 29 patients excluded for receiving anticoagulation therapy and 4 patients lost to follow-up; of the final 99 study patients 9% died from non-VTE causes; no VTE occurred during follow-up	Low N; only 1 autopsy performed; 29 patients excluded for receiving anticoagulation therapy during follow-up	III
Kavanagh et al[120]	2004	Prospective	Withholding anticoagulation in patients with a negative CTA result for PE	9-mo VTE, death	102 patients; 85 patients without PE; only 1 patient with VTE on follow-up	Low N; follow-up ranged from 4 to 13 mo	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Prologo et al[121]	2005	Prospective	Single-detector CT and multidetector CT	3- and 6-mo follow-up for VTE	N=221; 112 had single-detector CT and 109 had multidetector CT, patients with negative scan results followed up to 6 mo, if no VTE event recorded, then telephone survey at 3 and 6 mo; results: prevalence of PE: 10.4%; no comment but assumed 100% follow-up; 98 patients with negative single-detector CT results and none had VTE; 6 (6.1%) died of "unrelated" causes; 100 patients with negative multidetector CT results and 1 (1%) had PE, 1 (1%) had DVT, and 8 (8%) died of unrelated causes	Small sample size; retrospective; smaller prevalence of PE than in other studies; no comment as to how many patients had autopsy to confirm cause of death; variable follow-up from 3 to 6 mo; no comment but assumed 100% follow-up	III
Vigo et al[122]	2006	Prospective inpatients and outpatients	Multidetector CT combined with quantitative D-dimer	6-mo follow-up for VTE	N=279 patients with negative CT and positive D-dimer results, further workup positive for PE in 55 (19.7%); NPV of CT negative and D-dimer positive=79.6% (missed 5 patients with PE); sensitivity of CT alone as low as 83%; 257 patients with negative CT and negative D-dimer results followed for 6 mo, 3 lost to follow-up between 3 and 6 mo, 15 died after variable periods of time and 1 was confirmed to have PE soon after initial evaluation, 9 developed symptoms concerning for VTE and 3 of these were proven to have VTE; rate of VTE after negative CT and negative D-dimer results=1.17% (0.24% to 3.38%)	Did not define uneventful follow-up; no autopsy rates for patients who died; by studying patients at the time of the negative CT result they did not necessarily evaluate the implication of discharging these patients off of anticoagulation; excluded patients with positive ultrasound results; different D-dimer assays were used at different centers	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Subramaniam et al[123]	2007	Prospective nonlow clinical-risk inpatients and outpatients	Single-detector CT	3-mo follow-up for VTE	321 of 381 patients had direct patient interview and 60 patients had their primary care provider contacted; 14 (3.7%; 2.2% to 6.1%) patients underwent another CT pulmonary angiogram for new or progressive symptoms of suspected PE, and 8 (2.1%; 1.1% to 4.1%) underwent ultrasound; 1 patient was diagnosed with DVT and none with PE; 38 (10%; 7.4% to 13.4%) died (14 of the 38 within 10 days); only 2 patients had autopsy and only 1 was diagnosed with PE; VTE event rate=0.52% (0.14% to 1.89%) within 3 mo; NPV=99.5% (98.1% to 99.9%)	Positive D-dimer result is not analogous to moderate or high risk; 36 patients excluded for receiving lower extremity ultrasound before CT for symptoms concerning for DVT and 6 were positive; 6 with negative CT results were lost to follow-up and were excluded from the sample; 60 patients were not contacted directly during follow-up; 38 patients died and only 2 had autopsy; rate of subsequent VTE does not match that of previous studies with higher clinical risk patients	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Elias et al[124]	2004	Prospective observational design	Pretest probability, D-dimer, VQ scan, venous ultrasound and 3-mo follow-up performed in all patients; pulmonary angiogram was performed in cases in which PE diagnosis was inconclusive after pretest probability, D-dimer, and VQ testing results were inconclusive	PE diagnosed by positive high-probability VQ scan result plus high clinical probability, positive pulmonary angiogram result, or positive VTE result at 3-mo follow-up	210 patients enrolled with 96 (45.7%) (95% CI 38.8% to 52.7%) diagnosed with PE; positive venous ultrasound: 91/210 (LR+=5.7) (95% CI 4.4 to 6.9)	CT scanner: single detector; included inpatients and outpatients; venous ultrasound administered to all patients regardless of pretest probability; results for venous ultrasound testing in patient with negative CTA result not available	II
Le Gal et al[125]	2006	Prospective multicenter (3 sites) observational design	Pretest probability, D-dimer, CTA, venous ultrasound, and 3-mo follow-up	PE diagnosed by positive CTA, positive venous ultrasound, or positive VTE result at 3-mo follow-up	756 patients enrolled with 195 (25.8%) (95% CI 22.7% to 29.1%) diagnosed with PE; positive CTA: 187/524 (35.7%) (95% CI 31.6% to 40.0%); negative CTA and positive venous ultrasound result: 3/337 (0.9%) (95% CI 0.2% to 2.6%)	CT scanner: type not identified; not clear whether included inpatients; follow-up not well delineated	II
Au et al[126]	2001	Prospective observational design	CTA followed by CTV and venous ultrasound	PE diagnosed by positive CTA, positive CTV, or positive venous ultrasound result	50 patients enrolled; positive PE=18/50 (36%) (95% CI 23.0% to 50.8%); positive CTA: 12/50 (24%) (95% CI 13.1% to 38.2%); negative CTA and positive CTV: 3/38 (7.9%) (95% CI 1.7% to 21.4%); negative CTA and positive venous ultrasound: 1/38 (2.6%) (95% CI 0.1% to 13.8%)	CT scan: high speed; included inpatients and outpatients referred to radiology for CTA with clinically suspected PE; no pretest probability testing or follow-up	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Coche et al[127]	2001	Prospective observational study	CTA followed by CT venogram and venous ultrasound	PE diagnosed by positive CTA, positive CT venogram, or positive venous ultrasound result	65 patients enrolled; positive PE=25/65 (38.5%) (95% CI 26.7% to 51.4%); negative CTA and positive CT venogram: 2/43 (4.7%) (95% CI 0.6% to 15.8%); negative CTA and positive venous ultrasound: 1/43 (2.3%) (95% CI 0.1% to 12.3%)	CT scanner: double detector array; included inpatients and outpatients; 7/65 were from the ED referred to radiology for CTA with clinically suspected PE; no pretest probability testing or follow-up	III
Begemann et al[128]	2003	Prospective observational study	CTA followed by CT venogram	PE diagnosed by positive CTA or positive CT venogram result	41 patients enrolled; positive PE=20/41 (48.8%) (95% CI 32.9% to 64.9%); positive CTA: 20/41 (48.8%) (95% CI 32.9% to 64.9%); negative CTA and positive CTV: 0/21 (0.0%) (95% CI 0.0% to 16.1%)	CT scanner: 4-row multidetector scanner; included inpatients and outpatients; there was no 3-mo follow-up; excluded patients age <50 y	III
Johnson et al[129]	2006	Retrospective study design	CTA followed by CT venogram	PE diagnosed by positive CTA, positive CT venogram result	427 patients enrolled; positive PE=41/427 (9.6%) (95% CI 7.0% to 12.8%); positive CTA: 40/427 (9.4%) (95% CI 6.8% to 12.5%); negative CTA and positive CTV: 1/387 (0.3%) (95% CI 0.01% to 1.4%)	CT scanner: 4-row multidetector; retrospective design; included inpatients and outpatients referred to radiology for CTA with clinically suspected PE; no pretest probability testing or follow-up	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/ Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Loud et al[130]	2001	Retrospective multicenter (2 sites); observational design	CTA followed by CT venogram	PE diagnosed by positive CTA, positive CT venogram result	650 patients enrolled; positive PE=116/650 (17.9%) (95% CI 15.0%); positive CTA: 85/650 (13.1%) (95% CI 10.6% to 15.9%); negative CTA and positive CT venogram: 31/565 (5.5%) (95% CI 3.8% to 7.7%)	CT scanner: high speed; the 2 sites used slightly different protocols when performing the CT scans; retrospective design; included inpatients and outpatients referred to radiology for CTA with clinically suspected PE; no pretest probability testing or follow-up	III
Goodman et al[133]	2007	Substudy analysis of a prospective multicenter study	CT angiogram, CT venogram, and venous ultrasound	PE diagnosed by a composite reference standard requiring 1 of the following: high-probability VQ scan, positive pulmonary arteriogram, positive CT venogram, or positive venous ultrasound result	711 patients underwent CT angiogram, CT venogram, and venous ultrasound; positive CT venogram and positive venous ultrasound in 81 of 711 (11%) patients; positive CT venogram result and negative venous ultrasound result in 17 (2%) patients; negative CT venogram result and positive venous ultrasound result in 15 (2%) patients	CT scanner: single detector; included inpatients and outpatients; venous ultrasound administered to all patients regardless of pretest probability; results for venous ultrasound testing in patients with negative CTA not available	II
Konstantinides et al[144]	1998	Nonrandomized open label trial	Alteplase plus heparin vs heparin	Pulmonary artery systolic pressure; end-diastolic dimensions of right ventricle on ECHO	40 patients; 27 alteplase, 13 heparin; pulmonary artery pressure decreased more at 12 h in alteplase group (19 vs 4; P=0.02); ECHO demonstrated greater early improvements in alteplase group but by 1 wk, no differences were seen on ECHO between the 2 groups	Nonrandomized; small sample size; improvements in pulmonary artery pressure and ECHO may not be clinically relevant	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Dalla-Volta et al[146]	1992	Randomized multicenter open label trial	Alteplase plus heparin vs heparin	Primary outcomes: mean vascular obstruction as assessed by angiogram Miller index; secondary outcomes: mortality, bleeding, recurrent PE	36 patients; 20 alteplase and 16 heparin; mean vascular obstruction assessed by pulmonary angiogram decreased significantly in the alteplase-treated group vs heparin group at 2 h (28.3 to 24.8; $P<0.01$ vs 25.3 to 25.2; P=NS); mean pulmonary artery pressure decreased significantly in the alteplase group in mmHg (30.2 to 21.4; $P<0.01$ vs 22.3 to 24.8; P=NS); lung scanning at 7 and 30 days found no differences in perfusion in a subset of patients with available data; bleeding occurred in 14 of 20 patients in alteplase group vs 6 of 16 in heparin group (P=NS)	Small sample size; method of randomization not described; patients with shock excluded; lack of blinding; findings on pulmonary vascular obstruction and pulmonary artery pressure at 2 h may not be clinically relevant; study not powered to detect differences in patient mortality and morbidity; used in meta-analysis by Dong et al,[162] Wan et al,[161] and Agnelli et al[159]	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Goldhaber et al[147]	1993	Single-center randomized, open label trial; single blinded for interpretation of ECHO and lung scanning	Alteplase plus heparin vs heparin	Primary outcomes: RV wall motion and RV end-diastolic area at 3 h and 24 h; lung scanning at baseline and 24 h; secondary outcome: 14-day recurrent PEs	101 patients; 46 in alteplase group, 55 in heparin group; RV wall motion improved in 39% of alteplase group vs 17% in heparin group, and worsened in 2% and 17%, respectively (P=0.005); alteplase patients also had significant decrease in RV end-diastolic area and improvement in pulmonary perfusion (14.6% vs 1.5%); recurrent PE or death occurred in 5 heparin patients and in no alteplase patients (P=0.06); all 5 patients with recurrent PE or death had RV hypokinesis on baseline ECHO	Only hemodynamically stable patients included; study not designed to detect differences in recurrent PE or mortality; unknown whether improvement in RV function and perfusion is clinically relevant; 3 of 5 patients in heparin group with recurrent PE treated with thrombolytics; used in meta-analysis by Dong et al,[162] Thabut et al,[160] Wan et al,[161] and Agnelli et al[159]	II
Levine et al[148]	1990	Multicenter, randomized, double-blinded, placebo-controlled trial	Alteplase plus heparin vs heparin plus placebo	Primary endpoints: relative improvement of perfusion lung scan of 50% at 24 h and 7 days compared with baseline scan; secondary endpoints: bleeding, mortality, and recurrent PE	58 patients; 33 in alteplase and 25 placebo; 34% alteplase patients had improvements in perfusion at 24 h vs 12% in placebo group (P=0.026); by day 7, no differences were seen in perfusion; there were no differences in major bleeding, mortality, or recurrent PE	Small sample size; patients with hypotension excluded; improvement in perfusion at 24 h may not be clinically relevant because perfusion was the same at 7 days; used in meta-analysis by Dong et al,[162] Thabut et al,[160] Wan et al,[161] and Agnelli et al[159]	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Ly et al[149]	1978	Single-center, randomized trial; single blinded for interpretation of pulmonary angiogram	Streptokinase for 72 h vs heparin	Primary outcome: perfusion as assessed by 72-h angiogram score; secondary outcomes: clinical improvement, clinical deterioration, death	25 patients; 14 in streptokinase group and 11 in control group; the mean 72-h angiogram score revealed a greater improvement in streptokinase group (52.2% vs 20.6%; $P<0.01$)	Small sample size; patients with hypotension excluded; 5 patients were included who did not undergo randomization (4 in streptokinase group and 1 in heparin group); 72-h improvement in angiogram scores may not be clinically relevant; study not powered to investigate secondary endpoints; used in meta-analysis by Dong et al,[162] Thabut et al,[160] Wan et al,[161] and Agnelli et al[159]	III
PIOPED Investigators[150]	1990	Multicenter, double-blinded, randomized, placebo-controlled trial	Alteplase plus heparin vs heparin plus placebo	Primary outcomes: fragment D-dimer levels, total pulmonary vascular resistance at 1.5 h, angiogram at 2 h, and lung scanning at 24 h	13 patients; 9 alteplase and 4 placebo; modest improvement in pulmonary vascular resistance at 1.5 h and no improvement in angiogram scores; at 24 h there was a trend toward great improvement in perfusion in alteplase group	Small sample size; lack of clinically relevant outcome measures; heparin dose not standardized (at discretion of attending physician); used in meta-analysis by Dong et al,[162] Thabut et al,[160] Wan et al,[161] and Agnelli et al[159]	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
UPET Investigators[151]	1970	Multicenter randomized controlled trial; "modified" double blinded (physician administering study drug and laboratory personnel analyzing blood samples not blinded)	Urokinase for 12 h followed by heparin vs heparin	Primary outcomes: pulmonary angiogram scores, hemodynamic measurements, lung scanning; secondary outcomes: complications, mortality, morbidity	160 patients; 82 urokinase and 78 heparin; 53% of urokinase patients demonstrated moderate or greater improvement in 24-h angiogram scores compared with 9% in heparin group; mean hemodynamic abnormalities significantly improved for urokinase patients compared with heparin patients; 24-h lung scanning revealed degree of resolution of initial lesion of 22.1% in urokinase group vs 8.1% in heparin group though no differences were seen by day 14; no differences in mortality or recurrent PE between 2 treatment groups; patients in shock and patients with previous history of cardio-pulmonary disease had a trend for greater improvements with urokinase; urokinase patients had higher rates of major bleeding complications compared with heparin patients (45% vs 27%)	Only 14 patients had shock, thus preventing conclusion about whether urokinase is more effective in this subgroup; primary outcomes may not be clinically relevant; the primary statistical test used for data analysis was relative betting odds; statistical analysis not provided for a significant proportion of results presented; used in meta-analysis by Dong et al,[162] Thabut et al,[160] Wan et al,[161] and Agnelli et al[159]	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Konstantinides et al[152]	2002	Multicenter, randomized, double-blinded, placebo-controlled trial	Alteplase plus heparin vs heparin plus placebo	Primary endpoint was inhospital death or clinical deterioration that required an escalation of treatment (catecholamines, secondary thrombolysis), intubation, CPR, surgical embolectomy); secondary endpoints were recurrent PE, major bleeding, and ischemic stroke	256 patients; 118 alteplase and 138 placebo; the primary endpoint occurred in 11.0% of alteplase patients vs 24.6% of heparin patients (P=0.006); of the individual components of all of the individual primary endpoints, the only significant difference was seen in secondary thrombolysis (7.6% vs 23.2%; P=0.001); there were no differences in secondary endpoint	Patients with hypotension were excluded; the fact that randomization code was allowed to be broken before decision of whether to administer thrombolytics seriously calls into question the principal findings of this study because patients who initially are treated with alteplase are less likely to receive secondary thrombolysis; excluding the findings about escalation of treatment, the evidence provided in this study (contrary to investigators' conclusions) suggests that thrombolytics are not routinely indicated in hemodynamically stable patients; used in meta-analysis by Dong et al[162] and Wan et al[161]	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Dotter et al[153]	1979	Randomized open label trial	Intravenous streptokinase for 18-72 h, followed by heparin vs heparin	Angiogram scores pre- and post-treatment	31 patients (15 streptokinase and 16 heparin); patients in streptokinase group had significantly greater improvement in angiogram score than heparin group (2.08 vs 0.86; *P*=0.013); no differences seen in morbidity or mortality though study not designed or powered to investigate differences	Angiogram scores may not be clinically relevant; no report of method of randomization, how treatment allocation was concealed, or numbers of dropouts; repeated pulmonary angiogram was not uniform because it was "performed as soon after streptokinase therapy or 72 h of heparin therapy as the patient's clinical status permitted, usually on the fourth treatment day (range 2 to 5 days)"; only 1 patient with hypotension in each group; emboli were 24 h old or less in 5 streptokinase and 9 heparin patients; in "many patients" administration of heparin had already been started in streptokinase patients and had to be stopped during streptokinase infusion; used in meta-analysis of Wan et al[161] and Agnelli et al[159]	X

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Jerjes-Sanchez et al[154]	1995	Randomized open-label trial	Streptokinase over 1 h followed by heparin vs heparin	Mortality	Mortality was 0% in streptokinase group vs 100% in heparin group	Only 8 patients (original size of study 40 patients but terminated after 4 deaths in heparin group at recommendation of ethics committee); all 8 patients had systolic BP <90 mm Hg although hypotension alone was not a study requirement; patients in streptokinase group presented to study hospital within 1-4 h after symptom onset; all 4 patients in heparin group were admitted by an outlying hospital after sustaining a "minor PE" and transferred to study hospital 2 to 4 h after sustaining a massive PE requiring mechanical ventilation (mean time from first PE to study enrollment was 2.5 h in streptokinase group vs 34.8 h in heparin group); PE was not confirmed in all patients; used in meta-analysis of Wan et al,[161] Thabut et al,[160] and Agnelli et al[159]	X

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Marini et al[155]	1988	Prospective randomized open label trial	Heparin vs urokinase alone (2 doses of urokinase used)	Fibrinogen plasma concentration; resolution of PE on lung scanning	10 patients each group; 20 urokinase and 10 heparin; no differences were seen in lung perfusion and gas exchange recovery or in pulmonary artery pressure; no deaths or recurrent PE noted in study patients at 1 y; no major bleeding	Small sample size; methods for enrollment, randomization, and concealment are not clear; doses of urokinase used in 2 thrombolytic treatment arms are not standard doses; the fact that 10 patients were in each of the 3 treatment groups suggests that this study did not use true randomization, but rather a 1:1:1 selection randomization; outcomes may not be clinically relevant; used in meta-analysis of Thabut et al,[160] Wan et al,[161] and Agnelli et al[159]	X

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Tibbutt et al[156]	1974	Two-center, randomized open label trial; single blinded for analysis of angiographs	Streptokinase for 72 h through pulmonary artery catheter vs heparin	Primary outcome: pulmonary perfusion as measured by Miller angiography score; secondary outcomes: right atrial, right ventricular, and pulmonary arterial phasic and mean pressure measurements, oxygen saturation, cardiac index, and other hemodynamic measurements "if patient's condition allowed"	30 patients (17 streptokinase and 13 heparin); patients treated with streptokinase had greater improvements in degree of thrombolysis (13.3 vs 2.8; $P<.001$) and in systolic (15.4 vs 3.8; $P<0.05$) and mean pulmonary arterial pressure (12.3 vs 4.8; $P<0.02$)	Small sample size and lack of clinically relevant outcome measures limit conclusion; streptokinase infused over 72 h through pulmonary artery catheter cannot be assumed to be equivalent to IV thrombolytic therapy; 7 patients (23.3%; 5 streptokinase and 2 heparin) failed to complete 72 h of trial treatment and thus are not included in results (1 death and 6 with clinical deterioration; 4 of the deteriorating patients underwent successful embolectomy); 9 patients did not undergo pulmonary arterial systolic pressure measurements, and 13 patients did not have mean pulmonary arterial pressure measurements at baseline and 72 h; used in meta-analysis by Dong et al,[162] Wan et al,[161] and Agnelli et al[159]	X

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Becattini et al[157]	2010	Multicenter, randomized, double-blinded, placebo-controlled trial	Tenecteplase plus heparin vs placebo plus heparin	Primary outcome: RV dysfunction assessed by echocardiography at 24 h; secondary efficacy outcomes: RV dysfunction at 7 days, clinical deterioration within 7 days requiring escalation of treatment, 30-day recurrent PE or death; secondary safety outcomes: serious bleeding and serious adverse events within 7 days	58 patients (28 tenecteplase, 30 placebo); reduction in right to left ventricle end-diastolic dimension ratio at 24 h was 0.31+0.08 in tenecteplase group vs 0.10+0.07 in placebo group (P=0.04); no statistical differences in secondary efficacy or safety outcome variables	Small N; improvement in RV dysfunction is only statistically significant finding; however, only 51 patients had echocardiography data (23 tenecteplase, 28 placebo, dropout of 18% tenecteplase vs 7% of placebo); feasibility study not powered to detect differences in any of the secondary outcome variables; study prematurely terminated because of startup of the PEITHO trial; unknown whether improvement in RV dysfunction clinically relevant; inclusion criteria included patients up to 10 days after symptom onset	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Agnelli et al[159]	2002	Meta-analysis of 9 randomized studies	Thrombolytic therapy (with or without heparin) vs heparin	Composite endpoint of death, recurrent PE, and major bleeding events	461 patients; 241 patients in thrombolysis group vs 220 patients in heparin group; there was no difference in the composite endpoint of death, recurrent PE, and major bleeding events for thrombolysis vs heparin (23.2% vs 25.9%; RR 0.9; 95% CI 0.57-1.32); there was no difference in the individual components of the composite endpoints; there was a difference in composite of death or reoccurrence (10.4% for thrombolysis group vs. 17.3% in heparin group; RR 0.55; 95% CI 0.33-0.96); authors conclude that outcome trial is warranted in patients at high risk for death or reoccurrence	Only 2 of 9 trials (15.4% of patients) were double blinded; studies used 3 different thrombolytic agents; there were also multiple different doses and regimens within the individual thrombolytic agents; only 6 studies reported reoccurrence rates; low rate of death in heparin group suggests that patients in these studies were at low-risk for adverse outcome; majority of studies included were designed to compare the effect of thrombolysis on rate of lung reperfusion and not on adverse outcome; this meta-analysis was given an "X" primarily because it did not use fixed-effects or random-effects model for the meta-analyses; authors simply added all outcomes together for total, did not treat each study as a unit of analysis; also, 3 of 9 investigations used in this meta-analyses were given a grade of X by this subcommittee	X

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Thabut et al[160]	2002	Meta-analysis of 9 randomized trials	Thrombolytics (with or without heparin) vs heparin	Mortality, recurrent PE, and major hemorrhage	461 patients; 223 thrombolytics and 205 heparin; thrombolytic therapy had no effect on mortality (RR 0.63; 95% CI 0.32-1.23) or recurrent PE (RR 0.59; 95% CI 0.3 to 1.2); patients treated with thrombolytic therapy had greater risk of major hemorrhage (RR 1.76; 95% CI 1.04 to 2.98); the authors conclude that thrombolytic therapy does not appear to have therapeutic benefit in unselected patients with acute PE	Studies very heterogeneous with 3 different thrombolytic agents used in various dosages and regimens; 5 studies excluded hypotensive patients; outcome variables also vary with death being only outcome variable that could be calculated for all studies; low rate of death in heparin group suggests that majority of patients in these studies were at low risk for adverse outcome; many of the studies included were designed to compare the effect of thrombolytics on rate of lung reperfusion or hemodynamic variables and not on clinically relevant adverse outcome; 3 of 9 studies included in this meta-analyses were given a grade of X	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Wan et al[161]	2004	Meta-analysis of 11 randomized controlled trials	Thrombolytic therapy (with or without heparin) vs heparin	Primary outcome: death, recurrent PE, major bleeding; secondary outcome: nonmajor bleeding	748 patients; 374 thrombolytic patients and 374 heparin; thrombolytic therapy was associated with nonsignificant reduction in recurrent PE and death and a nonsignificant increase in major bleeding and significant increase in nonmajor bleeding (22.7% vs 10.0%; OR 2.63; 95% CI 1.53-4.54); in trials that also enrolled patients with hemodynamic instability, thrombolytic therapy was associated with a significant reduction in recurrent PE or death (9.4% vs 19.0%; OR 0.45; 95% CI 0.22 to 0.92), but not in trials that excluded these patients (5.3% vs 4.8%; OR 1.07; 95% CI 0.5 to 2.3)	Studies very heterogeneous with 3 different thrombolytic agents used in various dosages and regimens; outcome variables also vary with death being only outcome variable that could be calculated for all studies; low rate of death in heparin group suggests that majority of patients in these studies were at low risk for adverse outcome; many of the studies included were designed to compare the effect of thrombolysis on rate of lung reperfusion or hemodynamic variables and not on clinically relevant adverse outcome; data does support authors' conclusion that thrombolytic therapy is not indicated in unselected patients with PE; included 4 studies given a grade of X by this subcommittee; the results of subset analysis of the 5 trials that included patients with hemodynamic instability are suspect because 3 of these investigations were given a grade of X (see text for discussion)	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Dong et al[162]	2006	Cochran review; meta-analysis of randomized controlled trial	Thrombolytic therapy (with or without heparin) vs heparin	Primary outcome: death, recurrent PE, hemorrhage; secondary outcomes: hemodynamics as assessed by perfusion, angiogram, and/or ECHO	8 randomized trials with 679 total patients; no differences in primary outcomes for thrombolytics vs heparin for death rate (OR 0.89; 95% CI 0.45-1.78), recurrent PE (OR 0.63; 95% CI 0.33-1.2), major hemorrhage (OR 1.61; 95% CI 0.91-2.86), or minor hemorrhage (OR 1.98; 95% CI 0.68-5.75); thrombolytics improved hemodynamics though studies were inconsistent when hemodynamic parameters were investigated; improvements were also seen in perfusion lung scanning at 1-2 days (though these differences disappeared on follow-up lung scanning at 5 days, 14 days, and 1 y) and 72-h pulmonary lung assessment; no differences were seen in major hemorrhagic events	Studies very heterogeneous with 3 different thrombolytic agents used in various dosages and regimens; outcome variables also vary with death being the only outcome variable that could be calculated for all studies; low rate of death in heparin group suggests that majority of patients in these studies were at low risk for adverse outcome (the authors recommend a large study be performed in patients with hemodynamic instability); many of the studies included were designed to compare the effect of thrombolysis on the rate of lung reperfusion or hemodynamic variables and not on clinically relevant adverse outcome; 1 of the 10 studies used in this meta-analysis was given an X (Table 8)	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Nakamura et al[164]	2005	Multicenter registry in Japan	Thrombolytic therapy vs heparin	Primary outcomes: death and recurrent PE; secondary outcomes: major bleeding complications	221 patients, 121 thrombolytics and 100 heparin; no difference in outcome seen in hemodynamically stable patients; no difference in outcome in patients with right ventricular afterload stress on echo who were treated with thrombolytics (death: 5% vs 13%; *P*=0.28; recurrent PE: 20% vs 10%; *P*=0.36)	Nonrandomized, retrospective analysis of registry data; treatment at discretion of treating physician; study not powered to study primary and secondary outcomes; authors' conclusion that patients with RV afterload stress should receive consideration for thrombolytic therapy is unjustified based on findings reported in article; data support finding that no subgroup benefits from thrombolytic therapy	III
Wolfe et al[165]	1994	Retrospective analysis of 1993 Goldhaber et al study in hemodynamically stable patients	ECHO: perfusion lung scanning	RV hypokinesis on baseline ECHO; defects on baseline perfusion lung scanning	90 patients; 38 patients had RV hypokinesis; patients with RV hypokinesis had greater perfusion defects; all patients with recurrent PE were in the subgroup with RV hypokinesis; authors conclude that RV hypokinesis on ECHO may select a subgroup of hemodynamically stable patients who may benefit from thrombolytic therapy	Did not investigate outcome for thrombolytic vs heparin (lumped all patients into 1 subgroup); clinical endpoints may not be clinically relevant; data does demonstrate that hemodynamically stable patients with RV hypokinesis on ECHO are at higher risk of adverse outcome, though there are no data to suggest that these patients will benefit from thrombolytics	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Rose et al[171]	2002	Retrospective analysis of patients with right heart thromboemboli	Heparin vs thrombolysis vs surgical embolectomy	Mortality	177 patients; treatments administered were no treatment (9%), heparin (35%), thrombolytic therapy (19.8%), and embolectomy; mortality was 100%, 28.6%, 23.8%, and 11.3%, respectively; on multivariate analysis, only thrombolytic therapy ($P<0.05$) was associated with a decreased mortality	Patient population nonrandomized; significant selection bias because patient population derived from 95 reports that either consisted of case reports or case series; small N for each subgroup; data suggest that thrombolytics should be considered in patients with right heart thrombus on ECHO	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Konstantinides et al[173]	1997	Observational registry of 204 centers in Germany (Management Strategy and Prognosis of Pulmonary Embolism Registry)	Thrombolytic therapy vs no thrombolytic therapy during initial 24 h of hospitalization	Primary endpoint 30-day mortality; recurrent PE, major bleeding complications	719 "consecutive" hemodynamically stable patients with major PE; 23.5% of patients treated initially with thrombolytics; patients receiving thrombolytics had lower mortality (4.7% vs 11.1%; P=0.16); clinical factors associated with higher mortality were syncope, hypotension, history of CHF, history of COPD; multivariate analysis revealed that primary thrombolytics was the only independent predictor of survival (OR 0.46; 95% CI 0.21 to 1.0); patient also receiving thrombolytics had reduced rate of recurrent PE (7.7% vs 18.7%; P< 0.001) and higher rates of major bleeding (21.9% vs 7.8%; P<0.001)	Retrospective analysis of registry data; patients not consecutive (see comments above); decision to administer thrombolytics not randomized; thrombolytic treatment at discretion of treating physician; patients receiving thrombolytics were younger and less likely to have history of pre-existing pulmonary or cardiovascular disease, which by itself may explain differences in mortality	III

ABG, arterial blood gas; *AUC*, area under the curve; *BP*, blood pressure; *CHF*, congestive heart failure; *CI*, confidence interval; *COPD*, chronic obstructive pulmonary disease; *CPR*, cardiopulmonary resuscitation; *CT*, computed tomography; *CTA*, computed tomography angiogram; *CTPA*, computed tomography pulmonary angiogram; *CTV*, computed tomography venogram; *DVT*, deep venous thrombosis; *ECG*, electrocardiogram; *ECHO*, echocardiogram; *ED*, emergency department; *ELFA*, enzyme-linked immunofluorescence assay; *ELISA*, enzyme-linked immunosorbent assay; *h*, hour; *IV*, intravenous; *LR-*, negative likelihood ratio; *LR+*, positive likelihood ratio; *min*, minute; *mo*, month; *NPV*, negative predictive value; *NS*, not significant; *OR*, odds ratio; *PE*, pulmonary embolism; *PEITHO*, Pulmonary Embolism Thrombolysis Study; *PERC*, Pulmonary Embolism Rule-out Criteria; *PIOPED*, Prospective Investigation of Pulmonary Embolism Diagnosis; *PGY*, postgraduate year; *PPV*, positive predictive value; *ROC*, receiver operating characteristic; *RR*, relative risk; *RV*, right ventricular; SaO_2, arterial blood oxygen saturation; *VQ*, ventilation-perfusion; *vs*, versus; *VTE*, venous thromboembolism; *wk*, week; *y*, year.