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SPECIAL ARTICLE

Diagnosis of Venous Thromboembolism: 20 Years of Progress

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Many guidelines suggest incorporating clinical assessment, imaging, and D-dimer testing into diagnostic algorithms in patients with suspected deep venous thrombosis (DVT) and pulmonary embolism (PE). This special article reviews the evidence supporting the use of algorithms and their individual components for diagnosis of upper- and lower-extremity DVT and PE in adults, including pregnant women. The authors identified evidence through several electronic database searches to April 2017, evaluated the robustness of selected evidence, assessed whether diagnostic approaches that do not use algorithms are acceptable, and identified knowledge gaps that require further research.

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Venous thromboembolism (VTE), which includes deep venous thrombosis (DVT) and pulmonary embolism (PE), is the third most common cardiovascular disorder; it has an estimated annual incidence of 0.1% and affects up to 5% of the population during their lifetimes (1). Pulmonary embolism is implicated in the death of more than 10% of hospitalized patients (1). Because an estimated 20% of patients with PE will die on or before the first day after diagnosis, prompt detection is critical (2). Initiating anticoagulant therapy in cases of suspected VTE before a confirmatory diagnosis is safe in outpatients but has not been studied in hospitalized patients (3). Given the risk for death with no treatment in patients with VTE and the risk for major hemorrhage associated with anticoagulant therapy, accurate and timely diagnostic strategies must be used. However, data suggest that physicians are unaware of the options and default to—and overuse—diagnostic tests (4).

Gold standard diagnostic tests exist but are rarely used because of cost and inconvenience. Clinicians must strive to use tests and strategies that are as safe as the gold standard. Safety is measured by the risk for a VTE event in the 3 months after a negative finding: The ideal target is 1.3% for DVT (as achieved with intravenous contrast venography) and 1.6% for PE (with invasive contrast pulmonary angiography) (5, 6). Attempts to achieve the same VTE follow-up rate as with the gold standard may lead to an unacceptable tradeoff in increased imaging and false-positive diagnoses. Many studies have evaluated clinical prediction tools, imaging tests, D-dimer testing, and management strategies. We reviewed this work to summarize what is reliable and where future efforts should be directed.

Methods

We searched Embase Classic, Embase, Ovid MEDLINE, and other nonindexed citations from inception to 30 April 2017 to find English-language systematic reviews or meta-analyses and randomized controlled trials that evaluated diagnostic strategies for VTE. Of 1008 nonduplicate references identified in these searches, 280 articles were meta-analyses or systematic reviews. Two authors (P.S.W. and M.A.F.) independently evaluated these 280 articles and found that 245 were related to diagnosis and, of those, 200 were potentially relevant to our overview. For important topics not covered by the systematic reviews and meta-analyses, we reviewed the abstracts of the 728 randomized controlled trials identified in the searches for relevance. We also reviewed the ninth and tenth editions of the American College of Chest Physicians antithrombotic therapy guidelines, bibliographies of included studies, and our own literature database (RefMan, version 12) of 9238 articles to identify well-done prospective studies when no relevant randomized trials or meta-analyses were found.

We focused our overview on meta-analyses that we judged to be of medium or high quality using the AMSTAR tool (7). When we found several meta-analyses, we took the study with the best methodological quality; when reports had similar quality, we took the most recent. We focused our review of randomized trials and prospective studies on those that we judged to be "acceptable" using the SIGN (Scottish Intercollegiate Guidelines Network) 50 checklist (8). In the end, 27 meta-analyses or systematic reviews, 7 randomized trials, and 20 prospective studies informed our overview, which was not funded by any outside source. (**Appendix Tables 1** to **3**, available at Annals.org, show our quality assessments of these studies.)

Clinical Diagnosis of VTE

The signs and symptoms of DVT and PE are not specific, but determining pretest probability has value. Several prediction models and rules categorize pretest DVT and PE as low, moderate, or high probability or "likely" versus "unlikely" (9–11). As initially shown in the PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) study in patients with suspected PE (12), a low pretest probability of PE is associated with a higher likelihood that a positive finding will be false-positive because a high-probability ventilation–perfusion (V/Q) scan was diagnostic for PE in only 40%

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Table 1. Details of the DVT Clinical Probability Scores

Variable	Points
Wells rule*	
Active cancer (treatment ongoing or within the previous 6 mo or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for >3 d or major surgery, within 4 wk	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by >3 cm when compared with the asymptomatic leg (measured 10 cm below the tibial tuberosity)	1
Pitting edema (greater in the symptomatic leg)	1
Collateral superficial veins (nonvaricose)	1
History of DVT	1
Alternative diagnosis as likely as or more likely than DVT	−2
Oudega rule†	
Male sex	1
Oral contraceptive pill use	1
Presence of active cancer (within the past 6 mo)	1
Major surgery (within the past 3 mo)	1
Absence of leg trauma	1
Vein distention	1
Calf swelling ≥3 cm	2
Abnormal results on D-dimer testing	6

DVT = deep venous thrombosis.
* Using the original score, <0 points indicates low probability, 0–2 points indicates intermediate probability, and >2 points indicates high probability. Using the dichotomized score, ≤1 point indicates that DVT is unlikely and ≥2 points indicates that DVT is likely.
† ≤3 points indicates that that the patient should not be referred for compression ultrasonography and ≥4 points indicates that the patient should be directly referred for compression ultrasonography.

of patients with low clinical probability versus 96% of those with high clinical probability. Conversely, 56% of patients with high pretest probability had PE despite a low-probability V/Q scan, and only 4% of low-probability patients with a low-probability scan had PE (13). Table 1 shows variables and scoring for 2 clinical probability scores for DVT (Wells and Oudega). At least 14 studies involving more than 10 000 outpatients have shown that the Wells DVT model—the value of which we first demonstrated 20 years ago (14, 15)—is accurate and reproducible. Table 2 shows variables and scoring for 4 PE clinical probability scores (original Geneva, modified Geneva, Pulmonary Embolism Rule-out Criteria [PERC], and Wells).

The Wells and modified Geneva rules have been studied in more than 55 000 patients with suspected PE (16). We believe that the 2 rules have similar reliability and accuracy, although 1 study suggested that the Wells rule is more accurate as measured by the receiver-operating characteristic curves (17). Most studies showed moderate to substantial interrater agreement and reproducibility of the Wells rule (18–20). Another study showed that trainees can safely use the Wells rule for PE (21). Although not a pretest probability tool, the PERC rule will rule out PE without further testing when used for patients with low suspicion of PE (22). Some data suggest that a gestalt approach can be used (23); however, we believe that those results should be carefully interpreted because clinicians using gestalt often disagree on pretest probability and the physicians using that method in the studies likely had knowledge of existing prediction rules (24, 25).

Simpler models may be beneficial. Although recent studies suggest that the Geneva and Wells rules for PE can be simplified without loss of accuracy, prospective validation is required (25). The specificity of these rules decreases slightly in elderly persons, and fewer elderly than younger patients are classified as having low probability of PE (26). In addition, these DVT and PE rules have not been extensively studied in hospitalized patients. The DVT model was accurate in 1 prospective study but not in another (27, 28). Similarly, although 1 study reported successful use of the PE rules (29), data are limited, so neither can be recommended for use in hospitalized patients.

D-Dimer

D-dimer, a degradation product of cross-linked fibrin, is typically elevated not only in patients with acute VTE but also in those with nonthrombotic disorders. D-dimer is a diagnostic (not screening) test used as an exclusion tool; its value resides in a negative result. If VTE is not a diagnostic possibility, a D-dimer test should not be done because positive results may direct the clinician away from investigating the true cause of the symptoms toward unnecessary evaluation for VTE. Knowledge of the D-dimer result influences physician assessment of clinical probability (30).

In general, D-dimer testing has good sensitivity but poor specificity. The pooled sensitivity for the quantitative latex and enzyme-linked immunosorbent assays is more than 93% for DVT and 95% for PE, with corresponding specificities of 53% and 50% (31). High sensitivity is also possible with certain point-of-care D-dimer tests in outpatients (32).

High-sensitivity D-dimer assays cannot be used in isolation to exclude VTE. D-dimer assays have lower sensitivity for calf DVT (33) and are not useful in hospitalized patients.

Imaging Tests for DVT

Suspected First DVT

Compression ultrasonography is highly sensitive and specific for a first episode of DVT (34, 35) using 1 of the following 3 imaging strategies: stopping at the calf trifurcation where the veins of the calf join the popliteal vein, with negative findings followed by a repeated (serial) test in 1 week; 2-point ultrasonography, which involves scanning only the common femoral and popliteal trifurcation regions, with negative findings requiring a serial test; and scanning from the common femoral vein distally in approximately 3-cm increments, including the deep veins of the calf ("whole-leg ultrasonography"), with no need for a serial test. The risk for VTE after these strategies is remarkably low (<1%) (34, 35). Studies using computed tomography (CT) venography report a pooled sensitivity of 96% and a specificity of 95% (36). With magnetic resonance venography, sensitivity is 93% and specificity 96% for the diagnosis of DVT (37).

With 2 of the ultrasonography approaches, a repeated test is required 1 week after initially normal findings. In choosing a strategy, the clinician should consider patient adherence for the repeated test and patient convenience because whole-leg ultrasonography avoids serial testing. Although data show that ultrasonography is very accurate, it may be user-dependent. Accuracy data from studies where ultrasonography was done by dedicated technicians could have been influenced by training and experience. Data suggest that imaging done by emergency physicians, less trained than technologists, is accurate for diagnosis and exclusion of proximal DVT, but exact training requirements to achieve sufficient expertise remain poorly defined (38). The studies assessing the diagnostic value of CT and magnetic resonance venography were of low quality, so reported accuracy estimates cannot be considered definitive (36, 37). Studies informing the magnetic resonance venography meta-analysis were evaluated using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) criteria; the articles had average or poor methodology due to lack of detail in patient selection and differences in reference standards. Although we included 23 studies, only 1121 cases informed the results. This was similar for the meta-analysis of CT. Therefore, CT venography and magnetic resonance venography cannot be recommended for routine diagnosis.

Suspected Recurrent DVT

Ultrasonography findings suggestive of chronic thrombi include isolated wall thickening; venous synechiae; echogenicity; and nonocclusive, discrete, noncontinuous thrombi (39). Such findings, however, have not been validated as diagnostic of recurrent DVT. A validated approach is baseline ultrasonography on discontinuation of anticoagulation therapy to provide a comparison scan for future suspected events. A randomized trial showed higher levels of interobserver agreement on diagnosis of recurrent DVT with the availability of baseline ultrasonography (40). Baseline ultrasonography at the time of anticoagulant withdrawal in patients with low risk for recurrence is unlikely to be cost-effective. For patients with persistent thrombosis, a 4-mm increase in clot diameter or evidence of new areas of thrombosis is suggestive of recurrence (41).

The best criteria for diagnosing DVT in patients with prior DVT are not established, and compression ultrasonography may be falsely positive. The criterion of vein compressibility may not distinguish patients with acute recurrent DVT from those with chronic findings.

Imaging Tests for PE

Among the many imaging tests for PE, V/Q lung scans and CT pulmonary angiography (CTPA) are the best-validated and most widely used. Others include lower-extremity compression ultrasonography, thoracic ultrasonography, and magnetic resonance imaging (MRI). A randomized trial that compared V/Q scanning with CTPA found that CTPA detected approximately 5% more PE; however, patients in whom PE was excluded with V/Q scanning were not more likely to return with consequences of undetected VTE than those in whom PE was ruled out by CTPA (42). For most clinicians, CTPA is the preferred test because of its higher sensitivity and simpler reporting system. A meta-analysis suggested a sensitivity of 86% and a specificity of 94%

Table 2. Details of the PE Clinical Probability Scores

Variable	Points
Original Geneva rule*	
Age	
60–79 y	1
≥80 y	2
Previous DVT or PE	2
Recent surgery within 4 wk	3
Heart rate >100 beats/min	1
$Paco_2$	
<35 mm Hg	2
35–39 mm Hg	1
40–48 mm Hg	4
49–59 mm Hg	3
60–71 mm Hg	2
72–82 mm Hg	1
Band atelectasis on radiography	1
Elevation of hemidiaphragm on radiography	1
Modified Geneva rule†	
Age ≥65 y	1
Previous DVT or PE	3
Surgery or fracture within 1 mo	2
Active cancer	2
Unilateral lower limb pain	3
Pain on deep palpation of lower limb and unilateral edema	4
Hemoptysis	2
Heart rate	
75–94 beats/min	3
≥95 beats/min	5
PERC rule‡	
Hypoxia (Sao_2 <95%)	–
Unilateral leg swelling	–
Hemoptysis	–
Prior DVT or PE	–
Recent surgery or trauma	–
Age >50 y	–
Hormone use	–
Tachycardia	–
Wells rule§	
Signs or symptoms of DVT	3
Alternative diagnosis is less likely than PE	3
Heart rate >100 beats/min	1.5
Immobilization/surgery in previous 4 wk	1.5
History of DVT or PE	1.5
Hemoptysis	1
Active cancer	1

DVT = deep venous thrombosis; PE = pulmonary embolism; PERC = Pulmonary Embolism Rule-out Criteria.
* <5 points indicates low probability, 5–8 points indicates intermediate probability, and >8 points indicates high probability.
† Using the modified score, <3 points indicates low probability, 4–10 points indicates intermediate probability, and >10 points indicates high probability. Using the simplified score, ≤2 points indicates that PE is unlikely.
‡ Absence of all variables classifies the patient as having no risk for PE.
§ Using the traditional score, >6.0 points indicates high probability, 2.0–6.0 points indicates moderate probability, and <2.0 points indicates low probability. Using the simplified score, >4 points indicates that PE is likely and ≤4 points indicates that PE is unlikely.

for CTPA, whereas the sensitivity and specificity of V/Q scanning were 39% and 97%, respectively (43). This meta-analysis predated widespread use of more sensitive CT scanners, which likely have sensitivities much higher than 86%. Outcome studies suggest that normal CTPA alone has an overall negative predictive value approaching 99% (44).

Single-photon emission CT (SPECT) V/Q technology may have similar diagnostic accuracy to multislice CTPA (45). The most discriminant cutoff for PE may be at least 1 segmental or 2 subsegmental mismatches (46).

Lower-extremity ultrasonography may be used as the initial test in patients with suspected PE (47). Ultrasonography is particularly useful in the initial assessment of patients with symptoms of DVT (in whom the prevalence of DVT is up to 40% in patients with PE), where diagnostic imaging for PE is not widely available, or when CTPA is contraindicated (47, 48). Proximal vein ultrasonography has a sensitivity of 41% and a specificity of 96% (48). Patients with signs and symptoms of DVT are 4 times more likely to have DVT on ultrasonography. The sensitivity and specificity of MRI are about 81% and 96%, respectively, but 19% of scans may be inconclusive (49). The newer technique of transthoracic ultrasonography has a sensitivity of 85% and a specificity of 83% (50).

Because of widespread availability and direct visualization of emboli, CTPA is increasingly being used to evaluate patients with clinically suspected PE. However, use in isolation is somewhat limited by its sensitivity and detection of subsegmental PE, which are often false-positive findings (43, 51, 52). Its disadvantage compared with V/Q scanning is the radiation dose and contrast dye exposure, but accuracy can be preserved with a 30% reduction in radiation dose and a 25% lower volume of contrast media (53). Regardless of the preference for CTPA, planar V/Q scanning is a reliable test for PE; negative predictive value is very high; and it can be used when a low radiation dose is desirable, such as in young patients and women (12, 54). The use of planar V/Q scanning is also supported by the results of management studies (55), although the positive predictive value of a high-probability V/Q scan with low clinical probability was only 40% in PIOPED (12). Studies of SPECT V/Q scanning were heterogeneous, using different reference standards and designs, and all had high risk of bias. No studies assessed the diagnostic utility of SPECT V/Q scanning in management strategies. Prospective multicenter studies are needed to define the place of SPECT V/Q scanning; it is possible that combining this method with CT may be a better option. Magnetic resonance imaging technology is advancing but neither it nor transthoracic ultrasonography is accurate for detection of PE.

Diagnostic Algorithms for DVT

Algorithms use combinations of tools and tests; several for DVT have been studied. Initial normal findings from limited 2-point ultrasonography combined with a negative result on high-sensitivity D-dimer testing rule out DVT (56). This strategy has been directly compared with whole-leg ultrasonography. Patients received "limited" ultrasonography with serial compression ultrasonography if D-dimer results were positive and the initial findings from compression ultrasonography were negative, or 1 whole-leg ultrasound (57). Rates of VTE during follow-up in those in whom DVT was excluded were 7 of 801 (0.9%) and 9 of 763 (1.2%), respectively (57). In a second study, patients with a "likely" clinical probability or an elevated D-dimer level had either 2 serial "limited" scans or 1 whole-leg ultrasound; follow-up VTE rates were 2.0% and 1.2%, respectively (58). In the whole-leg ultrasound strategy, calf DVT was treated but clinical outcomes were the same, suggesting that many calf DVTs do not require anticoagulant treatment (58). From this and many earlier studies of serial limited ultrasonography, we can hypothesize that calf DVT that has not propagated after 7 days may be less clinically important. No study has used clinical probability in conjunction with a single whole-leg ultrasound, but modeling suggests an unacceptable 2.5% false-negative rate of normal ultrasonography findings in patients with high or likely clinical probability for DVT (59).

A strategy that uses serial "limited" ultrasonography only in patients with both a "likely" probability and an elevated D-dimer level after an initial normal finding from ultrasonography is as safe as serial ultrasonography on all patients to exclude DVT (60). Patients with an unlikely (or low or moderate) clinical pretest probability with a positive D-dimer test result can be managed with a single limited ultrasound, and if the D-dimer result is negative, DVT can be ruled out without ultrasonography (60). A negative D-dimer result should not be used to exclude VTE in patients who have a high pretest probability. However, using a negative D-dimer result to exclude DVT in patients at low and moderate risk is standard practice. High-quality data support the safety of this approach: The false-negative rate for exclusion of DVT with low and moderate clinical probability and a negative D-dimer result is 1.0% (11). A higher cut point for a negative D-dimer result (1000 μg/L) may be used if clinical probability is low (61).

The Oudega rule, a DVT clinical prediction rule with the D-dimer result embedded in the score, has been used in primary care (62). A prospective validation study in the Netherlands reported the false-negative rate of this rule as 1.4% (95% CI, 0.6% to 2.9%) (63). It has not been used outside the Netherlands or within hospitals and thus cannot be recommended.

Figure 1 shows the validated diagnostic approaches in outpatients with suspected DVT. Hospitalized patients with clinical suspicion of DVT should proceed directly to whole-leg ultrasonography. Many physicians struggle with the concept of not diagnosing and treating calf DVT. D-dimer testing has less utility in patients older than 80 years, but a recent high-quality meta-analysis reviewing the diagnostic accuracy of D-dimer testing in older patients (>50 years) suggested that varying the cut point (the value at which the test result is considered positive) by patient age (cut point is

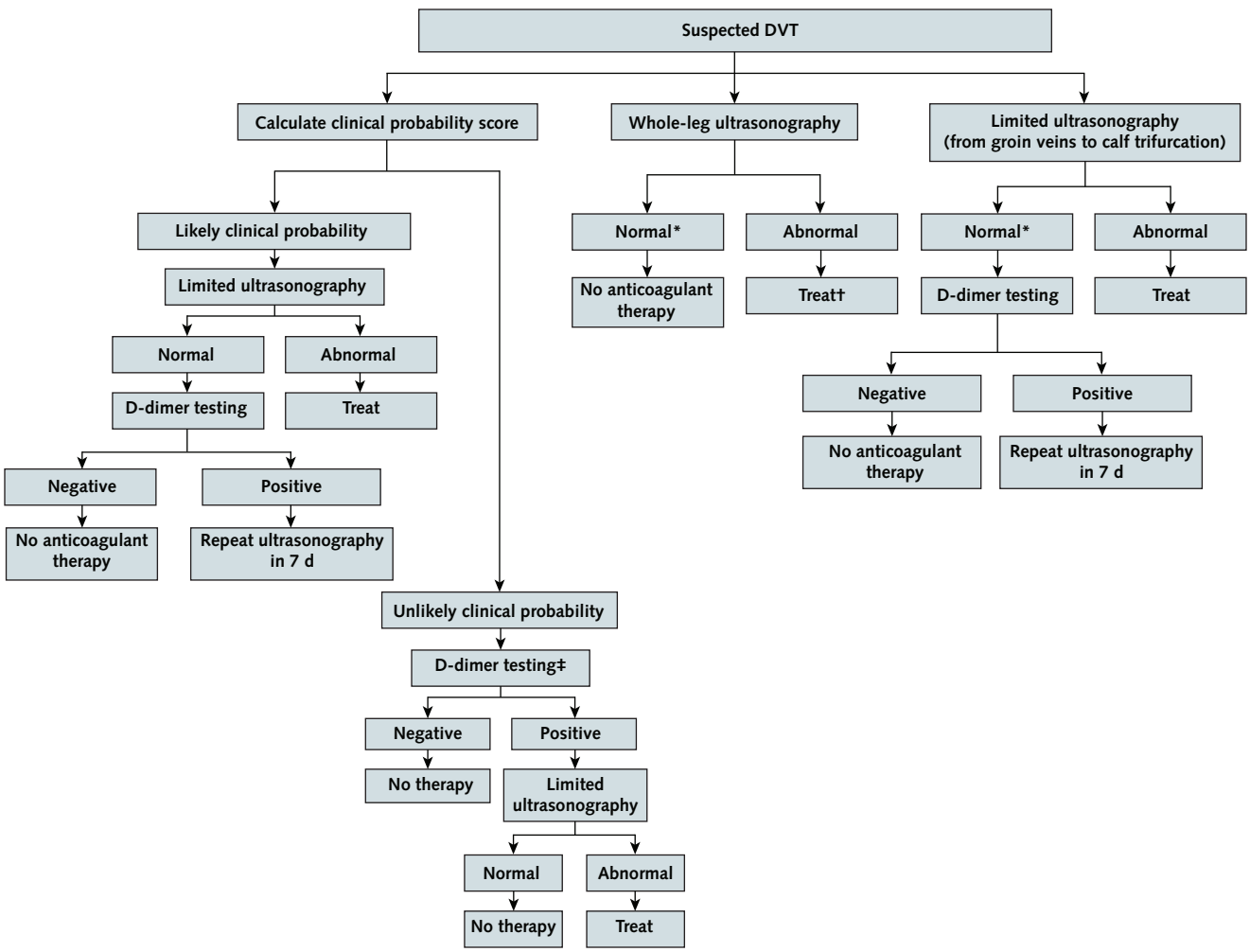
determined by age × 10 μg/L) can safely exclude more patients from imaging (64). This change in cut point enables sensitivity to remain above 97%, but specificity increases substantively–for example, from 25% to 44% in patients aged 71 to 80 years.

Diagnostic Algorithms for PE

Combining CTPA with clinical assessment has high positive and negative predictive value in both first and recurrent PE in outpatients (65, 66). Positive findings on CTPA can be considered diagnostic if the pretest probability is high or the PE is in a segmental vessel or larger, but not when the pretest clinical probability is low or "unlikely" or the PE is in the subsegmental arteries. In the latter cases, the results should be reviewed with a radiologist to consider a false-positive result because anticoagulation could lead to more harm than benefit (43, 65). The safety of using a pretest probability of low, moderate, or unlikely in combination with a negative quantitative D-dimer result to rule out PE without imaging tests is well-validated (negative predictive value, 99.6% [CI, 99.2% to 99.7%]) (16, 67). A prospective cohort study showed that an age-adjusted D-dimer cut point can be safely used in this algorithmic approach (68). The Wells model has been simplified by assigning 1 point to all variables, measuring D-dimer levels if the score is 0 or 1, and going directly to CTPA if the score is greater than 1. This simplified model, in combination with the age-adjusted D-dimer, performs as well as the more complex scoring system (69). In patients with low pretest probability, PERC can safely identify those in whom D-dimer and imaging tests are not necessary (22); however, it should not be applied to patients at intermediate or high risk for PE.

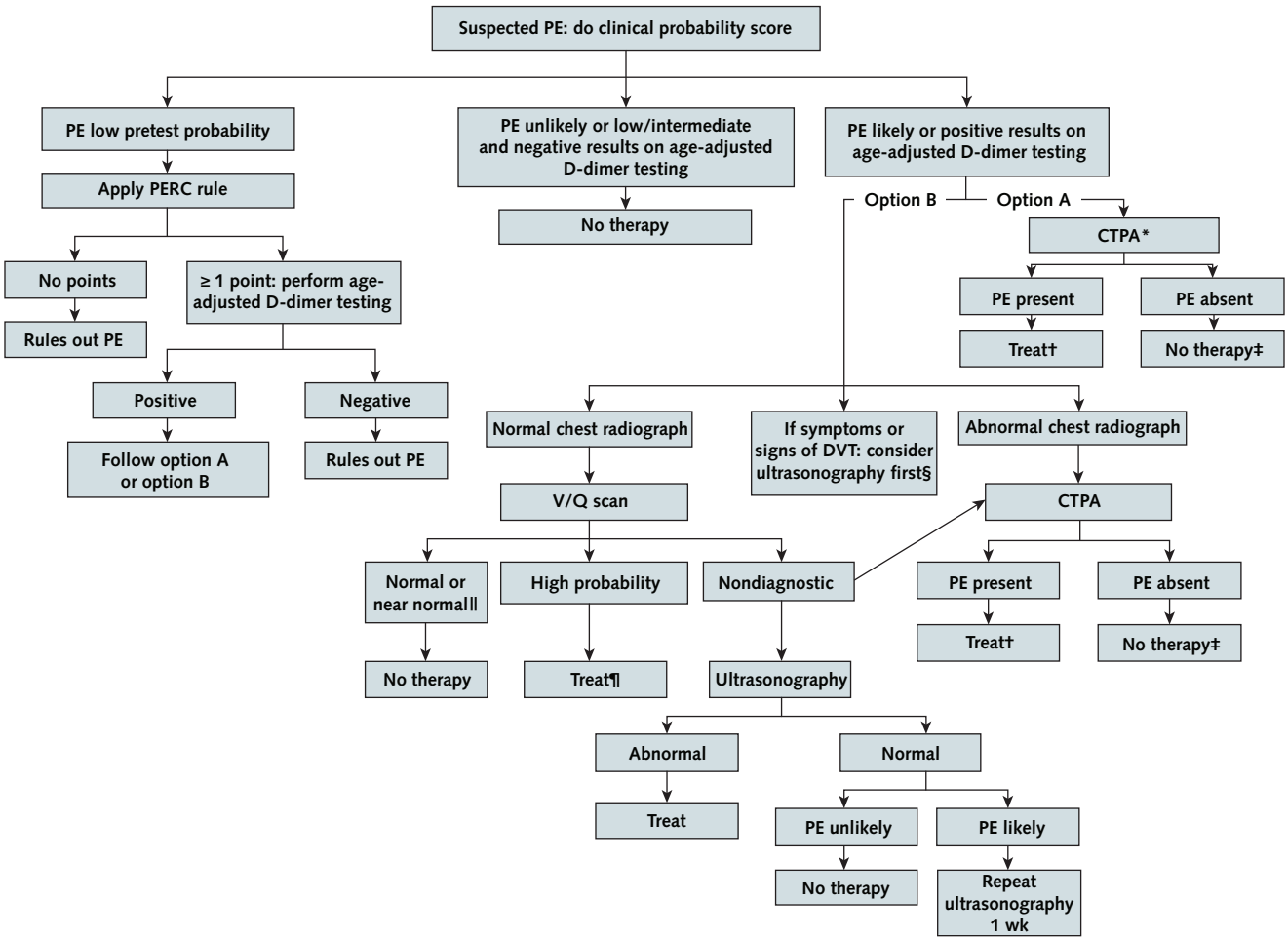
Appropriate use of V/Q scanning in a validated diagnostic algorithm yields similar outcomes to CTPA (42, 55), although angiography produces fewer nondi-

Figure 1. Diagnostic management of outpatients with suspected DVT.



DVT = deep venous thrombosis.
* Approximately 2.5% of results will be false-negative if clinical probability is high.
† Calf DVT will be up to 35% of DVT detected, and whether treatment is needed is unclear.
‡ Consider use of age-adjusted D-dimer.

Figure 2. Diagnostic management of outpatients with suspected PE.



CTPA = computed tomography pulmonary angiography; DVT = deep venous thrombosis; PE = pulmonary embolism; V/Q = ventilation–perfusion; PERC = Pulmonary Embolism Rule-out Criteria.

* Using CTPA as the only managing test in patients with PE likely or positive D-dimer results is an acceptable strategy, but if signs and symptoms of DVT are present, ultrasonography can be done first.

† Subsegmental or single segmental PE; confirm test result with radiology. Conventional angiography or V/Q scanning may help determine whether the diagnosis is correct. Withholding treatment and using serial ultrasonography can be considered.

‡ If (≥16-row) CTPA evidence suggests leg vein DVT, ultrasonography is not required, but we recommend ultrasonography if the patient has signs and symptoms of DVT.

§ Ultrasonography findings are positive in >20% of patients with symptoms and >50% of those with high clinical probability of PE and clinical symptoms of DVT. If ultrasonography findings are negative, proceed to CTPA or V/Q strategy. Avoid using ultrasonography alone if value is attached to images obtained by CTPA.

‖ If PE was likely and V/Q scan was near normal or low probability, age-adjusted D-dimer test (negative result is <500 μg/L if patient is aged <50 y; otherwise, negative result is <age × 10 μg/L) can be used to guide next steps. If D-dimer result is positive, serial ultrasonography or CTPA can be used at this point; if D-dimer result is negative, stop.

¶ If PE was "unlikely" or low probability, results will be false-positive in up to 30% of patients.

agnostic tests. With normal findings from a chest radiograph, an algorithm using V/Q scanning could be considered. In patients with either nondiagnostic V/Q results and high clinical probability or high-probability V/Q scans and low clinical probability, CTPA can be used. This strategy would avoid angiography in 89% of patients. The use of pretest probability in conjunction with imaging also allows for identification of potentially false-positive imaging findings. The posttest probability of PE with positive findings from CTPA was 30% (70% false-positive) in patients with low pretest probability and 84% in those with moderate pretest probability (43). If this is not acknowledged, many patients will incorrectly receive anticoagulants. Positive scans in low-probability patients should be reviewed with an imaging expert.

Acceptable algorithms for diagnosing PE are in Figure 2. The American Board of Internal Medicine Foundation Choosing Wisely campaign encourages evidence-based, quality-improving, resource-sparing medical practice. Both the American College of Radiology and American College of Physicians recommend using pretest probability in the investigation of suspected PE. A medium-quality systematic review of 13

studies evaluating the cost-effectiveness of incorporating CTPA into the diagnosis of PE concludes that CTPA combined with D-dimer testing or ultrasonography is the most cost-effective method for diagnosing PE (70). All included studies used clinical probability assessment.

High-quality data support the use of algorithms, although error rates are high if the algorithms are not followed carefully (71). Most studies were done in outpatients. Hospitalized patients should proceed directly to an imaging approach, usually CTPA, if PE is clinically suspected. Future research should aim to enroll inpatients, validate the simplified rules, create strategies around the high potential for false-positive results in patients with low pretest probability, and confirm the safety of D-dimer cut points that vary on the basis of pretest probability and age.

Diagnosis of DVT and PE in Pregnancy

Approximately 60% of pregnancy-related DVT is diagnosed before delivery, and 80% is found in the left leg (72, 73). Only 1 small review informs the use of objective testing and ultrasonography (74). If ultrasonography findings from the common femoral vein distally to the calf trifurcation were normal at presentation and D-dimer results were normal, or if an abnormal D-dimer finding was combined with normal results on serial ultrasonography, DVT was safely excluded (negative predictive value, 100% [CI, 92% to 100%]).

Diagnostic imaging algorithms for DVT in nonpregnant patients may be less applicable because routine ultrasonography has low sensitivity for DVT isolated to the iliac vein. In patients with swelling of the entire leg, buttock, or flank or back pain and normal findings on ultrasonography, we suggest using either ultrasonography to evaluate the iliac vein or MRI, rather than serial ultrasonography. Ultrasonography seems safe, but larger confirmatory studies are needed. For patients with clinically suspected PE, the initial test should be bilateral lower-extremity ultrasonography. If DVT is not detected, pulmonary imaging is indicated. The choice between V/Q scanning and CTPA is controversial, but for most patients with normal findings on chest radiography, V/Q scanning is the recommended test; otherwise, CTPA should be the first test (75). A V/Q scan results in more, albeit low, radiation exposure to the fetus; angiography results in more radiation and contrast dye exposure to the mother. Nondiagnostic V/Q scans require further investigation by angiography or serial ultrasonography, but neither approach has been well-studied.

Diagnosis of Upper-Extremity DVT

Upper-extremity DVT is uncommon, accounting for about 10% of all cases of DVT (76). Provoked DVT of the upper extremity is the most common (central venous catheters, pacemaker wires, and cancer-associated) (77). Although ultrasonography is the most commonly used test, visualization of the portion of the subclavian vein that lies beneath the clavicle and the location of the innominate veins and superior vena cava render compression in these areas impossible. Thus, upper-extremity DVT is generally diagnosed using combined-modality ultrasonography by demonstrating either noncompressibility of the vein or absence of a Doppler signal. A management study by Kleinjan and colleagues (78) showed that combining a clinical decision score, D-dimer testing, and ultrasonography (a strategy identical to that outlined for lower-extremity DVT) was safe and effective.

Kleinjan and colleagues' algorithm may be the ideal approach, but it requires validation. The ninth edition of the American College of Chest Physicians guidelines for antithrombotic therapy and prevention of thrombosis recommend further confirmatory testing with venography in patients with negative findings from combined-modality ultrasonography and a positive D-dimer result if no alternative explanation exists for their symptoms; however, the less invasive algorithmic approach may be a better strategy (59).

Conclusions and Relevance

Considerable evidence shows that an algorithmic approach using a combination of pretest clinical probability and D-dimer testing followed by accurate imaging tests in selected patients is the safest and most cost-effective diagnostic approach in outpatients with suspected VTE. The use of clinical decision rules in combination with D-dimer testing has standardized the diagnostic approaches for VTE. However, many gaps in knowledge remain. Imaging tests alone are reasonably accurate, but using them without considering pretest probability and D-dimer levels causes overtesting, with associated costs and risks. Many other imaging techniques, such as MRI and SPECT V/Q scanning, have been studied, but the quality of evidence from such studies is limited. Further research is needed in patients with suspected upper-extremity DVT and in pregnant women. Imaging without the use of clinical probability and D-dimer testing is appropriate in hospitalized patients.

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Appendix Table 1. Assessment of the Quality of Systematic Reviews and Meta-analyses Using AMSTAR

Study, Year (Reference)	1*	2†	3‡	4§	5‖	6¶	7**	8††	9‡‡	10§§	11‖‖	Overall Quality
Ceriani et al, 2010 (9)	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	High
Goodacre et al, 2005 (10)	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	Medium
Wells et al, 2006 (11)	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	No	Yes	Medium
Lucassen et al, 2011 (16)	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	High
Siccama et al, 2011 (26)	No	Yes	Yes	No	No	Yes	Yes	Yes	NA	Yes	Yes	Medium
Singh et al, 2013 (22)	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Medium
Chunilal et al, 2003 (23)	No	Yes	No	No	No	Yes	No	No	Yes	No	Yes	Medium
Di Nisio et al, 2007 (31)	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	Medium
Geersing et al, 2009 (32)	No	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Medium
Goodacre et al, 2005 (34)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	High
Johnson et al, 2010 (35)	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	High
Pomero et al, 2013 (38)	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	High
Thomas et al, 2008 (36)	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Carrier et al, 2010 (51)	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	High
Hayashino et al, 2005 (43)	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	Medium
Mos et al, 2009 (44)	No	Yes	Yes	No	No	Yes	No	Yes	No	No	Yes	Medium
Schouten et al, 2013 (64)	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	High
Abdalla et al, 2015 (37)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	High
Pasha et al, 2010 (67)	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	High
Raymakers et al, 2014 (70)	No	No	Yes	No	Yes	Yes	Yes	No	No	No	No	Medium
Nijkeuter et al, 2006 (74)	No	Yes	Yes	No	Yes	Yes	No	No	NA	No	No	Medium
Fabiá Valls et al, 2015 (66)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Jiang et al, 2015 (50)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Phillips et al, 2015 (45)	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Medium
Squizzato et al, 2017 (49)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	High
Da Costa Rodrigues et al, 2016 (48)	Yes	No	No	No	Yes	Yes	No	No	Yes	Yes	Yes	Medium
van Es et al, 2017 (69)	Yes	Yes	Yes	No	No	No	Yes	Yes	No	No	Yes	Medium

AMSTAR = A Measurement Tool to Assess Systematic Reviews; NA = not applicable.
* A priori design.
† Duplicate study selection and data extraction.
‡ Comprehensive literature search.
§ Gray literature used as an inclusion criterion.
‖ List of included and excluded studies provided.
¶ Characteristics of included studies provided.
** Scientific quality of included studies assessed and documented.
†† Scientific quality of included studies used to formulate conclusions.
‡‡ Appropriate methods used to combine findings.
§§ Likelihood of publication bias assessed.
‖‖ Conflict of interest included.

Appendix Table 2. Assessment of the Quality of Randomized Controlled Trials Using the Scottish Intercollegiate Guidelines Network 50 Checklist*

Study, Year (Reference)	1.1†	1.2‡	1.3§	1.4‖	1.5¶	1.6**	1.7††	1.8‡‡	1.9§§	1.10‖‖	2.1¶¶
Hamadah et al, 2011 (40)	Yes	Yes	Yes	No	Yes	Yes	Yes	NA	Yes	NA	Acceptable
Anderson et al, 2007 (42)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Acceptable
Szucs-Farkas et al, 2014 (53)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	NA	Acceptable
Righini et al, 2008 (47)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Acceptable
Bernardi et al, 2008 (57)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Acceptable
Wells et al, 2003 (60)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Acceptable
Linkins et al, 2013 (61)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Acceptable

NA = not applicable.
* High quality indicates that no criteria are poorly addressed, acceptable indicates that 1–3 criteria are poorly addressed, and low quality indicates that >3 criteria are poorly addressed.
† The study addresses an appropriate and clearly focused question.
‡ The assignment of participants to treatment groups is randomized.
§ An adequate concealment method is used.
‖ Participants and investigators are kept "blind" about treatment allocation.
¶ The treatment and control groups are similar at the start of the trial.
** The only difference between groups is the treatment under investigation.
†† All relevant outcomes are measured in a standard, valid, and reliable way.
‡‡ Did fewer than 5% of persons or clusters recruited into each group of the study drop out before the study was completed?
§§ All of the participants are analyzed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis).
‖‖ Where the study is carried out at more than 1 site, results are comparable for all sites.
¶¶ How well was the study done to minimize bias?

Appendix Table 3. Assessment of the Quality of Prospective Studies Using the Scottish Intercollegiate Guidelines Network 50 Checklist*

Study	1.1†	1.2‡	1.3§	1.4‖	1.5¶	1.6**	1.7††	1.8‡‡	1.9§§	1.10‖‖	1.11¶¶	1.12***	1.13†††	1.14‡‡‡	2.1§§§
Wells et al, 1995 (14)	Yes	NA	Yes	NA	Yes	NA	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	Acceptable
Wells et al, 1997 (15)	Yes	NA	Yes	NA	Yes	NA	Yes	Yes	NA	Yes	Yes	No	No	Yes	Acceptable
Ambid-Lacombe et al, 2009 (27)	Yes	Yes	Yes	NA	Can't say	No	Yes	No	No	Yes	Yes	NA	NA	No	Acceptable
Silveira et al, 2015 (28)	Yes	NA	No	NA	NA	NA	Yes	Yes	Yes	Yes	Yes	NA	NA	Yes	Acceptable
Penaloza et al, 2011 (17)	Yes	NA	No	NA	No	NA	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	Acceptable
Rodger et al, 2005 (19)	Yes	NA	Yes	NA	Yes	NA	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	Acceptable
Wolf et al, 2004 (20)	Yes	NA	Yes	NA	Yes	NA	Yes	Yes	NA	Yes	Yes	Yes	No	Yes	Acceptable
Runyon et al, 2005 (24)	Yes	NA	Yes	NA	NA	NA	Yes	Yes	NA	Yes	Yes	NA	NA	Yes	Acceptable
Penaloza et al, 2007 (21)	Yes	NA	Yes	NA	Yes	NA	Yes	No	No	Yes	Yes	NA	NA	Yes	Acceptable
Di Marca et al, 2015 (29)	Yes	NA	No	NA	NA	NA	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Acceptable
Luxembourg et al, 2012 (33)	Yes	NA	No	NA	Yes	No	Yes	Yes	NA	Yes	Yes	NA	No	Yes	Acceptable
Sostman et al, 2008 (54)	Yes	NA	Yes	NA	Yes	No	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Acceptable
PIOPED Investigators, 1990 (12)	Yes	NA	Yes	NA	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Acceptable
Bernardi et al, 1998 (56)	Yes	NA	Yes	NA	NA	NA	Yes	No	No	Yes	Yes	NA	NA	Yes	Acceptable
Gibson et al, 2009 (58)	Yes	NA	Yes	NA	Yes	Yes	Yes	No	No	Yes	Yes	NA	NA	Yes	Acceptable
Buller et al, 2009 (63)	Yes	NA	Yes	NA	Yes	Yes	Yes	No	Yes	Yes	Yes	NA	No	Yes	Acceptable
Stein et al, 2006 (65)	Yes	NA	Yes	NA	Yes	No	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Acceptable
Righini et al, 2014 (68)	Yes	NA	Yes	NA	Yes	No	Yes	Yes	NA	Yes	Yes	Yes	No	Yes	Acceptable
Wells et al, 2001 (55)	Yes	NA	Yes	NA	NA	NA	Yes	No	No	Yes	Yes	Yes	No	Yes	Acceptable
Kleinjan et al, 2014 (78)	Yes	NA	Yes	NA	Yes	Yes	Yes	NA	NA	Yes	Yes	No	No	Yes	Acceptable

NA = not applicable; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis.
* High quality indicates that no criteria are poorly addressed, acceptable indicates that 1–3 criteria are poorly addressed, and low quality indicates that >3 criteria are poorly addressed.
† The study addresses an appropriate and clearly focused question.
‡ The 2 groups being studied are selected from source populations that are similar in all respects other than the factor under investigation.
§ The study indicates how many of the persons asked to take part did so in each of the groups being studied.
‖ The likelihood that some eligible participants might have the outcome at the time of enrollment is assessed and taken into account in the analysis.
¶ Did fewer than 5% of persons or clusters recruited into each group of the study drop out before the study was completed?
** Comparison is made between full participants and those lost to follow-up, by exposure status.
†† The outcomes are clearly defined.
‡‡ The assessment of outcome is made blind to exposure status. If the study is retrospective, this may not be applicable.
§§ Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.
‖‖ The method of assessment of exposure is reliable.
¶¶ Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.
*** Exposure level or prognostic factor is assessed more than once.
††† The main potential confounders are identified and taken into account in the design and analysis.
‡‡‡ CIs have been provided.
§§§ How well was the study done to minimize the risk of bias or confounding?