Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department With Suspected Acute Venous Thromboembolic Disease

From the American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Thromboembolic Disease:
Stephen J. Wolf, MD (Subcommittee Chair; Committee Co-Chair)
Sigrid A. Hahn, MD, MPH
Lauren M. Nentwich, MD
Ali S. Raja, MD, MBA, MPH
Scott M. Silvers, MD
Michael D. Brown, MD, MSc (Committee Co-Chair)

Members of the American College of Emergency Physicians Clinical Policies Committee (Oversight Committee):

Michael D. Brown, MD, MSc (Chair 2014-2017; Co-Chair 2017-2018)
Stephen J. Wolf, MD (Co-Chair 2017-2018)
Richard Byyny, MD, MSc (Methodologist)
Deborah B. Diercks, MD, MSc
Seth R. Gemme, MD
Charles J. Gerardo, MD, MHS
Steven A. Godwin, MD
Sigrid A. Hahn, MD, MPH
Nicholas E. Harrison, MD (EMRA Representative 2017-2018)
Benjamin W. Hatten, MD, MPH
Jason S. Haukoos, MD, MSc (Methodologist)
Amy Kaji, MD, MPH, PhD (Methodologist)
Heemun Kwok, MD, MS (Methodologist)
Bruce M. Lo, MD, MBA, RDMS
Sharon E. Mace, MD
Devorah J. Nazarian, MD
Jean A. Proehl, RN, MN, CEN, CPEN, TCRN (ENA Representative 2015-2018)
Susan B. Promes, MD, MBA
Kaushal H. Shah, MD
Richard D. Shih, MD
Scott M. Silvers, MD
Michael D. Smith, MD, MBA
Molly E. W. Thiessen, MD
Christian A. Tomaszewski, MD, MS, MBA
Jonathan H. Valente, MD
Stephen P. Wall, MD, MSc, MAEd (Methodologist)
Stephen V. Cantrill, MD (Liaison with Quality and Patient Safety Committee, and E-QUAL Steering Committee)
Jon Mark Hirshon, MD, PhD, MPH (Board Liaison 2016-2018)
Travis Schulz, MLS, AHIP, Staff Liaison, Clinical Policies Committee
Rhonda R. Whitson, RHIA, Staff Liaison, Clinical Policies Committee and Subcommittee Revising the Venous Thromboembolic Disease Policy

Approved by the ACEP Board of Directors, February 8, 2018

Endorsed by the Emergency Nurses Association, March 20, 2018

0196-0644/$-see front matter

https://doi.org/10.1016/j.annemergmed.2018.03.006

[Ann Emerg Med. 2018;71:e59-e109.]

ABSTRACT

This clinical policy from the American College of Emergency Physicians addresses key issues in the evaluation and management of adult patients with suspected venous thromboembolism. A writing subcommittee conducted a systematic review of the literature to derive evidence-based recommendations to answer the following clinical questions: (1) In adult patients with suspected acute pulmonary embolism, can a clinical prediction rule be used to identify a group of patients at very low risk for the diagnosis of pulmonary embolism for whom no additional diagnostic workup is required? (2) In adult patients with low to intermediate pretest probability for acute pulmonary embolism, does a negative age-adjusted D-dimer result identify a group of patients at very low risk for the diagnosis of pulmonary embolism for whom no additional diagnostic workup is required? (3) In adult patients with subsegmental pulmonary embolism, is it safe to withhold anticoagulation? (4) In adult patients diagnosed with acute pulmonary embolism, is initiation of anticoagulation and discharge from the emergency department safe? (5) In adult patients diagnosed with acute lower-extremity deep venous thrombosis who are discharged from the ED, is treatment with a non–vitamin K antagonist oral anticoagulant safe and effective compared with treatment with low-molecular-weight heparin and vitamin K antagonist? Evidence was graded and recommendations were made based on the strength of the available data.

INTRODUCTION

Venous thromboembolism (VTE), a coagulation disorder encompassing both deep venous thrombosis (DVT) and pulmonary embolism (PE), is a major public health problem.[1,2] Undiagnosed, untreated patients are believed to be at substantial risk for progressive disease and sudden death, typically because of worsening right-sided heart strain and, ultimately, cardiovascular collapse. Treated patients are at risk for chronic sequelae (eg, vein scarring, leg swelling, pulmonary hypertension) and adverse events from ongoing anticoagulation (eg, hemorrhage, medication adverse effects).

Although the true incidence of VTE is not known, reports estimate that 600,000 to 900,000 individuals per year (1 to 2 per 1,000) may be affected in the United States, a number that increases with patient age.[2-4] Others estimate that upwards of 294,000 fatal cases of PE occur in the United States annually, accounting for up to 10% of all hospital deaths.[5,6] In selected patient populations, VTE has been reported to have an associated mortality rate as low as 2%[7] and as high as 30%, which is primarily attributed to PE.[2,3,8]

One significant challenge to health care providers evaluating patients for VTE lies in the variability of signs and symptoms of the disease that are related to the clot burden, location, and the individual patient's cardiopulmonary reserve. Without perfect, cost-effective tests for the diagnosis, providers have come to rely on Bayesian decisionmaking to guide their workup, using pretest probability to interpret diagnostic evaluations and generate posttest probability of disease.[9,10] Doing this allows providers to maximize diagnostic accuracy while minimizing overtesting and patient harm from the risks associated with unnecessary evaluation and treatment.

Efforts to refine this Bayesian approach in emergency medicine have been ongoing. Original studies to determine pretest probability and the accuracy of various screening tests[11-13] have been validated, and the limits of their efficacy are being explored.[14] These structured clinical prediction rules, whether diagnostic (eg, Pulmonary Embolism Rule-out Criteria [PERC], Wells criteria, revised Geneva score [RGS]), or prognostic (eg, Pulmonary Embolism Severity Index [PESI], Hestia criteria), offer an adjunct to gestalt clinical assessment to assist in risk stratification and determination of pretest probability (ie, low, intermediate, high, nonhigh, PE unlikely, PE likely) or predict prognosis. In consideration of the cost of evaluation, the risk of false positives, and the risk of complications related to testing, studies have supported using a predefined posttest probability threshold of less than 2.0% to exclude the diagnosis of VTE.[9,14-18] Last, substantial efforts are being made to advance the treatment of VTE by balancing outcomes, anticoagulation risks to patients, and patient preferences. New non–vitamin K antagonist oral anticoagulants (NOACs) (aka novel oral anticoagulants, direct oral anticoagulants, and target-specific oral anticoagulants) directly bind to specific clotting factors (ie, IIa or Xa) to induce anticoagulation, and have been proposed as safer alternatives to vitamin K antagonists (VKAs) (ie, warfarin), which more broadly reduce circulating clotting factors (ie, II, VI, IX, and X). NOACs are particularly appealing for long-term anticoagulation because of their simple oral dosing regimens with no need for routine laboratory monitoring. Examples of approved NOACs include apixaban (Eliquis), dabigatran (Pradaxa), edoxaban (Savaysa), and rivaroxaban (Xarelto).

The 2011 American College of Emergency Physicians (ACEP) clinical policy on this topic focused on 6 critical questions: pretest probability and clinical assessment, utility

of the PERC, the diagnostic role of highly sensitive D-dimer assays, computed tomography (CT) pulmonary angiogram, CT venogram, and the therapeutic role of thrombolysis in hemodynamically stable and unstable patients with PE.[9]

This revision will focus on 5 areas of interest or controversy that have developed or still exist since the 2011 policy was formulated. The first 2 critical questions address the role of unique clinical prediction rules and age-adjusted D-dimer testing in the diagnosis of PE, whereas the remaining 3 questions focus on optimal treatment and disposition for individuals receiving a diagnosis of venous thromboembolic disease.

METHODOLOGY

This clinical policy is based on a systematic review with critical analysis of the medical literature meeting the inclusion criteria. Searches of MEDLINE, MEDLINE InProcess, SCOPUS, EMBASE, Web of Science, and the Cochrane Database of Systematic Reviews, were performed. All searches were limited to English-language sources, adults, and human studies. Specific key words/phrases, years used in the searches, dates of searches, and study selection 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 reviewers were included.

This policy is a product of the ACEP clinical policy development process, including internal and external review, and is based on the existing literature; when literature was not available, consensus of Clinical Policies Committee members was used and noted as such in the recommendation (ie, consensus recommendation). Review comments were received from emergency physicians and residents, internal and cardiovascular medicine physicians, a pharmaceutical industry representative, an advocate for patient safety, ACEP's Medical-Legal Committee, the American College of Chest Physicians, and a member of the American College of Physicians. Comments were received during a 60-day open-comment period, with notices of the comment period sent in an e-mail to ACEP members, published in *EM Today*, posted on the ACEP Web site, and sent to other pertinent physician organizations. The responses were used to further refine and enhance this clinical policy; however, responses do not imply endorsement. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology, methodology, or the practice environment changes significantly. ACEP was the funding source for this clinical policy.

Assessment of Classes of Evidence

Two methodologists independently graded and assigned a preliminary Class of Evidence for all articles used in the formulation of this clinical policy. Class of Evidence is delineated whereby an article with design 1 represents the strongest study design and subsequent design classes (ie, design 2 and design 3) represent respectively weaker study designs for therapeutic, diagnostic, or prognostic studies, or meta-analyses (Appendix A). Articles are then graded on dimensions related to the study's methodological features, such as randomization processes, blinding, allocation concealment, methods of data collection, outcome measures and their assessment, selection and misclassification biases, sample size, generalizability, data management, analyses, congruence of results and conclusions, and conflicts of interest. Using a predetermined process combining the study's design, methodological quality, and applicability to the critical question, articles received a Class of Evidence grade. An adjudication process involving discussion with the original methodologist graders and at least one additional methodologist was then used to address any discordance in original grading, resulting in a final Class of Evidence assignment (ie, Class I, Class II, Class III, or Class X) (Appendix B). Articles identified with fatal flaws or ultimately determined to not be applicable to the critical question received a Class of Evidence grade "X" and were not used in formulating recommendations for this policy. However, content in these articles may have been used to formulate the background and to inform expert consensus in the absence of robust evidence. Grading was done with respect to the specific critical questions; thus, the Class of Evidence for any one study may vary according to the question for which it is being considered. As such, it was possible for a single article to receive a different Class of Evidence rating when addressing a different critical question. Question-specific Classes of Evidence grading may be found in the Evidentiary Table included at the end of this policy.

Translation of Classes of Evidence to Recommendation Levels

Based on the strength of evidence grading for each critical question (ie, Evidentiary Table), the subcommittee drafted the recommendations and the supporting text synthesizing the evidence using the following guidelines:

Level A recommendations. Generally accepted principles for patient care that reflect a high degree of clinical certainty (eg, based on evidence from 1 or more

Class of Evidence I or multiple Class of Evidence II studies).

Level B recommendations. Recommendations for patient care that may identify a particular strategy or range of strategies that reflect moderate clinical certainty (eg, based on evidence from 1 or more Class of Evidence II studies or strong consensus of Class of Evidence III studies).

Level C recommendations. Recommendations for patient care that are based on evidence from Class of Evidence III studies or, in the absence of any adequate published literature, based on expert consensus. In instances where consensus recommendations are made, "consensus" is placed in parentheses at the end of the recommendation.

The recommendations and evidence synthesis were then reviewed and revised by the Clinical Policies Committee, which was informed by additional evidence or context gained from reviewers.

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 consistency of results, uncertainty about effect magnitude, and publication bias, among others, might lead to a downgrading of recommendations.

When possible, clinically oriented statistics (eg, likelihood ratios, number needed to treat) are presented to help the reader better understand how the results may be applied to the individual patient (Appendix C).

This policy is not intended to be a complete manual on the evaluation and management of patients with suspected or known acute VTE but rather a focused examination of critical issues that have particular relevance to the current practice of emergency medicine. Potential benefits and harms of implementing recommendations are briefly summarized within each critical question.

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 adequate empirical data 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.

This clinical policy is not intended to represent a legal standard of care for emergency physicians. Recommendations offered in this policy are not intended to represent the only diagnostic or management options available to the emergency physician. ACEP recognizes the importance of the individual physician's judgment and patient preferences. This guideline provides clinical strategies for which medical literature exists to answer the critical questions addressed in this policy.

Scope of Application. This guideline is intended for physicians working in emergency departments (EDs).

Inclusion Criteria. This guideline is intended for adult patients presenting to the ED with suspected or known acute VTE (ie, PE or DVT).

Exclusion Criteria. This guideline is not intended to address the care of pediatric patients, or those with VTE in the setting of cardiac arrest or pregnancy.

CRITICAL QUESTIONS

1. **In adult patients with suspected acute PE, can a clinical prediction rule be used to identify a group of patients at very low risk for the diagnosis of PE for whom no additional diagnostic workup is required?**

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. For patients who are at low risk for acute PE, use the PERC to exclude the diagnosis without further diagnostic testing.

Level C recommendations. None specified.

Potential Benefits of Implementing the Recommendations:

- Reduced test-related complications (eg, contrast-induced nephropathy, contrast-related allergic reactions, contrast infiltrations, radiation exposure)
- Reduced costs associated with less diagnostic testing
- Reduced time in the ED associated with less diagnostic testing
- Better use of health care resources
- Improved patient satisfaction as a result of more efficient evaluation

Potential Harms of Implementing the Recommendations:

- A small increase in the incidence of missed PE
- Misapplication of the recommendation to individuals with intermediate or high pretest probability of PE

Key words/phrases for literature searches: pulmonary embolism, acute pulmonary embolism, diagnosis, decision support techniques, clinical decision making, clinical decision support, clinical decision rule, evidence based medicine, hospital emergency service, risk assessment, rule-out, low-risk, and variations and combinations of the key words/phrases. Searches included January 1, 2006, to search date of April 22, 2016.

Study Selection: Forty-seven articles were identified in this search. Nineteen relevant articles were selected from

the search results for further methodological review and grading. Four Class II articles and 4 Class III articles were included for this critical question.

During the past 2 decades, clinical prediction rules have been derived and validated to assist in determination of pretest probability and subsequent Bayesian decisionmaking for the evaluation of patients with suspected PE.[19-24] Most have focused on identifying populations for appropriate use of a given diagnostic test (eg, the D-dimer).[19-23] In 2004, Kline et al[24] took a different approach by aiming to derive a clinical prediction rule that would be able to exclude the diagnosis of PE in low-risk patients *without* additional diagnostic testing. Conventionally, clinicians identify these low-risk patients by either clinical gestalt assessment (eg, pretest probability <15%) or a structured clinical prediction rule (eg, Wells score <2).[25] The derivation of the PERC was described in a Class II multicenter study[24] with 3,148 patients undergoing evaluation for PE. Twenty-one descriptive variables relevant to the diagnosis were prospectively collected and compared with a primary outcome of a composite criterion standard for the diagnosis of PE that included 90-day clinical follow-up. The overall prevalence of VTE was 11%. Logistic regression analysis was used to identify criteria that could predict a patient population estimated to have a prevalence of disease below 1.8%, at which point the diagnosis was considered reasonably excluded. Eight criteria were identified: younger than 50 years, pulse rate less than 100 beats/min, room air SaO_2 greater than 94% (at sea level), no recent trauma or surgery, no unilateral leg swelling, no previous PE or DVT, no hormone use, and no hemoptysis. The authors proposed that when all 8 criteria are met in patients at low risk for PE, a patient could be considered PERC negative and that further diagnostic workup for PE, including a D-dimer test, would be unnecessary. Since its derivation, 3 Class II[24,26,27] and 4 Class III[28-31] validation studies, along with 1 Class II meta-analysis[32] have been published on the criteria's performance. Data from these studies will be discussed as they relate to sample cohort pretest probability, which directly determines posttest probability after application of the criteria.

PERC Performance in Low-Risk Cohorts

As mentioned, the original study by Kline et al[24] derived the PERC in a low-pretest-probability cohort. This Class II study also included an independent validation cohort of 1,427 patients determined to be at low risk by clinical gestalt with an 8% prevalence of PE. Twenty-five percent of all patients were PERC negative, yielding a sensitivity, specificity, and negative likelihood ratio for the criteria of 96%, 27%, and 0.16, respectively. Therefore, with the overall 8% prevalence of PE as the pretest probability, it was estimated that the posttest probability for PE among the PERC-negative patients was 1.4%, which was below the a priori testing threshold. The authors concluded that in patients with low suspicion for PE who are PERC negative, the probability of PE is so low that further testing will not yield a favorable risk-benefit ratio.[24] In 2008, a second Class II validation study by the same author[26] included 8,138 patients, of whom 66% were deemed to be at low pretest probability. The prevalence of VTE was 7% for the entire cohort and 3% for the low-risk cohort. The PERC performance was nearly identical to that of the original study, regardless of pretest probability.

Three additional external validation studies with low-risk cohorts have also been published.[27,30,31] The first, a Class II study by Hugli et al[27] in 2011, is the only study to challenge the use of the PERC in low-risk patients. This retrospective study included 1,675 total patients, 35% of whom were at low risk. The prevalence of PE was 21% for the total cohort and 10% for the low-risk cohorts. In this study, the PERC performed considerably worse, yielding a sensitivity, specificity, and negative likelihood ratio of 79%, 33%, and 0.63, respectively. In their study, the posttest incidence of VTE in PERC-negative, low-risk patients was 6.4%. Besides the significantly higher baseline prevalence of disease, this European study had a lower proportion of patients in the overall cohort considered to be at low risk, and the PERC were applied retrospectively to the prospectively collected database. It is unclear whether these factors or some other element of regional practice played a role in the criteria's poorer performance. In this study, when the PERC was applied to the entire cohort, regardless of previous probability, the PERC performed better than when applied to the low-risk cohort alone. Two Class III studies support the use of PERC, demonstrating 100% sensitivity in 459 low-risk patients with a combined prevalence of PE of 5.9%.[30,31]

Last, a 2012 Class II meta-analysis that included 13,885 low-risk patients with a 10% prevalence of PE found the PERC to be adequate to exclude the diagnosis of PE in a low-risk population.[32] Their analysis included 8 patient cohorts that were not included in this clinical policy (3 with abstract data only,[33-35] 4 graded Class X,[36-39] and 1 nonapplicable cohort included in the original Kline et al[24] derivation study). The meta-analysis found a pooled sensitivity, specificity, and negative likelihood ratio of 97%, 23%, and 0.18, respectively. Thus, based on these results, for a patient with a pretest probability for PE estimated to

Table 1. PERC performance.

Study Cohorts	Class	Pretest Probability	N	PE (%)	PERC Determination	PERC Performance			
						Sensitivity (95% CI), %	Specificity (95% CI), %	Negative LR (95% CI)	Posttest VTE (%) (95% CI)
Low-Risk Cohorts									
Kline et al[24]	II	Low	1,427	114 (8)	Prospective	96 (90-99)	27 (25-30)	0.16 (0.07-0.38)	1.4 (0.4-3.2)
Kline et al[26]	II	Low	5,425	163 (3)	Prospective	97 (96-99)	22 (21-23)	0.12 (0.07-1.19)	1.3 (0.8-1.9)
Hugli et al[27]	II	Low	587	57 (10)	Retrospective	79 (67-88)	33 (29-37)	0.63 (0.04-1.06)	6.4 (3.7-6.8)
Wolf et al[31]	III	Low	60	1 (2)	Retrospective	100 (25-100)	22 (12-35)	0 (*)	0 (0-24.7)
Penaloza et al[30]	III	Low	399	26 (7)	Retrospective	100 (99-100)	9 (6-11)	0 (*)	0 (0-5)
Undifferentiated-Risk Cohorts									
Kline et al[26]	II	All	8,138	561 (7)	Prospective	96 (94-97)	25 (24-26)	0.17 (0.11-0.25)	1.0 (0.6-1.6)
Hugli et al[27]	II	All	1,675	357 (21)	Retrospective	97 (94-98)	16 (14-18)	0.21 (0.12-0.37)	5.4 (3.1-9.3)
Wolf et al[31]	III	All	120	16 (12)	Retrospective	100 (79-100)	16 (10-24)	0 (*)	0 (0-17.6)
Crichlow et al[29]	III	All	152	18 (12)	Prospective	100 (78-100)	10 (6-17)	0 (*)	0 (0-23.2)
Penaloza et al[30]	III	All	959	286 (30)	Retrospective	99 (97-100)	10 (8-13)	0.13 (0.05-0.36)	5.4 (1.7-12.5)
Bozarth et al[28]	III	All	719	32 (5)	Retrospective	97 (94-100)	12 (10-15)	0.26 (0.04-1.82)	1.2 (0-6.5)

CI, confidence interval; *LR*, likelihood ratio; *PE*, pulmonary embolism; *PERC*, pulmonary embolism rule-out criteria; *VTE*, venous thromboembolism;
*Undefined given 100% sensitivity

be 10% who is determined to be PERC negative, the posttest probability for having PE would be 1.9%.

PERC Performance in Undifferentiated Cohorts

Although the PERC were not derived to exclude the diagnosis of PE in a population with an undifferentiated pretest probability for PE (ie, low, moderate, or high), several studies have looked at its performance in this context, with conflicting results. One Class II[26] and 3 Class III[28,29,31] studies support the use of PERC regardless of the pretest probability. Combined, these studies looked at 9,129 patients with a 6.9% prevalence of VTE, demonstrating negative likelihood ratios for PERC ranging from 0 to 0.26, with posttest incidence of VTE ranging from 0% to 1.2%.

Two studies (1 Class II[27] and 1 Class III[30]) demonstrated poorer PERC performance in patient populations with undifferentiated risk. Together, these studies enrolled 2,634 patients with suspected PE, 24.4% of whom ultimately received a diagnosis of VTE. Among these cohorts with higher risk for PE, the posttest probability in PERC-negative patients was 5.4%, which is a risk above the testing threshold and would require further diagnostic testing.

Pooling data from any of these studies is difficult because of substantial heterogeneity. Table 1 summarizes data from each of these studies. Therefore, there is insufficient evidence to recommend using the PERC to exclude PE in a non–low-risk population.

In summary, the existing literature supports the use of PERC to exclude PE in low-risk patients based on a moderate degree of certainty. However, these results are tempered by one study[27] with a point estimate greater than the commonly quoted threshold of 2.0% posttest prevalence. Additionally, there is insufficient evidence to support the use of PERC in higher-risk populations.

Future Research

Although evidence exists to support the use of PERC in low-risk patients with suspected PE, future research should focus on more accurately defining pretest probability risk cut offs and optimizing the diagnostic evaluation of PE in higher-risk subgroups.

2. **In adult patients with low to intermediate pretest probability for acute PE, does a negative age-adjusted D-dimer result identify a group of patients at very low risk for the diagnosis of PE for whom no additional diagnostic workup is required?**

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. In patients older than 50 years deemed to be low or intermediate risk for acute PE, clinicians may use a negative age-adjusted D-dimer* result to exclude the diagnosis of PE.

Level C recommendations. None specified.

*For highly sensitive D-dimer assays using fibrin equivalent units (FEU) use a cutoff of age×10 μg/L; for highly sensitive D-dimer assays using D-dimer units (DDU), use a cutoff of age×5 μg/L.

Potential Benefits of Implementing the Recommendations:

- Reduced test-related complications (eg, contrast-induced nephropathy, contrast-related allergic reactions, contrast infiltrations, radiation exposure)

- Reduced cost associated with less diagnostic testing
- Reduced time in ED associated with less diagnostic testing
- Better use of health care resources
- Improved patient satisfaction as a result of more efficient evaluation

Potential Harms of Implementing the Recommendations:

- A small increased incidence of missed PE
- Misapplication of the recommendation because of confusion with multiple D-dimer assay units

Key words/phrases for literature searches: pulmonary embolism, acute pulmonary embolism, diagnosis, lung embolism, fibrin degradation product, D-dimer, fibrin fragment, probability, age-adjusted, sensitivity and specificity, emergency service, hospital, predictive value of tests, and variations and combinations of the key words/phrases. Searches included January 1, 2006, to search date of April 22, 2016.

Study Selection: Fifty-nine articles were identified in this search. Forty-two relevant articles were selected from the search results for further methodological review and grading. Three Class II articles and 7 Class III articles were included for this critical question.

The diagnosis of PE poses a special challenge in the elderly, given that its prevalence increases with age,[4] as does the frequency of comorbid conditions that can present with similar signs and symptoms. Although the accuracy and clinical utility of prediction rules remain good in this population,[40,41] there is an age-dependent increase in D-dimer levels[42] that results in a decline in the specificity of D-dimer testing in the elderly when a conventional fixed cutoff is used. This can lead to high rates of unnecessary imaging in this group.

Raising the D-dimer threshold in older patients who are at nonhigh risk of VTE has been studied as a strategy to improve workup efficiency. Nonhigh risk refers to a low or intermediate pretest probability, or "PE unlikely" using a validated clinical prediction rule. Most of the studies included in our systematic review of the literature used a D-dimer cutoff based on the patient's age in years (age×10 μg/L) for patients older than 50 years (unless otherwise specified); however, other strategies have been studied such as using a cutoff that increases by decade, or simply applying a single higher threshold to patients older than 50 years or 70 years. All but one included study used one or more high-sensitivity D-dimer assays (eg, VIDAS, Tinaquant, STA-Liatest, Innovance, and D-dimer HS), which generally use a conventional cutoff of FEU at 500 μg/L.[43-51] One study used the HemosIL D-dimer assay, which reported results in DDU that are equivalent to approximately half of an FEU, and the formula for age adjustment was adjusted accordingly (age×5 μg/L).[52]

The primary concern when using an age-adjusted D-dimer cutoff is whether increasing the threshold increases the risk of missed PEs. This measure was expressed as sensitivity in some studies, yet was variably reported as the number of false negatives or "failure rate" in others. In this section, we use the analogous term "miss rate," defined here as the proportion of patients with a negative D-dimer result (cutoff defined in each study) who ultimately received a diagnosis of PE.

The practical consideration when using an age-adjusted D-dimer cutoff is how much it reduces the need for additional imaging. Many studies reported the "clinical usefulness" or "efficiency" of the test (ie, the proportion of patients with negative D-dimer test results), although this does not directly reflect whether the negative results were true or false.

Several other societies have reviewed the issue of age-adjusted D-dimers in their guidelines. The best practice advice put forth by the American College of Physicians recommends using age-adjusted D-dimer thresholds in patients older than 50 years, and not ordering imaging if the D-dimer level is below the cutoff.[10] The 2014 European Society of Cardiology guidelines on the diagnosis and management of PE discussed, but did not formally endorse, the use of age-adjusted D-dimers.[53] A majority of the studies included in this systematic review were conducted in Europe, where a higher prevalence of PE was reported compared with most study populations in the United States, thus limiting applicability to the ED patient population in the United States.

Safety of the Age-Adjusted D-dimer Strategy (Table 2)

Overall, the 3 Class II studies[43-45] found that the miss rate of the age-adjusted D-dimer was similar to a conventional D-dimer cutoff, and that the sensitivities were similar. The prospective study by Righini et al[43] took place at multiple centers in Europe and included 3,324 ED patients with a 19% overall prevalence of PE; 87% were at nonhigh risk, and if the D-dimer result was negative, these patients were discharged without additional testing and without anticoagulation. The 3-month risk of missed (nonfatal) PE was 1 among 810 patients with a negative conventional D-dimer result (0.1%). There was 1 additional missed PE among the 331 patients who had a negative D-dimer result, using the age-adjusted D-dimer cutoff, for a total of 2 missed (nonfatal) PEs among 1,141 patients (0.2%).

Table 2. D-dimer performance in VTE patients older than 50 years using a CDD versus AADD.

Study	Class	CPR	PTP	AADD cutoff (μg/L)	CDD Sensitivity (%; 95% CI)	AADD Sensitivity (%; 95% CI)	CDD Miss Rate (%; 95% CI)	AADD Miss Rate (%; 95% CI)	% Cohort With Negative CDD (95% CI)	% Cohort With Negative AADD (95% CI)
Righini et al[43]*	II	sRGS or Wells	Non-high or unlikely	Age×10†	NR	NR	1/810 (0.1; 0-0.7)	2/1,141 (0.2; 0-0.6)	28 (27-30)	40 (38-42)
Flores et al[45]	II	Wells	Non-high	Age×10†	100 (94-100)	100 (94-100)	0/92 (0; 0-3.9)	0/121 (0; 0-3.0)	28 (23-33)	37 (32-42)
van Es et al[44]	II	Wells	Unlikely	Age×10†	99 (99-100)	99 (98-99)	13/2,035 (0.7; 0.4-1.1)	22/2,369 (0.9; 0.6-1.5)	28 (21-37)	33 (25-42)
van Es et al[47]*	III	Wells	Unlikely	Age×10†	NR	NR	1/60 (1.7; 0-8.9)	2/92 (2.2; 0-7.6)	15 (11-18)	22 (18-26)
Gupta et al[49]	III	NR	Any	Age×10†	100 (94-100)	97 (90-100)	0/72 (0; 0-5.0)	2/165 (1.2; 0.1-4.3)	7 (7-9)	16 (14-19)
Friz et al[50]	III	NR	Any	Age×10†	100 (97-100)	98 (94-100)	0/8 (0; 0-36.9)	2/28 (7.1; 0.9-23.5)	2 (1-3)	6 (4-8)
Jaconelli et al[52]	III	Wells	Unlikely	Age×5‡	95 (86-99)	95 (86-99)	3/859 (0.3; 0.1-1.0)	3/989 (0.3; 0.1-0.9)	65 (62-68)	75 (72-77)
Sharp et al[48]	III	NR	Any	Age×10†	98 (96-99)	93 (90-95)	10/16,660 (0.1; 0-0.1)	36/19,584 (0.2; 0.1-0.3)	54 (53-54)	63 (62-64)
Douma et al[46]	III	Wells	Unlikely	Age×10†	NR	NR	2/983 (0.2; 0.1-0.7)	7/1,093 (0.6; 0.3-1.3)	46 (43-48)	51 (49-53)
Douma et al[46]	III	RGS	Non-high	Age×10†	NR	NR	0/561 (0; 0.0-0.7)	2/663 (0.3; 0.1-1.1)	34 (32-37)	40 (38-43)
Sharp et al[48]	III	NR	Any	1,000†	98 (96-99)	84 (81-87)	10/16,660 (0.1; 0.0-0.1)	80/23,146 (0.3; 0.3-0.4)	54 (53-54)	74 (74-75)
Friz et al[50]	III	NR	Any	1,000†	100 (97-100)	96 (91-99)	0/8 (0; 0-36.9)	4/61 (6.6; 1.8-15.9)	2 (1-3)	13 (10-16)
Kline et al[51]*§	III	sRGS or Wells	Any	1,000†	94 (88-97)	92 (86-96)	8/152 (5.3; 2-10.1)	10/185 (5.4; 2.6-9.7)	22 (19-26)	27 (24-31)

AADD, age-adjusted D-dimer; *CDD*, conventional D-dimer; *CI*, confidence interval; *CPR*, clinical prediction rule; *NR*, not reported; *PTP*, pretest probability; *RGS*, revised Geneva score; *sRGS*, simplified revised Geneva score.
*Multiple CPRs were used; for simplicity, only results for Wells are presented.
†D-dimer value reported in FEUs.
‡D-dimer value reported in DDUs;
§Applied AADD to patients older than 70 years.

Van Es et al[44] conducted a meta-analysis using patient-level data from 6 prospective studies (including data from the Righini et al study[43]) that included 7,268 patients with a 22% overall prevalence of PE. This meta-analysis found that among patients with "PE unlikely" based on the Wells criteria and a negative conventional D-dimer result, the incidence of symptomatic VTE during a 3-month follow-up period was 0.7%, and there were no fatal events. In comparison, the miss rate with the age-adjusted D-dimer was 0.9%, with 1 fatal event. The sensitivity of both the conventional D-dimer and age-adjusted D-dimer cutoffs was 99%.

Flores et al[45] conducted a study of 362 ED patients in Spain; all patients had imaging, with the D-dimer level tested for research purposes, and the prevalence of PE in this population was 27%. Among the 331 non–high-risk patients by Wells criteria, there were 0 missed PEs with either the conventional D-dimer or the age-adjusted D-dimer, thus yielding a 100% sensitivity for both the conventional D-dimer and age-adjusted D-dimer cutoffs.

Additionally, a majority of the 5 Class III studies found a low risk of missed PEs and a high sensitivity with the age-adjusted D-dimer cutoff.[46-50] Douma et[46] derived the age-adjusted formula and then validated it in 2 retrospective cohorts, showing miss rates of 0.3% and 0.6% with the age-adjusted D-dimer cutoff versus miss rates of 0.0% and 0.2% with the conventional D-dimer cutoff. Van Es et al[47] compared the age-adjusted D-dimer with the conventional D-dimer cutoff, using a number of well-validated clinical prediction rules. For non–high-risk patients, they reported age-adjusted D-dimer miss rates ranging from 2.2% to 2.5% compared with conventional D-dimer miss rates of 1.7% to 1.8%. The other 3 studies looked at cohorts of patients with suspected PE who had D-dimer tests, presumably not exclusively nonhigh risk, but the pretest probability was not provided.[48-50] Sharp et al[48] analyzed one such ED cohort in the United States with a low prevalence of PE and found a miss rate of 0.1% with the conventional D-dimer cutoff, 0.2% for the age-adjusted D-dimer cutoff, and 0.3% when applying a threshold of 1,000 μg/L. Gupta et al[49] applied 2 different age-adjusted strategies to an ED cohort in the United States (PE prevalence of 7%) and reported similar sensitivities for both the yearly cutoff (97.4%) and a decadal cutoff (98.7%); the sensitivity for the conventional D-dimer cutoff in this cohort was 100%. Finally, Friz et al[50] studied a cohort in Italy who all had D-dimer tests and CTs as part of standard practice for suspected PE in their ED, and in this higher-risk population (PE prevalence of 23%) the sensitivity was 98% based on the yearly age-adjusted D-dimer formula and 96% for a cutoff of 1,000 μg/L, compared with 100% for conventional D-dimer.

Clinical Usefulness of Using the Age-Adjusted D-dimer Cutoff (Table 2)

The 3 Class II studies found a modest increase (ranging from 5% to 12%) in the proportion of non–high-risk patients having a negative D-dimer result, using an age-adjusted cutoff versus a conventional cutoff.[43-45] Righini et al[43] showed a 12% increase in the proportion of patients with negative D-dimer results, using the age-adjusted D-dimer versus the conventional D-dimer, from 28% to 40%. Van Es et al[44] found an increase from 28% using the conventional D-dimer to 33% when the age-adjusted D-dimer was applied to a PE-unlikely group. Flores et al[45] reported an increase in the proportion of patients with a negative D-dimer result from 28% to 37%, using the conventional D-dimer and age-adjusted D-dimer, respectively, and an improvement in specificity from 36% to 47%.

The results of 5 Class III studies were similar.[46-50] Douma et al,[46] in 2 validation sets, found an increase in the proportion of patients with negative D-dimer results from 46% to 51% and from 34% to 40% with the age-adjusted D-dimer strategy. Van Es et al[47] separated the results by the clinical decision rule that was used and reported a 4% to 7% increase in the proportion of patients with a negative age-adjusted D-dimer result when using the Wells criteria, simplified Wells, RGS, or simplified RGS. In the study by Sharp et al,[48] the proportion of patients with a negative D-dimer result increased from 54% with the conventional D-dimer to 63% with the yearly age-adjusted D-dimer. Gupta et a[49] found an increase in specificity from 7% to 14% with the decadal age-adjusted D-dimer, and to 17% with the yearly age-adjusted D-dimer. Friz et al[50] reported a small increase, from 2% to 6%, with the yearly age-adjusted D-dimer formula, and from 2% to 13% with a cutoff of 1,000 μg/L.

Performance of the Age-Adjusted D-dimer Strategy in Geriatric Subgroups

A number of the studies discussed above also reported data for older subgroups of patients, in which the clinical usefulness of the age-adjusted D-dimer strategy appears greater. In the Class II study by Righini et al,[43] the proportion of non–high-risk patients older than 75 years and with a negative conventional D-dimer result was only 6% (95% confidence interval [CI] 5% to 9%) and increased to 30% (95% CI 26% to 33%) with the age-adjusted D-dimer, with 0 missed PEs (95% CI 0% to 2%).

The Class II study by van Es et al[44] also reported an increase in the proportion of PE-unlikely patients older than 75 years and with a negative D-dimer result from 8% to 20% when using the age-adjusted D-dimer cutoff, with a concomitant increase in the miss rate from 0% to 2.1% (95% CI 1% to 6%). The Class III study by van Es et al[47] found an increase in the proportion of patients with a negative D-dimer result, using conventional D-dimer versus age-adjusted D-dimer, of 6% to 21% using the Wells criteria, 5% to 17% with the simplified Wells, and 3% to 12% with the RGS or simplified RGS for patients older than 70 years. The Class III study by Friz et al[50] looked at the subgroup of patients older than 80 years and found that the sensitivity of the D-dimer with the age-adjusted D-dimer was maintained at 100% (95% CI 91% to 100%) and the proportion of patients with a negative D-dimer result increased from 0% to 5% compared with the conventional D-dimer. In the oldest subgroup (>80 years), Douma et al[46] also found an increase in the proportion of patients with a negative D-dimer result, using age-adjusted D-dimer versus conventional D-dimer (from 9% to 21% in one validation set and from 15% to 29% in a second validation set), with similar miss rates, 2% (95% CI 0% to 11%) and 0% (95% CI 0% to 7%), respectively.

In a Class III study, Kline et al[51] calculated the performance of a fixed cutoff of 1,000 μg/L in an ED cohort in the United States. Using a cutoff of 1,000 μg/L for patients older than 70 years yielded a sensitivity of 92% compared with 94% for a threshold of 500 μg/L among all age groups. These authors noted that of the 10 missed PEs using the higher threshold, 9 were subsegmental. However, using this strategy increased the specificity by only 6% (ie, from 26% to 32%).

Assays That Use a Conventional D-dimer Cutoff Other Than 500 μg/L

One Class III study[52] looked at whether the yearly age-adjusted strategy could be adapted to a setting that used the HemosIL-HS assay, reporting results using a DDU, with a manufacturer-recommended cutoff of 230 ng/mL. Quantitative D-dimer assay results are reported as either the concentration of DDU or as FEU, depending on the calibration method for the assay. The 2 numeric values are easily convertible because the mass of one FEU equals approximately half of one DDU (ie,1 FEU=2×DDU). For simplicity, this study compared a standard cutoff of 250 ng/mL with an age-adjusted formula of age×5 ng/mL for patients older than 50 years. This study included patients with nonhigh pretest probability for DVT and PE and found that specificity improved from 68% to 78%. There were no additional missed PEs.

In summary, using a strategy of adjusting the D-dimer for age modestly increases the proportion of patients with a negative D-dimer result, which may reduce the need for advanced imaging in approximately 5% to 10% of patients, without a significant increase in missed cases of PE.

Future Research

Although evidence exists to support the use of age-adjusted D-dimer results in the evaluation of non–high-risk patients with suspected PE, future research should focus on further defining the role of age-adjusted D-dimer in older subgroups (eg, >80 years).

3. **In adult patients with subsegmental PE, is it safe to withhold anticoagulation?**

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Given the lack of evidence, anticoagulation treatment decisions for patients with subsegmental PE without associated DVT should be guided by individual patient risk profiles and preferences. [Consensus recommendation]

Potential Benefits of Implementing the Recommendations:

- Reduced treatment-related complications (eg, major and minor medication-related bleeding, medication-related allergic reactions)
- Reduced time and costs associated with less frequent follow-up visits
- Better use of health care resources
- Improved patient satisfaction as a result of more efficient patient care and shared decisionmaking

Potential Harm of Implementing the Recommendations:

- PE-related complications due to inaccurate assessment of individual patient risk profiles.

Key words/phrases for literature searches: pulmonary embolism, venous thromboembolism, lung embolism, vein embolism, thromboembolism, venous thromboembolism, subsegmental, anticoagulation, decision making, anticoagulant agent, anticoagulants, diagnosis, treatment withdrawal, health status indicators, fibrin fibrinogen degradation products, emergency service, and variations and combinations of the key words/phrases. Searches included January 1, 2006, to search date of April 22, 2016.

Study Selection: Seventeen articles were identified in this search. Nine relevant articles were selected from the search

results for further methodological review and grading. Two Class III articles were included for this critical question.

Anticoagulation is typically considered standard treatment for PE, regardless of size. However, with advances in imaging technology and increased awareness of PE, the incidence of the disease has increased while its resultant mortality has remained unchanged.[54,55] Given the risk of anticoagulation, some have questioned whether it is beneficial for patients with subsegmental PE,[56,57] which has a lower morbidity than segmental or more central PE.[54] In addition, the distinction between isolated and nonisolated subsegmental PE is an important one. Isolated subsegmental PEs refer to those without an associated DVT, whereas nonisolated subsegmental PEs are those with an associated DVT; the latter are typically anticoagulated because of the DVT in and of themselves. In 2016, a Cochrane review on this topic found no credible evidence to evaluate whether anticoagulation is useful in patients with isolated subsegmental PE; however, this systematic review did not consider nonrandomized or cohort studies for inclusion.[57] Our systematic review of the literature similarly found no Class I or II studies; however, 2 Class III studies[58,59] were identified evaluating the effectiveness of anticoagulation therapy for patients with isolated subsegmental PE.

A Class III study by den Exter et al[58] compared outcomes for patients with subsegmental PE with those with larger PEs. Although all patients enrolled received anticoagulation, their results suggest that patients with subsegmental PE have risks of recurrent VTE similar to those of patients with larger PEs at 3-month follow-up (3.6% versus 2.5%, respectively). However, this study's applicability to the critical question was limited by the fact that all subjects enrolled were not confirmed to have "isolated" subsegmental PE (ie, all subjects did not undergo extremity ultrasonography or another imaging modality to rule out concomitant DVT). The other Class III study by Donato et al[59] included a total of 22 patients with confirmed, isolated subsegmental PE who did not receive anticoagulation; at 3-month follow-up, none had a recurrent VTE. In 20 of the 22 untreated patients, duplex ultrasonography of the lower extremities was found to be negative before the decision to not anticoagulate was made. This study also reported on the outcomes of 71 patients with isolated subsegmental PE who received anticoagulation; 1 of these patients had a recurrent (nonfatal) PE, but 8 experienced hemorrhage (5 major and 3 minor).[59]

Future Research

Given the lack of evidence on the prognosis and management of patients with isolated subsegmental PE, prospective randomized trials assessing the benefits and harms of anticoagulation are required. This information can then be used to inform shared decisionmaking between provider and patient.

4. In adult patients diagnosed with acute PE, is initiation of anticoagulation and discharge from the ED safe?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Selected patients with acute PE who are at low risk for adverse outcomes as determined by PESI, simplified PESI (sPESI), or the Hestia criteria may be safely discharged from the ED on anticoagulation, with close outpatient follow-up.

Potential Benefits of Implementing the Recommendations:

- Reduced inpatient treatment-related complications (eg, hospital-acquired infections)
- Reduced cost compared with inpatient patient care
- Reduced hospital inpatient crowding
- Reduced time associated with treatment follow-up
- Better use of health care resources
- Improved patient satisfaction as a result of more efficient patient care and the ability to be treated at home

Potential Harms of Implementing the Recommendations:

- Increased patient and provider anxiety with outpatient management of a potentially serious disease process
- Delay in evaluation and management of any change in clinical condition, resulting from the need to return to the ED or a health care setting for evaluation and management

Key words/phrases for literature searches: pulmonary embolism, acute pulmonary embolism, venous embolism, venous thromboembolism, thromboembolism, anticoagulants, anticoagulation, outpatients, patient discharge, home care services, outpatient, home treatment, discharge, risk factors, Hestia, sPESI, decision support techniques, patient selection, ambulatory care, risk assessment, time factors, treatment outcome, severity of illness, and variations and combinations of the key words/phrases. Searches included January 1, 2006, to search date of April 22, 2016.

Study Selection: Ninety-five articles were identified in this search. Twenty-four relevant articles were selected from the search results for further methodological review and grading. Two Class II and 7 Class III articles were included for this critical question.

Given the mortality historically associated with PE, patients have traditionally been hospitalized for monitoring and parenteral anticoagulant therapy.[60,61] With the development

of low-molecular-weight heparins (LMWH) that can be administered once or twice daily at home, protocols have been established allowing for safe outpatient treatment of patients with uncomplicated DVT.[60] More recently, NOACs (eg, rivaroxaban, apixaban, dabigatran, edoxaban) have been approved for the treatment of both DVT and PE after studies demonstrated that this regimen was noninferior to traditional treatment with heparin and a VKA.

More than 95% of patients who ultimately receive a diagnosis of acute PE are "hemodynamically stable" at presentation with an associated mortality of 1% to 15%.[62,63] The availability of newer anticoagulation agents (eg, NOACs) that are equally effective, more easily administered, and do not require laboratory monitoring has led to efforts aimed at treating low-risk patients with newly diagnosed PE as outpatients who can be directly discharged from the ED.

Multiple investigators have combined specific criteria into clinical prediction rules to identify which patients receiving a diagnosis of acute PE are at low risk for adverse outcomes.[60,61,64-71] Among these criteria, the PESI, sPESI, and Hestia criteria are the most well studied, with generalizability to the acute care setting of the ED. The PESI was initially developed to predict 30-day mortality, whereas the Hestia criteria were developed with the intention to help identify patients at lower risk of adverse outcomes. (Figures 1 and 2)

Although most studies included in our systematic review applied similar definitions and methodology, they varied in several important ways, such as the inclusion of asymptomatic patients with PE, recruitment of patients from settings outside of the ED such as an outpatient clinic or hospital, the application of exclusion criteria beyond those used to establish low risk, the proportion of patients with cancer, the anticoagulation regimen, the definition of "early discharge," and the length of follow-up for adverse outcomes.

For inpatients receiving traditional anticoagulation therapy, limited data exist on outcomes specific to low-risk subgroups. Two randomized controlled trials were identified that assessed outcomes of low-risk patients admitted to the hospital and treated with traditional anticoagulation for 90 days.[61,66] In these 2 studies, the incidence of recurrent VTE, major hemorrhage, and all-cause mortality was approximately 1%, 2%, and 2%, respectively.[61,66] Thus, an outpatient treatment strategy for newly diagnosed PE can be deemed safe and effective if the subsequent incidence of important adverse outcomes does not exceed those experienced by patients receiving traditional hospitalization followed by outpatient care.

Two Class II studies[61,68] and 7 Class III studies[60,67,72-76] addressed this critical question, 3 of which were deemed directly applicable.[60,61,68] In each of these studies, the

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*	Total Point Score†
I	<65
II	66–85
III	86–105
IV	106–125
V	>125

*Risk Classes I and II are considered low risk.
†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.

Reprinted with permission of the American Thoracic Society. Copyright ©2018 American Thoracic Society. 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.[13] The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society.

Simplified Pulmonary Embolism Severity Index

Age >80 years?
Cardiopulmonary co-morbidity?
History of cancer?
Arterial oxyhaemoglobin saturation level <90%?
Systolic blood pressure <100 mm Hg?
Pulse frequency ≥110 beats/min?

If one of the items is present the patient is regarded as high risk.

Reprinted with permission. Zondag W, den Exter PL, Crobach MJ, et al; on behalf of the HESTIA Study Investigators. Comparison of two methods for selection of out of hospital treatment in patients with acute pulmonary embolism. *Thromb Haemost.* 2013;109:47-52.[72]

Figure 1. PESI and sPESI.

Haemodynamically instable?*

Thrombolysis or embolectomy necessary?

High risk for bleeding?**

Oxygen supply to maintain oxygen saturation >90% >24 h?

Pulmonary embolism diagnosed during anticoagulant treatment?

Intravenous pain medication >24 h?

Medical or social reason for treatment in the hospital >24 h?

Creatinine clearance of less than 30 mL/min?***

Severe liver impairment****

Pregnant?

Documented history of heparin-induced thrombocytopenia?

If one of the questions is answered with YES, the patient cannot be treated at home.

*Include the following criteria, but are left to the discretion of the investigator: systolic blood pressure <100 mm Hg with heart rate >100 beats per minute; condition requiring admission to an intensive care unit.

**Gastrointestinal bleeding in the preceding 14 days, recent stroke (less than 4 weeks ago), recent operation (less than 2 weeks ago), bleeding disorder or thrombocytopenia (platelet count $<75\times10^9$/L), uncontrolled hypertension (systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg).

***Calculated creatinine clearance according to the Cockroft-Gault formula.

****Left to the discretion of the physician.

h, hour; *mL*, milliliter; *mm Hg*, millimeters of mercury; *min*, minute.

Reprinted with permission. Zondag W, den Exter PL, Crobach MJ, et al; on behalf of the HESTIA Study Investigators. Comparison of two methods for selection of out of hospital treatment in patients with acute pulmonary embolism. *Thromb Haemost.* 2013;109:47-52.[72]

Figure 2. Hestia criteria.

rates of important short-term adverse outcomes (eg, recurrent VTE, major hemorrhage, mortality) did not exceed that expected of admitted patients receiving traditional care.

First, a Class II study by Aujesky et al[61] prospectively randomized 344 consecutive, low-risk patients by the PESI score to either early discharge from the hospital within 24 hours (N=172) or admission to the hospital for traditional care (N=172). Both treatment arms received anticoagulation with subcutaneous LMWH for no more than 5 days followed by a VKA (ie, warfarin). Although the incidence of recurrent VTE, major hemorrhage, and all-cause mortality was similar in both treatment arms (Table 3), this open-label study had limitations.[61] First, 126 eligible patients were not enrolled for a variety of reasons (eg, declined to participate [N=99], physician was against study participation [N=17], not randomized [N=9]); if these patients had more severe disease, not including these subjects may have resulted in an underestimation of the incidence of adverse outcomes. Next, early-discharge patients spent up to 24 hours in a health care setting, which is significantly longer than the typical ED length of stay, thus limiting the direct applicability to the critical question. Finally, the study added additional exclusion criteria during patient enrollment that were not a part of the original PESI score (eg, requiring narcotics for pain, active bleeding, risk of bleeding, renal failure, extreme obesity, heparin allergy, currently taking anticoagulation, pregnancy, barriers to adherence of the treatment protocol). Therefore, when the application of these results is considered, these additional exclusion criteria should be considered, along with the PESI score, when one seeks to identify low-risk patients for adverse outcomes.

In another Class II study, Zondag et al[68] prospectively investigated the outcomes of 297 patients with acute PE who were determined to be at low risk by the Hestia criteria. All patients were discharged from the hospital within 24 hours of their presentation, and all were treated with subcutaneous LMWH followed by a VKA. The authors reported the incidence of recurrent VTE, major hemorrhage, and mortality at both 7 days and 90 days. Although deaths did occur in the study, the authors pointed out that no patient was adjudicated as having died from recurrent VTE. The incidence of adverse outcomes in this study was similar to that previously reported among patients receiving traditional care in the hospital (Table 3). Limitations of this study include that some of the patients came from outside the ED, 6.1% of patients received LMWH only as their anticoagulation, and 26 eligible patients (7.7%) refused to participate in the study. Zondag et al[72] went on to perform a Class III post hoc analysis of their original data, comparing the performance of the Hestia and sPESI low-risk rules. The authors found that the sPESI performed as well as the HESTIA criteria in identifying acute PE patients who were low risk for adverse outcomes.[72]

Table 3. Rates of Adverse Outcomes in Patients with PE who were treated as outpatients.

Study	Follow-up (Days)	Outcomes			
		Recurrent VTE, % (UCL)	Major Hemorrhage, % (UCL)	Mortality, % (UCL)	Unique Composite Outcome,* % (UCL)
Traditional inpatient care[61,66]		1.0 (3.3)	2.0 (5.0)	2.0 (11)	
Outpatient care					
Aujesky et al[61†]	14	0 (1.7)	1.2 (3.6)	0 (1.7)	
	90	0.6 (2.7)	1.8 (4.5)	0.6 (2.1)	
Zondag et al[68†]	7	0 (1.2)	0.3 (1.9)	0 (1.2)	
	90				
den Exter et al[60†]	10				0.3 (1.0)
	30				1.1 (3.2)
	90	1.1 (3.2)	1.1 (3.2)	1.1 (3.2)	
Zondag et al[74‡]		1.5 (3.0)	0.8 (1.4)	1.6 (2.8)	

UCL, upper confidence limit.
*Composite outcome included recurrent VTE, bleeding-related mortality, or need for cardiopulmonary resuscitation, ICU-level care, thrombolytic therapy, or embolectomy.
†Original data.
‡Meta-analysis.

A Class III study by den Exter et al[60] reported data from a prospective trial that followed 275 patients with acute PE who were determined to be at low risk by the Hestia criteria. All patients were treated with an LMWH followed by a VKA and discharged from the hospital within 24 hours of presentation. The 90-day incidence of recurrent VTE, major bleeding, and mortality was determined to be similar to that experienced by patients receiving traditional care in the hospital (Table 3). This study was limited by the fact that it was not clear whether the study enrolled consecutive patients or what proportion of patients were from the ED (if any). Additionally, 11 patients were excluded by their physician for a perceived "large clot burden" despite being deemed to be at low risk by the Hestia criteria.

The findings of these 3 studies are corroborated by 3 Class III meta-analyses.[73-75] The more notable of these, by Zondag et al,[74] included 8 retrospective studies of various quality and found similar rates of adverse outcome, which included rates of recurrent VTE, major hemorrhage, and mortality of 1.5%, 0.8%, and 1.6%, respectively.

Table 3 shows the summary outcomes data from these studies compared with traditional care.[60,61,68,74] This, combined with the fact that nearly 50% of patients who receive a diagnosis of acute PE meet low-risk criteria, implies that approximately half of patients with newly diagnosed PE may be eligible for discharge directly home from the ED.[60,61,68,74]

Currently, the additional discriminatory value of adding right ventricular dysfunction on imaging to decisionmaking in regard to low risk is controversial. Some guidelines have recommended that screening for right ventricular dysfunction on imaging be incorporated into the determination of low-risk PE despite that right ventricular dysfunction is not included as a predictive variable in the PESI, sPESI, or Hestia scores.[53] On the other hand, Zondag et al[76] and Barrios et al[77] found that screening patients for right ventricular dysfunction did not significantly improve the identification of low-risk patients with PE over the Hestia and sPESI rules, respectively; and in the case of the Hestia rule, it would have led to one-third of the truly low-risk patients who proved to have good outcomes being falsely classified as having nonlow risk.

In summary, although existing literature supports early discharge of patients with newly diagnosed PE who are deemed to be at low risk for adverse outcomes, the current evidence supported only a Level C recommendation. To make a recommendation with a high degree of clinical certainty, studies that enroll consecutive ED patients with symptomatic PE who are discharged within a reasonable timeframe (ie, a typical ED length of stay) are needed. Also, the studies that contributed to the final recommendation of this critical question only treated patients with a LMWH followed by a VKA. Although NOACs are an approved therapy for the treatment of VTE, there are limited data assessing the safety of early discharge of patients with PE who are receiving a NOAC. Nonetheless, no current data suggests any reason why a NOAC would be inferior as a treatment regimen for this group of patients.

Future Research

To achieve a higher-level recommendation, future high-quality studies need to focus on the identification of those low-risk patients with acute PE who are safe for discharge from the ED, including those identified as having concurrent DVT who may be at greater risk for subsequent

embolization and adverse outcome.[78,79] Comparative effectiveness studies are also needed to determine the balance of risks and benefits for outpatient treatment of VTE with the various NOACs.

5. **In adult patients diagnosed with acute lower-extremity DVT who are discharged from the ED, is treatment with a NOAC safe and effective compared with treatment with LMWH and VKA?**

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. In selected patients diagnosed with acute DVT, a NOAC may be used as a safe and effective treatment alternative to LMWH/VKA.

Level C recommendations. Selected patients with acute DVT may be safely treated with a NOAC and directly discharged from the ED.

Potential Benefit of Implementing the Recommendations:

- Reduced inpatient treatment-related complications (eg, hospital-acquired infections)
- Reduced cost compared with inpatient care or medication monitoring of VKAs
- Reduced hospital inpatient crowding
- Reduced time associated with treatment follow-up
- Better use of health care resources
- Improved patient satisfaction as a result of more efficient patient care and the ability to be treated at home
- Improved safety profile of NOACs with reduced major or clinically relevant nonmajor bleeding compared with standard therapy

Potential Harm of Implementing the Recommendations:

- Increased pharmacy expense for NOAC medications
- Lack of safe and effective reversal agents for NOACs for patients presenting with severe bleeding
- Increased patient and provider anxiety with outpatient management of a potentially serious disease process
- Delay in evaluation and management of changes in clinical condition, resulting from the need to return to the ED or a health care setting for evaluation and management

Key words/phrases for literature searches: venous thrombosis, venous thromboembolism, DVT, deep venous thrombosis, thromboembolism, leg thrombosis, lower extremity thrombosis, factor Xa inhibitors, NOAC, novel oral anticoagulant, antithrombins, DOAC, rivaroxaban, apixaban, edoxaban, dabigatran, pyridones, pyrazoles, pyridines, non–vitamin K antagonist, heparin, warfarin, anticoagulants, oral administration, recurrence, risk factors, treatment outcome, patient discharge, hospital emergency or emergency room, or emergency department, or outpatient, or ambulatory care, or home care, and variations and combinations of the key words/phrases. Searches included January 1, 2006, to search dates of April 22, 2016, and May 2, 2016.

Study Selection: Two hundred fifty-nine articles were identified in this search. Forty-five relevant articles were selected from the search results for further methodological review and grading. Three Class II and 8 Class III articles were included for this critical question.

Traditional therapy for patients with acute lower extremity DVT is subcutaneous LMWH with simultaneous bridging administration of an oral VKA until the patient achieves a therapeutic level of anticoagulation. It has been shown to be safe and effective as an outpatient treatment regimen.[80-82] This initiation of LMWH/VKA requires extensive resources and potential hospitalization to achieve essential patient goals, including ensuring appropriate patient education, patient access to medications for home administration, and patient follow-up for laboratory monitoring of anticoagulation. If shown to be safe and effective, the administration of NOACs with subsequent direct discharge from the ED could markedly simplify the initiation and monitoring requirements for patients with newly diagnosed acute DVT.[83] Furthermore, studies have shown reduced health care costs when a NOAC is used over traditional LMWH/VKA therapy in properly chosen patients.[84-86] A list of currently approved NOACs and dosing regimens is shown in Table 4. For both LMWHs and NOACs, physicians must pay attention to body mass index and renal function before initiating anticoagulation treatment.

For this critical question, 3 Class II studies[87-89] and 8 Class III studies[90-97] were identified comparing the efficacy and safety of NOACs with standard therapy in the treatment of acute VTE. All 3 of the Class II studies[87-89] and 3 of the Class III studies[90,91,94] specifically examined outcomes in patients receiving a diagnosis of isolated DVT, whereas the remaining 5 Class III studies[92,93,95-97] examined cohorts that included patients with DVT and PE.

Of the 11 Class II and Class III studies, only 1 directly addressed safety and efficacy outcomes in patients who began receiving a NOAC and were directly discharged from the ED.[90] This multicenter Class III study examined the safety and efficacy of a protocol for the outpatient treatment of patients with newly diagnosed VTE. Per protocol, patients at low risk for adverse outcomes based on a modified version of the Hestia criteria were treated with oral rivaroxaban and discharged from the ED with arranged outpatient follow-up. Of the 271 eligible VTE patients,

Table 4. Comparison of NOACs for treatment of VTE.

NOAC	Class	Treatment Regimen for VTE	Pretreatment Before Initiation of Further Treatment	Notes
Dabigatran (Pradaxa)	Direct thrombin inhibitor	150 mg BID	Parenteral anticoagulation× 5-10 days	Dialyzable; reversal agent idarucizumab
Edoxaban (Savaysa)	Factor Xa inhibitor	60 mg QD	Parenteral anticoagulation× 5-10 days	Lower dose of 30 mg QD for patients ≤60 kg or CrCl 15-50 mL/min
Rivaroxaban (Xarelto)	Factor Xa inhibitor	Initial: 15 mg BID×21 days Then: 20 mg QD	None	Take with food
Apixaban (Eliquis)	Factor Xa inhibitor	Initial: 10 mg BID×7 days Then: 5 mg BID	None	

BID, two times a day; *CrCl*, creatinine clearance; *kg*, kilogram; *mg*, milligram; *min*, minute; *mL*, milliliter; *QD*, once a day.

39% were deemed to be at low risk and treated per study protocol, and were discharged directly from the ED. These patients represented 51% of all new DVT diagnoses and 27% of all new PE diagnoses during the study period. No patient discharged on oral rivaroxaban had recurrent VTE or a clinically relevant bleeding event while receiving therapy (95% CI 0% to 3.4%). Three patients had recurrent DVT after cessation of therapy, and 2 patients experienced death unrelated to VTE or rivaroxaban. The authors concluded that ED discharge on oral rivaroxaban for properly selected patients with acute DVT diagnosis is safe and effective. The major limitation of this study was that subjects were not randomized, potentially leading to a biased sample based on clinician judgment to enroll patients in the study versus admit them to the hospital.[90]

Of the remaining 10 studies, 3 Class II studies[87-89] depicted the efficacy and safety of NOACs versus LMWH/VKA in patients with a diagnosis of isolated DVT or in patients with a diagnosis of VTE (ie, DVT or PE) but with clinical outcome data reported for index DVT. The Class II DVT study by the EINSTEIN Investigators[87] was the first to focus specifically on the treatment of acute DVT with a NOAC. In this open-label, noninferiority study, patients receiving a diagnosis of acute DVT were randomized to treatment with either oral rivaroxaban alone (N=1,731) or traditional therapy (n=1,718). The rivaroxaban arm had noninferior efficacy compared with standard therapy, as measured by recurrent VTE (2.1% versus 3.0%; hazard ratio 0.7; 95% CI 0.4 to 1.0) and major bleeding during treatment (8.1% versus 8.1%; hazard ratio 1; 95% CI 0.8 to 1.2).

The other 2 Class II studies[88,89] considered patients with isolated DVT, or PE with or without DVT, and analyzed outcomes stratified by the index event. The multicenter, double-blinded Apixaban for the initial management of PE and DVT as first-line therapy (AMPLIFY) study[88] randomized 5,395 patients with newly diagnosed VTE to either oral apixaban or standard therapy. Sixty-five percent of enrolled patients had an isolated acute DVT, and of these, the primary efficacy outcome of recurrent VTE occurred in 2.3% of those in the apixaban group versus 2.7% receiving conventional therapy (risk difference –0.5%; 95% CI –1.5% to 0.6%). The primary safety outcome of major bleeding occurred in 0.6% of patients in the apixaban arm versus 1.8% in the conventional arm (risk difference –1.1%; 95% CI –1.7 to –0.6), thus favoring the use of apixaban in terms of safety. The multicenter, double-blinded Hokusai-VTE study[89] randomized patients with acute VTE to either edoxaban or a VKA; all patients received at least 5 days of parenteral anticoagulation. Of the 8,292 patients enrolled, 59% presented with isolated DVT as the index event. Among this subgroup, a recurrent VTE during the study period occurred in 3.4% (83/2,468) of patients receiving edoxaban versus 3.3% (81/2,453) of patients receiving warfarin (hazard ratio 1; 95% CI 0.8 to 1.4). For all enrolled patients (eg, PE, DVT), the primary safety outcome of major or clinically relevant nonmajor bleeding was less in those treated with edoxaban versus standard therapy, occurring in 8.5% of patients treated with edoxaban versus 10.3% treated with VKA (hazard ratio 0.8; 95% CI 0.7 to 0.9). These 2 studies showed similar efficacy, but improved safety for treatments with a NOAC with or without LWMH versus traditional therapy in patients with acute DVT.[88,89]

Three Class III research studies[91-93] evaluated the use of NOACs alone or in combination with LMWH for the treatment of acute VTE. A phase 2 industry-sponsored dose-ranging study evaluated once-daily rivaroxaban (20, 30, or 40 mg) versus LMWH/VKA for acute symptomatic DVT without PE.[91] Efficacy and safety were similar among all 4 groups, justifying progression to the phase 3 EINSTEIN-DVT study described above.[87] In 2009, Schulman et al[92] (the RE-COVER trial) compared dabigatran versus warfarin in the treatment of acute VTE. This Class III study[92] was a double-blind noninferiority trial randomizing patients with newly diagnosed PE or

DVT to treatment with dabigatran or warfarin for 6 months. Sixty-nine percent of patients in this study had an isolated acute DVT, but outcomes were not stratified by index event. Patients in both groups received concurrent initial treatment with parenteral anticoagulation for at least 5 days. This trial found dabigatran to be noninferior to warfarin for the prevention of recurrent VTE (2.4% versus 2.1%). Rates of bleeding with dabigatran were similar to or lower than those with warfarin. The number of deaths, acute coronary syndromes, and abnormal liver function test results were also similar between the 2 groups.

The effect of prestudy heparin on the efficacy and safety of rivaroxaban relative to standard therapy and the incidence of bleeding compared with that of patients who did not receive prestudy heparin was evaluated in a Class III study by Prandoni et al.[93] This retrospective, post hoc analysis of the EINSTEIN-DVT[87] and EINSTEIN-PE[98] studies found that the majority of patients (84%) enrolled in the EINSTEIN-DVT and PE studies received prestudy heparin but with most (70%) receiving prestudy heparin for 1 day or less. There was no difference observed in the incidence of recurrent VTE or bleeding between the groups.

Four Class III meta-analyses[94-97] compared the safety and efficacy of NOACs versus traditional therapy. In 2015, Robertson et al[94] found NOACs with or without LMWH to be an effective and safe alternative to traditional anticoagulation treatment of acute DVT. This analysis included 11 randomized controlled trials of 27,945 patients, 5 of which are discussed above[87-89,91,92] and 6 of which are not included in this review (1 was deemed not directly relevant to the critical question,[98] 2 were reviewed and graded Class X,[99,100] 1 was abstract data only,[101] 1 was a proof-of-concept study,[102] and 1 was a study on a non–Food and Drug Administration– approved NOAC[103]). It included separate meta-analyses assessing the effectiveness of oral direct thrombin inhibitors (ie, dabigatran) or oral factor Xa inhibitors (ie, apixaban, edoxaban, rivaroxaban).[94] Meta-analysis comparing oral direct thrombin inhibitors versus traditional therapy showed no difference in the rate of recurrent VTE (odds ratio [OR] 1.09; 95% CI 0.80 to 1.49) but did show reduced bleeding rates (OR 0.68; 95% CI 0.47 to 0.98).[94] Similarly, meta-analysis comparing oral factor Xa inhibitors with traditional therapy showed similar rates of recurrent VTE (OR 0.89; 95% CI 0.73 to 1.07), with reduced rates of bleeding (OR 0.57; 95% CI 0.43 to 0.76).[94]

Two other Class III meta-analyses were conducted to compare the safety and efficacy of NOACs in the treatment of VTE (ie, DVT or PE)[95,96]; both included 6 phase 3 randomized controlled trials[87-89,92,98,100] and showed that there was no significant difference between the NOACs in regard to the risk of recurrent VTE, mortality, or safety. The fourth Class III meta-analysis by Di Minno et al[97] included the same 6 studies as above and showed similar safety and efficacy of treatment with NOACs versus VKA among patients of various body weights.

Future Research

Although evidence exists to support the use of NOACs to treat DVT, future research should focus on direct comparison of individual NOACs in relation to efficacy, bleeding risks, adverse effects, and patient preferences. Furthermore, high-quality research should focus on the efficacy and safety of NOACs for outpatient treatment of patients diagnosed with VTE and the need for LMWH as pretreatment before initiation of specific NOACs, including dabigatran and edoxaban.

Relevant industry relationships: There were no relevant industry relationships disclosed by the subcommittee members for this topic.

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

Introduction

1. Office of the Surgeon General (US); National Heart, Lung, and Blood Institute (US). *The Surgeon General's Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism*. Rockville, MD: Office of the Surgeon General; 2008.
2. Beckman MG, Hooper WC, Critchley SE, et al. Venous thromboembolism: a public health concern. *Am J Prev Med*. 2010; 38-S495-S501.
3. Heit JA. The epidemiology of venous thromboembolism in the community. *Arterioscler Thromb Vasc Biol*. 2008;28:370-372.
4. Oger E. Incidence of venous thromboembolism: a community-based study in Western France. EPI-GETBP Study Group. *Thromb Haemost*. 2000;83:657-660.
5. Heit JA, Cohen AT, Anderson FA Jr. Estimated annual number of incident and recurrent, non-fatal and fatal venous thromboembolism (VTE) events in the U.S. *Blood*. 2005;106:910.
6. Cohen AT, Agnelli G, Anderson FA, et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. *Thromb Haemost*. 2007;98:756-764.
7. Jiménez D, de Miguel-Díez J, Guijarro R, et al; for the RIETE Investigators. Trends in the management and outcomes of acute pulmonary embolism. Analysis from the RIETE registry. *J Am Coll Cardiol*. 2016;67:162-170.
8. Cushman M, Tsai AW, White RH, et al. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. *Am J Med*. 2004;117:19-25.
9. Fesmire FM, Brown MD, Espinosa JA, et al; American College of Emergency Physicians. Critical issues in the evaluation and management of adult patients presenting to the emergency department with pulmonary embolism. *Ann Emerg Med*. 2011;57:628-652.e75.

10. Raja AS, Greenberg JO, Qaseem A, et al; Clinical Guidelines Committee of the American College of Physicians. Evaluation of patients with suspected acute pulmonary embolism: best practice advice from the Clinical Guidelines Committee of the American College of Physicians. *Ann Intern Med*. 2015;163:701-711.
11. 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.
12. 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.
13. 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.
14. Fabiá Valls MJ, van der Hulle T, den Exter PL, et al. Performance of a diagnostic algorithm based on a prediction rule, D-dimer and CT-scan for pulmonary embolism in patients with previous venous thromboembolism. A systematic review and meta-analysis. *Thromb Haemost*. 2015;113:406-413.
15. Pauker SG, Kassirer JP. The threshold approach to clinical decision making. *N Engl J Med*. 1980;302:1109-1117.
16. 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.e1.
17. Pines JM, Lessler AL, Ward MJ, et al. The mortality benefit threshold for patients with suspected pulmonary embolism. *Acad Emerg Med*. 2012;19:E1109-1113.
18. Sikkens JJ, Beekman DG, Thijs A, et al. How much overtesting is needed to safely exclude a diagnosis? a different perspective on triage testing using Bayes' theorem. *PLoS One*. 2016;11:e0150891.

Q1

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. 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.
25. Kline JA. Diagnosis and exclusion of pulmonary embolism. *Thromb Res*. 2018;163:207-220.
26. 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.
27. Hugli O, Righini M, Le Gal G, et al. The pulmonary embolism rule-out criteria (PERC) rule does not safely exclude pulmonary embolism. *J Thromb Haemost*. 2011;9:300-304.
28. Bozarth AL, Bajaj N, Wessling MR, et al. Evaluation of the pulmonary embolism rule-out criteria in a retrospective cohort at an urban academic hospital. *Am J Emerg Med*. 2015;33:483-487.
29. Crichlow A, Cuker A, Mills AM. Overuse of computed tomography pulmonary angiography in the evaluation of patients with suspected pulmonary embolism in the emergency department. *Acad Emerg Med*. 2012;19:1219-1226.
30. Penaloza A, Verschuren F, Dambrine S, et al. Performance of the Pulmonary Embolism Rule-out Criteria (the PERC rule) combined with low clinical probability in high prevalence population. *Thromb Res*. 2012;129:e189-193.
31. 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.
32. Singh B, Parsaik AK, Agarwal D, et al. Diagnostic accuracy of pulmonary embolism rule-out criteria: a systematic review and meta-analysis. *Ann Emerg Med*. 2012;59:517-520.e1-4.
33. Beam D, Brewer K, Kline JA. Application of the pulmonary embolism rule-out criteria in a rural population. *Ann Emerg Med*. 2007;50:S132.
34. Courtney DM, Pribaz JR, Senh AC. Prospective evaluation of the pulmonary embolism rule-out criteria (PERC) rule: an 8-variable block rule to identify subjects at very low risk of pulmonary embolism. *Acad Emerg Med*. 2006;13:S157-158.
35. Crichlow A, Cuker A, Matsuura AC, et al. Underuse of clinical decision rules and D-dimer testing in the evaluation of patients presenting to the emergency department with suspected venous thromboembolism. *Acad Emerg Med*. 2011;18:S48.
36. Hogg K, Dawson D, Kline J. Application of pulmonary embolism rule-out criteria to the UK Manchester Investigation of Pulmonary Embolism Diagnosis (MIOPED) study cohort. *J Thromb Haemost*. 2005;3:592-593.
37. Righini M, Le Gal G, Perrier A, et al. More on: clinical criteria to prevent unnecessary diagnostic testing in emergency department patients with suspected pulmonary embolism. *J Thromb Haemost*. 2005;3:188-189.
38. Dachs RJ, Kulkarni D, Higgins GL. The pulmonary embolism rule-out criteria rule in a community hospital ED: a retrospective study of its potential utility. *Am J Emerg Med*. 2011;29:1023-1027.
39. Kline JA, Peterson CE, Steuerwald MT. Prospective evaluation of real-time use of the pulmonary embolism rule-out criteria in an academic emergency department. *Acad Emerg Med*. 2010;17:1016-1019.

Q2

40. Righini M, Le Gal G, Perrier A, et al. Effect of age on the assessment of clinical probability of pulmonary embolism by prediction rules. *J Thromb Haemost*. 2004;2:1206-1208.
41. Di Marca S, Cilia C, Campagna A, et al. Comparison of Wells and revised Geneva rule to assess pretest probability of pulmonary embolism in high-risk hospitalized elderly adults. *J Am Geriatr Soc*. 2015;63:1091-1097.
42. Haase C, Joergensen M, Ellervik C, et al. Age- and sex-dependent reference intervals for D-dimer: evidence for a marked increase by age. *Thromb Res*. 2013;132:676-680.
43. Righini M, Van Es J, Den Exter PL, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism. The ADJUST-PE study. *JAMA*. 2014;311:1117-1124.
44. van Es N, van der Hulle T, van Es J, et al. Wells rule and D-dimer testing to rule out pulmonary embolism. A systematic review and individual-patient data meta-analysis. *Ann Intern Med*. 2016;165:253-261.
45. Flores J, Garcia de Tena J, Galipienzo J, et al. Clinical usefulness and safety of an age-adjusted D-dimer cutoff levels to exclude pulmonary embolism: a retrospective analysis. *Intern Emerg Med*. 2016;11:69-75.
46. Douma RA, le Gal G, Söhne MD, 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.

47. van Es J, Mos I, Douma R, et al. The combination of four different clinical decision rules and an age-adjusted D-dimer cut-off increases the number of patients in whom acute pulmonary embolism can safely be excluded. *Thromb Haemost*. 2012;107:167-171.
48. Sharp AL, Vinson DR, Alamshaw F, et al. An age-adjusted D-dimer threshold for emergency department patients with suspected pulmonary embolus: accuracy and clinical implications. *Ann Emerg Med*. 2016;67:249-257.
49. Gupta A, Raja AS, Ip IK, et al. Assessing 2 D-dimer age-adjustment strategies to optimize computed tomographic use in ED evaluation of pulmonary embolism. *Am J Emerg Med*. 2014;32:1499-1502.
50. Friz HP, Pasciuti L, Meloni DF, et al. A higher d-dimer threshold safely rules-out pulmonary embolism in very elderly emergency department patients. *Thromb Res*. 2014;133:380-383.
51. Kline JA, Hogg MM, Courtney DM, et al. D-dimer threshold increase with pretest probability unlikely for pulmonary embolism to decrease unnecessary computerized tomographic pulmonary angiography. *J Thromb Haemost*. 2012;10:572-581.
52. Jaconelli T, Eragat M, Crane S. Can an age-adjusted D-dimer level be adopted in managing venous thromboembolism in the emergency department? A retrospective cohort study. *Eur J Emerg Med*. https://doi.org/10.1097/MEJ.0000000000000448.
53. Konstantinides SV, Torbicki A, Agnelli G, et al; Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2014;35:3033-3069; 3069a-3069k.

Q3

54. Carrier M, Righini M, Wells PS, et al. Subsegmental pulmonary embolism diagnosed by computed tomography: incidence and clinical implications. A systematic review and meta-analysis of the management outcome studies. *J Thromb Haemost*. 2010;8:1716-1722.
55. Wiener RS, Schwartz LM, Woloshin S. When a test is too good: how CT pulmonary angiograms find pulmonary emboli that do not need to be found. *BMJ*. 2013;347:f3368.
56. Kearon C, Akl EA, Omelas J, et al. Antithrombotic therapy for VTE disease. CHEST Guideline and Expert Panel report. *Chest*. 2016;149:315-352.
57. Yoo HH, Queluz TH, El Dib R. Anticoagulant treatment for subsegmental pulmonary embolism. *Cochrane Database Syst Rev*. 2016;(1):CD010222.
58. den Exter PL, van Es J, Klok FA, et al. Risk profile and clinical outcome of symptomatic subsegmental acute pulmonary embolism. *Blood*. 2013;122:1144-1149.
59. Donato AA, Khoche S, Santora J, et al. Clinical outcomes in patients with isolated subsegmental pulmonary emboli diagnosed by multidetector CT pulmonary angiography. *Thromb Res*. 2010;126:e266-e270.

Q4

60. den Exter PL, Zondag W, Klok FA, et al; for the Vesta Study Investigators. Efficacy and safety of outpatient treatment based on the Hestia clinical decision rule with or without N-terminal pro-brain natriuretic peptide testing in patients with acute pulmonary embolism: a randomized clinical trial. *Am J Respir Crit Care Med*. 2016;194:998-1006.
61. Aujesky D, Roy PM, Verschuren F, et al. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. *Lancet*. 2011;378:41-48.
62. Barco S, Lankeit M, Binder H, et al. Home treatment of patients with low-risk pulmonary embolism with the oral factor Xa inhibitor rivaroxaban. Rationale and design of the HoT-PE Trial. *Thromb Haemost*. 2016;116:191-197.
63. Yoo HH, Queluz TH, El Dib R. Outpatient versus inpatient treatment for acute pulmonary embolism. *Cochrane Database Syst Rev*. 2014;(11):CD010019.
64. Agterof MJ, Schutgens RE, Snijder RJ, et al. Out of hospital treatment of acute pulmonary embolism in patients with a low NT-proBNP level. *J Thromb Haemost*. 2010;8:1235-1241.
65. Erkens PM, Gandara E, Wells P, et al. Safety of outpatient treatment in acute pulmonary embolism. *J Thromb Haemost*. 2010;8:2412-2417.
66. Otero R, Uresandi F, Jiménez D, et al. Home treatment in pulmonary embolism. *Thromb Res*. 2010;126:e1-e5.
67. Davies CW, Wimperis J, Green ES, et al. Early discharge of patients with pulmonary embolism: a two-phase observational study. *Eur Respir J*. 2007;30:708-714.
68. Zondag W, Mos IC, Creemers-Schild D, et al; on behalf of the Hestia Study Investigators. Outpatient treatment in patients with acute pulmonary embolism: the Hestia study. *J Thromb Haemost*. 2011;9:1500-1507.
69. Barra SN, Paiva L, Providencia R, et al. A review on state-of-the-art data regarding safe early discharge following admission for pulmonary embolism: what do we know? *Clin Cardiol*. 2013;36:507-515.
70. Beam DM, Kahler ZP, Kline JA. Immediate discharge and home treatment with rivaroxaban of low-risk venous thromboembolism diagnosed in two US emergency departments: a one-year preplanned analysis. *Acad Emerg Med*. 2015;22:789-795.
71. Kline JA, Kahler ZP, Beam DM. Outpatient treatment of low-risk venous thromboembolism with monotherapy oral anticoagulation: patient quality of life outcomes and clinician acceptance. *Patient Prefer Adherence*. 2016;10:561-569.
72. Zondag W, den Exter PL, Crobach MJ, et al; on behalf of the Hestia Study Investigators. Comparison of two methods for selection of out of hospital treatment in patients with acute pulmonary embolism. *Thromb Haemost*. 2013;109:47-52.
73. Piran S, Le Gal G, Wells PS, et al. Outpatient treatment of symptomatic pulmonary embolism: a systematic review and meta-analysis. *Thromb Res*. 2013;132:515-519.
74. Zondag W, Kooiman J, Klok FA, et al. Outpatient versus inpatient treatment in patients with pulmonary embolism: a meta-analysis. *Eur Respir J*. 2013;42:134-144.
75. Vinson DR, Zehtabchi S, Yealy DM. Can selected patients with newly diagnosed pulmonary embolism be safely treated without hospitalization? a systematic review. *Ann Emerg Med*. 2012;60:651-662.
76. Zondag W, Vingerhoets LM, Durian MF, et al; on behalf of the Hestia Study Investigators. Hestia criteria can safely select patients with pulmonary embolism for outpatient treatment irrespective of right ventricular function. *J Thromb Haemost*. 2013;11:686-692.
77. Barrios D, Morillo R, Lobo JL, et al; for the PROTECT investigators. Assessment of right ventricular function in acute pulmonary embolism. *Am Heart J*. 2017;185:123-129.
78. Jiménez D, Aujesky D, Diaz G, et al; RIETE Investigators. Prognostic significance of deep vein thrombosis in patients presenting with acute symptomatic pulmonary embolism. *Am J Respir Crit Care Med*. 2010;181:983-991.
79. Becattini C, Cohen AT, Agnelli G, et al. Risk stratification of patients with acute symptomatic pulmonary embolism based on presence or absence of lower extremity DVT. Systematic review and meta-analysis. *Chest*. 2016;149:192-200.

Q5

80. Kurtoglu M, Koksoy C, Hasan E, et al. Long-term efficacy and safety of once-daily enoxaparin plus warfarin for the outpatient ambulatory treatment of lower-limb deep vein thrombosis in the TROMBOTEK trial. *J Vasc Surg*. 2010;52:1262-1270.

81. Lozano F, Trujillo-Santos J, Barrón M, et al. Home versus in-hospital treatment of outpatients with acute deep venous thrombosis of the lower limbs. *J Vasc Surg*. 2014;59:1362-1367.e1.
82. Othieno R, Abu Affan M, Okpo E. Home versus in-patient treatment for deep vein thrombosis. *Cochrane Database Syst Rev*. 2007;(3):CD003076.
83. Ahrens I, Lip GY, Peter K. New oral anticoagulant drugs in cardiovascular disease. *Thromb Haemost*. 2010;104:49-60.
84. Kahler ZP, Beam DM, Kline JA. Cost of treating venous thromboembolism with heparin and warfarin versus home treatment with rivaroxaban. *Acad Emerg Med*. 2015;22:796-802.
85. Lefebvre P, Coleman CI, Bookhart BK, et al. Cost-effectiveness of rivaroxaban compared with enoxaparin plus a vitamin K antagonist for the treatment of venous thromboembolism. *J Med Econ*. 2014;17:52-64.
86. Merli GJ, Hollander JE, Lefebvre P, et al. Costs of hospital visits among patients with deep vein thrombosis treated with rivaroxaban and LMWH/warfarin. *J Med Econ*. 2016;19:84-90.
87. Bauersachs R, Berkowitz SD, Brenner B, et al; EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363:2499-2510.
88. Agnelli G, Buller HR, Cohen A, et al; for the AMPLIFY investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369:799-808.
89. Büller HR, Décousus H, Grosso MA, et al; the Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013;369:1406-1415.
90. Beam DM, Kahler ZP, Kline JA. Immediate discharge and home treatment with rivaroxaban of low-risk venous thromboembolism diagnosed in two US emergency departments: a one-year preplanned analysis. *Acad Emerg Med*. 2015;22:789-795.
91. Buller HR, Lensing AW, Prins MH, et al; on behalf of the EINSTEIN-DVT Dose-Ranging Study Investigators. A dose-ranging study evaluating once-daily oral administration of the factor Xa inhibitor rivaroxaban in the treatment of patients with acute symptomatic deep vein thrombosis: the EINSTEIN-DVT Dose-Ranging Study. *Blood*. 2008;112:2242-2247.
92. Schulman S, Kearon C, Kakkar AK, et al; for the RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med*. 2009;361:2342-2352.
93. Prandoni P, Prins MH, Cohen AT, et al. Use of prestudy heparin did not influence the efficacy and safety of rivaroxaban in patients treated for symptomatic venous thromboembolism in the EINSTEIN DVT and EINSTEIN PE studies. *Acad Emerg Med*. 2015;22:143-149.
94. Robertson L, Kesteven P, McCaslin JE. Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis. *Cochrane Database Syst Rev*. 2015;(6):CD010956.
95. Cohen AT, Hamilton M, Mitchell SA, et al. Comparison of the novel oral anticoagulants apixaban, dabigatran, edoxaban, and rivaroxaban in the initial and long-term treatment and prevention of venous thromboembolism: systematic review and network meta-analysis. *PLoS One*. 2015;10:e0144856.
96. Kang N, Sobieraj DM. Indirect treatment comparison of new oral anticoagulants for the treatment of acute venous thromboembolism. *Thromb Res*. 2014;133:1145-1151.
97. Di Minno MN, Lupoli R, Di Minno A, et al. Effect of body weight on efficacy and safety of direct oral anticoagulants in the treatment of patients with acute venous thromboembolism: a meta-analysis of randomized controlled trials. *Ann Med*. 2015;47:61-68.
98. Büller HR, Prins MH, Lensing AW, et al; for the EINSTEIN-PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012;366:1287-1297.
99. Buller H, Deitchman D, Prins M, et al; on behalf of the Botticelli Investigators, the Writing Committee. Efficacy and safety of the oral direct factor Xa inhibitor apixaban for symptomatic deep vein thrombosis. The Botticelli DVT dose-ranging study. *J Thromb Haemost*. 2008;6:1313-1318.
100. Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation*. 2014;129:764-772.
101. Piazza G, Mani V, Grosso M, et al. Abstract 12074: a randomized, open-label, multicenter study of the efficacy and safety of edoxaban monotherapy versus low-molecular weight heparin/warfarin in patients with symptomatic deep vein thrombosis—Edoxaban Thrombus Reduction Imaging Study (eTRIS). *Circulation*. 2014;130:A12074.
102. Agnelli G, Gallus A, Goldhaber SZ, et al. Treatment of proximal deep-vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAY 59-7939): the ODIXa-DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in patients with acute symptomatic deep-vein thrombosis) study. *Circulation*. 2007;116:180-187.
103. Eriksson H, Wåhlander K, Gustafsson D, et al; for the THRIVE Investigators. A randomized, controlled, dose-guiding study of the oral direct thrombin inhibitor ximelagatran compared with standard therapy for the treatment of acute deep vein thrombosis: THRIVE I. *J Thromb Haemost*. 2003;1:41-47.

Appendix A. Literature classification schema.*

Design/Class	Therapy†	Diagnosis‡	Prognosis§
1	Randomized, controlled trial or meta-analysis 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 series	Case series

*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	Does not change pretest probability
1-5	0.5-1	Minimally changes pretest probability
10	0.1	May be diagnostic if the result is concordant with pretest probability
20	0.05	Usually diagnostic
100	0.01	Almost always diagnostic even in the setting of low or high pretest probability

LR, likelihood ratio.
*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).

Q1: In adult patients with suspected acute PE, can a clinical prediction rule be used to identify a group of patients at very low risk for the diagnosis of PE for whom no additional diagnostic workup is required?

Evidentiary Table.

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Kline et al[24] (2004)	II	Multicenter, prospective derivation study	21 PE-related predictive variables vs endpoints/outcomes variables; logistic regression analysis with stepwise backwards elimination yielding PERC and LPTP validation cohort; included VLPTP cohort (in which PE was not initially suspected) that was used for comparison; secondary primary outcome=VTE by criterion standard with 90-day follow-up	Derivation: N=3,148; VTE=11%; 8 PERC variables identified; PE % PERC negative=1.8%; LPTP validation: N=1,427; VTE=8%; PERC negative=25%; sensitivity=96%, specificity=27%, LR negative=0.15; VLPTP validation; N=328; VTE=2%; PERC negative=15%; sensitivity=100%, specificity=15%, LR negative=0	Unknown sampling; ill-defined inclusion/exclusion and enrollment criteria; VLPTP cohort=convenience sample without suspicion of PE not applicable for validation
Kline et al[26] (2008)	II	Prospective multicenter	PERC validation in low- to very-low-risk patients; primary outcome=VTE by criterion standard and 45-day follow-up; data form completed prospectively before test results; VTE status established by adjudicated review and required agreement between 2 independent clinicians using explicit criteria	Eligible=12,213; enrolled=8,138, VTE=6.9%; PERC negative=24%, LPTP=67%; PERC all: sensitivity=95.7%; specificity=25.4%; LR negative=0.17; PERC LPTP: sensitivity=94.7%; specificity=21.9%; LR negative=0.12	Enrollment rate was 66%; no follow-up on 304 patients; eligibility for enrollment was an order for an objective diagnostic test for PE (CT, V/Q, D-dimer); loss to follow-up in 304 patients, and it was not stated whether outcome was measured without knowledge of the risk factor or PERC result

Evidentiary Table (continued).

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Hugli et al[27] (2011)	II	Retrospective analysis of prospectively collected data	Consecutive patient population with suspicion for PE; primary outcome=VTE by criterion standard with 90-day follow-up	N=1,675; VTE%=21.3%; PERC negative=221 (13.2%); PE % PERC negative=5.4%; PE % PERC negative and LPTP=6.4%; PERC all: sensitivity=96.6%; specificity=16%; LR negative=0.70; PERC LPTP: sensitivity=79%; specificity=33.2; LR negative=0.63; only 1 patient lost to follow-up	LPTP cohort proportionally small; did not state whether outcomes were measured without knowledge of risk factors or whether radiology studies were measured in a valid or reliable way
Bozarth et al[28] (2015)	III	Retrospective cohort study	Consecutive patients evaluated for rule out of PE with CTA; excluded nondiagnostic imaging; primary outcome=PERC sensitivity and NPV; retrospective PERC calculation	N=729; 6-mo follow-up in 76/83 patients; PE%=4.5%; PERC sensitivity=96.9%; specificity=11.9%; NPV=98.9; LR negative=262	Retrospective PERC calculation; included all PTP; no blinding of reviewers of study hypothesis, and relatively small sample size of positive PE (32) patients
Crichlow et al[29] (2012)	III	Prospective cohort	Convenience sample; primary outcome was percentage of CTA scans avoidable by Wells/D-dimer negative or PERC negative; 90-day follow-up for CTA-negative patients	Enrolled=166; excluded 14 (including 8 lost to follow-up); analyzed=152; % PERC negative=9.2% (N=14); % PERC negative without PE=0	Convenience sample; single center, sampling missed the people who did not receive a CTPA; sample size small

Evidentiary Table (continued).

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Penaloza et al[30] (2012)	III	Prospective cohort study	PERC performance in LPTP patients by gestalt and revised Geneva score; retrospective PERC and revised Geneva score calculation	N=959; VTE all=29.8%; PERC negative=74 (7.7%); VTE and PERC negative=4 (5.4%); VTE and PERC negative and revised Geneva score LPTP=6.2%; VTE and PERC negative and gestalt LPTP was 0%	PERC-negative population relatively small; unknown reliability of retrospective application of PERC and revised Geneva score; essentially, it is using clinical gestalt to find a low-prevalence population in whom we know that PERC already works well
Wolf et al[31] (2008)	III	Prospective cohort study	Post hoc analysis on prospectively collected data (2001-2002 Kaiser data); primary outcome was VTE by criterion standard and 90-day follow-up; pretest probability calculated according to Wells prospectively; PERC was retrospectively applied	N=134; VTE=12%; PERC all: sensitivity=100%; specificity=16%; LR negative=0 PERC LPTP: sensitivity=100%; specificity=22%; LR negative=0; started with 176 patients but only 134 included, because excluded patients >85 y, morbid obesity, recent pregnancy, known thrombophilia other than cancer, D-dimer in recent past, critical illness, and non-English speaking; 16/134 (12%) had PE and 8 lost to follow-up	Small study size; post hoc analysis, large proportion excluded; only 19 were PERC negative; nothing stated as to validity and reliability of retrospective application of PERC or who the chart abstractors were, single center

Evidentiary Table (continued).

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Singh et al[32] (2012)	II	Systematic review/meta-analysis	Outcome=PERC accuracy; comprehensive search, appropriate methods used to assess heterogeneity, and random-effects models used to pool likelihood ratios; performed meta-regression	12 studies (13,885 patients with 1,391 PEs) with 10% VTE; 11 studies included; PERC: pooled sensitivity: 97%; specificity=23%; LR negative=0.18; there was heterogeneity in specificity and positive predictive value	Quality assessment on 8 but 11 studies included; abstracts included in the analysis; only 44/13,885 patients had PE, and there was heterogeneity; because of small number of studies could not assess publication bias

Q2: In adult patients with low to intermediate pretest probability for acute PE, does a negative age-adjusted D-dimer result identify a group of patients at very low risk for the diagnosis of PE for whom no additional diagnostic workup is required?

Evidentiary Table (continued).

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Righini et al[43] (2014)	II	Prospective cohort study; multicenter, multinational, study, involving 19 hospitals in Belgium, France, the Netherlands, and Switzerland	Included patients with clinical suspicion of PE defined as an acute onset or worsening shortness of breath or chest pain without another obvious cause; Wells criteria for PE or Geneva scoring for risk assessment; AADD=patient's age×10 ng/mL for those >50 y; 3-mo follow-up; evaluated diagnostic algorithm	3,324 patients met eligibility criteria; 2,898 (87.2%) were low or intermediate risk by Wells or Geneva criteria; 1,154 patients (39.8%) had a negative D-dimer result according to the age-adjusted cutoff (95% CI 38.1% to 41.6%); 817 patients (28.2%) had a D-dimer level lower than 500 μg/L (95% CI 26.6% to 29.9%); age-adjusted cutoff resulted in an 11.6% absolute increase (95% CI 10.5% to 12.9%) in proportion of negative D-dimer results; 3-mo thromboembolic risk was 1 of 810 patients in conventional D-dimer (0.1%; 95% CI 0.0% to 0.7%); failure rate of the AADD was 1 of 331 patients (0.3%; 95% CI 0.1% to 1.7%)	Unclear when Geneva or Wells criteria were used; multiple D-dimer assays were used, with various sensitivity; verification bias, if the D-dimer assay was normal, using AADD, then patients were only followed up without any additional testing (MDCT, V/Q), so subsegmental PEs may not have been detected or others not causing clinical suspicion for further testing were left undiagnosed

Evidentiary Table (continued).

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
van Es et al[44] (2016)	II	Systematic review and individual patient data meta-analysis of 6 prospective studies	Inpatients and outpatients with a "PE unlikely" Wells score; VIDAS, Tina-quant, STA-Liatest, high sensitivity D-dimer, or Innovance D-dimer tests were used	Included 7,268 patients for whom management of suspected PE was guided by Wells and D-dimer; mean age 56 y; PE diagnosed in 1,527 (21%); missed diagnosis in whom imaging was withheld based on a Wells criteria score of ≤4 and D-dimer level below age-adjusted threshold=0.94% (95% CI 0.58% to 1.5%) with 1 fatal event; proportion of patients who could forgo imaging increased from 28% to 33% with the AADD (an additional 1 of 20 patients); between-study heterogeneity	There was heterogeneity between studies (but used individual patient data), there was a high prevalence of PE (22%), inpatients were included, and different D-dimer assays were used; multiple imputation was used for missing data
Flores et al[45] (2016)	II	Prospective cohort; teaching hospital in Spain between September 2008 and October 2010	Included ED patients with low-moderate PTP of PE based on Wells criteria; D-dimer ELISA assay (VIDAS) on all patients, and did not influence more definitive diagnostic testing (multidetector CT or V/Q lung scanning); 3-mo follow up; AADD=patient's age×10 ng/mL for those >50 y	331 patients were included; 22% with PE diagnosis; 291 older than 50 y; 291 of 362 were >50 y and PE confirmed in 81; AADD sensitivity was 97.9 (95% CI 92.1% to 99.6%) and specificity was 46.2 (95% CI 40.1% to 52.4%); (higher than conventional D-dimer specificity of 35.2 [95% CI 29.5% to 41.3%] and the same sensitivity)	Initial cohort included low-, moderate-, and high-risk patients; this analysis excluded high-risk group; data was stratified by Wells score to compensate; small sample size with relatively wide CIs and high prevalence of PE (27%); D-dimer test was analyzed retrospectively at the end of the study; single center

Evidentiary Table (continued).

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Douma et al[46] (2010)	III	Secondary retrospective analysis; derivation and validation	Derivation set: combined 2 multicenter cohort studies with 1,721 patients with suspected PE; 3-mo telephone follow-up; validation set: one evaluating clinical effectiveness of algorithm using dichotomized Wells rule, D-dimer, and CT and the second was a randomized noninferiority trial (using Geneva score) analyzing whether adding ultrasound to CT improved PE detection	416/1,721 (24.2%) in derivation had PE, and Wells score could not be computed in 54 (no alternative diagnosis); using age-adjusted cutoff, D-dimer negative in 615/1,712 (46.2%, and number needed to test=2.2) and a 20.1% (95% CI 16.9% to 23.8%) increased proportion in whom D-dimer result was normal; 5/615 had PE during 3 mo (0.8%; 0.4% to 1.9%); in validation set 1, 674/3,306 (20.4%) had PE; 983 had negative D-dimer result with conventional cutoff, of whom 2 (0.2%; 0.1% to 0.7%) had PE, whereas with age-adjusted cutoff, 1,093 had negative D-dimer result, of whom 6 (0.6%; 0.3% to 1.3%) had PE; age-adjusted cutoff resulted in an 11.2% (9.3% to 13.3%) increase in patients with a negative D-dimer result; in validation set 2, there was an 18.2% (15.2% to 21.4%) increase in number of patients in whom D-dimer result was negative, with 2 false negatives (0.3; 0.1% to 1.1%)	Prevalence of PE was extremely high in these cohorts; used different D-dimer assays, as well as both Geneva score and Wells score; missing D-dimer results in those who were "high risk," and no imputation performed

Evidentiary Table (continued).

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
van Es et al[47] (2012)	III	Secondary analysis of a prospective cohort of inpatients and outpatients at academic and non-academic medical centers and with clinically suspected PE in the Netherlands between July 2008 and November 2009	Patients >50 y with suspected PE; VIDAS D-dimer assay (BioMerieux, Marcy L'Etoile, France), Tinaquant assay (Roche Diagnostica, Indianapolis, IN), STA-Liatest D-di (Diagnostica Stago, Asnieres, France) or Innovance D-dimer (Siemens, Erlangen, Germany)	414 nonhigh-probability patients included (20% inpatients); 456/807 (57%) were >50 y; no D-dimer tested in 42/456 (all high probability); 110/414 (27%) patients had PE; with age-adjusted cutoff, D-dimer result was normal in 105/414 patients (25.4%), 2 of whom had PE (false negative=1.9%, 0.2% to 6.7%); true-negative rate of conventional D-dimer was 16% vs 25% with age-adjusted; 1 patient missed with the conventional D-dimer and 2 with the AADD	Revised Geneva score may have limited applicability in the elderly because it incorporates age as a risk factor already; studied in both inpatients and outpatients; few patients in some of the risk strata led to wide CIs; combining clinical decision rules with D-dimer was done retrospectively (no interrater reliability of this); 95% CI of false-negative rate wide because of small numbers with PE; different D-dimer assays used; not clear whether investigators assessing patients at follow-up were blinded to D-dimer

Evidentiary Table (continued).

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Sharp et al[48] (2016)	III	Secondary analysis of Kaiser database for patients >50 y who presented between 2008 and 2013 with suspected PE	Used *ICD-10* codes to identify the patients; primary outcome was acute PE	N=31,094 patients >50 y and had D-dimer test; primary outcome=PE in 507/11,999 (4.2%); among 18,608 who did not have imaging, 17.6% had D-dimer >500; AADD was more specific (64% vs 54%) but less sensitive (93% vs 98%) than standard 500; among 12,486 patients who received imaging, 1,323 (10.6%) had negative D-dimer result; age-adjusted would avert 2,492 low-value imaging tests while resulting in 26 additional cases of missed PE	Used *ICD-10* codes to identify the patients and used the Elixhauser comorbidity index; chart review was conducted, but no methods are described; not clear that outcome was measured in a valid or reliable way, and there was no mention of attrition, and there were 3,278/18,608 (17.6%) who had a D-dimer result >500 but no imaging; 1,323 patients had a negative D-dimer result and got a CT angiogram

Evidentiary Table (continued).

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Gupta et al[49] (2014)	III	Single center, urban, academic; retrospective cohort	Adult ED patients with suspected PE who were evaluated with D-dimer (STA-Liatest immunoturbidimetric D-dimer assay)	N=1,055; prevalence 7%; specificity 7% (95% CI 6% to 9%) with standard threshold of 500 ng/mL, vs 17% (95% CI 14% to 19%) with yearly age-adjusted threshold, vs 14% (95% CI 12% to 17%) with decade age-adjusted threshold; sensitivity 100% (95% CI 94% to 100%) for standard threshold of 500 ng/mL, vs 97% (95% CI 90% to 100%) yearly age-adjusted threshold, vs 99% (95% CI 92% to 100%) with decade age-adjusted threshold	Selection bias

Evidentiary Table (continued).

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Friz et al[50] (2014)	III	Single center, community; retrospective cohort	Adults with suspected PE who were evaluated with D-dimer (Innovance D-dimer, Siemens Medical Solutions Diagnostics, Deerfield, IL) and CTA	N=481; prevalence of PE=23%; specificity=2% (95% CI 1% to 4%) with standard threshold of 490 ng/mL vs 7% (95% CI 4% to 10%) with age-adjusted threshold; sensitivity=100% (95% CI 97% to 100%) with standard threshold of 490 ng/mL vs 98% (95% CI 94% to 100%) with age-adjusted threshold	Selection bias; a single fixed binary cutoff of 1,000 ng/mL; cohort included low-, moderate- and high-risk patients
Kline et al[51] (2012)	III	Prospective multicenter study including 4 centers; enrolled patients between January 30, 2007, and April 27, 2008; patients were enrolled in the ED, inpatient wards, ICU, and radiology suites; patients were enrolled 6 days/wk 12 h/day	Adult patients with PE evaluated with D-dimer (via VIDAS ELISA)	N=678 patients; PE was found in 126/678 patients, 19% (95% CI 16% to 22%); sensitivity and specificity of <500 ng/mL 97.2% and 15.6%, respectively; sensitivity and specificity of <1,000 ng/mL 93.7% and 26.1%, respectively; sensitivity and specificity of <1,000 ng/mL and 70 y were 92.1% and 31.7%, respectively	Convenience sampling; single binary higher cut point for D-dimer applied; included inpatients, ED patients, and outpatients

Evidentiary Table (continued).

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Jaconelli et al[52] (2017)	III	Single center; retrospective cohort (chart review) of all patients in whom PE or lower extremity DVT was suspected and who had a D-dimer ordered; separated out low risk, as defined by Wells criteria; follow-up through 3 mo; chart review methods defined; criterion standard was ultrasound, V/Q scan, and CTPA	Adults with proximal DVT and/or PE; primary efficacy outcome was VTE or PE in age-adjusted vs conventional D-dimer cutoff (<230 ng/mL)	N=1,649 (986 patients with suspected PE) including both PE and DVT; 1,324 with follow-up; 60/1,324 patients with confirmed VTE, 1,264 with no VTE; conventional D-dimer sensitivity 95% CI 95% (86.1% to 99%), specificity 95% CI 67.7% (65.1% to 70.3%), LR- 95% CI 0.07 (0.02 to 0.22), LR+ 95% CI 2.94 (2.67 to 3.25); AADD sensitivity 95% CI 95% (86.1% to 99%), specificity 95% CI 78% (75.6% to 80.3%), LR- 95% CI 0.06 (0.02 to 0.19), and LR+ 95% CI 4.32 (3.84 to 4.87)	Both DVT and PE were included, and test characteristics were difficult to discern when only PE patients were considered; loss to follow-up relatively high, and confirmatory criterion standard not performed on patients with negative standard D-dimer cut-point

Q3: In adult patients with subsegmental PE, is it safe to withhold anticoagulation?

Evidentiary Table (continued).

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
den Exter et al[58] (2013)	III	Urban, multicenter, academic center; prospective cohort	Adults with suspected PE; no PE vs isolated subsegmental PE vs proximal PE; outcomes: symptomatic, recurrent PE and death within 3 mo	N=3,769: isolated subsegmental PE (116) vs proximal PE (632) vs no PE (2,980); recurrent PE 3.6% in subsegmental PE vs 2.5% in proximal PE, adjusted HR=1.6 (95% CI 0.5 to 4.8); mortality 10.3% in subsegmental PE vs 6.3% in proximal PE, adjusted HR=1.5 (95% CI 0.8 to 2.8)	All patients with PE received anticoagulation; underpowered because of small number of outcome events; outcome assessment not blinded
Donato et al[59] (2010)	III	Urban, single-center, community hospital; retrospective cohort	Adults with isolated subsegmental PE; variable treatment with anticoagulation; outcome: recurrent PE and death within 3 mo	N=93; treatment with anticoagulation (71) vs no anticoagulation (22); recurrent PE 1.4% in anticoagulated group vs 0% in no-anticoagulation group; all-cause mortality 3% in anticoagulated group vs 0% in nonanticoagulated group	Underpowered because of small number of outcome events; CT interpretation and outcome assessment not blinded

Q4 In adult patients diagnosed with acute PE, is initiation of anticoagulation and discharge from the ED safe?

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
den Exter et al[60] (2016)	III	Prospective, randomized, noninferiority, open-label trial at 17 hospitals; to validate the utility and safety of selecting PE patients for outpatient treatment by the Hestia criteria; compares the safety of Hestia criteria alone with the Hestia criteria combined with NT-proBNP testing; compared PE patients with elevated NT-pro BNP whether admitted or discharged and if NT-pro BNP added value to Hestia screening	PE patients who were low risk by Hestia were randomized to immediate discharge or NT-pro BNP; of BNP group if level ≤500, then discharged home and if >500, then admitted; discharged all patients randomized to the direct discharge arm within 24 h of diagnosis and also studied those with post hoc elevated BNP; all patients received LMWH and VKAs; outpatient evaluation at 5 to 9 days; 4 to 6 wk; then 3 mo; primary endpoint: 30-day adverse outcome (PE, bleeding-related mortality, CPR, ICU, lytic or embolectomy); 3.4% difference was set as the noninferiority margin for primary endpoint; secondary outcomes: 90-day recurrent symptomatic VTE, major bleeding and all-cause mortality	Randomized 550 patients with PE, 275 had NT-pro BNP; 34/275 (12.4%) had BNP level >500 and were treated as inpatients; 34 were also compared with 23 immediately discharged patients who were found to have NT-pro BNP level ≥500 post hoc protocol violations; 30-day primary endpoint: no inpatient with elevated BNP (0/34; 0% to 10.2%) or immediately discharged patient with elevated BNP (0/23; 0% to 14.8%) experienced primary endpoint; 0/275 with NT-pro BNP testing had primary outcome (0%; 0% to 1.3%) 3/275 (1.1%; 0.2% to 3.2%) (*P*=.25); in immediately discharged group without NT-pro BNP had primary outcome, and 1 of the 3 died on day 15 from PE; post hoc analysis of BNP level of those 3 patients revealed NT-pro BNP level was <500; absolute difference between BNP and immediately discharged group 1.1% (0.46% to 3.2%); after 10 days the primary endpoint (30-day measure) was met in no BNP patient (0/275) and 1 of the immediately discharged group who died (1/275=0.4%); 3-mo recurrent VTE: NT-pro BNP group: 2 (0.73%; 0.1% to 2.6%) met outcome; immediately discharged group: 3 patients (1.1%; 0.2% to 3.2%) met outcome (*P*=.65)	Patients could have symptoms for ≤14 days and be included; treatment with LMWH-warfarin; not blinded treatment arms in follow-up; underpowered for a noninferiority design; unknown if ED study or outpatient clinic study (all authors outside emergency medicine); 28 patients excluded for reasons beyond Hestia because of large clot burden (11), positive troponin result/ECG result abnormal (10), delirium or cognitive dysfunction (7); patients in immediately discharged group were discharged within 24 h: 6 to 24 h, seemed more like observation unit stay; no breakdown of times by patient; Hestia-negative patients' upper limit of 95% CI of 3.2% of patients who may be discharged and experience primary endpoint, one third died, ≈1% of discharged patients at most and the 1 in this study occurred day 15 after likely admission if had been admitted; admission may not prevent death; Hestia-negative patients may still experience as much as 3.2% VTE during 3 mo as well; slightly more cancer in NT-pro BNP group than immediately discharged group; unable to determine value of elevated NT-pro BNP because of low number of patients with elevated levels ≥500

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Aujesky et al[61] (2011)	II	Prospective open-label randomized noninferiority trial in 19 international EDs from 2007 to 2010; adult patients with acute symptomatic objectively verified PE with low risk for death by PESI; chest pain or shortness of breath and PE on CT, arteriography, high-probability V/Q scan result or documentation of DVT by ultrasound or venography	Excluded: oxygen saturation <90%, partial pressure of oxygen <60 mm Hg, systolic blood pressure <100 mmHg, requiring narcotics for pain, active bleeding, risk of bleeding, renal failure, extreme obesity, heparin allergy or history of heparin-induced thrombocytopenia, receiving anticoagulation already, pregnancy, or barriers to treatment adherence or follow-up; had to be low risk of death by PESI (risk classes 1 or 2); patients randomized 1:1 inpatient or outpatient; treatment: enoxaparin injection with early warfarin for both inpatient and outpatient groups for 90 days; follow contact every day for first wk and then days 14, 30, 60, and 90 for recurrent (primary) VTE within 90 days, but also (secondary) major bleeding within 14 and 90 days, and death within 90 days	Randomized PESI 1 or 2 patients: 172 patients to the inpatient group and 172 patients to the outpatient group; 1 outpatient and 2 inpatients lost to follow-up, 2 inpatients withdrew; 1 (0.6%) outpatient had recurrent VTE and no inpatients had recurrent VTE meeting criteria for noninferiority; 3 episodes of major bleeding (1 after 14 days though) exceeded noninferiority threshold and were therefore notable; 1 patient in each treatment group died, supporting noninferiority for mortality (outpatient died of trauma and inpatient died of pneumonia)	Open-label trial: 17 of 470 patients (3.6%) eligible for the enrollment were not enrolled because the doctor declined enrollment of the patient; unknown outcomes for these patients; occurred before randomization; long duration ≥13 h before randomization for both groups; outpatient group remained in ED <24 h from randomization; most discharged patients leave in <6 h, so they were cared for much longer than normal; more major bleeding in outpatient group by 1 of the 3 occurred after day 14; if this one were excluded, then major bleeding would have been noninferior between groups; 30% of PE patients met criteria for outpatient management and 73% enrolled

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Davies et al[67] (2007)	III	Prospective multicenter cohort study in 2 phases; patients >18 y with signs or symptoms of possible PE, diagnosis of PE based on V/Q scan result, CT result, or positive lower-limb ultrasound; phase 1 was used to derive low-risk criteria for outcomes; phase 2 was performed to validate the criteria derived from phase 1	Exclusion: (1) Admission to hospital for another medical reason (eg, significant respiratory and/or cardiovascular disease and/or treatment for active malignancy); (2) additional monitoring required, such as ECG monitoring, or administration of any form of oxygen therapy for hypoxemia or of any intravenous drugs, including analgesia; (3) history of PE or further PEs developing while receiving anticoagulation treatment; (4) showing coexisting major DVT (high-segment femoral and above) confirmed by radiologic imaging; (5) bleeding disorders or active bleeding; (6) pregnancy; (7) likelihood of poor compliance or difficulty ensuring appropriate follow-up, including elderly patients with complex disease, the infirm, and those with significant immobility, geographic inaccessibility, or a history of noncompliance, and intravenous drug abusers; (8) patient preference; outcome measures included (1) early bleeding complications (during acute in-patient anticoagulation with LMWH); (2) later bleeding complications (ie, taking oral anticoagulants); (3) thromboembolic complications (with objective confirmation); and (4) mortality at 3 mo (the cause of death was taken from the death certificate entry and clarified by the lead clinician at the relevant site where possible)	Phase 1: N=225 among whom 202 were followed for 3 mo; during 3-mo follow-up there were 9 deaths, 6 major bleeding episodes,4 minor bleeding episodes, and 6 thromboembolic events; 85 of 202 patients were considered suitable for outpatient management; phase 2: N=157 patients among whom the median length of hospital stay before discharge was 1 day; there were no deaths during the initial 7 days of treatment; 3 patients were admitted with complications unrelated to PE; during the 3-mo follow-up there were 3 deaths (1.9%) and 1 minor bleeding event	Many patients spent more than 1 day in the hospital in the phase 2 validation; several of the reasons that were derived for hospitalization were largely subjective; no comparison group, all patients received the treatment; study not powered for safety and efficacy; unclear whether outcome assessors were blinded to risk factors

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Zondag et al[68] (2011)	II	Prospective cohort study of patients with objectively proven acute PE from 12 hospitals in the Netherlands; study objective: to determine incidences of VTE recurrence, major bleeding, and mortality in select patients deemed safe for outpatient management of PE	Excluded patients with asymptomatic PE or PE with symptoms >14 days; predefined criteria for outpatient therapy (Hestia) included whether capable of 3-mo follow-up and whether life expectancy >3 mo; treatment with LMWH (nadroparin) followed by VKA (procoumon or acenocoumarol); eligible patients sent home immediately or within 24 h after PE objectively diagnosed; primary outcomes: recurrent VTE (both DVT or PE) at 3 mo; secondary outcomes: major hemorrhage and mortality during 3-mo follow-up; patients evaluated at the outpatient clinic at 1 wk and 3 mo after presentation; 6-wk telephone contact planned; used acceptable outpatient recurrent VTE rate of 7%	N=297 (51%) of consecutive patients with PE; 3-mo follow-up completed for all patients; recurrent VTE 6 (2%; 0.8% to 4.3%) (5 PE and 1 DVT); mortality: 3 patients (1%; 0.2% to 2.9%) during 3-mo follow-up (none from PE); major bleeding: 2 patients (0.7%; 0.08% to 2.4%); 1 patient within 7 days (0.3%; 0.008% to 1.9%) and this patient had LMWH treatment violation; no patient with adequate treatment experienced a VTE or death within 7 days; wk 2 to 3 mo: 5 patients had recurrent VTE (4 PE, 1 DVT); 3 mo: total of 6 patients (2%; 0.8% to 4.3%) had recurrent VTE; safety: 2 patients (0.7%; 95% CI 0.08% to 2.4%) had major bleeding episode; mortality: 3 patients (1%; 0.2% to 2.9%) died during the study (1 intracranial bleeding and 2 cancer)	6.1% of patients were treated with LMWH alone for 6 mo for malignancy or allergy to VKA; 23% of patients admitted before diagnosis as a result of unavailability of a CT scan to make the diagnosis; considered acceptable outpatient recurrent VTE rate of 7% and it was 4%, none fatal; 68 of 297 (23%) admitted to hospital for <24 h "mainly because CT not available at night"; not able to blind endpoint ascertainment because single arm but performed according to predefined criteria; included patients from ED and outpatient clinic and never stratified by group

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Zondag et al[72] (2013)	III	Post hoc analysis of Hestia validation study	Compared Hestia vs sPESI rules; outcome: 3-mo occurrence of recurrent VTE, major bleeding, mortality	297 patients Hestia negative treated at home, and 233 excluded by Hestia and treated in the hospital; sPESI could be calculated in 468 of 530 patients, with 247 patients being treated at home; of 247 patients treated at home as part of Hestia screening, 189 (77%) would have been in low-risk sPESI group; at 7-day follow-up, 1 (0.4%) of the low-risk sPESI vs none of the Hestia experienced VTE; at 30-day follow-up, 4 (1.5%) low-risk sPESI vs 4 (1.6%) Hestia experienced VTE; 7-day major bleeding in 3 (1.1%) of low-risk sPESI vs 1 (0.4%) of Hestia negative, and 30-day major bleeding in 3 (1.1%) low-risk sPESI vs 1 (0.4%) of Hestia negative; mortality sensitivity: sPESI 91%, Hestia 82%; mortality NPV: sPESI 100%, Hestia 99%; mortality ROC curve AUCs: sPESI 0.756 (0.642 to 0.871), Hestia 0.679 (0.536 to 0.822); 7-day mortality sensitivity/specificity/NPV: sPESI 100%, 59.7%, 100%, respectively; Hestia 100%, 53.6%, 100%, respectively; 39% of low-risk sPESI could not have been treated at home by Hestia; one fourth of low-risk Hestia patients would not have been low risk by sPESI; Hestia allows low-risk patients with cancer to be treated at home as opposed to the sPESI	62 of 530 patients (11.7%) could not have sPESI calculated; sPESI calculated retrospectively; low incidence of mortality in the sample; unplanned post hoc analysis

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Piran et al[73] (2013)	III	Systematic review, meta-analysis of prospective diagnostic test evaluation, and randomized controlled trial studies	Only included prospective trials with PE proven by CT segmental or larger or high-probability V/Q scan (did not include indeterminate studies with DVT); assessed the methodologic quality of included studies using the Risk of Bias Assessment Tool from Cochrane; random-effects model used for pooling data; heterogeneity assessed	11 studies included (8 prospective cohort studies and 3 randomized controlled trials); 1,258 total patients; (8 of 11 studies treated the patients exclusively as outpatients and 2 studies treated patients after early discharge <3 days); recurrent VTE 1.47% (0.47% to 3.0%); fatal PE 0.47% (0.16% to 1.0%); major bleeding 0.81% (0.37% to 1.42%); fatal intracranial hemorrhage 0.29% (0.06% to 0.68%); overall mortality 1.58% (0.71% to 2.8%); no difference between groups risk stratifying using clinical gestalt and exclusion criteria vs published low-risk models; short-term outcome (<14 days) reported in 2 studies; pooled rate of VTE recurrence within 14 days: 0.28% (95% CI 0.13% to 0.89%); pooled rate of major bleeding 0.46% (95% CI 0.022% to 1.46%)	Many patients from the individual studies were not from the ED; combined patients from studies of lower quality with different definitions and different screening; Table 3 did not list upper limit of 95% CIs from studies; evidence-based on class II open-label randomized controlled trials, Class III, and even studies scored as an X by the methodology panel

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Zondag et al[74] (2013)	III	Systemic review, meta-analysis of randomized controlled trials, prospective and retrospective observational studies; objective: to evaluate whether outpatient treatment and early discharge are as safe as traditional inpatient treatment in patients with PE	Only included randomized controlled trials or cohort studies of acute symptomatic PE; early discharge had to be ≤ 3 days; main outcome: 3-mo pooled incidence of recurrent VTE, major bleeding and all cause-mortality; logistic regression used with random effects for study used to pool the data	Included 15 studies; all patients treated with LMWH and VKA or LMWH alone if indicated; recurrent VTE: no difference; 13 studies 1,657 patients; 33 recurrent VTE 1.7% (0.92% to 3.1%), none fatal; 3 studies 256 patients discharged early; 3 had recurrent VTE (1.1%; 0.22% to 5.43%); inpatient 4 studies 329 patients, 6 recurrent VTE (1.2%; 0.16% to 8.14%); major bleeding: no difference; outpatients 1,657 patients, 15 had major bleeding (0.97%; 0.58% to 1.6%); 256 patients discharged early and 2 patients major bleeding, both fatal (0.78%; 0.16% to 2.75%); inpatients: 383 patients, 4 major bleeding, nonfatal (1.0%; 0.39% to 2.75%); all-cause mortality: no difference; 1,657 PE outpatients, 49 died, none from PE (1.9%; 0.79% to 4.6%); 256 patients early discharge, 6 died (2.3%; 1.08% to 5.12%); 383 inpatients, 8 died (0.74%; 0.04% to 11.14%); estimates did not change after controlling for malignancies	Composed of many weaker studies with differing definitions; unknown how many patients were ED patients; no assessment of study quality; no assessment of heterogeneity; no sensitivity analysis using higher-quality studies; despite limitations, this analysis provides some information about patients with cancer who may be eligible for discharge

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Vinson et al[75] (2012)	III	Systematic review of 1 randomized controlled trial and 7 observational studies; planned meta-analysis to answer question: can selected outpatients with newly diagnosed PE be treated safely and effectively without hospitalization?	Excluded studies not defining objective outcome measures; assessed quality of studies using GRADE criteria; 3 studies used explicit risk stratification, the Geneva rule, a single laboratory value, BNP, and PESI; 5 studies did not use a risk-stratification tool and instead used general inclusion and exclusion criteria; treatment with LMWH while awaiting an oral VKA if prescribed; follow-up in 7 to 10 days often preceded by a telephone call; 5 studies included patient preferences; measured recurrent VTE, major bleeding and death	24 prospective studies that discharged patients with acute symptomatic PE without hospitalization; 17 excluded primarily for outcome measures not described; selected 8 studies; N=777 patients among 8 studies; no patients in any study were lost to follow-up; in 7 of 8 studies pooling 741 patients there was no case of VTE-related or hemorrhage-related death, 0% (0% to 0.62%); even if included the 1 study of 180-day follow-up then 2 deaths (0.26% upper CI=1%); 7 of 8 studies reporting 90-day follow-up reported nonfatal recurrent VTE 0% to 6.2% and major hemorrhage 0% to 1.2%; 2 studies 7- to 14-day follow-up (outcome rates not reviewed); in 1 study the patient satisfaction score did not differ between inpatients and outpatients	Patients were not necessarily from the ED; unable to perform meta-analysis with a random-effects model because of inherent heterogeneity and varying quality of studies; unpublished data were reported from larger studies queried; some patients transferred to “thrombosis unit” before discharge home; slightly different definitions of PE; studies included different types of patients (eg, some less cancer); variability in the use of risk-stratification tools; all observational studies were graded as “very low” evidence; some classified as X by methodology panel; exception was one that was classified as moderate

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Zondag et al[76] (2013)	III	Post hoc analysis of prospective data from the Hestia study; evaluated the clinical utility of Hestia criteria and the ESC criteria by assessing the specific test characteristics for predicting adverse events	RV function assessed by CT; patients divided into 3 groups: low risk (hemodynamically stable without RV dysfunction), intermediate risk (hemodynamically stable with asymptomatic RV dysfunction), high risk (if hemodynamically unstable, systolic blood pressure <100 mm Hg regardless of RV dysfunction); patients followed for 3 mo; outcomes: PE-related mortality, resuscitation after respiratory or cardiac arrest, need for mechanical ventilation or use of inotropic agents, administration of thrombolytic drugs or surgical embolectomy; CT measure of RV dysfunction; RV dysfunction considered absent if RV/LV ratio was 1.0 or less, modest RV dysfunction defined as a ratio >1.0 but ≤1.5, severe dysfunction defined as ratio >1.5; radiology reviewers blinded to clinical condition of patient	34 (6%) CT parameters could not be measured because of use of V/Q scan (18) or technical problems (16); CT: 275 patients treated at home and 221 treated in hospital; 3 hospital patients lost to follow-up; less RV dysfunction in patients treated at home (35%) than in hospital (59%) (P<.001); no RV dysfunction patient treated at home had an adverse event; moderate RV dysfunction had 6 times greater likelihood of adverse event; severe RV dysfunction had 47 times greater likelihood of adverse event; Hestia-negative patients were 65% no RV dysfunction and 35% with moderate RV dysfunction; no severe dysfunction; 3 outpatients died during 3 mo, all non-PE-related events; Hestia allowed more patients than the RV screen alone to be sent home safely	ESC criteria applied retrospectively; could not measure the added value of troponins; RV function measured by 1 radiologist; however, interobserver reliability of subset of patients was good; wide OR around RV association with adverse outcome so difficult to make firm conclusions; variability of CT equipment; 34 patients excluded because CT not used or there were technical problems; unclear about the accuracy of CT for RV dysfunction vs video echocardiography

Q5: In adult patients diagnosed with acute lower-extremity DVT who are discharged from the ED, is treatment with a NOAC safe and effective compared with treatment with LMWH and VKA?

Evidentiary Table (continued).

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Bauersachs et al[87] (2010)	II	Multicenter; randomized clinical trial of rivaroxaban vs conventional therapy	Adult patients with acute DVT without symptomatic PE; primary efficacy outcome: recurrent symptomatic VTE; primary safety outcome: major or clinically relevant nonmajor bleeding	N=3,449 patients; efficacy outcome: rivaroxaban 2.1% vs conventional 3.0%, HR=0.68 (95% CI 0.44 to 1.0); safety outcome: rivaroxaban 8.1% vs conventional 8.1%, HR=0.97 (95% CI 0.76 to 1.2)	Open label
Agnelli et al[88] (2013)	II	Multicenter; randomized, double-blinded, clinical trial of apixaban vs conventional therapy (enoxaparin followed by warfarin)	Adults with proximal DVT and/or PE; primary efficacy outcome was recurrent symptomatic VTE or death related to VTE; safety outcome was major bleeding	N=5,395 (total); N=3,532 with proximal DVT only; recurrent VTE in DVT group: apixaban 2.2% vs conventional 2.7%, risk difference: -0.5% (95% CI -1.5% to 0.6%); major bleeding: apixaban 0.6% vs conventional 1.8%, risk difference: -1.1% (95% CI -1.7% to -0.6%)	Double blinded, placebo controlled; minimal loss to follow-up; excluded patients with cancer, hemoglobin <9 mg, platelet count <100,000, and creatinine >2.5

Evidentiary Table (continued).

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Büller et al[89] (2013)	II	Randomized, double-blind, event-driven, noninferiority trial to compare patients with VTE to treatment with heparin plus edoxaban vs heparin plus warfarin for 3 to 12 mo; 439 centers, 37 countries	Diagnosed with acute DVT or PE and >18 y; randomized to heparin with edoxaban vs warfarin; all patients received initial therapy with open-label enoxaparin or unfractionated heparin for at least 5 days; edoxaban was started after discontinuation of initial heparin, warfarin started concurrently with heparin; primary efficacy outcome: recurrent symptomatic VTE; principal safety outcome: major or clinically relevant nonmajor bleeding	4,921 patients with DVT, 3,319 with PE; primary efficacy was recurrent VTE; primary efficacy for DVT-only cohort: 83 of 2,468 (3.4%) in edoxaban group, 81 of 2,453 (3.3%) in warfarin group, HR 1 (95% CI 0.8 to 1.4); primary safety for entire VTE cohort: 349/4,118 (8.5%) edoxaban, and 423/4,122 (10.3%) warfarin, HR 0.8 (95% CI 0.7 to 0.9; *P*=.004)	Sponsored by Daiichi Sankyo; edoxaban started only after treatment with heparin for 5 days; included both PE and DVT but broke the clinical outcomes data down by index DVT and index PE for primary efficacy outcomes but not primary safety outcomes; drug sponsor was responsible for the collection and maintenance of the data, but an independent committee (blinded to assignment) adjudicated the outcomes
Beam et al[90] (2015)	III	ED discharge and home treatment with rivaroxaban of low-risk VTE, included PE and DVT patients but broke it down by category; 2 urban EDs; prospective observational study at 2 academic EDs; standard care protocol	Standard care protocol: ED phase with VTE diagnosis and follow-up clinic phase; modified version on Hestia criteria used to identify low-risk patients; eligible patients received enoxaparin 1 mg/kg and one dose rivaroxaban 15 mg before discharge; clinic follow-up continued rivaroxaban treatment; call at 1-2 days post-discharge, clinic follow-up at 3 wk, second follow-up 3-5 mo; outcomes of protocol reported in 1 y	Outcomes – recurrent VTE, clinically significant bleeding (major bleeding or clinically relevant nonmajor bleeding; 106 patients, 71 with DVT, 30 with PE, 5 with DVT and PE; no patient developed a new or recurrent VTE during treatment; 6 mo after final patient enrolled, 3 patients had recurrent VTE; 82% of patients followed up in clinic first time, 63% followed up for second visit; 2 patients died, unrelated to VTE or rivaroxaban; no major bleeding event	Not randomized, biased sample; clinician judgment to enroll patient vs admit; one fourth of patients did not follow up

Evidentiary Table (continued).

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Buller et al[91] (2008)	III	Multicenter; randomized clinical trial of rivaroxaban (20-, 30-, and 40-mg arms) vs open-label standard therapy	Adult patients with acute, symptomatic DVT without PE; primary efficacy outcome was symptomatic recurrent VTE or asymptomatic deterioration in thrombotic burden at 3 mo; primary safety outcome was any clinically relevant bleeding	N=449 (per-protocol analysis); primary efficacy outcome: rivaroxaban 5.4% to 6.6% vs standard 9.9%; primary safety outcome: rivaroxaban 2.2% to 6.0% vs standard 8.8%	Phase 2 dose-finding trial; 17% randomized patients were excluded from per-protocol analysis

Evidentiary Table (continued).

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Schulman et al[92] (2009)	III	Randomized, double-blinded, noninferiority trial of patients with acute VTE given parenteral anticoagulation and then dabigatran vs warfarin	Patients from 228 clinical centers in 29 countries; >18 y with acute DVT or PE and for whom 6 mo of anticoagulant therapy was acceptable; all patients initially treated with parenteral anticoagulant (unfractionated heparin administered intravenously or subcutaneously administered LMWH) before randomization with dabigatran vs warfarin; primary outcome: 6-mo incidence of symptomatic recurrent VTE, objectively confirmed VTE, and deaths; safety outcomes: bleeding events, acute coronary syndrome, other adverse events, liver function tests	2,564 patients, 78.5% from Europe or North America; study drug stopped before 6 mo in 16.0% dabigatran, 14.5% warfarin; primary outcome for efficacy 2.4% dabigatran, 2.1% warfarin, no significant difference in efficacy; major bleeding episode 1.6% dabigatran, 1.9% warfarin; 9.0% dabigatran, 6.8% warfarin had adverse event that led to stopping study drug; dyspepsia more common in dabigatran group: 2.9% vs 0.6%	Funded, designed, conducted and analyzed by Boehringer Ingelheim; included both DVT and PE; parenteral anticoagulation required for both medications; patients in both arms received heparins; unclear whether patients were treated as inpatients or outpatients

Evidentiary Table (continued).

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Prandoni et al[93] (2015)	III	Retrospective, post hoc analysis of data collected in the EINSTEIN-DVT and EINSTEIN-PE studies; EINSTEIN was multicenter randomized open-label trial comparing efficacy and safety of rivaroxaban with standard therapy (enoxaparin and VKA) in patients with acute, symptomatic DVT and/or PE	Primary efficacy outcome was acute, symptomatic recurrent VTE; principal safety outcome was clinically relevant bleeding, which was defined as a composite of major and nonmajor clinically relevant bleeding; bleeding was defined as major if associated with a decrease in the hemoglobin level of ≥2.0 g/dL, led to the transfusion of ≥2 units of RBCs, was intracranial or retroperitoneal or occurred in another critical site, or contributed to death; nonmajor clinically relevant bleeding was associated with medical intervention, unscheduled contact with a physician, interruption or discontinuation of a study drug, or discomfort or impairment of activities of daily life	N=8,281 patients; 6,937 (83.8%) patients received prestudy heparin and 1,344 (16.2%) patients did not receive prestudy heparin; duration of prestudy heparin (LMWH, unfractionated heparin) limited to 1 day or less in most patients; incidence of recurrent VTE: patients who did not receive prestudy heparin: rivaroxaban 15 of 649 (2.3%) and enoxaparin and VKA13 of 695 (1.9%) (adjusted HR=1.11; 95% CI 0.52 to 2.37); patients who did receive prestudy heparin: rivaroxaban 54 of 3,501 (1.5%) and enoxaparin and VKA 69 of 3,436 (2.0%) (adjusted HR=0.74; 95% CI 0.52 to 1.06; *P*-value interaction=.32); incidence of major and nonmajor clinically relevant bleeding: patients who did not receive prestudy heparin: rivaroxaban vs enoxaparin and VKA 24 of 645 (3.7%) vs 30 of 688 (4.4%), adjusted HR=0.81 (95% CI 0.46 to 1.40; *P*-value interaction=.68); patients who received prestudy heparin: rivaroxaban vs enoxaparin and VKA 105 of 3,485 (3.0%) vs 104 of 3,428 (3.0%); adjusted HR=0.98 (95% CI 0.75 to 1.29)	Unplanned secondary analysis of EINSTEIN trials; indirect evidence, patients received heparin before NOAC, limited data for those who did not; study underpowered to detect interaction

Evidentiary Table (continued).

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Robertson et a[94] (2015)	III	Meta-analysis; Cochrane review to assess the effectiveness of oral DTIs and oral factor Xa inhibitors for the treatment of DVT	Included randomized controlled trials in which people with a DVT confirmed by standard imaging techniques were allocated to receive an oral DTI or an oral factor Xa inhibitor for the treatment of DVT; 2 primary outcomes were recurrent VTE and PE; other outcomes included all-cause mortality and major bleeding	11 randomized controlled trials of 27,945 participants; 3 studies tested oral DTIs (2 dabigatran and 1 ximelagatran), 8 tested oral factor Xa inhibitors (4 rivaroxaban, 2 apixaban and 2 edoxaban); meta-analysis of 3 studies (7,596 participants) comparing oral DTIs with standard anticoagulation groups showed no difference in the rate of recurrent VTE (OR 1.09; 95% CI 0.80 to 1.49), recurrent DVT (OR 1.08; 95% CI 0.74 to 1.58), fatal PE (OR 1.00; 95% CI 0.27 to 3.70), nonfatal PE (OR 1.12; 95% CI 0.66 to 1.90) or all-cause mortality (OR 0.84; 95% CI 0.62 to 1.15); oral DTIs were associated with reduced bleeding (OR 0.68; 95% CI 0.47 to 0.98); meta-analysis of 8 studies (16,356 participants) comparing oral factor Xa inhibitors with standard anticoagulation demonstrated a similar rate of recurrent VTE between the 2 treatments (OR 0.89; 95% CI 0.73 to 1.07); oral factor Xa inhibitors were associated with a lower rate of recurrent DVT (OR 0.75; 95% CI 0.57 to 0.98); however, this was a weak association, heavily dependent on 1 study; the rate of fatal PE (OR 1.20; 95% CI 0.71 to 2.03), nonfatal PE (OR 0.94; 95% CI 0.68 to 1.28), and all-cause mortality (OR 0.84; 95% CI 0.64 to 1.11) was similar between the 2 treatment groups; oral factor Xa inhibitors were also associated with reduced bleeding (OR 0.57; 95% CI 0.43 to 0.76)	100% of the included studies were funded by pharmaceutical industry; not clear whether the patients in the included studies were discharged from the ED

Evidentiary Table (continued).

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Cohen et al[95] (2015)	III	Meta-analysis of randomized clinical trials comparing NOACs vs conventional therapy	Adult patients with DVT and/or PE; efficacy outcome was recurrent VTE; safety outcomes were major bleeding, any clinically relevant bleeding, and mortality	6 trials included	Fixed-effect network meta-analysis
Kang and Sobieraj[96] (2014)	III	Adjusted indirect comparison meta-analysis to evaluate the comparative efficacy and safety of NOACs: rivaroxaban, apixaban, dabigatran, edoxaban	Systemic literature search in MEDLINE and Cochrane Central databases through November 2013 for randomized controlled trials evaluating patients with VTE treated with NOAC; Cochrane Risk of Bias tool used to assess the methodologic quality of the included trials; efficacy outcomes: mortality, recurrent symptomatic VTE, recurrent DVT, recurrent PE; safety outcomes: major bleeding	6 randomized controlled trials met inclusion criteria; total of 27,069 patients with acute VTE; included both DVT and PE patients; there were 21% to 31% of patients with PE, and both DVT and PE in 8% to 10% of included patients; NOACs did not differ significantly in the risk of mortality, recurrent VTE, recurrent PE or recurrent DVT; dabigatran increased major bleeding risk compared with apixaban (RR 2.7; 1.2 to 6.1) as did edoxaban compared with apixaban (RR 2.7; 1.4 to 5.4)	Includes both DVT and PE; adjusted indirect treatment comparison meta-analysis: data were generated with indirect evidence, not as precise as direct evidence; patients could have been treated with therapeutic anticoagulation doses before randomization; quality of individual studies not described and no comment made about heterogeneity

Evidentiary Table (continued).

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Di Minno et al[97] (2015)	III	Meta-analysis of randomized clinical trials comparing NOACs vs conventional therapy	Adult patients with DVT and/or PE; low body weight vs normal body weight vs high body weight; efficacy outcome was symptomatic recurrent VTE or VTE-related death; safety outcomes were major bleeding or clinically relevant nonmajor bleeding	6 trials included; efficacy outcome: (1) high body weight: NOACs 2.7% vs conventional 2.8%, RR 0.98 (95% CI 0.72 to 1.4); (2) normal body weight: NOACs 2.4% vs conventional 2.6%, RR 0.91 (95% CI 0.75 to 1.1); (3) low body weight: NOACs 2.6% vs 3.1%, RR 0.84 (95% CI 0.57 to 1.24); safety outcome: (1) high body weight: NOACs 6.7% vs conventional 7.1%, RR 0.93 (95% CI 0.65 to 1.3); (2) NOACs 6.5% vs conventional 7.9%, RR 0.82 (95% CI 0.67 to 1.0); (3) low body weight: NOACs 8.4% vs 10.1%, RR 0.80 (95% CI 0.54 to 1.2)	Fixed-effect network meta-analysis

AADD, age-adjusted D-dimer; *AUC*, area under the curve; *BNP*, b-type natriuretic peptide; *CI*, confidence interval; *CPR*, clinical prediction rule; *CT*, computed tomography; *CTA*, computed tomographic angiography; *CTPA*, computed tomographic pulmonary angiography; *dL*, deciliter; *DTI*, direct thrombin inhibitors; *DVT*, deep venous thrombosis; *ECG*, electrocardiogram; *ED*, emergency department; *ELISA*, enzyme-linked immunosorbent assay; *ESC*, European Society of Cardiology; *g*, gram; *GRADE*, Grading of Recommendations Assessment, Development and Evaluation; *h*, hour; *HR*, hazard ratio; *ICD-10*, International Classification of Disease, 10th Revision; *ICU*, intensive care unit; *INR*, international normalized ratio; *L*, liter; *LPTP*, low pretest probability; *LR*, likelihood ratio; *LMWH*, low-molecular-weight heparin; *LV*, left ventricular; *MDCT*, multidetector computed tomography; *mL*, milliliter; *mm Hg*, millimeters of mercury; *mo*, month; *N*, number; *ng*, nanogram; *NOAC*, non–vitamin K antagonist oral anticoagulant; *NPV*, negative predictive value; *NT-proBNP*, N-terminal pro b-type natriuretic peptide; *OR*, odds ratio; *PE*, pulmonary embolism; *PERC*, pulmonary embolism rule-out criteria; *PESI*, Pulmonary Embolism Severity Index; *PTP*, pretest probability; *RBC*, red blood cell; *ROC*, receiver operating characteristic; *RR*, relative risk; *RV*, right ventricular; *sPESI*, simplified Pulmonary Embolism Severity Index; *VKA*, vitamin K antagonist; *VLPTP*, very low pretest probability; *V/Q*, ventilation-perfusion; *vs*, versus; *VTE*, venous thromboembolism; *wk*, week; *y*, year.