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ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Diagnosis of DVT

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Shannon M. Bates, MDCM; Roman Jaeschke, MD; Scott M. Stevens, MD; Steve Goodacre, MBChB, PhD; Philip S. Wells, MD; Matthew D. Stevenson, PhD; Clive Kearon, MD, PhD; Holger J. Schunemann, MD, PhD, FCCP; Mark Crowther, MD; Stephen G. Pauker, MD; Regina Makdissi, MD; and Gordon H. Guyatt, MD, FCCP

Background: **Objective testing for DVT is crucial because clinical assessment alone is unreliable and the consequences of misdiagnosis are serious. This guideline focuses on the identification of optimal strategies for the diagnosis of DVT in ambulatory adults.**
Methods: **The methods of this guideline follow those described in Methodology for the Development of Antithrombotic Therapy and Prevention of Thrombosis Guidelines: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.**
Results: **We suggest that clinical assessment of pretest probability of DVT, rather than performing the same tests in all patients, should guide the diagnostic process for a first lower extremity DVT (Grade 2B). In patients with a low pretest probability of first lower extremity DVT, we recommend initial testing with D-dimer or ultrasound (US) of the proximal veins over no diagnostic testing (Grade 1B), venography (Grade 1B), or whole-leg US (Grade 2B). In patients with moderate pretest probability, we recommend initial testing with a highly sensitive D-dimer, proximal compression US, or whole-leg US rather than no testing (Grade 1B) or venography (Grade 1B). In patients with a high pretest probability, we recommend proximal compression or whole-leg US over no testing (Grade 1B) or venography (Grade 1B).**
Conclusions: **Favored strategies for diagnosis of first DVT combine use of pretest probability assessment, D-dimer, and US. There is lower-quality evidence available to guide diagnosis of recurrent DVT, upper extremity DVT, and DVT during pregnancy.** ***CHEST 2012; 141(2)(Suppl):e351S–e418S***

Abbreviations: aOR = adjusted OR; CUS = compression ultrasonography; GRADE = Grades of Recommendation, Assessment, Development, and Evaluation; IPG = impedance plethysmography; MR = magnetic resonance; PE = pulmonary embolism; US = ultrasonography

Summary of Recommendations

Note on Shaded Text: Throughout this guideline, shading is used within the summary of recommendations sections to indicate recommendations that are newly added or have been changed since the publication of Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Recommendations that remain unchanged are not shaded.

3.1. In patients with a suspected first lower extremity DVT, we suggest that the choice of diagnostic tests process should be guided by the clinical assessment of pretest probability rather than by performing the same diagnostic tests in all patients (Grade 2B)**.**

Note: In considering this recommendation, five panelists voted for a strong recommendation and four voted for a weak recommendation (one declined to vote and two did not participate). According to predetermined criteria, this resulted in weak recommendation.

3.2. In patients with a low pretest probability of first lower extremity DVT, we recommend one of the following initial tests: (i) a moderately sensitive D-dimer, (ii) a highly sensitive D-dimer,

or (iii) compression ultrasound (CUS) of the proximal veins rather than (i) no diagnostic testing (Grade 1B for all comparisons)**, (ii) venography** (Grade 1B for all comparisons), **or (iii) whole-leg ultrasound (US)** (Grade 2B for all comparisons)**. We suggest initial use of a moderately sensitive** (Grade 2C) **or highly sensitive** (Grade 2B) **D-dimer rather than proximal CUS.**

Remarks: The choice between a moderately sensitive D-dimer test, a highly sensitive D-dimer test, or proximal CUS as the initial test will depend on local availability, access to testing, costs of testing, and the probability of obtaining a negative D-dimer result if DVT is not present. Initial testing with US would be preferred if the patient has a comorbid condition associated with elevated D-dimer levels and is likely to have a positive D-dimer result, even if DVT is absent. In patients with suspected first lower extremity DVT in whom US is impractical (eg, when leg casting or excessive subcutaneous tissue or fluid prevent adequate assessment of compressibility) or nondiagnostic, we suggest CT scan venography or magnetic resonance (MR) venography, or MR direct thrombus imaging could be used as an alternative to venography.

If the D-dimer is negative, we recommend no further testing over further investigation with (i) proximal CUS, (ii) whole-leg US, or (iii) venography (Grade 1B for all comparisons)**. If the proximal CUS is negative, we recommend no further testing compared with (i) repeat proximal CUS after 1 week, (ii) whole-leg US, or (iii) venography** (Grade 1B for all comparisons)**.**

If the D-dimer is positive, we suggest further testing with CUS of the proximal veins rather than (i) whole-leg US (Grade 2C) **or (ii) venography** (Grade 1B)**. If CUS of the proximal veins is positive, we suggest treating for DVT and performing no further testing over performing confirmatory venography** (Grade 2C)**.**

Remarks: In circumstances when high-quality venography is available, patients who are not averse to the discomfort of venography, are less concerned about the complications of venography, and place a high value on avoiding treatment of false-positive results are likely to choose confirmatory venography if findings for DVT are less certain (eg, a short segment of venous noncompressibility).

3.3. In patients with a moderate pretest probability of first lower extremity DVT, we recommend one of the following initial tests: (i) a highly sensitive D-dimer or (ii) proximal CUS, or (iii) whole-leg US rather than (i) no testing (Grade 1B for all comparisons) **or (ii) venography** (Grade 1B for all comparisons)**. We suggest initial use of a highly sensitive D-dimer rather than US** (Grade 2C)**.**

Remarks: The choice between a highly sensitive D-dimer test or US as the initial test will depend on local availability, access to testing, costs of testing, and the probability of obtaining a negative D-dimer result if DVT is not present. Initial testing with US may be preferred if the patient has a comorbid condition associated with elevated D-dimer levels and is likely to have a positive D-dimer result even if DVT is absent. Whole-leg US may be preferred in patients unable to return for serial testing and those with severe symptoms consistent with calf DVT. In patients with suspected first lower extremity DVT in whom US is impractical (eg, when leg casting or excessive subcutaneous tissue or fluid prevent adequate assessment of compressibility) or nondiagnostic, we suggest CT scan venography, MR venography, or MR direct thrombus imaging could be used as an alternative to venography.

If the highly sensitive D-dimer is negative, we recommend no further testing over further investigation with (i) proximal CUS, (ii) whole-leg US, or (iii) venography (Grade 1B for all comparisons)**. If the highly sensitive D-dimer is positive, we**

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Affiliations: From the Department of Medicine (Drs Bates and Crowther), McMaster University and Thrombosis and Atherosclerosis Research Institute; the Departments of Medicine and Clinical Epidemiology and Biostatistics (Drs Jaeschke, Schunemann, and Guyatt), McMaster University, Hamilton, ON, Canada; the Department of Medicine (Dr Stevens), Intermountain Medical Center, Murray, UT; the School of Health and Related Research (Drs Goodacre and Stevenson), University of Sheffield, Sheffield, England; the Department of Medicine (Dr Wells), University of Ottawa, Ottawa, ON, Canada; the Department of Medicine (Dr Pauker), Tufts New England Medical Center, Boston, MA; and the Department of Medicine (Dr Makdissi), University of Buffalo, Buffalo, NY.
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Correspondence to: Shannon M. Bates, MDCM, HSC 3W11, Department of Medicine, 1280 Main St W, Hamilton, ON, L8S 4K1, Canada; e-mail: batesm@mcmaster.ca

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recommend proximal CUS or whole-leg US rather than no testing (Grade 1B for all comparisons) **or venography** (Grade 1B for all comparisons)**.**

If proximal CUS is chosen as the initial test and is negative, we recommend (i) repeat proximal CUS in 1 week or (ii) testing with a moderate or highly sensitive D-dimer assay over no further testing (Grade 1C) **or venography** (Grade 2B)**. In patients with a negative proximal CUS but a positive D-dimer, we recommend repeat proximal CUS in 1 week over no further testing** (Grade 1B) **or venography** (Grade 2B)**.**

In patients with (i) negative serial proximal CUS or (ii) a negative single proximal CUS and negative moderate or highly sensitive D-dimer, we recommend no further testing rather than further testing with (i) whole-leg US or (ii) venography (Grade 1B for all comparisons)**.**

If whole-leg US is negative, we recommend no further testing over (i) repeat US in one week, (ii) D-dimer testing, or (iii) venography (Grade 1B for all comparisons)**. If proximal CUS is positive, we recommend treating for DVT rather than confirmatory venography** (Grade 1B)**. If isolated distal DVT is detected on whole-leg US, we suggest serial testing to rule out proximal extension over treatment** (Grade 2C)**.**

Remarks: Patients with abnormal isolated distal US findings on whole-leg US who place a high value on avoiding the inconvenience of repeat testing and a low value on avoiding treatment of false-positive results are likely to choose treatment over repeat US. Patients with severe symptoms and risk factors for extension as outlined in Perioperative Management of Antithrombotic Therapy. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines are more likely to benefit from treatment over repeat US.

3.4. In patients with a high pretest probability of first lower extremity DVT, we recommend either (i) proximal CUS or (ii) whole-leg US over no testing (Grade 1B for all comparisons) **or venography** (Grade 1B for all comparisons)**.**

Remarks: Whole-leg US may be preferred to proximal CUS in patients unable to return for serial testing and those with severe symptoms consistent with calf DVT. In patients with extensive unexplained leg swelling, if there is no DVT on proximal CUS or whole-leg US and D-dimer testing has not been performed or is positive, the iliac veins should be imaged to exclude isolated iliac DVT. In patients with suspected first lower extremity DVT in whom US is impractical (eg, when leg casting or excessive subcutaneous tissue or fluid prevent adequate assessment of compressibility) or nondiagnostic, we suggest CT scan venography, MR venography, or MR direct thrombus imaging could be used as an alternative to venography.

If proximal CUS or whole-leg US is positive for DVT, we recommend treatment rather than confirmatory venography (Grade 1B)**.**

In patients with a negative proximal CUS, we recommend additional testing with a highly sensitive D-dimer or whole-leg US or repeat proximal CUS in 1 week over no further testing (Grade 1B for all comparisons) **or venography** (Grade 2B for all comparisons)**. We recommend that patients with a single negative proximal CUS and positive D-dimer undergo whole-leg US or repeat proximal CUS in 1 week over no further testing** (Grade 1B) **or venography** (Grade 2B)**. In patients with negative serial proximal CUS, a negative single proximal CUS and negative highly sensitive D-dimer, or a negative whole-leg US, we recommend no further testing over venography or additional US** (Grade 1B for negative serial proximal CUS and for negative single proximal CUS and highly sensitive D-dimer; Grade 2B for negative whole-leg US)**.**

We recommend that in patients with high pretest probability, moderately or highly sensitive D-dimer assays should not be used as standalone tests to rule out DVT (Grade 1B)**.**

3.5. If risk stratification is not performed in patients with suspected first lower extremity DVT, we recommend one of the following initial tests: (i) proximal CUS or (ii) whole-leg US rather than (i) no testing (Grade 1B)**, (ii) venography** (Grade 1B)**, or D-dimer testing** (Grade 2B)**.**

Remarks: Whole-leg US may be preferred to proximal CUS in patients unable to return for serial testing and those with severe symptoms consistent with calf DVT or risk factors for extension of distal DVT. In patients with suspected first lower extremity DVT in whom US is impractical (eg, when leg casting or excessive subcutaneous tissue or fluid prevent adequate assessment of compressibility) or nondiagnostic, we suggest that CT scan venography, MR venography, or MR direct thrombus imaging could be used as an alternative to venography.

We recommend that patients with a negative proximal CUS undergo testing with a moderate- or

high-sensitivity D-dimer, whole-leg US, or repeat proximal CUS in 1 week over no further testing (Grade 1B) **or venography** (Grade 2B)**. In patients with a negative proximal CUS, we suggest D-dimer rather than routine serial CUS** (Grade 2B) **or whole-leg US** (Grade 2C)**. We recommend that patients with a single negative proximal CUS and positive D-dimer undergo further testing with repeat proximal CUS in 1 week or whole-leg US rather than no further testing** (Grade 1B for both comparisons)**.**

We recommend that in patients with (i) negative serial proximal CUS, (ii) a negative D-dimer following a negative initial proximal CUS, or (iii) negative whole-leg US, no further testing be performed rather than venography (Grade 1B)**.**

If proximal US is positive for DVT, we recommend treatment rather than confirmatory venography (Grade 1B)**. If isolated distal DVT is detected on whole-leg US, we suggest serial testing to rule out proximal extension over treatment** (Grade 2C)**.**

Remarks: Patients with abnormal isolated distal US findings on whole-leg US who place a high value on avoiding the inconvenience of repeat testing and a low value on avoiding treatment of false-positive results are likely to choose treatment over repeat US. Patients with severe symptoms and risk factors for extension as outlined in Perioperative Management of Antithrombotic Therapy. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines are more likely to benefit from treatment over repeat US.

3.6. In patients with suspected first lower extremity DVT, we recommend against the routine use of CT venography or MRI (Grade 1C)**.**

4.1. In patients suspected of having recurrent lower extremity DVT, we recommend initial evaluation with proximal CUS or a highly sensitive D-dimer over venography, CT venography, or MRI (all Grade 1B)**.**

Remarks: Initial D-dimer testing with a high-sensitivity assay is preferable if prior US is not available for comparison.

If the highly sensitive D-dimer is positive, we recommend proximal CUS over venography, CT venography, or MRI (Grade 1B for all comparisons)**.**

In patients with suspected recurrent lower extremity DVT in whom initial proximal CUS is negative (normal or residual diameter increase of <2 mm), we suggest at least one further proximal CUS (day 7 ± 1) or testing with a moderately or highly sensitive D-dimer (followed by repeat CUS [day 7 ± 1] if positive) rather than no further testing or venography (Grade 2B)**.**

Remarks: In patients with an abnormal proximal CUS at presentation that does not meet the criteria for the diagnosis of recurrence, an additional proximal CUS on day 2 ± 1 in addition to that on (day 7 ± 1) may be preferred. Patients who place a high value on an accurate diagnosis and a low value on avoiding the inconvenience and potential side effects of a venography are likely to choose venography over missed diagnosis (in the case of residual diameter increase of <2 mm).

We recommend that patients with suspected recurrent lower extremity DVT and a negative highly sensitive D-dimer or negative proximal CUS and negative moderately or highly sensitive D-dimer or negative serial proximal CUS undergo no further testing for suspected recurrent DVT rather than venography (Grade 1B)**.**

If CUS of the proximal veins is positive, we recommend treating for DVT and performing no further testing over performing confirmatory venography (Grade 1B for the finding of a new noncompressible segment in the common femoral or popliteal vein, Grade 2B for a ≥ 4-mm increase in venous diameter during compression compared with that in the same venous segment on a previous result)**.**

Remarks: Patients with US abnormalities at presentation that do not include a new noncompressible segment who place a high value on an accurate diagnosis and a low value on avoiding the inconvenience and potential side effects of a venography are likely to choose venography over treatment (in the case of ≥ 4-mm increase in venous diameter).

4.2. In patients with suspected recurrent lower extremity DVT and abnormal but nondiagnostic US results (eg, an increase in residual venous diameter of <4 but ≥ 2 mm), we recommend further testing with venography, if available (Grade 1B)**; serial proximal CUS** (Grade 2B) **or testing with a moderately or highly sensitive D-dimer with serial proximal CUS as above if the test is positive** (Grade 2B)**, as opposed to other testing strategies or treatment.**

4.3. In patients with suspected recurrent ipsilateral DVT and an abnormal US without a prior result for comparison, we recommend further

testing with venography, if available (Grade 1B) **or a highly sensitive D-dimer** (Grade 2B) **over serial proximal CUS. In patients with suspected recurrent ipsilateral DVT and an abnormal US without prior result for comparison and a negative highly sensitive D-dimer, we suggest no further testing over venography** (Grade 2C)**. In patients with suspected recurrent ipsilateral DVT and an abnormal US without prior result for comparison and a positive highly sensitive D-dimer, we suggest venography if available over empirical treatment of recurrence** (Grade 2C)**.**

Remarks: Patients who place a high value on avoiding the inconvenience and potential side effects of a venography are likely to choose treatment over venography.

5.1. In pregnant patients suspected of having lower extremity DVT, we recommend initial evaluation with proximal CUS over other initial tests, including a whole-leg US (Grade 2C)**, moderately sensitive D-dimer** (Grade 2C)**, highly sensitive D-dimer** (Grade 1B)**, or venography** (Grade 1B)**.**

5.2. In pregnant patients with suspected DVT in whom initial proximal CUS is negative, we suggest further testing with either serial proximal CUS (day 3 and day 7) (Grade 1B) **or a sensitive D-dimer done at the time of presentation** (Grade 2B) **over no further testing for DVT. We recommend that patients with an initial negative proximal CUS and a subsequent negative sensitive D-dimer or negative serial proximal CUS undergo no further testing for DVT** (Grade 1B) **and that patients with positive D-dimer have an additional follow-up proximal CUS (day 3 and day 7) rather than venography** (Grade 1B) **or whole-leg US** (Grade 2C)**.**

5.3. In pregnant patients with symptoms suggestive of isolated iliac vein thrombosis (swelling of the entire leg, with or without flank, buttock, or back pain) and no evidence of DVT on standard proximal CUS, we suggest further testing with either Doppler US of the iliac vein (Grade 2C)**, venography** (Grade 2C)**, or direct MRI** (Grade 2C)**, rather than standard serial CUS of the proximal deep veins.**

6.1. In patients suspected of having upper extremity DVT, we suggest initial evaluation with combined modality US (compression with either Doppler or color Doppler) over other initial tests, including highly sensitive D-dimer or venography (Grade 2C)**.**

6.2. In patients with suspected upper extremity DVT in whom initial US is negative for thrombosis despite a high clinical suspicion of DVT, we suggest further testing with a moderate or highly sensitive D-dimer, serial US, or venographic-based imaging (traditional, CT scan, or MRI), rather than no further testing (Grade 2C)**.**

In patients with suspected upper extremity DVT and an initial negative combined-modality US and subsequent negative moderate or highly sensitive D-dimer or CT or MRI, we recommend no further testing, rather than confirmatory venography (Grade 1C)**. We suggest that patients with an initial combined negative modality US and positive D-dimer or those with less than complete evaluation by US undergo venography rather than no further testing, unless there is an alternative explanation for their symptoms** (Grade 2B)**, in which case testing to evaluate for the presence an alternative diagnosis should be performed. We suggest that patients with a positive D-dimer or those with less than complete evaluation by US but an alternative explanation for their symptoms undergo confirmatory testing and treatment of this alternative explanation rather than venography** (Grade 2C)**.**

Remarks: Further radiologic testing (serial US or venographic-based imaging or CT/MR to seek an alternative diagnosis) rather than D-dimer testing is preferable in patients with comorbid conditions typically associated with elevated D-dimer levels.

DVT is a common condition that affects approximately one in 1,000 persons per year.[1,2] Objective testing for DVT is crucial because clinical assessment alone is unreliable,[3-6] and the consequences of misdiagnosis are serious, including fatal pulmonary embolism (PE).[7,8] Although anticoagulant therapy is effective,[9] its unnecessary use entails expense, inconvenience, and risk of major hemorrhage.[9] Only a minority of patients evaluated for suspected DVT actually have the disease.[10] Therefore, diagnostic strategies must be able to correctly rule in DVT when it is present and safely rule out DVT when it is absent.

Three categories of tests are typically used to determine the probability of DVT: (1) clinical probability assessment based on patient history and clinical findings, (2) D-dimer assays, and (c) imaging studies (most commonly venous ultrasonography [US] and less frequently venography, CT scan, or MRI). Diagnostic testing often requires that the results of more than one assessment are combined. The goal of choosing one strategy over another is to improve patient outcomes in the most efficient manner.

This article focuses on the identification of optimal strategies for the diagnosis of clinically suspected DVT in adults. Consecutive sections of this chapter concentrate on first DVT, recurrent DVT, upper extremity DVT, and DVT during pregnancy. Most of the data come from evaluations of patients in the ambulatory setting (ie, outpatient or ED), and our recommendations are most applicable to this patient population. Recommendations for the treatment of DVT once diagnosed can be found in Kearon et al.[11]

1.0 Methods

Article panelists identified questions related to the evaluation of adults with suspected DVT (Table 1). A broad overview search was performed centrally and provided to all coauthors, who followed it with more specific searching as required. Recommendations were developed from this evidence.

Eligible studies included both those addressing diagnostic accuracy (cross-sectional accuracy studies) and studies that assessed clinical outcomes such as DVT or PE during follow-up (prospective cohort management studies and randomized controlled trials [RCTs]). In typical management studies, investigators follow untreated patients with negative test results and record the proportion of patients who develop VTE. For each section, we developed corresponding methodology tables that included information on the study question (in terms of population, intervention, comparator, and outcome), the type of evidence assessed (meta-analysis or original study; cross-sectional study or management cohort or randomized trial), and selected details of study execution (inclusion of consecutive patients and independence of test result assessment). Findings of individual studies and meta-analyses are presented in descriptive tables and, when feasible, overall findings relating to each question are summarized as Evidence Profiles and Summary of Findings tables.

For accuracy studies, we extracted sensitivity and specificity and then estimated the effect on patient-important outcomes (eg, DVT, PE, death, bleeding in treated patients) that would be associated with this level of accuracy, assuming prevalences of DVT that correspond to high, moderate, and low pretest probability categories. For studies in which the diagnostic test was used to manage patients (ie, management studies), the incidence of VTE during follow-up was determined for patients in whom anticoagulation and additional diagnostic testing were withheld on the basis of negative test results.

Following the approach articulated by Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) for formulation of recommendations related to diagnosis,[12] we first considered the quality of evidence (representing our confidence that the testing strategy would result in patient outcomes that support a particular recommendation). We initially considered studies as providing high quality of evidence, unless rated down because of the following factors: risk of bias (eg, unrepresentative patients, lack of independent assessment of test and criterion standard), inconsistency (differences among study results), indirectness (with respect to the population studied, the tests performed, or the outcome measured), lack of precision, and risk of publication bias. Unless otherwise explicitly stated, the quality of evidence obtained from cross-sectional accuracy studies was lowered by one level because of the indirectness with which sensitivity and specificity corresponds to patient-important outcomes.

Typically, diagnostic strategies for DVT have been deemed acceptable if they have demonstrated no more than a 2% frequency of VTE during follow-up (a rate comparable to that seen when DVT is excluded by venography) in management studies in which treatment is withheld on the basis of a negative result.[13] Management studies that assess the follow-up frequency of VTE after negative diagnostic testing provide no information regarding false-positive diagnoses for DVT. Patients who are misdiagnosed with DVT will be prescribed unnecessary anticoagulants and some will suffer major bleeding as a result.

To overcome this limitation, we estimated the risk of major bleeding associated with different diagnostic strategies. These estimates were based on (1) the proportion of patients diagnosed with DVT (derived from sensitivity and specificity, with the assumption that all diagnosed DVT are treated), and (2) the frequency of major bleeding with 3 months of therapeutic-dose anticoagulants in cohort studies and randomized trials of patients with VTE. Because the evidence regarding major bleeding emerging from these models is indirect, it is generally rated as no higher than moderate quality.

For those diagnostic tests that have been robustly evaluated in management studies (ie, in patients with suspected first lower extremity DVT), we have assessed the impact of various strategies on major bleeding (both fatal and nonfatal, in patients prescribed anticoagulants on the basis of a positive test result) and mortality, as well as on the frequency of PE during follow-up (fatal and nonfatal) after application of a given diagnostic strategy (see Table S1 for list of strategies) (tables that contain an "S" before the number denote supplementary tables not contained in the body of the article and available instead in an online data supplement; see the "Acknowledgments" for more information). Management studies that followed cohorts of patients subjected to specific strategies for DVT diagnosis were used to determine the proportion of patients initially judged to be DVT-free who returned with symptomatic VTE. In order to identify the proportion and clinical course of patients incorrectly classified as having DVT and to estimate the risk of PE (fatal and nonfatal) in patients incorrectly categorized, we used a decision analytic model based on methodology described in detail in previous publications.[14,15] The model was originally developed to estimate the cost-effectiveness of diagnostic strategies. It was updated to include estimates of the outcomes (see below) of patients with DVT treated with anticoagulation for at least 3 months reported in a recent meta-analysis.[9] Sensitivities and specificities from meta-analyses were used to determine the proportion of patients with proximal, distal, and no DVT subjected to each diagnostic strategy who would be treated with anticoagulant therapy.

Based on the results of a previous meta-analysis of patients with suspected symptomatic DVT of the leg, we estimated an overall prevalence of proximal DVT of 19.0%,[10] with prevalences of 56.2%, 12.4%, and 3.4% in the high, moderate, and low pretest probability groups, respectively. The overall prevalence of distal DVT was estimated to be 5%. Untreated distal DVT was assumed not to directly cause PE; we estimated the probability of propagation to proximal veins of 21.4%. We estimated the probability that patients with treated proximal DVT would suffer a fatal PE to be 0.3% and a nonfatal PE to be 1.4% over 3 months.

The model assumed that all bleeding events were attributable to anticoagulation (ie, bleeding rates are not reported for untreated patients). Patients receiving treatment had a 0.3% probability of fatal bleeding, a 0.1% probability of nonfatal intracranial bleeding, and a 2.1% probability of major nonfatal non-intracranial bleeding over 3 months.[9,14,15] All parameters were modeled with a probability distribution to generate a credible range for the outcomes in question. The outputs from the model were the proportion of patients suffering the following events over the 3 months after diagnostic assessment: (1) fatal PE, (2) nonfatal PE, (3) fatal bleeding, (4) nonfatal intracranial bleeding, and (5) major nonfatal, non-intracranial bleeding. Table S1 lists the 21 diagnostic algorithms evaluated with this model.[16-35]

Table 1—*Structured Clinical Questions*

Informal Question	PICO Question: Population	Intervention	Comparator	Outcome	Methodology
			Suspected first DVT (Section 3.0)		
What are the consequences of using venography to diagnose first DVT?	Patients with suspected first DVT	Persistent intraluminal filling defect		Morbidity caused by test strategy Number of nonevaluable test results	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using venography to rule out first DVT?	Patients with suspected first DVT	Negative venography	VTE during additional testing or 3-6 mo follow-up if intervention negative for DVT	FN/1,000 of negatives (eg, post-TP of a negative test) Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using CUS to diagnose proximal DVT	Patients with suspected first DVT	Noncompressible venous segment from common femoral vein down to and including the trifurcation veins In all patients If low pre-TP If moderate pre-TP If high pre-TP If positive highly sensitive DD If positive moderately sensitive (SimpliRED) DD If negative highly sensitive DD If negative moderately sensitive (SimpliRED) DD	Venography	FP/1,000 of positive (eg, post-TP of a positive test) if management study Specificity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)

(Continued)

Table 1—*Continued*

Informal Question	PICO Question				Methodology
	Population	Intervention	Comparator	Outcome	
What are the consequences of using serial proximal CUS to exclude DVT (regardless of pre-TP)?	Patients with suspected first DVT	Proximal CUS on presentation and if negative a follow-up test approximately 1 wk later	Venography or VTE during additional testing or 3-6 mo follow-up if intervention negative for DVT	FN/1,000 of negatives (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using whole-leg US to diagnose distal DVT	Patients with suspected first DVT	Noncompressible venous segment isolated to the calf veins (eg, posterior tibial, anterior tibial, and peroneal veins) In all patients If low pre-TP If moderate pre-TP If high pre-TP If positive highly sensitive DD If positive moderately sensitive (SimpliRED) DD If negative highly sensitive DD If negative moderately sensitive DD	Venography or serial proximal CUS plus VTE during additional 3-6 mo if negative for proximal DVT	FP/1,000 of positive (eg, post-TP of a positive test) if management study Specificity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using a single whole-leg US to exclude DVT (regardless of pre-TP)?	Patients with suspected first DVT	Negative single whole-leg US on day of presentation	Venography or serial proximal CUS plus VTE during additional 3-6 mo if negative for proximal DVT	FN/1,000 of negatives (eg, post-TP of a negative test) Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)

(Continued)

Table 1—*Continued*

Informal Question	PICO Question				Methodology
	Population	Intervention	Comparator	Outcome	
What are the consequences of using a highly sensitive DD as a stand-alone test to exclude DVT?	Patients with suspected first DVT	Negative highly sensitive DD on day of presentation	Venography or serial proximal CUS plus VTE during additional 3-6 mo if negative for proximal DVT	FN/1,000 of negatives (eg, post-TP of a negative test) Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using DD and pre-TP to exclude DVT?	Patients with suspected first DVT	Negative moderately sensitive (SimpliRED) DD plus low/moderate/high pre-TP at presentation or Negative highly sensitive DD plus low/moderate/high pre-TP at presentation	Venography or serial proximal CUS plus VTE during additional 3-6 mo if negative for proximal DVT	FN/1,000 of negatives (eg, post-TP of a negative test) Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using a negative proximal CUS and negative DD to exclude DVT?	Patients with suspected first DVT	Negative moderately sensitive (SimpliRED) DD plus negative proximal CUS at presentation or Negative highly sensitive DD plus negative proximal CUS at presentation	Venography or serial proximal CUS plus VTE during additional 3-6 mo if negative for proximal DVT	FN/1,000 of negatives (eg, post-TP of a negative test) Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using pre-TP with a negative proximal CUS to exclude DVT?	Patients with suspected first DVT	Negative proximal CUS plus low/moderate/high pre-TP at presentation	Venography or serial proximal CUS plus VTE during additional 3-6 mo if negative for proximal DVT	FN/1,000 of negatives (eg, post-TP of a negative test) Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)

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Table 1—*Continued*

Informal Question	PICO Question: Population	Intervention	Comparator	Outcome	Methodology
What are the consequences of using serial proximal CUS to exclude DVT in patients with a low/moderate/high pre-TP?	Patients with suspected first DVT	Repeat proximal CUS (within approximately 1 wk)	Venography or serial proximal CUS plus VTE during additional 3-6 mo if negative for proximal DVT	FN/1,000 of negatives (eg, post-TP of a negative test) Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using serial proximal CUS to exclude DVT in patients with a positive DD? Negative proximal CUS plus positive moderately sensitive (SimpliRED) or highly sensitive DD plus low pre-TP Negative proximal CUS plus positive moderately sensitive (SimpliRED) or highly sensitive DD plus moderate pre-TP Negative proximal CUS plus positive highly sensitive DD plus high pre-TP	Patients with suspected first DVT	Repeat proximal CUS (within approximately 1 wk)	Venography or serial proximal CUS plus VTE during additional 3-6 mo if negative for proximal DVT	FN/1,000 of negatives (eg, post-TP of a negative test) Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using a negative DD to obviate the need for serial testing in patients with a negative proximal CUS and moderate or high pre-TP at presentation? Negative proximal CUS plus moderate pre-TP Negative proximal CUS plus high pre-TP	Patients with suspected first DVT	Negative highly sensitive DD or negative moderately sensitive (SimpliRED) DD	Venography or serial proximal CUS plus VTE during additional 3-6 mo if negative for proximal DVT	FN/1,000 of negatives (eg, post-TP of a negative test) Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)

(Continued)

Table 1—*Continued*

Informal Question	PICO Question				Methodology
	Population	Intervention	Comparator	Outcome	
What are the consequences of using CT scan venography to diagnose DVT	Patients with suspected first DVT	Intraluminal filling defect	Venography or serial proximal CUS plus VTE during additional 3-6 mo if negative for proximal DVT or single whole-leg US plus VTE during additional 3-6 mo if negative for DVT	FP/1,000 of positive (eg, post-TP of a positive test) if management study Specificity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using CT scan venography to exclude DVT?	Patients with suspected first DVT	Negative CT scan venography	Venography or VTE during additional testing or 3-6 mo follow-up if intervention negative for DVT	FN/1,000 of negatives (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using contrast MR venography to diagnose DVT?	Patients with suspected first DVT	Intraluminal filling defect	Venography or serial proximal CUS plus VTE during additional 3-6 mo if negative for proximal DVT or single whole-leg US plus VTE during additional 3-6 mo if negative for DVT	FP/1,000 of positive (eg, post-TP of a positive test) if management study Specificity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using contrast MR venography to exclude DVT?	Patients with suspected first DVT	Negative MR venography	Venography or VTE during additional testing or 3-6 mo follow-up if intervention negative for DVT	FN/1,000 of negatives (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using MR direct thrombus imaging to diagnose DVT	Patients with suspected first DVT	High signal intensity	Venography or serial proximal CUS plus VTE during additional 3-6 mo if negative for proximal DVT or single whole-leg US plus VTE during additional 3-6 mo if negative for DVT	FP/1,000 of positive (eg, post-TP of a positive test) if management study Specificity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)

(Continued)

Table 1—*Continued*

Informal Question	PICO Question				Methodology
	Population	Intervention	Comparator	Outcome	
What are the consequences of using MR direct thrombus imaging to exclude DVT?	Patients with suspected first DVT	Negative MR direct thrombus imaging	Venography or VTE during additional testing or 3-6 mo follow-up if intervention negative for DVT	FN/1,000 of negatives (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
Suspected recurrent DVT (Section 4.0)					
What are the consequences of using venography to diagnose recurrent DVT?	Patients with suspected recurrent DVT	Persistent intraluminal filling defect		Morbidity caused by test strategy Number of nonevaluable tests	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using venography to rule out recurrent DVT?	Patients with suspected recurrent DVT	Negative venography or venography with no new intraluminal filling defects	VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of recurrence	FN/1,000 (eg, post-TP of a negative test) Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using serial proximal CUS to diagnose recurrent DVT in the presence of the following?	Patients with suspected recurrent DVT		Venography	FP/1,000 of positive (eg, post-TP of a positive test) if management study Specificity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)

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Table 1—*Continued*

Informal Question	PICO Question: Population	Intervention	Comparator	Outcome	Methodology
New noncompressible segment		New noncompressible segment compared with previous proximal CUS either at presentation or on follow-up test(s) over next 7-10 d			
Increase in residual venous diameter		New increase in residual venous diameter greater than specified compared with previous proximal CUS either at presentation or on follow-up test(s) over next 7-10 d			
New noncompressible segment or increase in residual venous diameter		New noncompressible segment or change in residual diameter greater than specified compared with previous proximal CUS at presentation or on follow-up test(s) over next 7-10 d			
What are the consequences of using serial proximal CUS to exclude recurrent DVT in the absence of the following?	Patients with suspected recurrent DVT		Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of recurrence	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
New noncompressible segment		Proximal CUS on presentation and if negative or no new noncompressible segment compared with previous, follow-up test(s) over next 5-10 d, examining for new noncompressible segment			

(Continued)

Table 1—*Continued*

Informal Question	PICO Question: Population	Intervention	Comparator	Outcome	Methodology
Change in residual venous diameter		Proximal CUS on presentation and if negative or change in residual venous diameter less than specified compared with previous, follow-up test(s) over next 5-10 d, examining for change in residual venous diameter			
New noncompressible segment or change in residual venous diameter		Proximal CUS on presentation and if negative or no new noncompressible segment or change in residual diameter greater than specified compared with previous, follow-up test(s) over next 5-10 d, examining for new noncompressible segment or change in residual venous diameter			
What are the consequences of using DD and pre-TP to exclude suspected recurrent DVT?	Patients with suspected recurrent DVT	Negative moderately sensitive (SimpliRED) DD plus low/moderate/high pre-TP at presentation OR Negative highly sensitive DD plus low/moderate/high pre-TP at presentation	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of recurrence	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)

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Table 1—*Continued*

Informal Question	PICO Question: Population	Intervention	Comparator	Outcome	Methodology
What are the consequences of using a negative DD and proximal CUS (or proximal CUS unchanged from previous with respect to noncompressible segment and/or residual venous diameter) to exclude recurrent DVT?	Patients with suspected recurrent DVT	Negative moderately sensitive (SimpliRED) DD plus negative/unchanged (with respect to noncompressible segments and/or residual venous diameter) proximal CUS at presentation or Negative highly sensitive DD plus negative proximal CUS (with respect to noncompressible segments and/or residual venous diameter) at presentation	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of recurrence	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using a negative DD to exclude recurrent DVT?	Patients with suspected recurrent DVT	Negative moderately sensitive (SimpliRED) or Negative highly sensitive DD	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of recurrence	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using CT scan venography to diagnose recurrent DVT	Patients with suspected recurrent DVT	Intraluminal filling defect	Venography	FP/1,000 of positive (eg, post-TP of a positive test) if management study Specificity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using CT scan venography to exclude recurrent DVT?	Patients with suspected recurrent DVT	Negative CT scan venography	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of recurrence	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)

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Table 1—*Continued*

Informal Question	PICO Question: Population	Intervention	Comparator	Outcome	Methodology
What are the consequences of using contrast MR venography to diagnose recurrent DVT	Patients with suspected recurrent DVT	Intraluminal filling defect	Venography	FP/1,000 of positive (eg, post-TP of a positive test) if management study Specificity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using contrast MR venography to exclude recurrent DVT?	Patients with suspected recurrent DVT	Negative MR venography	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of recurrence	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using MR direct thrombus imaging to diagnose recurrent DVT?	Patients with suspected recurrent DVT	High signal intensity	Venography	FP/1,000 of positive (eg, post-TP of a positive test) if management study Specificity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using MR direct thrombus imaging to exclude recurrent DVT?	Patients with suspected recurrent DVT	Negative MR direct thrombus imaging	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of recurrence	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
Suspected DVT in pregnancy (Section 5.0)					
What are the consequences of using venography to diagnose DVT during pregnancy	Patients with suspected recurrent DVT	Persistent intraluminal filling defect		FP/1,000 of positive (eg, post-TP of a positive test) Morbidity caused by test strategy Radiation exposure to the fetus (also teratogenicity, increase in the risk of childhood cancer, fetal loss)	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)

(Continued)

Table 1—*Continued*

Informal Question	PICO Question				Methodology
	Population	Intervention	Comparator	Outcome	
What are the consequences of using venography to rule out DVT during pregnancy?	Patients with suspected recurrent DVT	Negative venography	VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) Morbidity caused by test strategy Radiation exposure to the fetus (also teratogenicity, increase in the risk of childhood cancer, fetal loss)	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using CUS to diagnose proximal DVT during pregnancy	Pregnant women with suspected DVT	Noncompressible venous segment from common femoral vein down to and including the trifurcation veins and/or absence of Doppler flow in the iliac vein In all patients If low pre-TP If moderate pre-TP If high pre-TP If positive highly sensitive DD If positive moderately sensitive (SimpliRED) DD If negative highly sensitive DD If negative moderately sensitive (SimpliRED) DD	Venography	FP/1,000 of positive (eg, post-TP of a positive test) if management study Specificity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using serial proximal CUS to exclude DVT during pregnancy, regardless of pre-TP?	Pregnant women with suspected DVT	Proximal CUS on presentation and if negative follow-up tests within 5-10 d	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)

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Table 1—*Continued*

Informal Question	PICO Question: Population	Intervention	Comparator	Outcome	Methodology
What are the consequences of using a negative proximal CUS and negative DD to exclude DVT during pregnancy?	Pregnant women with suspected DVT	Negative moderately sensitive (SimpliRED) plus negative proximal CUS at presentation OR Negative highly sensitive DD plus negative proximal CUS at presentation	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using pre-TP with a negative proximal CUS to exclude DVT during pregnancy?	Pregnant women with suspected DVT	Negative proximal CUS plus low/moderate/high pre-TP at presentation	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using serial proximal CUS to exclude DVT in patients with a low/moderate/high pre-TP during pregnancy?	Pregnant women with suspected DVT	Repeat proximal CUS (within approximately 1 wk)	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using serial proximal CUS to exclude DVT in patients with a positive DD during pregnancy? Negative proximal CUS plus positive moderately sensitive (SimpliRED) or highly sensitive DD plus low pre-TP Negative proximal CUS plus positive moderately sensitive (SimpliRED) or highly sensitive DD plus moderate pre-TP Negative proximal CUS plus positive highly sensitive DD plus high pre-TP	Pregnant women with suspected DVT	Repeat proximal CUS (within approximately 1 wk)	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)

(Continued)

Table 1—*Continued*

Informal Question	PICO Question				Methodology
	Population	Intervention	Comparator	Outcome	
What are the consequences of using a negative DD to obviate the need for serial testing in patients with a negative proximal CUS and moderate or high pre-TP at presentation during pregnancy? Negative proximal CUS plus moderate pre-TP Negative proximal CUS plus high pre-TP	Pregnant women with suspected DVT	Negative highly sensitive DD or negative moderately sensitive (SimpliRED) DD	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using pre-TP with a negative proximal CUS to exclude DVT?	Pregnant women with suspected DVT	Negative proximal CUS plus low/moderate/high pre-TP at presentation	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using serial proximal CUS to exclude DVT in patients with a low/moderate/high pre-TP?	Pregnant women with suspected DVT	Repeat proximal CUS (within approximately 1 wk)	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)

(Continued)

Table 1—*Continued*

Informal Question	PICO Question				Methodology
	Population	Intervention	Comparator	Outcome	
What are the consequences of whole-leg US to diagnose distal DVT during pregnancy	Pregnant women with suspected DVT	Noncompressible venous segment isolated to the calf veins (eg, posterior tibial, anterior tibial, and peroneal veins) In all patients If low pre-TP If moderate pre-TP If high pre-TP If positive highly sensitive DD If positive moderately sensitive (SimpliRED) DD If negative highly sensitive DD If negative moderately sensitive (SimpliRED) DD	Venography or serial proximal CUS plus VTE during additional 3-6 mo if negative for proximal DVT	FP/1,000 of positive (eg, post-TP of a positive test) if management study Specificity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using a single whole-leg US to exclude DVT during pregnancy?	Pregnant women with suspected DVT	Negative single whole-leg US on day of presentation	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using a highly sensitive DD as a stand-alone test to exclude DVT during pregnancy?	Pregnant women with suspected DVT	Negative highly sensitive DD on day of presentation	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)

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Table 1—*Continued*

Informal Question	PICO Question: Population	Intervention	Comparator	Outcome	Methodology
What are the consequences of using a moderately sensitive (SimpliRED) DD as a stand-alone test to exclude DVT pregnancy?	Pregnant women with suspected DVT	Negative moderately sensitive (SimpliRED) DD on day of presentation	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using CT scan venography to diagnose DVT during pregnancy?	Pregnant women with suspected DVT	Intraluminal filling defect	Venography	FP/1,000 of positive (eg, post-TP of a positive test) if management study Specificity if accuracy study Morbidity caused by test strategy Radiation exposure to the fetus (also teratogenicity, increase in the risk of childhood cancer, fetal loss)	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using CT scan venography to exclude DVT during pregnancy?	Pregnant women with suspected DVT	Negative CT scan venography	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy Radiation exposure to the fetus (also teratogenicity, increase in the risk of childhood cancer, fetal loss)	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using contrast MR venography to diagnose DVT during pregnancy	Pregnant women with suspected DVT	Intraluminal filling defect	Venography	FP/1,000 of positive (eg, post-TP of a positive test) if management study Specificity if accuracy study Morbidity caused by test strategy Teratogenicity, increase in the risk of childhood cancer, fetal loss	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)

(Continued)

Table 1—*Continued*

Informal Question	PICO Question				Methodology
	Population	Intervention	Comparator	Outcome	
What are the consequences of using MR venography to exclude DVT during pregnancy?	Pregnant women with suspected DVT	Negative MR venography	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy Teratogenicity, increase in the risk of childhood cancer, fetal loss	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using MR direct thrombus imaging to diagnose DVT during pregnancy?	Pregnant women with suspected DVT	High signal intensity	Venography	FP/1,000 of positive (eg, post-TP of a positive test) if management study Specificity if accuracy study Morbidity caused by test strategy Teratogenicity, increase in the risk of childhood cancer, fetal loss	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using MR direct thrombus imaging to exclude DVT during pregnancy?	Pregnant women with suspected DVT	Negative MR direct thrombus imaging	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Specificity if accuracy study Morbidity caused by test strategy Teratogenicity, increase in the risk of childhood cancer, fetal loss	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
Suspected upper extremity DVT (Section 6.0)					
What are the consequences of using venography diagnose upper extremity DVT?	Patient with suspected upper extremity DVT	Intraluminal filling defect		Morbidity caused by test strategy Number of nonevaluable test results	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)

(Continued)

Table 1—*Continued*

Informal Question	PICO Question				Methodology
	Population	Intervention	Comparator	Outcome	
What are the consequences of using venography to rule out upper extremity DVT?	Patients with suspected upper extremity DVT	Negative venography	VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of recurrence	FN/1,000 (eg, post-TP of a negative test) Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using CUS to diagnose upper extremity DVT?	Patients with suspected upper extremity DVT	Noncompressible venous segment or visualization of echogenic material (intraluminal thrombus)	Venography	FP/1,000 of positive (eg, post-TP of a positive test) if management study Specificity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using a single CUS to exclude upper extremity DVT	Patients with suspected upper extremity DVT	Negative CUS on presentation	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using serial CUS to exclude upper extremity DVT	Patients with suspected upper extremity DVT	CUS on presentation and if negative follow-up tests within 5-10 d	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using Doppler US to diagnose upper extremity DVT?	Patients with suspected upper extremity DVT	Absent flow/absence of phasic flow	Venography	FP/1,000 of positive (eg, post-TP of a positive test) if management study Specificity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)

(Continued)

Table 1—*Continued*

Informal Question	PICO Question: Population	Intervention	Comparator	Outcome	Methodology
What are the consequences of using a single Doppler US to exclude upper extremity DVT?	Patients with suspected upper extremity DVT	Negative US on presentation	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using serial Doppler US to exclude upper extremity DVT?	Patients with suspected upper extremity DVT	Negative US on presentation and negative follow-up 5-10 d later	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using duplex US (compression plus Doppler flow) to diagnose upper extremity DVT?	Patients with suspected upper extremity DVT	Noncompressible segment or visualization of echogenic material (intraluminal thrombus) or absent flow/absence of phasic flow	Venography	FP/1,000 of positive (eg, post-TP of a positive test) if management study Specificity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using a single duplex US (compression plus Doppler flow) to exclude upper extremity DVT?	Patients with suspected upper extremity DVT	Negative US on presentation	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using a serial duplex US (compression plus Doppler flow) to exclude upper extremity DVT?	Patients with suspected upper extremity DVT	Negative US on presentation and negative follow-up 5-10 d later	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)

(Continued)

Table 1—*Continued*

Informal Question	PICO Question				Methodology
	Population	Intervention	Comparator	Outcome	
What are the consequences of using a negative CUS and negative DD to exclude upper extremity DVT?	Patients with suspected upper extremity DVT	Negative moderately sensitive (SimpliRED) DD plus negative CUS at presentation or Negative highly sensitive DD plus negative CUS at presentation	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using a negative Doppler US and negative DD to exclude upper extremity DVT?	Patients with suspected upper extremity DVT	Negative moderately sensitive (SimpliRED) DD plus negative doppler us at presentation or Negative highly sensitive DD plus negative Doppler US at presentation	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using a negative duplex US and negative DD to exclude upper extremity DVT?	Patients with suspected upper extremity DVT	Negative moderately sensitive (SimpliRED) DD plus negative duplex US at presentation or Negative highly sensitive DD plus negative duplex US at presentation	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using pre-TP with a negative CUS to exclude upper extremity DVT?	Patients with suspected upper extremity DVT	Negative CUS plus low/moderate/high pre-TP at presentation	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)

(Continued)

Table 1—*Continued*

Informal Question	PICO Question				Methodology
	Population	Intervention	Comparator	Outcome	
What are the consequences of using pre-TP with a negative Doppler US to exclude upper extremity DVT?	Patients with suspected upper extremity DVT	Negative Doppler US plus low/moderate/high pre-TP at presentation	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using pre-TP with a negative duplex US to exclude upper extremity DVT?	Patients with suspected upper extremity DVT	Negative duplex US plus low/moderate/high pre-TP at presentation	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using serial CUS to exclude DVT in patients with a low/moderate/high pre-TP of upper extremity DVT?	Patients with suspected upper extremity DVT	Repeat CUS (within approximately 1 wk)	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using serial Doppler US to exclude DVT in patients with a low/moderate/high pre-TP of upper extremity DVT?	Patients with suspected upper extremity DVT	Repeat Doppler US (within approximately 1 wk)	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using serial duplex US to exclude DVT in patients with a low/moderate/high pre-TP of upper extremity DVT?	Patients with suspected upper extremity DVT	Repeat duplex US (within approximately 1 wk)	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)

(Continued)

Table 1—*Continued*

Informal Question	PICO Question				Methodology
	Population	Intervention	Comparator	Outcome	
What are the consequences of using serial CUS to exclude upper extremity DVT in patients with a positive DD? Negative CUS plus positive moderately (SimpliRED) or highly sensitive DD plus low pre-TP Negative CUS plus positive moderately sensitive (SimpliRED) or highly sensitive DD plus moderate pre-TP Negative CUS plus positive highly sensitive DD plus high pre-TP	Patients with suspected upper extremity DVT	Repeat CUS (within approximately 1 wk)	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using serial Doppler US to exclude upper extremity DVT in patients with a positive DD? Negative Doppler US plus positive moderately sensitive (SimpliRED) or highly sensitive DD plus low pre-TP Negative Doppler US plus positive moderately sensitive (SimpliRED) or highly sensitive DD plus moderate pre-TP Negative Doppler US plus positive highly sensitive DD plus high pre-TP	Patients with suspected upper extremity DVT	Repeat Doppler US (within approximately 1 wk)	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)

(Continued)

Table 1—*Continued*

Informal Question	PICO Question				Methodology
	Population	Intervention	Comparator	Outcome	
What are the consequences of using serial duplex US to exclude upper extremity DVT in patients with a positive DD? Negative duplex US plus positive moderately sensitive (SimpliRED) or highly sensitive DD plus low pre-TP Negative duplex US plus positive moderately sensitive (SimpliRED) or highly sensitive DD plus moderate pre-TP Negative duplex US plus positive highly sensitive DD plus high pre-TP	Patients with suspected upper extremity DVT	Repeat duplex US (within approximately 1 wk)	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using a negative DD to obviate the need for serial testing in patients with suspected upper extremity DVT and a negative CUS and moderate or high pre-TP at presentation? Negative CUS plus low pre-TP Negative CUS plus low pre-TP Negative CUS plus high pre-TP	Patients with suspected upper extremity DVT	Negative highly sensitive DD or negative moderately sensitive (SimpliRED) DD	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)

(Continued)

Table 1—*Continued*

Informal Question	PICO Question				Methodology
	Population	Intervention	Comparator	Outcome	
What are the consequences of using a negative DD to obviate the need for serial testing in patients with suspected upper extremity DVT and a negative Doppler US and moderate or high pre-TP at presentation? Negative Doppler US plus low pre-TP Negative Doppler US plus moderate pre-TP Negative Doppler US plus high pre-TP	Patients with suspected upper extremity DVT	Negative sensitive DD or negative moderately sensitive (SimpliRED) DD	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using a negative DD to obviate the need for serial testing in patients with suspected upper extremity DVT and a negative duplex US and moderate or high pre-TP at presentation? Negative duplex US plus low pre-TP Negative duplex US plus low pre-TP Negative duplex US plus high pre-TP	Patients with suspected upper extremity DVT	Negative highly sensitive DD or negative moderately sensitive (SimpliRED) DD	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)

(Continued)

Table 1—*Continued*

Informal Question	PICO Question				Methodology
	Population	Intervention	Comparator	Outcome	
What are the consequences of using a highly sensitive DD as a stand-alone test to exclude upper extremity DVT?	Patients with suspected upper extremity DVT	Negative highly sensitive DD on day of presentation	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using a moderately sensitive (SimpliRED) DD as a stand-alone test to exclude upper extremity DVT?	Patients with suspected upper extremity DVT	Negative moderately sensitive (SimpliRED) DD on day of presentation	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using CT scan venography to diagnose upper extremity DVT?	Patients with suspected upper extremity DVT	Intraluminal filling defect	Venography	FP/1,000 of positive (eg, post-TP of a positive test) if management study Specificity if accuracy study Morbidity caused by test strategy)	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using CT scan venography to exclude upper extremity DVT?	Patients with suspected upper extremity DVT	Negative CT scan venography	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)

(Continued)

Table 1—*Continued*

Informal Question	PICO Question				Methodology
	Population	Intervention	Comparator	Outcome	
What are the consequences of using contrast MR venography to diagnose upper extremity DVT?	Patients with suspected upper extremity DVT	Intraluminal filling defect	Venography	FP/1,000 of positive (eg, post-TP of a positive test) if management study Specificity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using MR venography to exclude upper extremity DVT?	Patients with suspected upper extremity DVT	Negative MR venography	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if management study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)
What are the consequences of using MR direct thrombus imaging to diagnose upper extremity DVT?	Patients with suspected upper extremity DVT	High signal intensity	Venography	FP/1,000 of positive (eg, post-TP of a positive test) if management study Specificity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)

(Continued)

Table 1—*Continued*

Informal Question	PICO Question				Methodology
	Population	Intervention	Comparator	Outcome	
What are the consequences of using MR direct thrombus imaging to exclude upper extremity DVT?	Patients with suspected upper extremity DVT	Negative MR direct thrombus imaging	Venography or VTE during additional testing or 3-6 mo follow-up if intervention shows no evidence of DVT	FN/1,000 (eg, post-TP of a negative test) if accuracy study Sensitivity if accuracy study Morbidity caused by test strategy	RCTs Observational studies Prospective cohort studies (can be single group or single arm that used diagnostic intervention specified in question) Cross-sectional accuracy studies (if insufficient data from randomized controlled management trials or prospective management studies)

For Pre-TP use available model and specify. Management study is one in which patient is managed (or treated) according to test results. CUS = compression ultrasonography; DD = D-dimer; FN = false negative; FP = false positive; MR = magnetic resonance; RCT = randomized controlled trial; sensitive DD = D-dimer with sensitivity ≥ 95% in general population of patients with suspected VTE; TP = test probability; US = ultrasound.

We have judged diagnostic strategies acceptable if we are confident that they meet all of the following conditions: (1) management studies have established that the probability of objective diagnosis of symptomatic VTE during 3 to 6 months of follow-up after initial classification as DVT negative is ≤ 2%; (2) modeling suggests a < 0.1% (one in 1,000) risk of fatal PE (to illustrate, the calculated risk is 0.065% for routine venography and 0.076% for routine serial proximal compression US [CUS]) and nonfatal PE of < 0.5% (five in 1,000) (to illustrate, the calculated risk is 0.31% for routine venography and 0.37% for routine serial proximal CUS); (3) modeling suggests a < 0.1% (one in 1,000) risk of fatal hemorrhage (to illustrate, the calculated risk is 0.071% for routine venography and 0.084% for routine serial CUS) and nonfatal intracranial hemorrhage of ≤ 0.035% (0.35/1,000) (to illustrate, the calculated risk is 0.025% for routine venography and 0.03% for routine serial proximal CUS); and (4) modeling suggests a risk of death from PE or hemorrhage of < 0.17% (1.7/1,000) (to illustrate, the calculated risk is 0.137% for routine venography and 0.159% for routine serial proximal CUS). These thresholds are admittedly arbitrary; those who choose different threshold may reach different conclusions. In the accompanying evidence profiles, we have rated down the quality of evidence if the CI around the estimate of a false-negative result after initial diagnostic testing crosses our 2% threshold.

1.1 Implications of Values and Preferences in the Diagnostic Process

When evaluating alternative diagnostic strategies in patients with suspected DVT, harmful effects, cost, and patient preference (eg, test discomfort, inconvenience, and diagnostic uncertainty) need to be considered. Unless stated, the cost (eg, to the patient, a third-party payer, or society) associated with different diagnostic strategies did not influence our recommendations.

Harmful effects of a given diagnostic strategy include not only acute (eg, renal toxicity) and long-term (eg, cancer secondary to radiation exposure) complications but also indirect complications associated with the incorrect diagnosis (eg, bleeding) or exclusion (subsequent DVT and/or PE) of DVT. A systematic review of patient preferences suggests that the disutility (unpleasantness) associated with an episode of nonfatal VTE and major nonfatal bleeding are similar.[36] This assessment is also supported by the results of a subsequent survey of all panelists for these guidelines that rated values and preferences associated with different standardized clinical scenarios, including episodes of nonfatal VTE and nonfatal major bleeding, as well as the use of different antithrombotic therapies.[36] Therefore, on average, we assume that patients attach equal value to nonfatal VTE and nonfatal major bleeding events. However, we also took into account that values and preferences vary markedly between individual patients and that there is often appreciable uncertainty about the average patient values we used.

We generally recommend against invasive diagnostic strategies when a comparably accurate noninvasive alternative is available. This is because invasive tests are generally associated with greater patient discomfort, side effects (eg, reactions to contrast) and radiation exposure than noninvasive tests. However, we recommend invasive testing over noninvasive testing if the benefits of a more accurate diagnosis outweigh these disadvantages. Individual patient preferences relating to test discomfort and tolerance for diagnostic uncertainty influence this decision. We also acknowledge that access to types of diagnostic testing differs (eg, many centers do not perform ascending venography) and that it is appropriate for such factors to influence the choice of diagnostic testing.

In making recommendations, we have placed the burden of proof with those who would claim a benefit with a more complex, invasive, or expensive diagnostic strategy. In the absence of such

proof (eg, the strategy has not been assessed in management studies), we generally recommend against such strategies. When recommendations were considered controversial by the panel (Recommendation 3.1), the results of panel votes are presented, along with the recommendation.

2.0 Venography: Reference Standard for Diagnosis of DVT

Contrast venography is the criterion standard (eg, the benchmark or best-performing test) for the diagnosis of DVT.[13,37-39] In this technique, iodinated contrast is injected into a dorsal foot vein to outline the entire deep venous system of the lower extremity. DVT is diagnosed by the presence of a constant intraluminal filling defect that is present in more than one view; nonfilling of a venous segment despite repeated injection is suspicious, but not diagnostic, of DVT.[40] Tables S2 to S4 present methods, descriptive results, and evidence profiles for diagnostic studies assessing venography in patients with first suspected lower extremity DVT. Withholding anticoagulants in patients with suspected first DVT who have a technically adequate normal venogram is associated with a low frequency of symptomatic DVT or PE during 3 months of follow-up (1.2%; 95% CI, 0.2%-4.4%).[13] This frequency of subsequent disease is the standard against which all tests or diagnostic strategies used to exclude DVT are typically judged.

Venography is expensive, not uniformly available, uncomfortable for patients, and contraindicated in patients with renal insufficiency and severe allergic reactions to contrast medium. In 5% of patients, the dorsal foot vein cannot be cannulated.[41] Even when venography is performed by experienced radiologists, inadequate imaging is common; in up to 20% of venograms there is inadequate visualization of a venous segment.[13,42-46] Further, venography can be difficult to interpret and the designation of "DVT present" or "DVT absent" is subject to a considerable degree of both intraobserver (κ values ranging from 0.56-0.95) and interobserver (κ values ranging from 0.47-0.92) variation.[43,47-52] Adverse reactions to contrast media include dizziness and nausea (complicating between 1% and 4% of procedures[53,54]), severe allergic reactions (in 0% [95% CI, 0%-2.4%][54] to 0.4% [95% CI, 0.1%-0.4%][53] of patients) and post-venography DVT (confirmed by repeat venography in between 0% [95% CI, 0%-13.3%][55] to 2% [95% CI, 0%-12.6%][53] of patients).

The above limitations make venography unsuitable for routine use in patients presenting with suspected DVT. Venography is now rarely used in clinical practice and many hospitals are unable to perform the procedure. However, venography can serve as a reference standard and be used when other tests are unable to definitely establish or exclude the diagnosis of DVT.

3.0 Diagnosis of Suspected First Lower Extremity DVT

The limitations of contrast venography have led to the development of other testing strategies for the evaluation of patients with suspected DVT.

3.1 Alternatives to Venography for the Evaluation of Suspected First Lower Extremity DVT

3.1.1 Pretest Probability Assessment: Although the clinical diagnosis of DVT is nonspecific and individual clinical features are of little value in diagnosing DVT,[56] clinical prediction or pretest probability estimates (structured and based on specific criteria or unstructured and empirical) are able to stratify patients into groups according to their probability of DVT.[56] Several structured scoring systems have been developed[10,31,32,56-60]; the most well studied is the Wells score.[6,10,31,56] This rule incorporates signs, symptoms, and risk factors for VTE to categorize patients as having a low, moderate, or high probability of DVT,[31] with a prevalence of DVT of 5.0% (95% CI, 4%-8%), 17% (95% CI, 13%-23%), and 53% (95% CI, 44%-61%), respectively.[10] A modification of the Wells score stratifies patients as being likely (prevalence of DVT, 28%; 95% CI, 24%-32%) or unlikely (prevalence of DVT, 6%; 95% CI, 4%-8%) to have DVT.[32] The Wells score has limitations. Interobserver reliability has not been widely evaluated, although one study confirmed its reproducibility when used by resident physicians.[61] One study found that the model performed less well in a primary care setting.[62]

3.1.2 D-Dimer: D-dimer, a degradation product of cross-linked fibrin, is typically elevated in patients with acute DVT. However, because D-dimer levels may also be increased in a variety of nonthrombotic disorders (eg, malignancy, disseminated intravascular coagulation, increasing age, infection, pregnancy, following surgery or trauma, inflammatory conditions, atrial fibrillation, and stroke), D-dimer is a sensitive but nonspecific marker for VTE. Consequently, although a positive result is not useful in confirming the diagnosis of DVT, a negative result can aid in the exclusion of this diagnosis. In hospitalized and other acutely ill patients commonly affected by the conditions listed above, D-dimer testing has less usefulness because of the high frequency of false-positive results. A wide variety of D-dimer assays are available. In a

meta-analysis of 217 studies, enzyme-linked immunofluorescence assays (sensitivity 96%; 95% CI, 89%-98%), microplate enzyme-linked immunosorbent assays (ELISAs) (sensitivity 94%; 95% CI, 86%-97%), and quantitative latex or immunoturbidimetric assays (sensitivity 93%; 95% CI, 89%-95%) were more sensitive for DVT than were the whole blood D-dimer assay (sensitivity 83%; 95% CI, 67%-93%) and latex semiquantitative assays (sensitivity 85%; 95% CI, 68%-93%).[63] Based on these data, ELISAs and enzyme-linked immunofluorescence assays, along with the latex immunoturbidimetric assays, are generally termed "highly sensitive," whereas the whole blood D-dimer assay is considered "moderately sensitive."[10] Of these tests, the whole blood D-dimer assay had the highest specificity (71%; 95% CI, 57%-82% vs 46% [95% CI, 31%-61%] for enzyme-linked immunofluorescence assays; 53% [95% CI, 38%-68%] for microplate ELISAs, and 53% [95% CI, 46%-61%] for quantitative latex or immunoturbidimetric assays).[63]

3.1.3 Venous US: Venous US is the most widely used imaging study for the diagnosis of DVT.[64] Proximal CUS assesses compressibility of the femoral and popliteal veins. The inability to fully collapse a venous segment under gentle US probe pressure is considered diagnostic of DVT. Although distal DVT may be present in patients with a normal proximal US, it is seldom if ever associated with important clinical sequelae (PE or postthrombotic syndrome). However, as distal DVT may propagate proximally and lead to PE, additional investigations, such as pretest probability assessment, D-dimer testing, or a second proximal CUS performed 5 to 7 days later (serial or repeat US), are needed to exclude distal DVT or, if distal DVT cannot be excluded, to detect early extension into the proximal veins.[22,65,66] Whole-leg US assesses the deep veins of both the proximal leg and calf. This technique has been studied as a means of excluding DVT as a stand-alone test, eliminating the need for a return visit for serial US. As whole-leg US results in treatment of distal DVT that will not extend,[67,68] it carries the risk of overtreatment.

3.1.4 CT Scan Venography: CT scan venography typically involves injection of contrast media into an arm vein followed by helical CT imaging timed to coincide with opacification of the deep veins of the legs to allow assessment of these veins for thrombus. It therefore shares the disadvantage with conventional contrast venography of requiring administration of IV contrast but does not require cannulation of a foot vein (although this technique can be used). CT scan venography can be combined with CT scan pulmonary angiography to provide imaging for both suspected DVT and suspected PE. Most studies of CT scan venography have been done this way.

3.1.5 MRI: MRI can be applied using a variety of techniques. Some techniques visualize blood flow without the need for contrast agents because they rely on the intrinsic properties of flowing blood (time-of-flight or phase-contrast venography). However, the imaging of vascular structures is often improved by the use of contrast agents, such as in IV gadolinium. MR contrast agents can be either injected into a vein in the foot or into the arm with imaging timed for optimal imaging of lower limb veins. Alternatively, MR can identify DVT by direct thrombus imaging. This technique involves visualizing thrombus (high signal due to red cell methemoglobin in the clot) against a suppressed background. This technique has the advantages of being noninvasive and not requiring IV contrast agents. However, MRI is not routinely accessible for this purpose in most centers.

3.2 Evaluation of Diagnostic Strategies for Suspected First Lower Extremity DVT

Pretest probability assessment, D-dimer testing, and venous US have been extensively investigated and are widely used either alone or in combination in patients with a suspected first DVT. Evaluation of CT scan venography and MRI in this patient population has been limited to accuracy studies.

Details of management studies in patients with suspected first DVT that used pretest probability, D-dimer, and proximal CUS are summarized in Table 2 and Tables S5 to S16.[10,16-19,21-23,25,30-32,41,60,62,63,65,69-86] Table 2 describes the consequences of using specific strategies in terms of the probability of VTE being diagnosed during clinical follow-up when a given diagnostic strategy suggests that DVT is not present.

As shown in Table 2 and Tables S5 to S16, the pretest assessment (ie, prevalence of DVT) has a significant effect on the usefulness of D-dimer and proximal US. Categorizing patients as having a low pretest probability for DVT eliminates the need for (1) radiologic imaging (eg, US) in those with a negative D-dimer, and (2) serial or repeat testing in those with a normal proximal US. Although most patients with a positive CUS have a proximal DVT, this is progressively less true as pretest probability declines. In a study of 529 symptomatic patients, the posttest probability of DVT in those with a positive CUS (as assessed by venography) was 100% in patients with a high pretest probability, 96% in those with a moderate pretest probability, and 63% in patients with a low pretest probability.[6]

Tables 3 and 4 and Tables S17 to S23 summarize the methodology and results of studies assessing whole-leg

Table 2—*[Sections 3.1-3.5] Summary of Outcomes for Diagnostic Studies Assessing DD, Pre-TP, and Proximal US for the Diagnosis of Suspected First Lower Extremity DVT*

Pre-TP	Diagnostic Strategy Used to Exclude DVT	No. of Studies[a]	Quality of Evidence	Number of Patients Subjected to Given Diagnostic Strategy → Number Considered Negative for DVT at Completion of Testing	Overall Prevalence in Population of Interest → Incidence of VTE During Follow-up[b] Among Those Judged to Have DVT Excluded by Specified Diagnostic Strategy (ie, Post-TPof Disease), % (95% CI)
Low	Moderately sensitive DD negative	1[79]	Moderate	206 → 177	2.4 → 0.6 (0.03-2.7)
		Meta-analysis, 3[10,70,74]			0.9
					0.5 (0.07-1.1)
					1.1 (0.9-1.5)
	Highly sensitive DD negative	5[16,18,25,81,82]	High	1,270 → 824	6.7 → 1.0 (0.5-1.7)
		Meta-analysis, 3[10,70,74]	Moderate		0.5
					0.4 (0.04-1.1)
					Cardiac: 0.4 (0.2-0.8) or Triage: 0.9 (0.9-2.2)
	Single proximal US negative	4[17,30,31,78]	High	944 → 885	7.1→ 0.9 (0.5-1.6)
	DD (mixed) positive → single proximal US negative	2[16,32]	High	765 → 198	5 → 0 (0-1.5)
Low/moderate or unlikely	Moderately sensitive DD negative	1[60]	Moderate	852 → 500	9.6 → 1.4 (0.7-2.6)
	DD (mixed) negative	1[32]	Moderate	317 → 218	5.0 → 0.92 (0.2-2.9)
	Highly sensitive DD negative	1[21]	Moderate	749 → 481	N/A → 0.42 (0.04-1.5)
		Meta-analysis, 1[74]	Moderate		0.4 (0.04-1.1)
	Single proximal US negative	1[32]	Moderate	284 → 272	5.6 → 1.5 (0.5-3.3)
	DD (mixed) positive → single proximal US negative	1[32]	Moderate	317 → 85	5 → 0 (0-3.5)
Moderate	Moderately sensitive DD negative	Meta-analysis, 3[10,70,74]	Moderate		4.4
					3.5 (1.4-6.9)
					SimpliRED 4.9 (3.6-6.8) or Clearview Simplify: 5.2 (4.1-6.5)
	Highly sensitive DD negative	3[18,25,77]	Moderate	655 → 214	25.7 → 0.57 (0.02-2.2)
		Meta-analysis, 2[10,70]	Low		NPV: 99 (96-100); LR (negative) 0.05 (0.01-0.21); estimated post-test prevalence, 1
					Cardiac: 1.7 (1.0-3.8) for point of care and Triage: 4.3 (2.0-9.7)
	Single proximal US negative	1[78]	Moderate	144 → 114	21.5 → 0.9 (0.05-4.1)
	Single proximal US negative → DD (mixed) negative	2[16,32]	High	675 → 325	22.4 → 0 (0-0.9)
	Serial proximal US negative	3[17,31,80]	Moderate	N/A → 365	15.8 (Based on 2 out of 3 studies) → 1.1 (0.4-2.5) 0.6 (0.4-0.9)
		Meta-analysis[85]	Moderate		
	Highly sensitive DD positive → Single proximal US negative	1[77]	Moderate	134 → 73	19.4 → 0 (0-4.0)
	Single proximal US negative → DD (mixed) positive → single proximal US negative	1[16]	Moderate	426 → 94	18.8 → 0 (0-3.1)

(Continued)

Table 2—*Continued*

Pre-TP	Diagnostic Strategy Used to Exclude DVT	No. of Studies[a]	Quality of Evidence	Number of Patients Subjected to Given Diagnostic Strategy → Number Considered Negative for DVT at Completion of Testing	Overall Prevalence in Population of Interest → Incidence of VTE During Follow-up[b] Among Those Judged to Have DVT Excluded by Specified Diagnostic Strategy (ie, Post-TPof Disease), % (95% CI)
Moderate/high or likely	Single proximal US negative → moderately sensitive DD negative	1[30]	Moderate	531→ 148	58.8 → 0 (0-2.0)
	Single proximal US negative → DD (mixed) negative	1[32]	Moderate	249 → 81	49.5 → 0 (0-3.6)
	Serial proximal US negative	1[32]	Moderate	246 → 181	27.1 → 1.1 (0.2-3.4)
	Single proximal US negative → DD (mixed) positive → single proximal US negative	1[32]	Moderate	249 → 97	28.5 → 0 (0-3.0)
	Single proximal US negative → moderately sensitive DD positive → single proximal US negative	1[30]	Moderate not to use, low to use	531→ 83	58.9 → 3.6 (1.0-9.1)
High	Moderately sensitive DD negative	Meta-analysis, 2[10,74]	Moderate		19
					21.4 (8.5-37.9)
	Highly sensitive DD negative	Meta-analysis, 3[10,70,74]	Moderate		NPV: 92 (81-97)
					6.4 (1.7-14.5)
					Cardiac: 6.5 (3.8-13.7) or Triage: 15.3 (7.4-30.1)
	Highly sensitive DD negative → single proximal US negative	2[18,25]	Low	350 → 59	53.4 → 1.7 (0-7.8)
	Serial proximal US negative	4[18,78,80,81]	Moderate	291 → 221	36.4 → 0.9 (0.2-2.8)
	Single proximal US negative → highly sensitive DD positive → single proximal US negative	1[25]	Low	279 → 36	59.5 → 2.8 (0.1-12.5)
	Single proximal US negative → venogram negative	3[17,23,31]	Low	168 → 43	78.0 → 0 (0-6.7)

(Continued)

Table 2—*Continued*

Pre-TP	Diagnostic Strategy Used to Exclude DVT	No. of Studies[a]	Quality of Evidence	Number of Patients Subjected to Given Diagnostic Strategy → Number Considered Negative for DVT at Completion of Testing	Overall Prevalence in Population of Interest → Incidence of VTE During Follow-up[b] Among Those Judged to Have DVT Excluded by Specified Diagnostic Strategy (ie, Post-TPof Disease), % (95% CI)
Not specified	Highly sensitive DD negative	Meta-analysis, 5[63,70-72,74]	Moderate		Highest sensitivity: 97
					Sensitivity: 97.7 (96.1-99.0) and specificity: 45.7 (28.0-66.6)
					Sensitivity: 93-96
					Sensitivity: up to 94
					Highest sensitivity: 96 (91-100)
					Sensitivity: 93-96
					Sensitivity: up to 94
					Highest sensitivity: 96 (91-100)
	Single proximal US negative, except if high pre-TP then venography	1[23]	Moderate	474 → 343	25.3 → 2.6 (1.4-4.5)
	Single proximal US negative → moderately sensitive DD –	1[80]	High	470 → 309	13.2 → 1.0 (0.3-2.5)
	Single proximal US and moderately sensitive DD negative	1[22]		1739 → 828	24.4 → 0.7 (0.3-1.4)
	Combined			2,209 → 1,137	22.1 → 0.8 (0.4-1.4)
	Single proximal US negative→ sensitive DD negative	1[76]	High	686 → 598	39.1 → 0.2 (0.2-0.8)
	Serial proximal US	3[41,65,80]	High	2,662 → 2,071	20.9 → 1.0 (0.7-1.5)
		Meta-analysis, 1[86]	Moderate		0.6 (0.4-0.9)
	Single proximal US and moderately s ensitive DD positive → single proximal US negative	1[22]	Moderate	1,739 →520	24.4 → 2.1 (1.2-3.5)
	Single proximal US and moderately s ensitive DD, if negative stop; if positive → single proximal US	1[19]	Moderate	1,045 → 828	23.3 → 1.1 (0.6-1.9)
	Single proximal US negative → highly sensitive DD positive → single proximal US negative	1[76]	Moderate	946 → 83	28.3 → 2.4 (0.4-7.4)
	Highly sensitive DD positive → serial proximal US negative	2[18,25]		1,065 → 494	34.5 → 2.2 (1.3-3.7)
	Combined (3 above)			2,011 → 577	31.6 → 2.3 (1.3-3.5)
	Single proximal US negative → moderately sensitive DD positive → venogram negative	1[80]	Low	470 → 58	13.2 → 3.5 (0.6-10.5)

Consequences in terms of presenting with VTE during clinical follow-up when specified strategies are used to rule out suspected first lower extremity DVT. LR = likelihood ratio; N/A = not available; NPV = negative predictive value. See Table 1 legend for expansion of other abbreviations.

[a]Meta-analyses and management studies are reported separately. All meta-analyses include both management and accuracy studies. Results of meta-analyses are reported separately for each meta-analysis. Where feasible, results of management studies are pooled.

[b]Duration of follow-up usually 3 mo; occasionally 6 mo.

US for the diagnosis of first DVT.[14,19-21,24,26-29,64,87-123] Although whole-leg US generates a larger number of false-negative results than venography for the diagnosis of isolated calf vein thrombosis, almost all positive results will be true positives. Pooling data from 34 studies comparing US with venography for calf-vein DVT in symptomatic patients yielded a specificity of 96.0% (95% CI, 95.2%-96.8%).[87-122] Eight management studies have assessed the safety of withholding anticoagulants based a negative whole-leg US.[19-21,24,26-29] The results of seven of these studies were pooled in a recent meta-analysis[123] that found that the 3-month rate of VTE after a single negative whole-leg US was 0.57% (95% CI, 0.25%-0.89%) (Table 3, Table S19).

Individual patient data from two studies were combined in order to ascertain the incidence rate of VTE following a negative whole-leg US in patients with varying pretest probabilities for DVT based on the three-category Wells score[27,28,123] (Table S22). The 3-month incidence of VTE was 0.3% (95% CI, 0%-0.7%) for low, 0.8% (0%-1.8%) for moderate, and 2.5% (0%-7.11%) for patients with high pretest probability.

In an RCT not included in the meta-analysis, patients with either an abnormal sensitive D-dimer or a score corresponding to "DVT likely" using the Wells two-level prediction rule were randomized to either serial proximal CUS or whole-leg US (Table 3, Table S23). The 3-month rate of VTE was 2.0% (95% CI, 0.6%-5.1%) in the group with negative serial proximal US (n = 198) and 1.2% (95% CI, 0.2%-4.3%) in the negative whole-leg US group (n = 165), (absolute difference in frequency of VTE during follow-up: 0.8%; 95% CI, −1.8 to 3.4).[21]

A subsequent management study of 431 patients explored the net effect of using whole-leg US vs serial proximal US (Tables 4, 5).[124] Patients with no proximal DVT and either an abnormal sensitive D-dimer or a score corresponding to "DVT likely" using the Wells two-level prediction rule were managed with serial proximal US. Whole-leg US was also performed, but results were blinded and not used for management. Sixty-five patients (15.3%; 95% CI, 12.0%-18.8%) were found to have DVT isolated to the calf. Of the 64 who completed follow-up, two patients with isolated calf DVT experienced extension into the proximal system, which was detected on serial proximal US.

Tables S24 to S26 present the results of our modeling and decision analysis. In all tables, the denominator is 1,000 patients managed according to each diagnostic strategy; Table S24 presents the number of expected clinical events, and Table S25 presents the incremental number of events compared with a strategy of serial proximal US. Table S26 contains the number of tests performed with each strategy and the incremental number of tests compared with a serial proximal US strategy. The latter was used for comparative purposes as it is one of the strategies least likely to produce false-negative results.

Although a whole-leg US strategy reduces the number of US sessions compared with serial proximal US, routine anticoagulation of patients with isolated calf DVT will result in a larger number receiving treatment and an increase in bleeding complications. As only a relatively small portion of isolated calf DVT would propagate or embolize without treatment, some patients undergoing whole-leg US will receive anticoagulation for a disease with a benign prognosis if left untreated (Kearon et al).[11] The absence of a clear safety advantage for the whole-leg US strategy is demonstrated in Table S24, wherein the point estimate for the risk of fatal PE with a serial proximal US strategy is no higher than one involving whole-leg US. Guidelines for determining which patients are likely to most benefit from anticoagulant

Table 3—*[Sections 3.2-3.5] Summary of Findings for Diagnostic Studies Evaluating Whole-Leg US in First Suspected Lower Extremity DVT: Prospective Cohort Management Studies*

Diagnostic Strategy Used to Exclude DVT	No. of Participants (Studies)[a]	Outcome	Incidence of VTE During Follow-up in Those Judged to Have DVT Excluded (ie, Post-TP of DVT), % (95% CI)	Quality of Evidence
Single negative whole-leg US	4,731 (7)[72,114-119]	VTE during clinical follow-up (3 mo)	0.57 (0.25-0.89)	Moderate[b]

Consequences in terms of presenting with VTE during clinical follow-up when a single whole-leg US is used to rule out suspected first lower extremity DVT. GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. GRADE = Grades of Recommendation, Assessment, Development, and Evaluation; See Table 1 legend for expansion of other abbreviations.

[a]Includes six management studies and one arm from an RCT.

[b]Pooled management studies are of high methodologic quality and results are highly concordant. Moderate quality due to only one RCT among the analyzed studies.

Table 4—*[Sections 3.2-3.5] Summary of Findings for Diagnostic Studies Evaluating Whole-Leg US in First Suspected Lower Extremity DVT: Randomized Trial (Single Whole-Leg US vs Serial Proximal US and DD)*[19]

Outcomes	Illustrative Comparative Risks (95% CI): Assumed Risk, Proximal US and DD	Illustrative Comparative Risks (95% CI): Corresponding Risk, Single Whole-Leg US	Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)	Comments
VTE follow-up: mean, 3 mo	9 per 1,000	12 per 1,000 (0-16)	1.3 (0-1.8)	1,564 (1)	High[a]	Whole-leg US and the serial US/DD arms met predefined criteria for equivalence

Single whole-leg US compared with serial proximal US and DD for patients with suspected DVT.[19] Patient or population: Patients with suspected DVT. Intervention: Single whole-leg US. Comparison: Serial proximal US (if moderately sensitive DD positive) or single proximal US (if moderately sensitive DD negative). GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. See Table 1 and 3 legends for expansion of abbreviations.

[a]Trial was RCT without significant methodologic limitations.

therapy when isolated distal DVT is detected by whole-leg US (vs. surveillance to rule detect extension) are found in the article by Kearon et al[11] in this supplement.

Strategies involving CT scan venography and MRI were not included in the decision analysis. The methodology of a meta-analysis of CT scan diagnostic accuracy,[125] along with individual accuracy studies,[126-143] is summarized in Table S27 (Recommendations 3.2-3.6). Most of the studies were of patients with suspected PE rather than suspected DVT. Only one compared CT scan venography with contrast venography;[143] the remainder compared CT scan venography to US.[126-142] The results of the meta-analysis[125] and five primary studies that were not included in the meta-analysis (mostly because they were subsequently published)[126-129,133] are described in Tables S28 and S29, with the Summary of Findings in Table 6.[144-146]

All the studies reported results as sensitivity and specificity, rather than the frequency of VTE during follow-up in patients who had normal test results. The meta-analysis reported summary estimates of sensitivity and specificity despite evidence of heterogeneity between the individual studies.[125] Causes of heterogeneity were not formally explored. In the meta-analysis, the summary estimate of sensitivity was 95.2% (95% CI, 93.6%-96.5%), whereas the range in individual studies was from 93% to 100%. The summary estimate of specificity was 95.9% (95% CI, 93.0%-97.8%), whereas the range in individual studies was from 71% to 100%. Sensitivity was lower in the five studies not included in the meta-analysis. Across all studies, the range for sensitivity was 59% to 100%, whereas the range for specificity remains 71% to 100%.

The quality of the evidence for CT scan venography is low (Table 6, Tables S27, S28, and S30)

Table 5—*[Section 3.2-3.5] Summary of Findings for Diagnostic Studies Evaluating Whole-Leg US in First Suspected Lower Extremity DVT: Randomized Trial (Single Whole-Leg US vs Serial Proximal US and DD in High-Risk Patients)*[21]

Outcomes	Illustrative Comparative Risks (95% CI): Assumed Risk, Serial Proximal US	Illustrative Comparative Risks (95% CI): Corresponding Risk, Single Whole-Leg US	Relative Effect	No. of Participants (Studies)	Quality of the Evidence (GRADE)	Comments
VTE follow-up: mean, 3 mo	20 per 1,000 (6-51)	12 per 1,000 (2-43)	0.6	521 (1)	High[a]	Reported $P = .69$ for difference in VTE events between strategies. Absolute difference, 0.8% (95% CI, −1.8 to −3.4)

Single whole-leg US compared with serial proximal US and DD for high-risk patients with suspected DVT.[21] Patient or population: High-risk patients with suspected DVT. Settings: Symptomatic patients with likely Wells score or positive highly sensitive DD (Tina-quant). Intervention: Single whole-leg CUS. Comparison: Serial proximal CUS. GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. See Table 1 and 3 legends for expansion of abbreviations.

[a]Trial was RCT without significant methodologic limitations.

Table 6—*[Sections 3.2-3.6] Summary of Findings of Diagnostic Studies Evaluating CT Scan Venography, MR Venography, and MR Direct Thrombus Imaging in Patients with Suspected First Lower Extremity DVT: Accuracy Studies*

Technique	Population and Reference Standard	Number of Studies	Quality of Evidence	Illustrative Comparative Numbers: Effect/1,000[a] True Positives (Correctly Classified as Having DVT)	True Negatives (Correctly Classified as Not Having DVT)	False Positives (Incorrectly Classified as Having DVT)	False Negatives (Incorrectly Classified as Not Having DVT)
CT scan venography[b]	Population: predominantly suspected PE	Meta-analysis of 13 plus 5 additional primary studies[125-129,133]	Low[c]	Prevalence 5%, 48	Prevalence 5%, 904	Prevalence 5%, 46	Prevalence 5%, 2
	Reference standard: predominantly US			Prevalence 17%, 163	Prevalence 17%, 790	Prevalence 17%, 40	Prevalence 17%, 7
				Prevalence 53%, 508	Prevalence 53%, 447	Prevalence 53%, 23	Prevalence 53%, 22
MR venography[d]	Population: predominantly suspected DVT	Meta-analysis of 13 plus 1 additional primary studie[144,145]	Low[e]	Prevalence 5%, 46	Prevalence 5%, 901	Prevalence 5%, 49	Prevalence 5%, 4
	Reference standard: predominantly contrast venography			Prevalence 17%, 158	Prevalence 17%, 787	Prevalence 17%, 43	Prevalence 17%, 14
				Prevalence 53%, 486	Prevalence 53%, 446	Prevalence 53%, 24	Prevalence 53%, 45
MR direct thrombus imaging[f]	Population: suspected DVT	1 Primary study[146]	Low[g]	Prevalence 5%, 47	Prevalence 5%, 874	Prevalence 5%, 76	Prevalence 5%, 3
	Reference standard: contrast venography			Prevalence 17%, 160	Prevalence 17%, 764	Prevalence 17%, 66	Prevalence 17%, 10
				Prevalence 53%, 498	Prevalence 53%, 432	Prevalence 53%, 38	Prevalence 53%, 32

GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. PE = pulmonary embolism. See Table 1 and 3 legends for expansion of other abbreviation.

[a]Prevalences for high (53%), moderate (17%), and low (5%) taken from Wells et al.[10]

[b]Based on a combined specificity of 95.2% (95% CI, 93.6%-96.5%) and sensitivity of 95.9% (95% CI, 93.0%-97.8%).

[c]Serious limitations (in adequate reference standard), moderate inconsistency (significant heterogeneity between studies), serious indirectness (most studies were in suspected PE, few in suspected DVT; no management studies), and moderate imprecision (reported specificities range from 93%-100%; reported sensitivities range from 59%-100%).

[d]Based on a combined specificity of 94.8% (95% CI, 92.6%-96.5%) and sensitivity of 91.5% (95% CI, 87.5%-94.5%).

[e]No major limitations, moderate inconsistency (significant heterogeneity between studies), moderate indirectness (no management studies), and serious imprecision (reported specificities range from 43%-100%, reported sensitivities range from 0-100%).

[f]Based on a specificity of 92% (95% CI, 80%-98%) and sensitivity of 94.9% (95% CI, 84%-97%).

[g]No significant limitations, only single study, and moderate indirectness (management studies).

because studies generally used an inadequate reference standard, there was marked unexplained heterogeneity between studies, most studies were in patients with suspected PE rather than DVT, and there are no management studies to determine the consequences of using CT scan venography in practice. In summary, there is currently insufficient evidence to draw reliable conclusions about the consequences of using CT scan venography to diagnose or exclude suspected first lower extremity DVT.

Tables S31 and S32 summarize the methodology of a meta-analysis of 14 studies[144] and individual accuracy studies[145-159] of MR diagnostic accuracy. Most of the studies in the meta-analysis were of MR venography (n = 13), but one study evaluated MR direct thrombus imaging.[146] The meta-analysis included all but one of the accuracy studies of MR venography.[145] The results of the meta-analysis and the additional primary study are described in Tables S33 and S34, with the Summary of Findings in Table 6. All the studies reported results as sensitivity and specificity rather than rates for VTE during follow-up in patients with negative test results.

The meta-analysis reported summary estimates of sensitivity and specificity despite evidence of heterogeneity between the individual studies.[144] The causes of heterogeneity were not formally explored. It also included the study of MR direct thrombus imaging.[146] In the meta-analysis, the summary estimate of sensitivity was 91.5% (95% CI, 87.5-94.5), whereas the range in individual studies was from 0% to 100%. The summary estimate of specificity was 94.8% (95% CI, 92.6%-96.5%), whereas the range in individual studies was from 43% to 100%. The additional study reported a sensitivity of 100% and a specificity of 78%.[145]

As outlined in Table 6 and Tables S31 and S32 the quality of the evidence for MR venography is low. There was marked unexplained heterogeneity between studies and there were no management studies to determine the consequences of using MR venography in practice. In summary, MR venography may have similar diagnostic accuracy to US for patients with suspected DVT. However, as the evidence consists of diagnostic accuracy studies, the consequences of basing treatment decisions on the results of MR venography are not clear.

The methodology and results of the single study examining the accuracy of MR direct thrombus imaging[146] are described in Tables S35 to S37 and Table 6 (Summary of Findings, Recommendations 3.2-3.6). The study evaluated diagnostic accuracy compared with a reference standard of contrast venography in patients with suspected DVT. Sensitivity was 94% (95% CI, 84%-97%), and specificity was 92% (95% CI, 80%-98%). As outlined in Tables S35 and S37 and Table 6, the evidence is of low quality, with only an accuracy study and no management studies to determine the consequences of using MR direct thrombus imaging in practice. In summary, MR direct thrombus imaging may have similar diagnostic accuracy to US for patients with suspected DVT, but the consequences of basing treatment decisions on the results of MR direct thrombus imaging are not clear.

As outlined above, patients who have had DVT excluded by diagnostic testing still have a small possibility of having thrombosis that could progress. Therefore, once testing has ruled out DVT, we recommend clinical follow-up, by which we mean that patients are aware of the need for further assessment if symptoms worsen or fail to resolve or if they develop symptoms suggestive of PE and there is a means to see and investigate patients promptly. It is also anticipated that patients with marked symptoms who have had DVT excluded will undergo assessment to identify an alternative diagnosis.

Recommendations (see Figs 1-5)

One approach to the evaluation of suspected first DVT is to begin by applying a pretest probability assessment to estimate the probability of DVT based on history and physical examination. We offer sets of recommendations both with and without their use.

3.1. In patients with a suspected first lower extremity DVT, we suggest that the choice of diagnostic tests process should be guided by the clinical assessment of pretest probability, rather than by performing the same diagnostic tests in all patients (Grade 2B)**.**

Note: In considering this recommendation, five panelists voted for a strong recommendation and four voted for a weak recommendation (one declined to vote and two did not participate). According to predetermined criteria, this resulted in weak recommendation.

Testing Using Risk Stratification

3.2. In patients with a low pretest probability of first lower extremity DVT (see Fig 1**), we recommend one of the following initial tests: (i) a moderately sensitive D-dimer, (ii) a highly sensitive d-dimer, or (iii) CUS of the proximal veins rather than (i) no diagnostic testing** (Grade 1B for all comparisons)**, (ii) venography** (Grade 1B for all comparisons)**, or (iii) whole-leg US** (Grade 2B for all comparisons)**. We suggest initial use of a moderately sensitive** (Grade 2C) **or highly sensitive** (Grade 2B) **D-dimer rather than proximal CUS.**

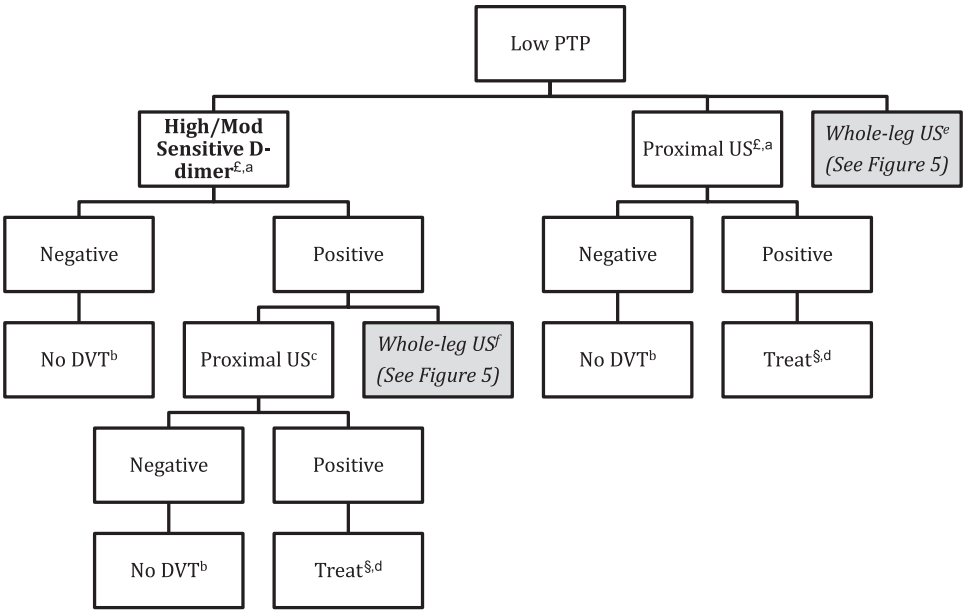

FIGURE 1. [Section 3.2] Recommendations for evaluation of suspected first lower extremity DVT: patients with low pretest probability (PTP) for DVT. Where there are preferred strategies, these are indicated by boldface print; less preferred strategies are indicated by italicizing/shading. Venography is not generally indicated in the figure, as it is not routinely used. §See Kearon et al.[11] £Beginning with moderately sensitive D-dimer (Grade 2C) or highly sensitive D-dimer (Grade 2B) is suggested over beginning with US. [a]Grade 1B vs no testing and vs venography; Grade 2B vs whole-leg US. [b]Grade 1B vs further testing. [c]Grade 1B vs venography; Grade 2C vs whole-leg US. [d]Grade 2C for treating DVT vs confirmatory venography. [e]Grade 2B for high/moderate sensitivity D-dimer or proximal US over whole-leg US. [f]Grade 2C for proximal US over whole-leg US. PTP = pretest probability; US = ultrasound.

Remarks: The choice between a moderately sensitive D-dimer test, a highly sensitive D-dimer test, or proximal CUS as the initial test will depend on local availability, access to testing, costs of testing, and the probability of obtaining a negative D-dimer result if DVT is not present. Initial testing with US would be preferred if the patient has a comorbid condition associated with elevated D-dimer levels and is likely to have a positive D-dimer result, even if DVT is absent. In patients with suspected first lower extremity DVT in whom US is impractical (eg, when leg casting or excessive subcutaneous tissue or fluid prevent adequate assessment of compressibility) or nondiagnostic we suggest CT scan venography, MR venography, or MR direct thrombus imaging could be used as an alternative to venography.

If the D-dimer is negative (see Fig 1), we recommend no further testing over further investigation with (i) proximal CUS, (ii) whole-leg US, or (iii) venography (Grade 1B for all comparisons)**. If the proximal CUS is negative, we recommend no further testing compared with (i) repeat proximal CUS after 1 week, (ii) whole-leg US, or (iii) venography** (Grade 1B for all comparisons)**.**

If the D-dimer is positive (see Fig 1), we suggest further testing with CUS of the proximal veins rather than (i) whole-leg US (Grade 2C) **or (ii) venography** (Grade 1B)**. If CUS of the proximal veins is positive, we suggest treating for DVT and performing no further testing over performing confirmatory venography** (Grade 2C)**.**

Remarks: In circumstances when high-quality venography is available, patients who are not averse to the discomfort of venography, are less concerned about the complications of venography, and place a high value on avoiding treatment of false-positive results are likely to choose confirmatory venography if findings for DVT are less certain (eg, a short segment of venous noncompressibility).

3.3. In patients with a moderate pretest probability of first lower extremity DVT (see Fig 2**), we recommend one of the following initial tests: (i) a highly sensitive D-dimer, or (ii) proximal CUS, or (iii) whole-leg US, rather than (i) no testing** (Grade 1B for all comparisons) **or (ii) venography** (Grade 1B for all comparisons)**. We suggest initial use of a highly sensitive D-dimer rather than US** (Grade 2C)**.**

Remarks: The choice between a highly sensitive D-dimer test or US as the initial test will depend on local availability, access to testing, costs of testing,

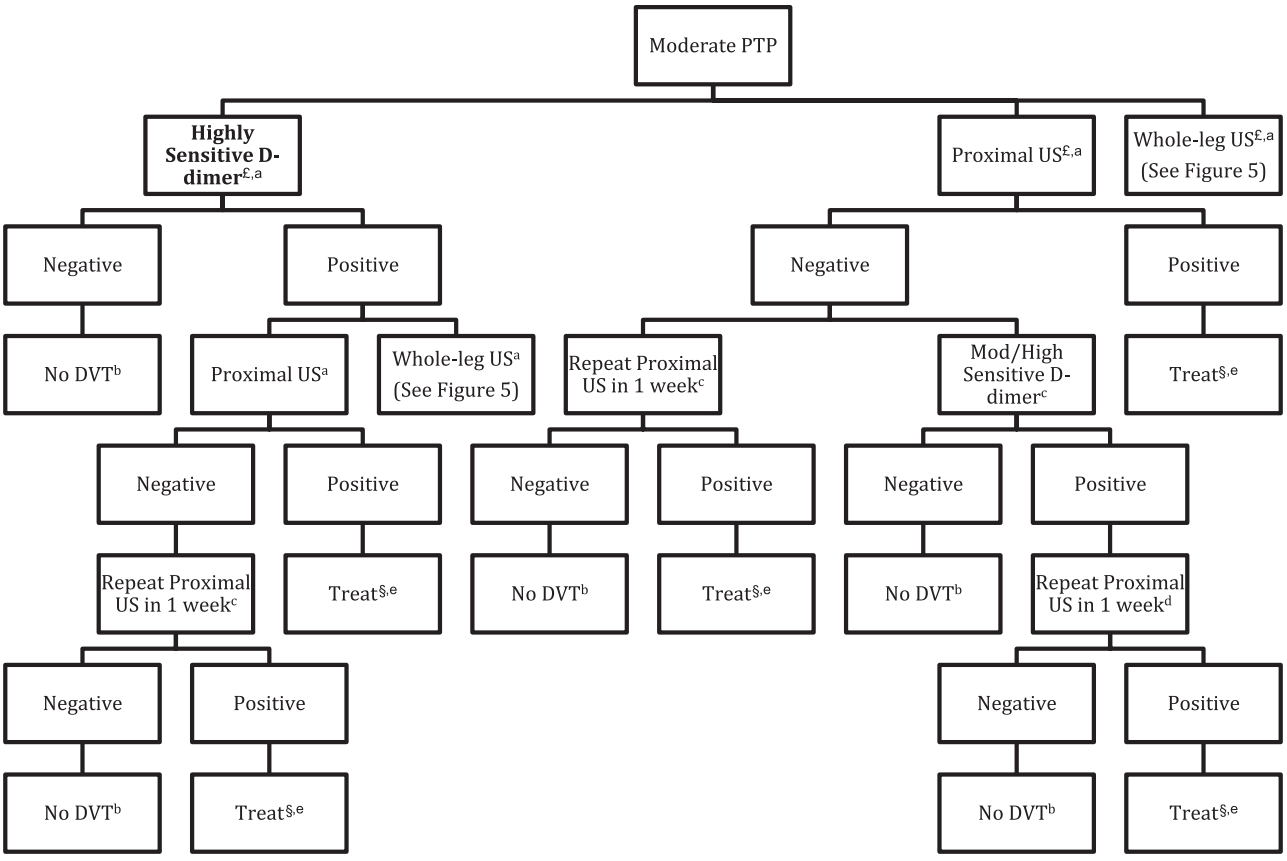

FIGURE 2. [Section 3.3] Recommendations for evaluation of suspected first lower extremity DVT: patients with moderate pretest probability (PTP) for DVT. Where there are preferred strategies, these are indicated by boldface print; less preferred strategies are indicated by italicizing/shading. Venography is not generally indicated in the figure, as it is not routinely used. §See Kearon et al.[11] £Beginning with highly sensitive D-dimer is suggested over beginning with US (Grade 2C). [a]Grade 1B vs no testing and vs venography. [b]Grade 1B vs further testing. [c]Grade 1C vs no further testing; Grade 2B vs venography. [d]Grade 1B vs no further testing; Grade 2B vs venography. [e]Grade 1B for treating DVT vs confirmatory venography. See Figure 1 legend for expansion of abbreviation.

and the probability of obtaining a negative D-dimer result if DVT is not present. Initial testing with US may be preferred if the patient has a comorbid condition associated with elevated D-dimer levels and is likely to have a positive D-dimer result even if DVT is absent. Whole-leg US may be preferred in patients unable to return for serial testing and those with severe symptoms consistent with calf DVT. In patients with suspected first lower extremity DVT in whom US is impractical (eg, when leg casting or excessive subcutaneous tissue or fluid prevent adequate assessment of compressibility) or nondiagnostic we suggest CT scan venography, MR venography, or MR direct thrombus imaging could be used as an alternative to venography.

If the highly sensitive D-dimer is negative (see Fig 2), we recommend no further testing over further investigation with (i) proximal CUS, (ii) whole-leg US, or (iii) venography (Grade 1B for all comparisons)**. If the highly sensitive D-dimer is positive, we recommend proximal CUS or whole-leg US rather than no testing** (Grade 1B for all comparisons) **or venography** (Grade 1B for all comparisons)**.**

If proximal CUS is chosen as the initial test and is negative (see Fig 2), we recommend (i) repeat proximal CUS in 1 week or (ii) testing with a moderate or highly sensitive D-dimer assay over no further testing (Grade 1C) **or venography** (Grade 2B)**. In patients with a negative proximal CUS but a positive D-dimer, we recommend repeat proximal CUS in 1 week over no further testing** (Grade 1B) **or venography** (Grade 2B)**.**

In patients with (i) negative serial proximal CUS or (ii) a negative single proximal CUS and negative moderate or highly sensitive D-dimer (see Fig 2), we recommend no further testing rather than further testing with (i) whole-leg US or (ii) venography (Grade 1B for all comparisons)**.**

If whole-leg US is negative (see Fig 2), we recommend no further testing over (i) repeat US in 1 week, (ii) D-dimer testing, or (iii) venography

(Grade 1B for all comparisons). **If proximal CUS is positive, we recommend treating for DVT rather than confirmatory venography** (Grade 1B). **If isolated distal DVT is detected on whole-leg US, we suggest serial testing to rule out proximal extension over treatment** (Grade 2C).

Remarks: Patients with abnormal isolated distal US findings on whole-leg US who place a high value on avoiding the inconvenience of repeat testing and a low value on avoiding treatment of false-positive results are likely to choose treatment over repeat US. Patients with severe symptoms and risk factors for extension as outlined in Kearon et al[11] are more likely to benefit from treatment over repeat US.

3.4. In patients with a high pretest probability of first lower extremity DVT (see Fig 3**), we recommend either (i) proximal CUS or (ii) whole-leg US over no testing** (Grade 1B for all comparisons) **or venography** (Grade 1B for all comparisons).

Remarks: Whole-leg US may be preferred to proximal CUS in patients unable to return for serial testing and those with severe symptoms consistent with calf DVT. In patients with extensive unexplained leg swelling, if there is no DVT on proximal CUS or whole-leg US and D-dimer testing has not been performed or is positive, the iliac veins should be imaged to exclude isolated iliac DVT. In patients with suspected first lower extremity DVT in whom US is impractical (eg, when leg casting or excessive subcutaneous tissue or fluid prevent adequate assessment of compressibility) or nondiagnostic, we suggest CT scan venography, MR venography, or MR direct thrombus imaging could be used as an alternative to venography.

If proximal CUS or whole-leg US is positive for DVT (see Fig 3), we recommend treatment rather than confirmatory venography (Grade 1B).

In patients with a negative proximal CUS (see Fig 3), we recommend additional testing with a highly sensitive D-dimer or whole-leg US or repeat proximal CUS in 1 week over no further testing (Grade 1B for all comparisons) **or venography** (Grade 2B for all comparisons). **We recommend that patients with a single negative proximal CUS and positive D-dimer undergo whole-leg US or repeat proximal CUS in 1 week over no further testing** (Grade 1B) **or venography** (Grade 2B). **In patients with negative serial**

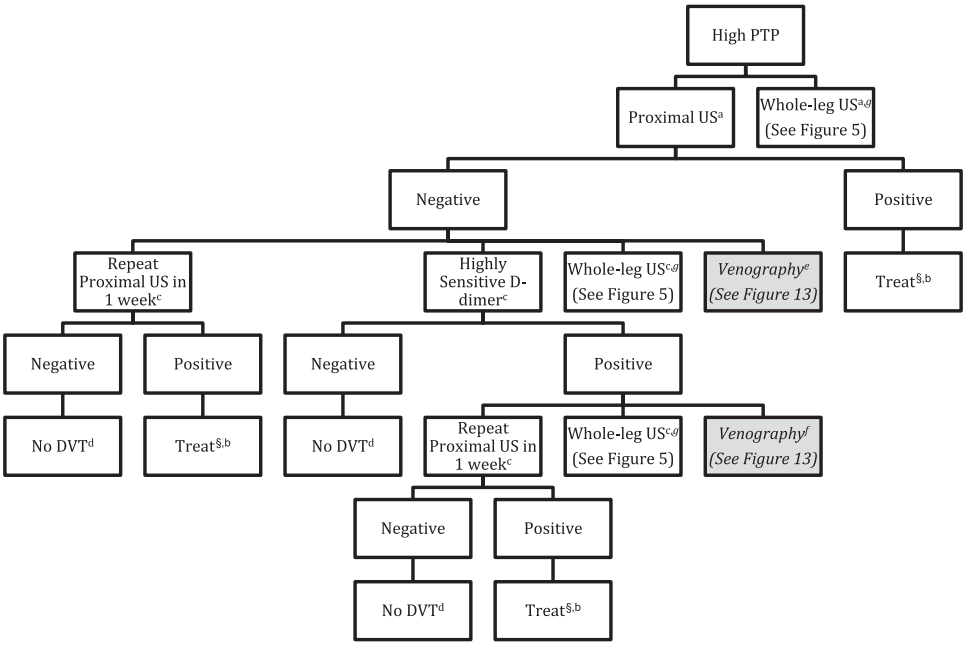

FIGURE 3. [Section 3.4] Recommendations for evaluation of suspected first lower extremity DVT: patients with high pretest probability (PTP) for DVT. Where there are preferred strategies, these are indicated by boldface print; less preferred strategies are indicated by italicizing/shading. Venography is not generally indicated in the figure, as it is not routinely used. [a]Grade 1B vs no testing and vs venography. [b]Grade 1B for treating DVT vs confirmatory venography. [c]Grade 1B vs no further testing; Grade 2B vs venography. [d]Grade 1B vs further testing. [e]Grade 2B for repeat proximal US, highly sensitive D-dimer or whole-leg US over venography. [f]Grade 2B for repeat proximal US over venography. [g]Grade 2B for no further testing over venography if whole-leg US is negative (see also Figure 5). See Figure 1 legend for expansion of abbreviation.

proximal CUS, a negative single proximal CUS and negative highly sensitive D-dimer, or a negative whole-leg US, we recommend no further testing over venography or additional US (Grade 1B for negative serial proximal CUS and for negative single proximal CUS and highly sensitive D-dimer; Grade 2B for negative whole-leg US).

We recommend that in patients with high pretest probability (see Fig 3), moderately or highly sensitive D-dimer assays should not be used as stand-alone tests to rule out DVT (Grade 1B).

3.5. If risk stratification is not performed in patients with suspected first lower extremity DVT (see Fig 4**), we recommend one of the following initial tests: (i) proximal CUS or (ii) whole-leg US, rather than (i) no testing** (Grade 1B)**, (ii) venography** (Grade 1B)**, or D-dimer testing** (Grade 2B).

Remarks: Whole-leg US may be preferred to proximal CUS in patients unable to return for serial testing and those with severe symptoms consistent with calf DVT or risk factors for extension of distal DVT. In patients with suspected first lower extremity DVT in whom US is impractical (eg, when leg casting or excessive subcutaneous tissue or fluid prevent adequate assessment of compressibility) or nondiagnostic, we suggest that CT scan venography, MR venography, or MR direct thrombus imaging could be used as an alternative to venography.

We recommend that patients with a negative proximal CUS (see Fig 4) undergo testing with a moderate or high sensitivity D-dimer, whole-leg US, or repeat proximal CUS in 1 week over no further testing (Grade 1B) **or venography** (Grade 2B). **In patients with a negative proximal CUS, we suggest D-dimer rather than routine serial CUS** (Grade 2B) **or whole-leg US** (Grade 2C). **We recommend that patients with a single negative proximal CUS and positive D-dimer undergo further testing with repeat proximal CUS in 1 week or whole-leg US rather than no further testing** (Grade 1B for both comparisons).

We recommend that in patients with (i) negative serial proximal CUS, (ii) a negative D-dimer following a negative initial proximal CUS, or

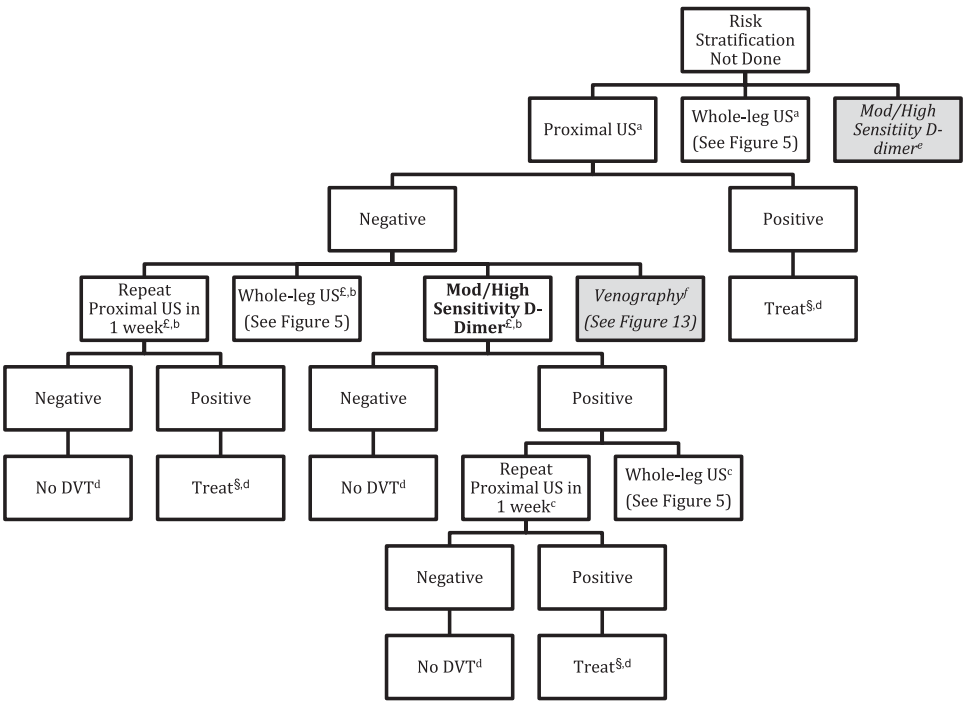

FIGURE 4. [Section 3.5] Recommendations for evaluation of suspected first lower extremity DVT: risk stratification not performed. Where there are preferred strategies, these are indicated by boldface print; less preferred strategies are indicated by italicizing/shading. §See Kearon et al.[11] £Use of D-dimer is suggested over use of repeat proximal US (Grade 2B) or whole-leg US (Grade 2C). [a]Grade 1B vs no testing and vs venography; Grade 2B vs D-dimer. [b]Grade 1B vs no further testing; Grade 2B vs venography. [c]Grade 1B vs no further testing. [d]Grade 1B vs venography. [e]Grade 2B for proximal US or whole-leg US over D-dimer. [f]Grade 2B for repeat proximal US, moderate or highly sensitive D-dimer, or whole-leg US over venography. [d]Grade 1B for treating DVT vs confirmatory venography. See Figure 1 legend for expansion of abbreviation.

(iii) negative whole-leg US (see Figs 4 and 5), no further testing be performed rather than venography (Grade 1B)**.**

If proximal US is positive for DVT (see Fig 4), we recommend treatment rather than confirmatory venography (Grade 1B). If isolated distal DVT is detected on whole-leg US, (see Fig 5**) we suggest serial testing to rule out proximal extension over treatment** (Grade 2C)**.**

Remarks: Patients with abnormal isolated distal US findings on whole-leg US who place a high value on avoiding the inconvenience of repeat testing and a low value on avoiding treatment of false-positive results are likely to choose treatment over repeat US. Patients with severe symptoms and risk factors for extension as outlined in Kearon et al[11] are more likely to benefit from treatment over repeat US.

3.6. In patients with suspected first lower extremity DVT, we recommend against the routine use of CT venography or MRI (Grade 1C)**.**

4.0 Diagnosis of Suspected Recurrent Lower Extremity DVT

Recurrent leg pain is common in patients after an episode of DVT and can be caused by recurrent disease, acute exacerbation of postthrombotic syndrome, or nonthrombotic problems. Accurate diagnosis of recurrence is important because the consequences of misdiagnosis are great. Incorrectly concluding that recurrent DVT is present commits the patient to prolonged (perhaps lifelong) anticoagulation, with its attendant costs, inconvenience, and bleeding risks. However, incorrectly concluding that recurrent DVT is absent places the patient at high risk of potentially fatal PE.

Unfortunately, few well-designed studies have been performed evaluating diagnostic strategies for suspected recurrent disease. Tables S38 and S39 summarize the methodology of diagnostic studies in patients with suspected recurrent DVT, and Table S40 provides a description of the study results. Tables S41 to S47 present the evidence profiles for the various diagnostic strategies that have been evaluated and are included in Recommendations 4.1 to 4.3. Tables 7 and 8 summarize the quality of evidence and frequency of potential clinical outcomes for the various diagnostic strategies.[160-168]

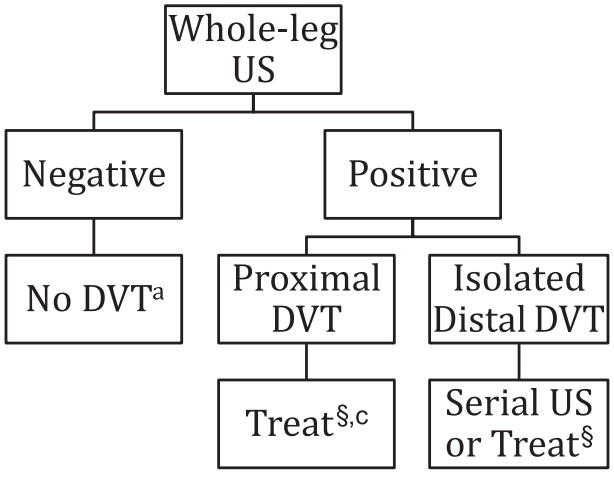

Figure 5. Use of whole-leg US (Referenced from Figures 1-4, 6). §See Kearon et al.[11] £If whole-leg US shows only isolated calf vein DVT, we suggest treating, rather than serial testing to rule out proximal extension only in patients with a high pretest probability or if high risk of extension or severe symptoms, see Kearon et al.[11] [a]Grade 1B vs repeat proximal US in 1 week, vs D-dimer testing and vs venography in patients with suspected first lower extremity DVT and a low, moderate, or unspecified pretest probability; Grade 2B vs venography and vs additional US in patients with suspected first lower extremity DVT and a high pretest probability. [b]Grade 2C vs treating DVT in patients with suspected first lower extremity DVT and a low, moderate, or unspecified pretest probability. [c]Grade 1B for treating DVT vs confirmatory venography. See Figure 1 legend for expansion of abbreviation.

4.1 Venography

Although contrast venography is the reference standard in patients with an initial episode of suspected DVT,[13,40] it can be of limited value in patients with previous disease. Although, intuitively, a normal venogram would exclude recurrent thrombosis, no empirical investigation has established this is the case. Although one might consider the presence of an intraluminal-filling defect diagnostic of acute DVT, it may be due to residual disease (scarring). Finally, as many as one-third of patients with suspected recurrence have a venogram that is considered inadequate because of nonfilling of venous segments.[169] In addition, as discussed in Section 2.0, venography is expensive, has complications,[13,40,53-55,170-172] is not available in many centers, and cannot be completed in many patients for technical reasons.

4.2 Compression Ultrasonography

The evaluation of suspected ipsilateral recurrence using CUS is problematic because persistent abnormalities of the deep veins are common following a first episode of thrombosis. Prospective follow-up studies have reported residual US abnormalities (noncompressibility) in approximately 80% of patients at 3 months[161,173] and 50% of patients 1 year after the diagnosis of proximal DVT.[161,173-175] Thus, the presence of a noncompressible venous segment on CUS is not diagnostic of recurrent thrombosis, and recurrence can only be confirmed if there is evidence of new thrombus formation.

Table 7—*[Sections 4.1-4.3] Summary of Findings for Diagnostic Studies in Patients With Suspected Recurrent Lower Extremity DVT: Accuracy Studies*

Criteria	Population and Reference Standard	No. of Studies (Participants)	Quality of Evidence	Illustrative Comparative Numbers: Effect/1,000[a] True Positives (Correctly Classified as Having DVT)	True Negatives (Correctly Classified as Not Having DVT)	False Positives (Incorrectly Classified as Having DVT)	False Negatives (Incorrectly Classified as Not Having DVT)
New noncompressible segment or increased residual venous diameter of 1-2 mm[b]	Population: suspected recurrent DVT	1 Study (16 participants)[160]	Low[c]	Prevalence 5%, 14	Prevalence 5%, 741	Prevalence 5%, 209	Prevalence 5%, 36
	Reference standard: venography			Prevalence 17%, 49	Prevalence 17%, 647	Prevalence 17%, 183	Prevalence 17%, 121
				Prevalence 53%, 154	Prevalence 53%, 367	Prevalence 53%, 103	Prevalence 53%, 376
New noncompressible segment or increased residual venous diameter of ≥ 2 mm[d]	Population: suspected recurrent DVT	2 Studies (115 participants)[161,162]	Low[e]	Prevalence 5%, 49	Prevalence 5%, 921	Prevalence 5%, 29	Prevalence 5%, 5
	Reference standard: venography			Prevalence 17%, 456	Prevalence 17%, 805	Prevalence 17%, 25	Prevalence 17%, 15
				Prevalence 53%, 482	Prevalence 53%, 155	Prevalence 53%, 14	Prevalence 53%, 49
New noncompressible segment or increased residual venous diameter of > 4 mm[f]	Population: suspected recurrent DVT	2 Studies[160,163]; however, estimates of both sensitivity and specificity only in 1 (16 participants)[163]	Moderate[g]	Prevalence 5%, 36	Prevalence 5%, 950	Prevalence 5%, 0	Prevalence 5%, 14
	Reference standard: venography			Prevalence 17%, 121	Prevalence 17%, 830	Prevalence 17%, 0	Prevalence 17%, 50
				Prevalence 53%, 376	Prevalence 53%, 470	Prevalence 53%, 0	Prevalence 53%, 154

GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. See Table 1 and 3 legends for expansion of abbreviation.

[a]Prevalences for high (53%), moderate (17%), and low (5%) taken from Wells et al.[10]

[b]Based on a specificity of 78% (95% CI, 45%-94%) and sensitivity of 29% (95% CI, 8%-64%).

[c]Serious limitations (published only in abstract form, unclear if consecutive or selected patients, technique requires local expertise and previous CUS for comparison), single study, serious indirectness (accuracy study only; no management studies), and moderate imprecision (wide 95% CI).

[d]Based on a specificity of 97% and sensitivity of 91%.

[e]Serious limitations (one study published only in abstract form,[162] unclear if consecutive or selected patients; technique requires local expertise and previous CUS for comparison), serious indirectness (accuracy study only; no management studies), and moderate imprecision (wide 95% CI).

[f]Based on a specificity of 100% (95% CI, 70%-100%) and sensitivity of 71% (95% CI, 36%-92%)[160]; positive predictive value only of 100% (95% CI, 84%-100%)[170]

[g]Serious limitations (published only in abstract form, unclear if consecutive or selected patients; technique requires local expertise and previous CUS for comparison), single study, serious indirectness (accuracy study only; no management studies), and very serious imprecision (wide 95% CI).

Table 8—*[Sections 4.1-4.3] Summary of Findings for Diagnostic Studies in Patients with Suspected Recurrent Lower Extremity DVT: Prospective Management Cohort Studies*

Diagnostic Strategy Used to Exclude Recurrent DVT	No. of Participants (Studies)	Outcome	Incidence of VTE During Follow-up Among Patients Judged to Have Recurrent DVT Excluded (ie, Post-TP of DVT), % (95% CI)%	Quality of Evidence
Negative serial proximal CUS[162-165]	Normal serial US			Moderate[a]
	Day of presentation, day 2 [± 1], day 7 [± 1]: 150 (1)[163]	VTE diagnosed during 6 mo of follow-up[163]	1.3 (95 CI, 0.02-4.7)[163]	
	Day of presentation, day 1-3 and 6-10 (in patients with a positive DD): 129 (2)[165]	VTE diagnosed during 3 mo of follow-up[165]	2.3 (95 CI, 0.8-6.6)[165]	
	Normal or unchanged/ improved residual venous diameter serial US			Low[b]
	Day of presentation, day 2 [± 1], day 7 [± 1]: 86 (1)[162]	VTE diagnosed during 6 mo of follow-up[162]	3.1 (95 CI, 0.4-10.7)[162]	
	Unchanged residual venous diameter (< 4 mm)	VTE diagnosed during 3 mo of follow-up[164]	4.8 (95 CI, 1.3-15.8)[164]	Low[c]
	Day of presentation and day 7: 42 (1)[164]			
Unchanged residual venous diameter (< 4 mm increase) on proximal CUS and a negative highly sensitive DD (Biopool AutoDimer)[166]	75 (1)	VTE diagnosed during 3 mo of follow-up	0 (95 CI, 0-4.8)	Moderate[d]
Unlikely pre-TP and negative highly sensitive DD (STA Liatest)[167]	16 (1)	VTE diagnosed during 3 mo of follow-up	0 (95 CI, 9-19.4)	Low[e]
Negative highly sensitive DD	STA Liatest DD: 134 (1)[168]	VTE diagnosed during 3 mo of follow-up	0.75 (95 CI, 0.02-4.1)	Moderate[f]
	MDA DD: 229 (1)[165]		1.71 (95 CI, 0.7-4.4)	

Consequences in terms of presenting with VTE during clinical follow-up when specific strategies are used to rule out suspected recurrent DVT. GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. See Table 1 and 3 legends for expansion of abbreviations.

[a]Bates et al[165] published only in abstract.

[b]Single study; point estimate for post-TP of DVT > 2%; very serious imprecision, wide 95% CI.

[c]Single study; unclear if consecutive or selected patients used; point estimate for post-TP of DVT > 2%; wide 95% CI.

[d]Single-center study; wide 95% CI.

[e]Only 15% of patients presenting to the ED with suspected DVT could be managed with this strategy, single study, very wide 95% CI.

[f]No data on patients with various pre-TPs; unable to determine exact overall prevalence of recurrent DVT[168]; published in abstract only[165]; for both studies, wide 95% CI.

Although the finding of a new noncompressibility of the common femoral or popliteal vein when compared with a previous US is considered diagnostic of recurrence, this finding occurs in only 10% to 20% of patients with recurrent thrombosis.[161,162,176] Although complete resolution of thrombus is slow to occur, the diameter of residual disease as assessed by CUS decreases substantially (by up to 62% in the common femoral vein and by as much as 50% in the popliteal vein) during the first 3 months of therapy.[161]

Two small studies suggest that recurrent ipsilateral DVT can be diagnosed in the presence of new noncompressibility of a previously normal popliteal or common femoral vein and/or a ≥ 2-mm increase in the residual venous diameter of one of these two veins (when measured in the transverse plane during maximal compression) and compared with the results of previous venous US (specificity of 100% and 95% against a reference standard of venography in both studies).[161,162] However, another study does not support these findings (14% of those with a positive test proved not to have thrombosis when venography performed).[163] Further, in a study assessing interobserver agreement on measurement of residual vein diameter, the mean difference between paired measurements was 2.2 mm (95th centile, 8.0 mm).[177]

An increase in venous diameter ≥ 4 mm during compression compared with a previous result on venous US appears more accurate for the diagnosis of recurrence (specificity of 100%).[160,163] However, interobserver variability in the measurement of residual thrombus suggests that, in the absence of a new noncompressible common femoral or popliteal vein, even an apparent increase in residual venous diameter of 4 mm may be associated with false positives. Furthermore, for a quantitative US assessment to be performed, a previous US must be available for comparison.

Rigorous evaluation and validation of other proposed venous US criteria for the diagnosis of recurrent DVT (eg, changes in thrombus length, Doppler flow, and intraluminal appearance) have not been published. Moreover, like residual vein diameter assessment, these characteristics have only moderate interobserver agreement.[177,178]

Extrapolating from studies in symptomatic patients with a suspected first DVT who have normal results on serial CUS, a similar strategy is expected to reliably exclude DVT in patients with suspected recurrence. Theoretically, development of collateral vessels in patients with previous disease might result in false-negative results (ie, a normal collateral vessel may be mistaken for one of the deep veins, preventing the ultrasonographer from detecting new DVT). Nonetheless, several management cohort studies suggest that it is safe to withhold anticoagulant therapy in patients with suspected recurrent DVT who have repeatedly normal results or unchanged residual venous diameter measurements on serial testing performed either on days 2 (±1) and 7 (±1),[162,163] day 7,[32,164] or days 1 to 3 and 7 to 10[165] (frequency of false negatives, 1%,[162] 2%,[165] 3%,[163] and 5%[164]).

4.3 Pretest Probability Assessment

Although the most recent version of the Wells pretest probability model for suspected DVT includes a history of previous VTE as one of items used to determine clinical probability,[32] it has not been validated in a large population of patients with suspected recurrence.

4.4 D-Dimer Alone and in Combination With Pretest Probability Assessment or CUS

D-Dimer assays have been less extensively evaluated in patients with suspected recurrent DVT than in those with a suspected first event. In many patients, D-dimer levels appear to return to normal values within 3 months of starting treatment of acute DVT[179] and remain within the normal range after anticoagulant therapy is withdrawn in the majority of patients.[180] Therefore, D-dimer testing should be useful in patients with suspected recurrence.

Five prospective cohort management studies have reported results for strategies involving D-dimer testing in patients with suspected recurrent DVT.[32,165,167-168] In two studies in which a negative sensitive D-dimer was used either in combination with an unlikely pretest probability using the modified Wells model (n = 16 patients)[167] or a CUS at presentation that was either normal or showed an increase in residual diameter of < 4 mm (n = 75)[166] to exclude recurrence, no patients experienced VTE during 3 months of follow-up. However, the first strategy may have limited usefulness, as the combination of D-dimer and pretest probability assessment was able to exclude recurrence in only 15% of patients.[167] Two larger prospective cohort studies suggest that negative results of sensitive assays exclude DVT in outpatients with suspected recurrent DVT (false-negative frequencies of 2%[165] and 5%[168]). In a randomized trial of 1,096 outpatients with suspected DVT, of whom 102 had prior VTE, the combination of an unlikely pretest probability (using the modified Wells model) and negative D-dimer (either moderate or high sensitivity) had a frequency of VTE during 3-month follow-up of 0.9% (95% CI, 0.3%-3.3%). Results for the 102 patients with suspected recurrence were not presented separately.

4.5 CT Scan Venography

There are no accuracy or management studies of CT scan venography in patients with suspected recurrent DVT.

4.6 MRI

One prospective study of 43 patients with a first episode of DVT suggests that the high T1 signal normalizes within 6 months.[181] However, there has been no evaluation of this technique's accuracy in patients with suspected recurrent DVT. MR venography has not been evaluated in patients with suspected DVT.

Recommendations (see Figs 6-9)

4.1. In patients suspected of having recurrent lower extremity DVT (see Fig 6**), we recommend initial evaluation with proximal CUS or a highly sensitive D-dimer over venography, CT venography or MRI** (all Grade 1B)**.**

Remarks: Initial D-dimer testing with a high-sensitivity assay is preferable if prior US is not available for comparison.

If the highly sensitive D-dimer is positive (see Fig 7**), we recommend proximal CUS over**

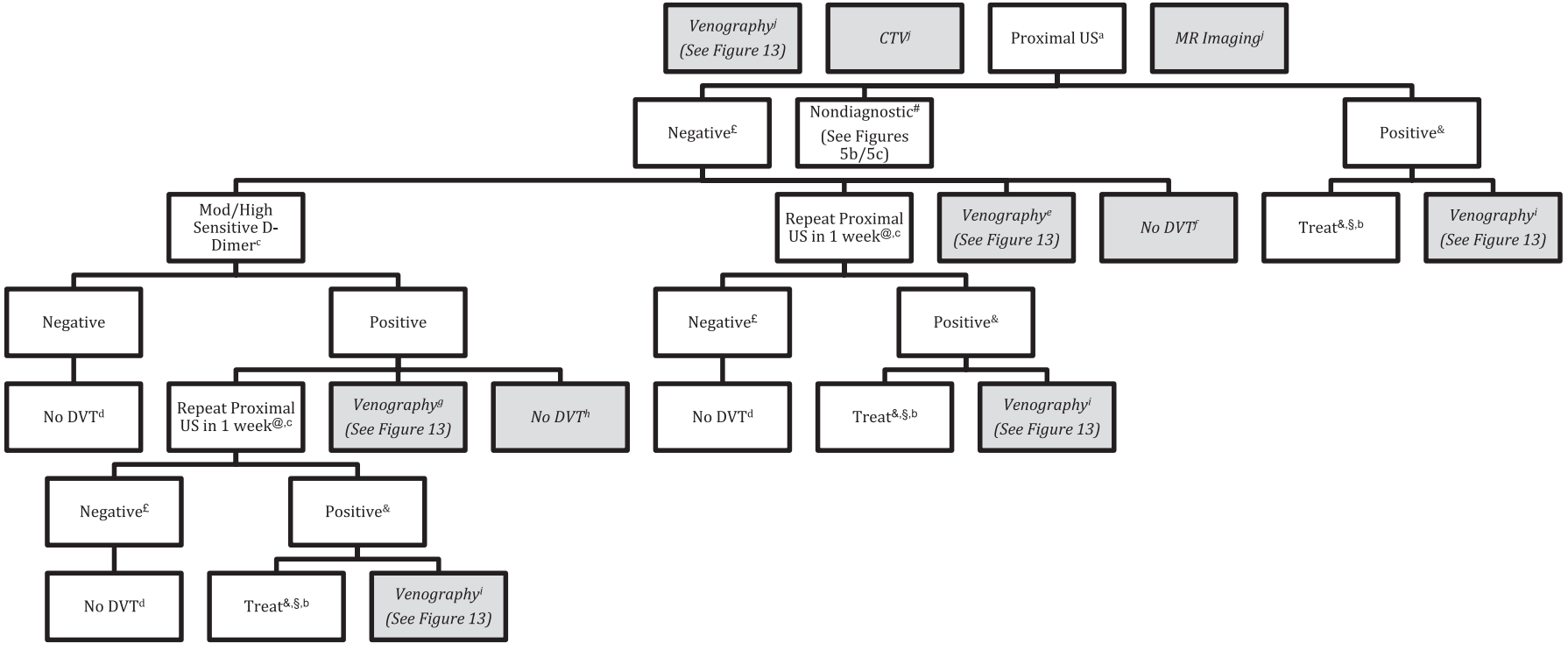

FIGURE 6. [Section 4.1] Recommendations for evaluation of suspected lower extremity recurrent DVT: proximal US as initial test. Where there are preferred strategies, these are indicated by boldface print; less preferred strategies are indicated by italicizing/shading. §See Kearon et al.[11] £"Negative" refers to a normal US or an area of prior noncompressibility with a stable or decreased residual diameter or an interval increase in residual diameter of <2 mm. #"Nondiagnostic" refers to a technically limited US, an area of prior noncompressibility with increase in residual venous diameter of <4 mm but ≥ 2 mm, or an area of prior noncompressibility without prior measurement of residual diameter for comparison. &"Positive" refers to a new noncompressible segment or an area of prior noncompressibility with an interval increase in residual diameter of ≥ 4 mm. @Consider additional serial proximal US. [a]Grade 1B vs venography, CTV, or MR venography. [b]Grade 1B for treating DVT vs venography if new noncompressible segment in the common femoral or popliteal vein; Grade 2B for treating DVT vs venography for a ≥ 4-mm increase in venous diameter during compression compared with that in the same venous segment on a previous result. [c]Grade 2B vs no further testing and vs venography. [d]Grade 1B vs further testing with venography. [e]Grade 2B for at least one additional proximal US or moderate or highly sensitive D-dimer over venography. [f]Grade 2B for at least one additional proximal US or moderate or highly sensitive D-dimer over no further testing. [g]Grade 2B for at least one additional proximal US over venography. [h]Grade 2B for at least one additional proximal US over no further testing. [i]Grade 1B for treating DVT over venography for new noncompressible segment compared to previous CUS result; Grade 2B for treating DVT over venography for a ≥ 4-mm increase in venous diameter during compression compared with that in the same venous segment on a previous result. [j]Grade 1B for proximal US (or highly sensitive D-dimer; see Figure 7) over venography, CTV, or MRI. CTV = CT scan venography; MR = magnetic resonance.

venography, CT venography, or MRI (Grade 1B for all comparisons)**.**

In patients with suspected recurrent lower extremity DVT in whom initial proximal CUS is negative (normal or residual diameter increase of < 2 mm) (see Fig 6), we suggest at least one further proximal CUS (day 7 ± 1) or testing with a moderately or highly sensitive D-dimer (followed by repeat CUS [day 7 ± 1] if positive) rather than no further testing or venography (Grade 2B)**.**

Remarks: In patients with an abnormal proximal US at presentation that does not meet the criteria for the diagnosis of recurrence, an additional proximal CUS on day 2 ± 1 in addition to that on (day 7 ± 1) may be preferred. Patients who place a high value on an accurate diagnosis and a low value on avoiding the inconvenience and potential side effects of a venography are likely to choose venography over missed diagnosis (in the case of residual diameter increase of < 2 mm).

We recommend that patients with suspected recurrent lower extremity DVT and a negative highly sensitive D-dimer or negative proximal CUS and negative moderately or highly sensitive D-dimer or negative serial proximal CUS (see Figs 6 and 7) undergo no further testing for suspected recurrent DVT rather than venography (Grade 1B)**.**

If CUS of the proximal veins is positive (see Figs 6 and 7), we recommend treating for DVT and

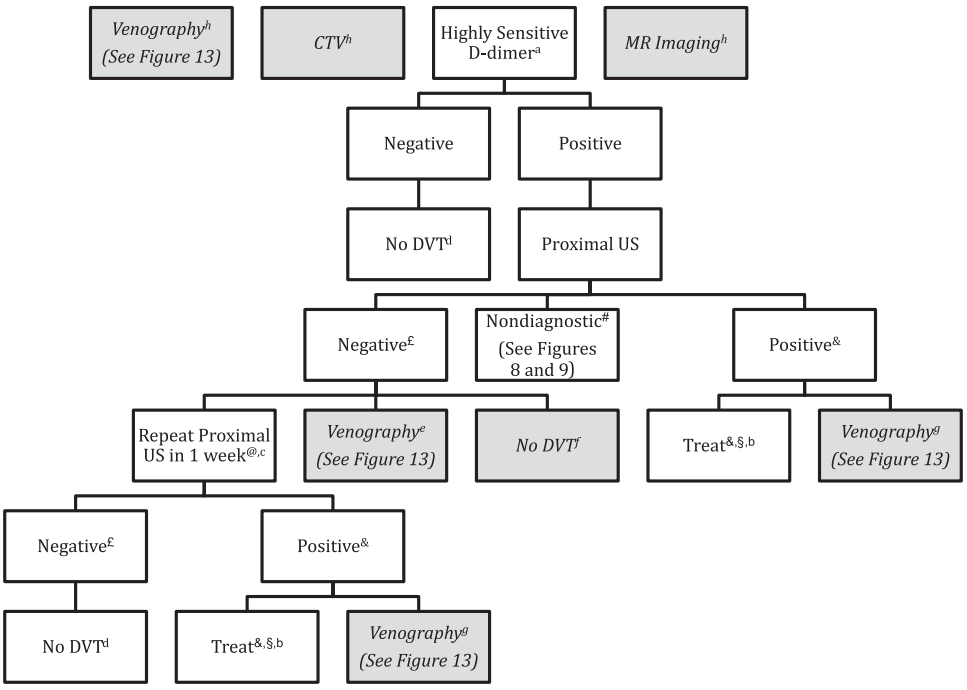

FIGURE 7. [Section 4.1] Recommendations for evaluation of suspected lower extremity recurrent DVT: highly sensitive D-dimer as initial test. Where there are preferred strategies, these are indicated by boldface print; less preferred strategies are indicated by italicizing/shading. §See Kearon et al.[11] £"Negative" refers to a normal US or an area of prior noncompressibility with a stable or decreased residual diameter or an interval increase in residual diameter of < 2 mm. #"Nondiagnostic" refers to a technically limited US, an area of prior noncompressibility with increase in residual venous diameter of < 4 mm but ≥ 2 mm, or an area of prior noncompressibility without prior measurement of residual diameter for comparison. &"Positive" refers to a new noncompressible segment or an area of prior noncompressibility with an interval increase in residual diameter of ≥ 4 mm. @Consider additional serial proximal US. [a]Grade 1B vs venography, CTV, or MR venography; preferred initial assay if prior US not available for comparison. [b]Grade 1B for treating DVT vs venography if new noncompressible segment in the common femoral or popliteal vein; Grade 2B for treating DVT vs venography for a ≥ 4-mm increase in venous diameter during compression compared with that in the same venous segment on a previous result. [c]Grade 2B vs no further testing and vs venography. [d]Grade 1B vs further testing with venography. [e]Grade 2B for at least one additional proximal US over venography. [f]Grade 2B for at least one additional proximal US over no further testing. [g]Grade 1B for treating DVT over venography if new noncompressible segment in the common femoral or popliteal vein; Grade 2B for treating DVT over venography for a ≥ 4-mm increase in venous diameter during compression compared with that in the same venous segment on a previous result. [h]Grade 1B for highly sensitive D-dimer (or proximal US; see Figure 6) over venography, CTV, or MRI. See Figure 1 and 6 legends for expansion of abbreviations.

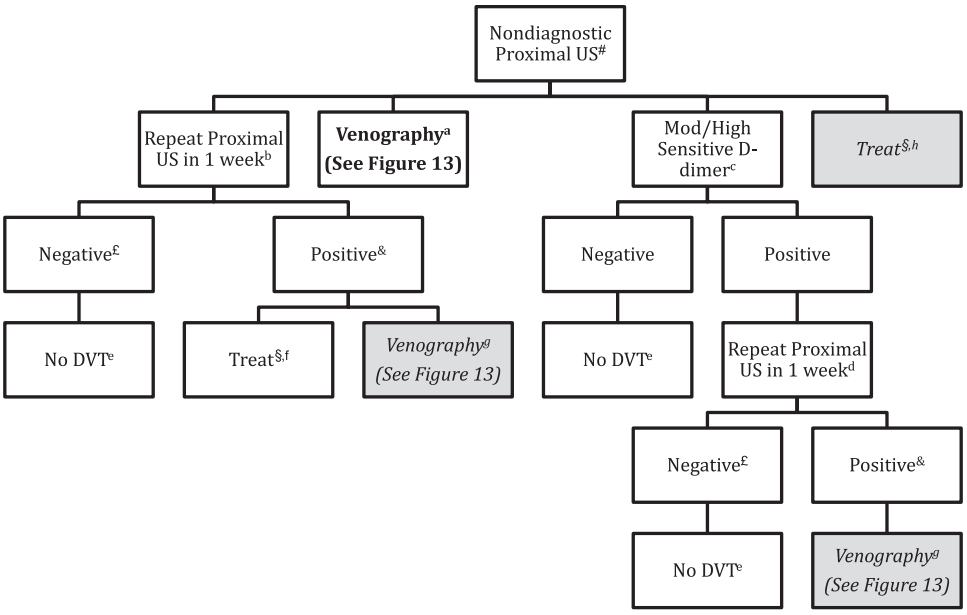

FIGURE 8. [Section 4.2] Recommendations for evaluation of suspected lower extremity recurrent DVT: evaluation following nondiagnostic proximal US and prior US result available for comparison. Where there are preferred strategies, these are indicated by boldface print; less preferred strategies are indicated by italicizing/shading. §See Kearon et al.[11] #Previous US with residual diameter measurements is available for comparison. Current US is nondiagnostic (technically limited or only abnormality an area of prior noncompressibility with increase in residual venous diameter of <4 mm but ≥ 2 mm). £"Negative" refers to a normal US or an area of prior noncompressibility with a stable or decreased residual diameter or an interval increase in residual diameter of <2 mm. &"Positive" refers to a new noncompressible segment or an area of prior noncompressibility with an interval increase in residual diameter of ≥ 4 mm. [a]Grade 1B vs treating for DVT and vs alternative test strategies. [b]Grade 2B vs treating for DVT and vs alternative test strategies. [c]Grade 2B vs treating for DVT and vs alternative test strategies. [d]Grade 2B vs no further testing and vs venography. [e]Grade 1B vs further testing with venography. [f]Grade 1B for treating DVT vs venography if new noncompressible segment in the common femoral or popliteal vein; Grade 2B for treating DVT vs venography for a ≥ 4-mm increase in venous diameter during compression compared with that in the same venous segment on a previous result. [g]Grade 2B for treating DVT over venography if a ≥ 4-mm increase in venous diameter during compression compared with that in the same venous segment on a previous result (Grade 1B for treating DVT over venography if new noncompressible segment in the common femoral or popliteal vein). [h]Grade 2B for repeat proximal US in 1 week or moderate or highly sensitive D-dimer over treating for DVT (Grade 1B for venography over treating for DVT). See Figure 1 legend for expansion of abbreviation.

performing no further testing over performing confirmatory venography (Grade 1B for the finding of a new noncompressible segment in the common femoral or popliteal vein, Grade 2B for a ≥ 4-mm increase in venous diameter during compression compared with that in the same venous segment on a previous result).

Remarks: Patients with US abnormalities at presentation that do not include a new noncompressible segment who place a high value on an accurate diagnosis and a low value on avoiding the inconvenience and potential side effects of a venography are likely to choose venography over treatment (in the case of a ≥ 4-mm increase in venous diameter).

4.2. In patients with suspected recurrent lower extremity DVT and abnormal but nondiagnostic US results (eg, an increase in residual venous diameter of <4 but ≥ 2 mm) (see Fig 8**), we recommend further testing with venography, if available** (Grade 1B)**; serial proximal CUS** (Grade 2B) **or testing with a moderately or highly sensitive D-dimer with serial proximal CUS as above if the test is positive (Grade 2B), as opposed to other testing strategies or treatment.**

4.3. In patients with suspected recurrent ipsilateral DVT and an abnormal US without a prior result for comparison (see Fig 9**), we recommend further testing with venography, if available** (Grade 1B) **or a highly sensitive D-dimer** (Grade 2B) **over serial proximal CUS. In patients with suspected recurrent ipsilateral DVT and an abnormal US without prior result for comparison and a negative highly sensitive D-dimer, we suggest no further testing over venography** (Grade 2C)**. In patients with suspected recurrent ipsilateral**

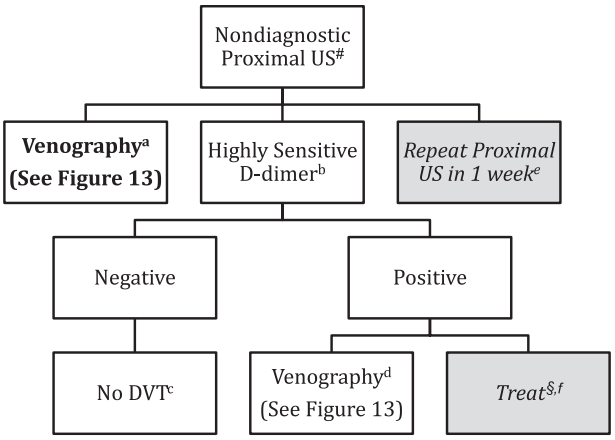

FIGURE 9. [Section 4.3] Recommendations for evaluation of suspected lower extremity recurrent DVT: evaluation following nondiagnostic proximal US and prior US result not available for comparison. Where there are preferred strategies, these are indicated by boldface print; less preferred strategies are indicated by italicizing/shading. §See Kearon et al.[11] Previous US with residual diameter measurements is not available for comparison. Current US is nondiagnostic (technically limited or only abnormality an area of prior noncompressibility). [a]Grade 1B vs repeat proximal US in 1 week. [b]Grade 2C vs repeat proximal US in 1 week. [c]Grade 2C vs further testing with venography. [d]Grade 2C vs treating for DVT. [e]Grade 2B for highly sensitive D-dimer (Grade 1B for venography) over repeat proximal US in 1 week. [f]Grade 2C for venography over treating for DVT. MRV = magnetic resonance venography. See Figure 1 legend for expansion of other abbreviation.

DVT and an abnormal US without prior result for comparison and a positive highly sensitive D-dimer, we suggest venography if available over empirical treatment of recurrence (Grade 2C)**.**

Remarks: Patients who place a high value on avoiding the inconvenience and potential side effects of a venography are likely to choose treatment over venography.

5.0 Diagnosis of Pregnancy-Related DVT

Roughly two-thirds of all pregnancy-related DVT occur antepartum, with risk distributed across all three trimesters.[182] During pregnancy, DVT is found in the left leg in > 80% of cases.[182,183] A recent systematic review confirmed a high frequency of iliofemoral (64%) and isolated iliac vein (17%) thromboses among those with confirmed DVT.[183]

Tables S48 and S49 summarize the methodology of diagnostic studies in patients with suspected pregnancy-related DVT; Table S50 provides a description of the study results. Evidence profiles for the various diagnostic strategies that have been evaluated are included in Tables S51 to S55. Tables 9 and 10 summarize the quality of evidence and potential clinical outcomes for the various diagnostic strategies.[184-187]

5.1 Venography

Although venography is the reference standard test for the diagnosis and exclusion of DVT,[13,40] concerns about fetal radiation exposure during testing have limited the number of studies involving this technique in pregnant women with suspected DVT. Potential adverse effects of in utero radiation exposure include oncogenicity and teratogenicity. Investigators using simulation techniques have calculated the radiation to the fetus during the performance of unilateral venography with abdominal shielding to be < 0.05 rads and 0.32 rads when shielding is removed.[188] Radiation doses of ≤ 5 rads do not appear to be associated with an increased risk of pregnancy loss,[189,190] and it has been suggested that the risk of fetal malformation only increases above background levels at radiation doses > 15 rads.[189,190] However, studies have reported up to a twofold increase in the risk of childhood malignancies with radiation exposures of up to 5 rads.[188] In absolute terms, this equates to a potential increase in the incidence of cancer in the first year of life from 0.1% to 0.2%.[191] A recent record linkage of administrative and health-care use databases in Ontario, Canada that identified 1.8 million mother-child pairs reported no significant increase in the risk of cancer in children of mothers who underwent CT scan or radionuclide imaging in pregnancy compared with offspring of mothers with no exposure, although a small harmful effect could not be excluded (adjusted hazard ratio: 0.68; 95% CI, 0.25-1.80).[192] These data suggest that a fear of fetal irradiation as consequence of maternal venography is likely overstated.

5.2 Compression Ultrasonography

Diagnostic imaging algorithms for DVT in the nonpregnant population are often extrapolated to pregnant women. However, these strategies may be inadequate as they do not take into account the increased frequency of pelvic and iliac vein thrombosis seen during pregnancy and the lack of sensitivity of standard CUS for DVT isolated to these areas.[193,194] Although modifications of standard CUS technique that include Valsalva maneuvers and the assessment of flow changes with respiration can be used to assess for patency of the iliac veins,[186,195-197] the accuracy of these techniques has not been rigorously assessed.

A multicentre prospective cohort study of 149 pregnant women with suspected first DVT evaluated the role of proximal CUS in the exclusion of DVT.[186] All patients underwent CUS with compression along the proximal veins and the calf trifurcation. Direct imaging and Doppler flow examination of the iliac veins were conducted if isolated iliac vein thrombosis was suspected. DVT was diagnosed when a venous

Table 9—*[Sections 5.1-5.3] Summary of Findings of Diagnostic Studies in Patients With Suspected Pregnancy-Related DVT: Accuracy Studies*

Criteria	Population and Reference Standard	No. of Studies (Patients)	Quality of Evidence	Illustrative Comparative Numbers: Effect/1,000[a]			
				True Positives (Correctly Classified as Having DVT)	True Negatives (Correctly Classified as Not Having DVT)	False Positives (Incorrectly Classified as Having DVT)	False Negatives (Incorrectly Classified as Not Having DVT)
Clinical model[b]	Population: suspected pregnancy-related DVT	1 (195)[184]	Low[c]	Prevalence 1.5%, 15	Prevalence 1.5%, 493	Prevalence 1.5%, 492	Prevalence 1.5%, 0
	Reference standard: proximal CUS and 3 mo of follow-up			Prevalence 8.7%, 87	Prevalence 8.7%, 457	Prevalence 8.7%, 456	Prevalence 8.7%, 0
				Prevalence 24.6%, 246	Prevalence 24.6%, 377	Prevalence 24.6%, 377	Prevalence 24.6%, 0
Highly sensitive DD (standard threshold)[d]	Population: suspected pregnancy-related DVT	1 (249)[185]	Low[e]	Prevalence 1.5%, 15	Prevalence 1.5%, 101	Prevalence 1.5%, 884	Prevalence 1.5%, 0
	Reference standard: proximal CUS and 3 mo of follow-up			Prevalence 8.7%, 87	Prevalence 8.7%, 84	Prevalence 8.7%, 819	Prevalence 8.7%, 0
				Prevalence 24.6%, 246	Prevalence 24.6%, 78	Prevalence 24.6%, 676	Prevalence 24.6%, 0
Moderately sensitive DD	Population: suspected pregnancy-related DVT	1 (149)[186]	Low[g]	Prevalence 1.5%, 15	Prevalence 1.5%, 591	Prevalence 1.5%, 394	Prevalence 1.5%, 0
	Reference standard: proximal CUS and 3 mo of follow-up			Prevalence 8.7%, 87	Prevalence 8.7%, 548	Prevalence 8.7%, 306	Prevalence 8.7%, 0
				Prevalence 24.6%, 247	Prevalence 24.6%, 452	Prevalence 24.6%, 302	Prevalence 24.6%, 0

GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. See Table 1 and 3 legends for expansion of abbreviation.

[a]Prevalences taken from Chan et al.[184]

[b]Based on a specificity of 50% (95% CI, 43%-58%) for absence of left leg symptoms, difference in calf circumference of at least 2 cm, and first trimester presentation and sensitivity of 100% (95% CI, 71%-100%) for at least one of these characteristics.

[c]Very serious limitations (not clearly a sample of consecutive patients, accepted reference standard not used, reference standard results not blinded, internal validation only, small number of events [17]), single study, serious indirectness (accuracy study only, no management studies), and very serious imprecision (wide 95% CI).

[d]Based on a specificity of 10.3% (95% CI, 6.6%-15.5%) and sensitivity of 100% (95% CI, 74.7%-100%) for the VIDAS DD using the standard cut point of 0.5 μg FEU/mL.

[e]Very serious limitations (not clearly a sample of consecutive patients, accepted reference standard not used, frozen samples, reference standard results not blinded, small number of events [15]), single study, serious indirectness (accuracy study only, no management studies), and very serious imprecision (wide 95% CI).

[f]Based on a specificity of 60% (95% CI, 52%-68%) and sensitivity of 100% (95% CI, 77%-100%) for the SimpliRED DD.

[g]Serious limitations (accepted reference standard not used, frozen samples, reference standard results not blinded, small number of events [13]), single study, serious indirectness (accuracy study only, no management studies), and very serious imprecision (wide 95% CI).

Table 10—*[Sections 5.1-5.3] Summary of Findings of Diagnostic Studies in Patients with Suspected Pregnancy-Related DVT: Prospective Cohort Management Studies*

Diagnostic Strategy Used to Exclude DVT	Number of Participants (Studies)	Outcome	Incidence of VTE During Follow-up Among Those Judged to Have DVT Excluded (ie, Post-TP of DVT), % (95% CI)	Quality of Evidence
Negative serial CUS of the proximal veins and calf trifurcation (with imaging of the iliac veins in women with symptoms of isolated iliac vein thrombosis) on day of presentation, day 3, and day 7[186]	149 (1)	VTE diagnosed during 3 mo of follow-up	0.7 (95% CI, 0.1-4.0)	Moderate[a]
Single whole-leg US[187]	194 (1)	VTE diagnosed during 3 mo of follow-up	1.7 (95% CI, 0.6-5.0)	Low[b]

Consequences in terms of presenting with VTE during clinical follow-up when specified strategies are used to rule out pregnancy-related DVT. GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. See Table 1 and 3 legends for expansion of abbreviations.

[a]Serious limitations (proportion of patients who underwent single CUS vs those who underwent serial testing on days 3 and 7 not specified and proportion of patients who required imaging of the iliac veins not specified), single study with overall prevalence of DVT of 8.7%, wide 95% CI.

[b]Serious limitations (an unspecified number were postpartum, of 176 women without DVT at presentation, three received full-dose anticoagulants despite negative US, complete follow-up only on 164 women), single study, study published only in abstract.

segment was noncompressible, when iliac vein thrombus was visualized, or when flow was absent in the iliac veins. Some patients with negative US at presentation underwent follow-up testing on day 3 and day 7, according the clinician's standard of practice (proportion not specified). All patients with normal CUS had anticoagulants withheld and were followed for 3 months. Twelve patients were diagnosed with DVT on CUS either at presentation or during serial testing. The false-negative rate of the CUS testing strategy during 3 months of follow-up was 0.7% (95% CI, 0%-4%).

Two studies[187,198] have examined the role of complete whole-leg US in the exclusion of pregnancy-related DVT. Both, however, have important limitations (Table S52).

5.3 Pretest Probability

Studies evaluating clinical prediction rules have excluded pregnant women. These models might not be applicable in this patient population because pregnant women frequently develop leg swelling unrelated to thrombosis and are less likely to have comorbidities included as risk factors in these models.[199]

In a multicenter accuracy study of 194 unselected pregnant women with suspected first DVT, of whom 17 had objectively confirmed disease, experienced physicians were able to empirically classify patients into low- and non-low-risk categories.[184] The majority of patients were classified as having a low pretest probability (67.5%). In this group, the prevalence of DVT was 1.5% (95% CI, 0.4%-5.4%) and the likelihood ratio associated with a low pretest probability was 0.16 (95% CI, 0.04-0.59). DVT was diagnosed in 24.6% of those with a moderate or high pretest probability. The likelihood ratio of a positive test (moderate or high pretest probability) was 12.9 (95% CI, 5.9-28.2). Inexperienced physicians are likely to be less accurate in their assessments.

The investigators identified three variables for inclusion in their model: (1) left leg symptoms (adjusted OR [aOR], 44.3; 95% CI, 3.2-609.7), (2) a difference in calf circumference $\geq$2 cm (aOR, 26.9; 95% CI, 6.1-118.5), and (3) first trimester presentation (aOR, 63.4; 95% CI, 7.1-401.0). Among the 17 pregnant women with confirmed DVT, all had at least one of these variables. With none of these criteria, DVT was never diagnosed (0%; 95% CI, 0%-4.2%). With one variable, DVT occurred in 16.4% of cases (95% CI, 10.5%-24.7%), whereas the frequency of thrombosis was 58.3% (95% CI, 35.8%-75.5%) when two or three criteria were present. Although the authors conducted an internal bootstrap validation, this model has not undergone prospective validation in an independent population.

5.4 D-Dimer

Although D-dimer has assumed an increasingly prominent role in the exclusion of acute DVT in the nonpregnant population, it has not yet been rigorously evaluated in pregnant patients. D-Dimer levels increase with gestational age and during complicated

pregnancies.[200-203] This reduces the test's specificity, and by the third trimester, only a minority of healthy pregnant women will have a negative D-dimer result when highly sensitive assays and the same cut point as in the nonpregnant population are used.[203-206]

A prospective cohort study of a moderately sensitive but more specific D-dimer assay for DVT during pregnancy reported a sensitivity of 100% (95% CI, 77%-100%) and a specificity of 60% (95% CI, 62%-68%).[186] False-positive results were documented in only 51% of third-trimester patients, suggesting that this test warrants further investigation. The usefulness of this assay in pregnant women has not been evaluated in prospective management studies.

The specificity of highly sensitive D-dimer assays for pregnancy-related DVT may be improved without sacrificing sensitivity by using higher D-dimer cut-point values.[185] Validation in prospective management studies is required.

5.5 CT Scan Venography

CT scan venography may be useful in detecting pelvic vein thrombi in nonpregnant subjects[125] but is associated with significant radiation exposure to the fetus.[207] There are no accuracy or management studies of CT scan venography in this patient population.

5.6 MRI

MR direct imaging does not require gadolinium contrast and appears to have similar accuracy to venography for iliac vein thrombi in the nonpregnant population.[150] However, access to this technique is limited and it has not been evaluated in pregnant women with suspected DVT. Although one study has assessed agreement between MR venography (time-of-flight technique) and US,[208] MRI has not been systematically evaluated in pregnant patients with suspected DVT.

Recommendations (see Figs 10 and 11)

5.1. In pregnant patients suspected of having lower extremity DVT (see Fig 10**), we recommend initial evaluation with proximal CUS over other initial tests, including a whole-leg US** (Grade 2C)**, moderately sensitive D-dimer** (Grade

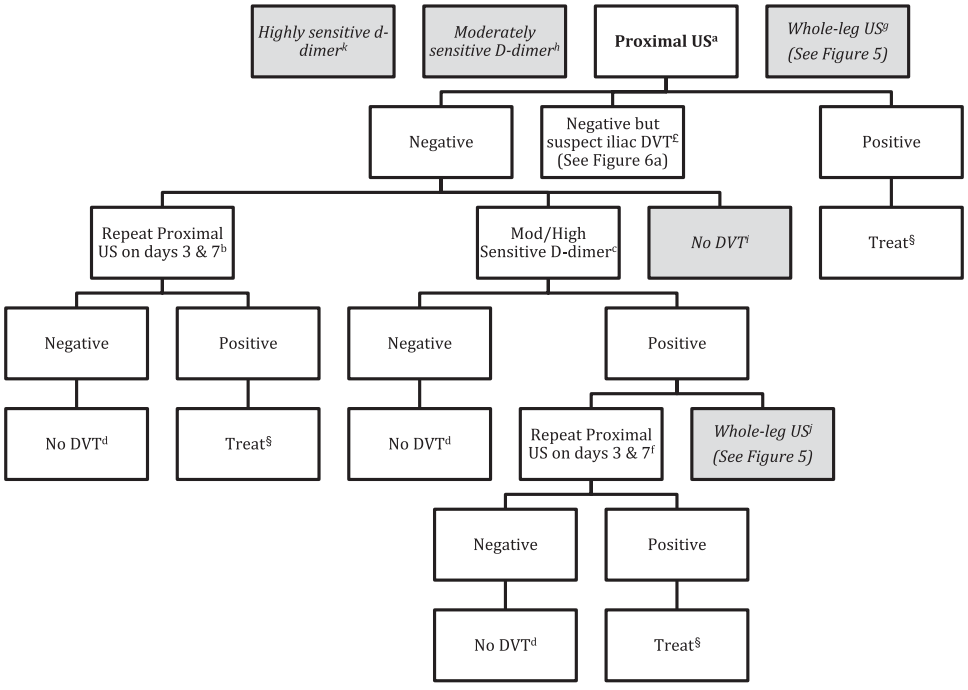

FIGURE 10. [Sections 5.1, 5.2] Recommendations for evaluation of suspected pregnancy-related lower extremity DVT. Where there are preferred strategies, these are indicated by boldface print; less preferred strategies are indicated by italicizing/shading. Venography is not generally indicated in the figure, as it is not routinely used. §See Kearon et al.[11] £Symptoms suggestive of iliac DVT include swelling of the entire leg, with or without flank, buttock, or back pain. [a]Grade 2C vs whole-leg US and vs moderately sensitive D-dimer; Grade 1B vs highly sensitive D-dimer and vs venography. [b]Grade 1B over no further testing. [c]Grade 2B over no further testing. [d]Grade 1B vs further testing. [e]Grade 1B vs venography; Grade 2C vs whole-leg US. [f]Grade 1B vs venography; Grade 2C vs whole-leg US. [g]Grade 2C for proximal US over whole-leg US. [h]Grade 2C for proximal US over moderately sensitive D-dimer. [i]Grade 2B for moderate or highly sensitive D-dimer over no further testing (Grade 1B for serial proximal US over no further testing). [j]Grade 2C for serial proximal US over whole-leg US. [k]Grade 1B for serial proximal US over highly sensitive D-dimer. See Figure 1 legend for expansion of abbreviation.

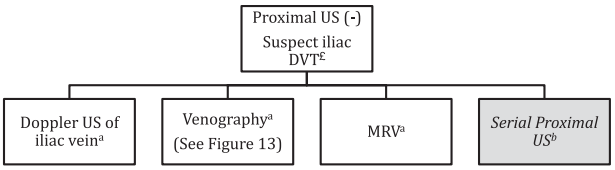

FIGURE 11. [Section 5.3] Recommendations for evaluation of suspected pregnancy-related lower extremity DVT: suspected isolated iliac vein DVT. £Symptoms suggestive of iliac DVT include swelling of the entire leg, with or without flank, buttock, or back pain. [a]Grade 2C vs standard serial proximal US. [b]Grade 2C for Doppler US of iliac vein, venography, or MRV over standard serial proximal US. See Figure 1 legend for expansion of abbreviation.

2C), **highly sensitive D-dimer** (Grade 1B), **or venography** (Grade 1B).

5.2. In pregnant patients with suspected DVT in whom initial proximal CUS is negative (see Fig 10), we suggest further testing with either serial proximal CUS (day 3 and day 7) (Grade 1B) **or a sensitive D-dimer done at the time of presentation** (Grade 2B) **over no further testing for DVT. We recommend that patients with an initial negative proximal CUS and a subsequent negative sensitive D-dimer or negative serial proximal CUS undergo no further testing for DVT** (Grade 1B) **and that patients with positive D-dimer have an additional follow-up proximal CUS (day 3 and day 7), rather than venography** (Grade 1B) **or whole-leg US** (Grade 2C).

5.3. In pregnant patients with symptoms suggestive of isolated iliac vein thrombosis (swelling of the entire leg, with or without flank, buttock, or back pain) and no evidence of DVT on standard proximal CUS (see Fig 11**), we suggest further testing with either Doppler US of the iliac vein** (Grade 2C), **venography** (Grade 2C), **or direct MRI** (Grade 2C), **rather than standard serial CUS of the proximal deep veins.**

6.0 Diagnosis of Upper Extremity DVT

Venous thrombosis involving the upper extremities is uncommon.[209-212] The annual incidence of upper extremity DVT in the general population is estimated to be three per 100,000 persons.[210,212-215] Secondary events, which are more common than primary thrombosis, are predominantly due to central venous catheters, pacemaker wires, and malignancies. Primary events include both idiopathic and effort-related (Paget-Schroetter syndrome) thrombosis.[216] The latter is a consequence of narrowing of the thoracic outlet at the level of the first rib and the clavicle resulting in compression of the subclavian vein.

A paucity of studies have evaluated diagnostic strategies for suspected upper extremity DVT. It is not clear that diagnostic research for lower extremity DVT can be extrapolated to upper extremity DVT. The anatomy of the upper extremity venous system creates diagnostic difficulties. The midportion of the subclavian vein runs beneath the clavicle, whereas the innominate veins and superior vena cava lie in the thoracic cavity. US visualization of these areas is difficult, and the standard diagnostic criterion of compression is impossible in these locations. Contrast venography has the ability to visualize the entire deep venous system of the upper extremity. However, as outlined in section 2.0, this technique has significant drawbacks. It would be preferable to use alternate techniques in routine clinical practice and, indeed, US is the most commonly used test.

Tables S56 and S57 summarize the methodology of diagnostic studies in patients with suspected upper extremity DVT. Table S58 provides a description of the study results, and Tables S59 to S65 present evidence profiles for the various diagnostic strategies that have been evaluated. Table 11 summarizes the quality of evidence and frequency of potential clinical outcomes for the various diagnostic strategies.[217-228]

6.1 Ultrasonography

Upper extremity DVT is diagnosed in the presence of noncompressibility of a venous segment (CUS) or in the absence of a color or Doppler signal within the lumen of the vein (visible intraluminal thrombus) and excluded in the absence of these findings.[216,219,223-227] Only two studies (total of 65 patients) have evaluated the accuracy of a single CUS compared with venography.[216,219] Although the pooled sensitivity and specificity were 97% (95% CI, 90%-100%) and 94% (95% CI, 80%-99%), respectively, the studies were of low quality and the CIs are wide. No management studies have been undertaken evaluating the safety of single or serial CUS for the exclusion of upper extremity DVT.

The sensitivities and specificities of Doppler and color Doppler combined with CUS or color Doppler alone were similar to that for CUS.[222-228] All of the available accuracy studies have significant limitations. No management studies using these techniques have been performed. Again, the available evidence is generally of low quality.

6.2 Clinical Pretest Probability Assessment

Evidence for the use of clinical pretest probability assessment in this patient population is of low quality. One prospective study of 214 patients evaluated a clinical score that categorized patients as "unlikely" and "likely" to have upper extremity DVT based on the presence of a central venous catheter or pacemaker,

Table 11—*Summary of Findings for Diagnostic Studies in Patients with Suspected Upper Extremity DVT: Accuracy Studies*

Diagnostic Test	Population and Reference Standard	No. of Studies (Participants)	Quality of Evidence	Illustrative Comparative Numbers: Effect/1,000[a]			
				True Positives (Correctly Classified as Having DVT)	True Negatives (Correctly Classified as Not Having DVT)	False Positives (Incorrectly Classified as Having DVT)	False Negatives (Incorrectly Classified as Not Having DVT)
Clinical model[b]	Population: suspected upper extremity DVT	1 (214)[217]	Low[c]	Prevalence 5%, 39	Prevalence 5%, 608	Prevalence 5%, 342	Prevalence 5%, 11
	Reference standard: single US			Prevalence 17%, 133	Prevalence 17%, 531	Prevalence 17%, 299	Prevalence 17%, 37
				Prevalence 53%, 413	Prevalence 53%, 301	Prevalence 53%, 169	Prevalence 53%, 117
Negative highly sensitive DD (VIDAS)[d]	Population: suspected upper extremity DVT	1 (52)[218]	Low[e]	Prevalence 5%, 50	Prevalence 5%, 133	Prevalence 5%, 817	Prevalence 5%, 0
	Reference standard: single US			Prevalence 17%, 170	Prevalence 17%, 116	Prevalence 17%, 714	Prevalence 17%, 0
				Prevalence 53%, 530	Prevalence 53%, 66	Prevalence 53%, 404	Prevalence 53%, 0
Negative single CUS[f]	Population: suspected upper extremity DVT	2 (65)[216,219]	Low[g]	Prevalence 5%, 49	Prevalence 5%, 893	Prevalence 5%, 57	Prevalence 5%, 1
	Reference standard: venography			Prevalence 17%, 165	Prevalence 17%, 780	Prevalence 17%, 50	Prevalence 17%, 5
				Prevalence 53%, 514	Prevalence 53%, 442	Prevalence 53%, 28	Prevalence 53%, 16
Negative single Doppler US[h]	Population: suspected upper extremity DVT	3 (101)[220]	Low[i]	Prevalence 5%, 42	Prevalence 5%, 912	Prevalence 5%, 38	Prevalence 5%, 8
	Reference standard: venography			Prevalence 17%, 143	Prevalence 17%, 797	Prevalence 17%, 33	Prevalence 17%, 27
				Prevalence 53%, 445	Prevalence 53%, 451	Prevalence 53%, 19	Prevalence 53%, 85
Negative single Doppler plus CUS[j]	Population: suspected upper extremity DVT	6 (320)[220]	Low[k]	Prevalence 5%, 45	Prevalence 5%, 883	Prevalence 5%, 67	Prevalence 5%, 5
	Reference standard: venography			Prevalence 17%, 155	Prevalence 17%, 772	Prevalence 17%, 58	Prevalence 17%, 15
				Prevalence 53%, 482	Prevalence 53%, 447	Prevalence 53%, 33	Prevalence 53%, 48
Negative MRI (time of flight)[l]	Population: suspected upper extremity DVT	1 (31)[221]	Low[m]	Prevalence 5%, 35	Prevalence 5%, 845	Prevalence 5%, 105	Prevalence 5%, 15
	Reference standard: venography			Prevalence 17%, 121	Prevalence 17%, 739	Prevalence 17%, 91	Prevalence 17%, 49
				Prevalence 53%, 376	Prevalence 53%, 418	Prevalence 53%, 62	Prevalence 53%, 154

(Continued)

Table 11—*Continued*

Diagnostic Test	Population and Reference Standard	No. of Studies (Participants)	Quality of Evidence	Illustrative Comparative Numbers: Effect/1,000[a]			
				True Positives (Correctly Classified as Having DVT)	True Negatives (Correctly Classified as Not Having DVT)	False Positives (Incorrectly Classified as Having DVT)	False Negatives (Incorrectly Classified as Not Having DVT)
Negative MRI (gadolinium)[n]	Population: suspected upper extremity DVT	1 (31)[221]	Low[o]	Prevalence 5%, 25	Prevalence 5%, 760	Prevalence 5%, 190	Prevalence 5%, 25
	Reference standard: venography			Prevalence 17%, 81	Prevalence 17%, 664	Prevalence 17%, 166	Prevalence 17%, 85
				Prevalence 53%, 265	Prevalence 53%, 376	Prevalence 53%, 94	Prevalence 53%, 265

GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. See Table 1 and 3 legends for expansion of abbreviations.

[a]Prevalences for high (53%), moderate (17%), and low (5%) taken from Wells et al.[10]

[b]Based on a specificity of 64% (95% CI, 57%-72%) and sensitivity of 78% (95% CI, 68%-66%).

[c]Very serious limitations (not clearly a representative sample, accepted reference standard not used, reference standard results no blinded, no data on withdrawals), single study, serious indirectness (accuracy study only, no management studies), and serious imprecision (wide 95% CI).

[d]Based on a specificity of 14% (95% CI, 4%-29%) and sensitivity of 100% (95% CI,78%-100%)

[e]Very serious limitations (differential verification, accepted reference standard no used, no data on withdrawals), single study, serious indirectness (accuracy study only; no management studies), and very serious imprecision (wide 95% CI).

[f]Based on a specificity of 94% (95% CI, 80%-99%) and a sensitivity of 97% (95% CI, 90%-100%).

[g]Very serious limitations (in one study, CUS results unverified against reference standard in 26 of 33 patients, unclear if representative sample, unclear if reference standard test blinded, no data on withdrawals), serious indirectness (accuracy study only, no management studies), and serious imprecision (wide 95% CI).

[h]Based on a specificity of 96% (95% CI, 86%-100%) and a sensitivity of 84% (95% CI, 72%-87%).

[i]Very serious limitations (in one study, three of 12 Doppler US results unverified against reference standard and 4 of 18 verified against CT scan, rather than venography; in another study, CUS also performed with potential for bias), serious indirectness (accuracy study only, no management studies), and serious imprecision (wide 95% CI).

[j]Based on a specificity of 93% (95% CI, 80%-100%) and a sensitivity of 91% (95% CI, 85%-97%).

[k]Very serious limitations (in one study, 19 of 42 Duplex US results unverified against reference standard; in another, nine of 130 results unverified against reference standard and 22 of 121 Duplex results verified against venography with remainder against CT scan, MRI, and clinical follow-up; four of six studies unclear if representative patient spectrum; two of six studies unclear if blinding of reference standard and index test results), serious indirectness (accuracy study only, no management studies), and serious imprecision (wide 95% CI).

[l]Based on a specificity of 89% (95% CI, 52%-100%) and a sensitivity of 71% (95% CI, 26%-96%).

[m]Very serious limitations (23 of initial 44 patients were lost), single study, serious indirectness (accuracy study only, no management studies), and very serious imprecision (wide 95% CI).

[n]Based on a specificity of 80% (95% CI, 44%-97%) and a sensitivity of 50% (95% CI, 12%-88%).

[o]Very serious limitations (23 of initial 44 patients were lost), single study, serious indirectness (accuracy study only, no management studies), and very serious imprecision (wide 95% CI)

FIGURE 12. [Section 6.1, 6.2] Recommendations for evaluation of suspected upper extremity DVT. Where there are preferred strategies, these are indicated by boldface print; less preferred strategies are indicated by italicizing/shading. §See Kearon et al.[11] §Combined modality US refers to CUS combined with either Doppler or color Doppler. [a]Grade 2C vs venography, vs sensitive D-dimer and vs other strategies. [b]Grade 2C vs no further testing. [c]Grade 1C vs venography. [d]Grade 2C vs venography. [e]Grade 2C for combined modality US over venography. [f]Grade 2C for combined modality US over moderate or highly sensitive D-dimer. [g]Grade 2C for moderate or highly sensitive D-dimer, MRV, CTV, or serial combined modality US over no further testing. [h]Grade 2C for pursuing alternate diagnosis over venography. See Figure 1 legend for expansion of abbreviation.

localized pain, unilateral pitting edema, and the presence of another likely possible diagnosis.[217,220] The sensitivity of this score was 78% (95% CI, 68%-88%), and the specificity was 64% (95% CI, 57%-72%). The score has not been evaluated in a prospective management study.

6.3 D-Dimer Testing

One study evaluated the accuracy of a rapid quantitative ELISA in 52 consecutive patients.[218,219] Although the sensitivity was 100% (95% CI, 78%-100%), the specificity was only 14% (95% CI, 57%-72%). Moreover, Doppler combined with CUS was used as the reference standard test, making this determination potentially unreliable.

6.5 MR Venography

Time-of-flight and gadolinium-enhanced MR venography were compared with contrast venography in a 44-patient accuracy study with important limitations.[220,221] For time of flight, the sensitivity was 71% (95% CI, 29%-96%) and the specificity was 89% (95% CI, 52%-100%). The sensitivity of gadolinium MR venography was 50% (95% CI, 12%-88%), and the specificity was 80% (95% CI, 44%-97%). No management studies have been performed with this technique.

6.6 Combinations of Tests

No studies have addressed strategies involving combinations of D-dimer, clinical assessment, and imaging studies.

Recommendations (see Fig 12)

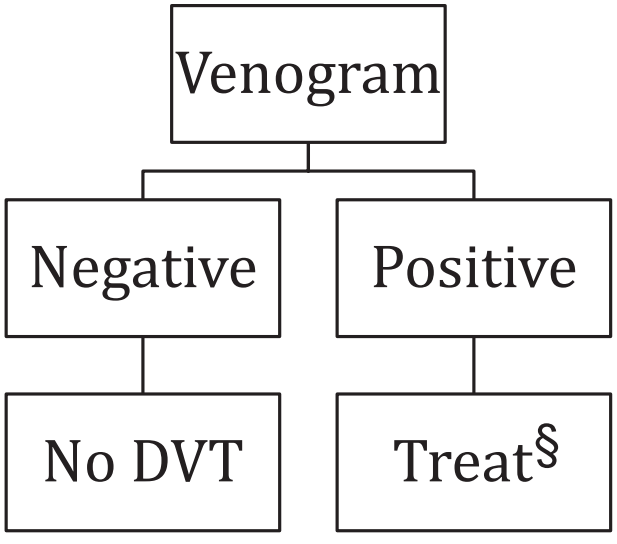

FIGURE 13. Use of venography (Referenced from Figures 1-12). §See Kearon et al.[11]

6.1. In patients suspected of having upper extremity DVT (see Fig 12), we suggest initial evaluation with combined-modality US (compression with either Doppler or color Doppler) over other initial tests, including highly sensitive D-dimer or venography (Grade 2C)**.**

6.2. In patients with suspected upper extremity DVT in whom initial US is negative for thrombosis despite a high clinical suspicion of DVT (see Fig 12), we suggest further testing with a moderate or highly sensitive D-dimer, serial US, or venographic-based imaging (traditional, CT scan, or MRI) rather than no further testing (Grade 2C)**.**

In patients with suspected upper extremity DVT and an initial negative combined modality US and subsequent negative moderate or highly sensitive D-dimer or CT scan or MRI, we recommend no further testing, rather than confirmatory venography (Grade 1C)**. We suggest that patients with an initial negative combined-modality US and positive D-dimer or those with less than complete evaluation by US undergo venography rather than no further testing, unless there is an alternative explanation for their symptoms** (Grade 2B)**, in which case testing to evaluate for the presence of an alternative diagnosis should be performed. We suggest that patients with a positive D-dimer or those with less than complete evaluation by US but an alternative explanation for their symptoms undergo confirmatory testing and treatment of this alternative explanation rather than venography** (Grade 2C)**.**

Remarks: Further radiologic testing (serial US or venographic-based imaging or CT scan/MRI to seek an alternative diagnosis) rather than D-dimer testing is preferable in patients with comorbid conditions typically associated with elevated D-dimer levels.

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Dr Stevens: contributed as a panelist.
Dr Goodacre: contributed as a panelist.
Dr Wells: contributed as a panelist.
Dr Stevenson: contributed as a panelist.
Dr Kearon: contributed as a panelist.
Dr Schunemann: contributed as a panelist.
Dr Crowther: contributed as a panelist.
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Additional information: The supplement Tables can be found in the Online Data Supplement at http:// chestjournal.chestpubs.org/content/141/2_suppl/e351S/suppl/DC1.

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CHEST Online Data Supplement

Diagnosis of DVT

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Shannon M Bates, MDCM; Roman Jaeschke, MD; Scott M. Stevens, MD; Steven Goodacre, MBChB, PhD; Philip S. Wells, MD; Matthew D. Stevenson, PhD; Clive Kearon, MD, PhD; Holger J. Schünemann, MD, PhD, FCCP; Mark Crowther, MD; Stephen G. Pauker, MD; Regina Makdissi, MD; and Gordon H. Guyatt, MD, FCCP

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Table S1—*Modeled Diagnostic Strategies*

Number	Strategy	Source
0	No testing or treatment	
1	Venography for all patients	
2	Proximal US, repeat if negative	
3	Whole-leg US, repeat if isolated calf vein DVT diagnosed	
4	Whole-leg US, treat if calf vein DVT diagnosed	Gibson et al,[1] Bernardi et al,[2] Johnson et al,[3] Elias et al,[4] Schellong et al,[5] Sevestre et al,[6] Sevestre et al,[7] Stevens et al,[8] Subramaniam et al[9]
5	Proximal US, no repeat	
6	Wells score and proximal US. If PTP low, discharge if US negative; venogram if positive. If PTP moderate, repeat US if negative, treat if positive. If high PTP, venogram if US negative, treat if US positive.	Anderson et al,[10] Wells et al,[11] Wells et al[12]
7	SimpliRED DD and proximal US. If US positive, then treat. If both are negative, then discharge. If DD positive and US negative, repeat US.	Kraaijenhagen et al[13]
8	Wells score and proximal US. If PTP high or moderate, perform proximal US. If positive treat, venogram if negative. If PTP low, perform proximal US. If positive treat, discharge if negative.	Walsh et al[14]
9	Wells score and full-leg US. If PTP high or moderate, perform full-leg US; treat if positive, venogram if negative. If PTP low, full-leg US; treat if positive, discharge if negative.	Walsh et al[14]
10	Quantitative latex DD. If positive, perform proximal US and repeat. If DD negative, perform Wells score. If high, perform proximal US and repeat if negative. If PTP moderate or low, discharge.	Bates et al[15]
11	Quantitative latex DD: if positive, perform above-knee US and repeat. If DD negative, perform Wells score. If PTP high, perform proximal US. PTP low or moderate, discharge.	Schutgens et al[16]
12	Wells score. If PTP high, perform proximal US, treat if positive, perform SimpliRED DD if negative. If DD positive, perform venogram, if negative repeat US. If PTP moderate, perform US; treat if positive, SimpliRED DD if negative. If DD positive, repeat proximal US. If DD negative, discharge. If PTP low, perform SimpliRED DD. If DD positive, perform proximal US. Discharge if DD negative.	Anderson et al[17]
13	Wells score and SimpliRED DD. If PTP high or moderate, or DD positive, perform full-leg US. If PTP low and DD negative, then discharge.	Janes and Ashford[18]
14	ELISA DD. If negative, discharge. If DD positive, perform proximal US. Treat if US positive. If US negative, perform Wells score. If PTP high, perform venogram. If PTP moderate or low, discharge.	Perrier et al[19]
15	Wells score. If PTP high or moderate, perform proximal US. If positive treat, if negative perform SimpliRED DD. Repeat US if DD positive, discharge if DD negative. If PTP low, perform US. Discharge if negative, treat if positive.	Tick et al[20]
16	Wells score. If PTP high or moderate, perform proximal US. If positive treat, if negative perform SimpliRED DD. Repeat US if DD positive and discharge if DD negative. If PTP low, perform SimpliRED DD; discharge if negative, perform proximal US if positive.	Wells et al,[21] intervention group (high and moderate combined)
17	Wells score. If PTP high, perform proximal US. If positive treat, if negative perform SimpliRED DD. Repeat US if DD positive, discharge if DD negative. If PTP moderate or low, perform SimpliRED DD. Discharge if negative, perform proximal US if positive.	Wells et al,[21] intervention group (moderate and low combined)
18	Wells score. If PTP high or moderate, perform proximal US. If positive treat, if negative repeat US. If PTP low, perform proximal US; treat if positive, discharge if negative.	Wells et al,[21] control group (high and moderate combined)
19	Wells score. If PTP high, perform proximal US. If positive treat, if negative repeat US. If PTP moderate or low, perform proximal US; treat if positive, discharge if negative.	Wells et al,[21] control group (moderate and low combined)
20	Wells score. If PTP high or moderate, perform proximal US. Treat if positive, if negative discharge. If PTP low, discharge.	UK survey
21	Perform SimpliRED DD. Discharge if negative, perform above-knee US if positive. Treat if US positive, repeat US if initial US is negative.	UK survey

In all algorithms, repeat US means that a proximal US is performed 1 week later. DD = D-dimer; ELISA = enzyme-linked immunosorbent assay; PTP = pretest probability; US = ultrasound.

Table S2—*Methodology Table for Diagnostic Studies Assessing Venography in Patients With Suspected Lower Extremity DVT: Individual Management Studies With Cohorts*

Study Details								
Patient Population	Diagnostic Test	Outcome	Methods (Single-Arm Cohort vs Cohort From RCT)	Consecutive Patients	Follow-up	Received Alternative Tests	Comments	Source
Suspected DVT	Technically adequate, normal venogram	Probability of VTE during follow-up	Single-arm cohort	Yes	3 mo	No	N = 160 outpatients with normal venography; 2 patients returned for investigation of new symptoms in the same leg during follow-up (day 2, day 8). New DVT was diagnosed by abnormal IPG in one (venography unsuccessful) and by repeat venography in another (calf vein DVT)	Hull et al[22]

Cohorts from single-arm studies or cohorts representing one of the arms of an RCT. IPG = impedance plethysmography; RCT = randomized controlled trial.

Table S3—*Descriptive Table for Cross-sectional Accuracy and Prospective Cohort Studies Assessing Venography for Evaluation of Suspected Lower Extremity DVT*

Question From Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Reference Standard	Patient Population	Outcome Measure[a]	Result	Comments	Reference
Suspected lower extremity DVT (Section 2.0)	What are the consequences of using venography to diagnose lower extremity DVT?	N/A	N/A	Patients with suspected DVT	N/A	N/A	Implied reference standard	N/A
	What are the consequences of using venography to rule out lower extremity DVT?	Primary study	3-mo follow-up	Patients with suspected DVT	3 mo follow-up	DVT diagnosed during follow-up in 2 of 160 patients (NPV, 98.8%; 95% CI, 95.6%-99.8%)	N = 160 outpatients with normal venography; 2 patients returned for investigation of new symptoms in the same leg during follow-up (day 2, day 8). New DVT was diagnosed by abnormal IPG in one (venography unsuccessful) and by repeat venography in another (calf vein DVT)	Hull et al[22]

N/A = not applicable; NPV = negative predictive value; TP = test probability. See Table S1 and S2 legends for expansion of other abbreviations.

[a]eg, Post-TP during 3 mo follow-up; sensitivity or specificity, and so forth.

Table S4—*Evidence Profile Table for Diagnostic Studies Assessing Venography in Patients With Suspected DVT: Should a Normal Venogram Be Used to Rule Out DVT?*

Quality Assessment							Summary of Findings		
							Accuracy Indices % (95% CI)		
No of Studies (Patients)	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Normal Venogram	Quality	Importance
Negative predictive value of a normal venogram for DVT compared with confirmed recurrent VTE during 3-mo follow-up									
1 (160)	Single-arm prospective cohort study	Serious[a]	Single study	N/A	95% CI, 95.6%-99.8%	3-mo follow-up as reference standard	98.8%	Moderate	Critical

Bibliography: Hull R, Hirsh J, Sackett DL, et al. Clinical validity of a negative venogram in patients with clinically suspected venous thrombosis. *Circulation*. 1981;64(3):622-625. Settings: outpatients.

[a] Prevalence of DVT in original population not specified.

Table S5—*[Sections 3.1-3.5] Methodology of Diagnostic Studies Assessing DD, PTP, and Proximal US for the Diagnosis of Suspected First Lower Extremity DVT: Meta-analysis of Accuracy Studies*

	Study Eligibility				
Study/Year	Patient Population	Diagnostic Test	Outcome (Criterion Standard)	Exploration of Heterogeneity	Comments
Goodacre et al[23]/2005	Clinically suspected DVT	US	Venography	Tested for influence of consecutive patients, blind reading of tests, underlying prevalence	Accuracy
Geersing et al[24]/2009	Suspected DVT, point of care, 23 studies, 13,959 patients	Point of care DD	US, venography, or 3 mo clinical follow-up or combined	Tested for a number of factors (ie, recurrent DVT, % with malignancy or surgery, DVT vs PE)	VTE (PE or DVT examined). Both accuracy and management studies (no imaging for some groups) included
Goodacre et al[25]/2005	Suspected DVT	DD	US, venography and/or plethysmography	Tested for patient-mix, ED only, outpatients only, and so forth	
DiNisio et al[26]/2007	Suspected DVT	DD	US, venography, and/or plethysmography	17 patient and design characteristics examined	VTE (DVT and PE) included
Stein et al[27]/2004	Suspected DVT	DD	US, venography, and/or plethysmography	Tested for DD used	

All studies are cross-sectional unless otherwise indicated under Comments. PE = pulmonary embolism. See Table S1 legend for expansion of other abbreviation.

Table S6—*[Sections 3.1-3.5] Methodology of Diagnostic Studies Assessing DD, PTP, and Proximal US for the Diagnosis of Suspected First Lower Extremity DVT: Individual Accuracy Studies*

	Study Details				
Study/Year	Patient Population	Diagnostic Test	Outcome (Criterion Standard)	Consecutive Patients	Independent Test Assessment
Subramaniam et al[28] 2006	ED patients	Wells score (likely or unlikely), moderately sensitive DD	Whole-leg US plus 3-mo follow-up in those with a negative US result at presentation	Yes	Yes

See Table S1 legend for expansion of abbreviations.

Table S7—*[Sections 3.1-3.5] Methodology of Diagnostic Studies Assessing DD, PTP, and Proximal US for the Diagnosis of Suspected First Lower Extremity DVT: Meta-analysis of Management Cohort Studies*

	Study Eligibility				
Study/Year	Patient Population	Diagnostic Test	Outcome	Methods (Single-Arm Cohort vs Cohort From RCT)	Exploration of Heterogeneity
Fancher et al[29]/2004	Clinically suspected DVT, primary vs referred not specified; 12 studies, 5,431 patients	DD combined with different PTP	3-mo probability of symptomatic VTE	Cohorts from both single-arm prospective studies and RCT	Presence of previous VTE, type of DD used
Wells et al[30]/2006	Mixed; 14 studies, 8,329 patients	PTP and DD	3-mo probability of VTE	Single-arm cohorts	
Righini et al[31]/2008	Clinically suspected DVT; 6 studies, 5,876 patients	Serial proximal CUS (one did CUS once)	3-mo probability of symptomatic VTE	Single-arm cohorts	No formal analysis

Cohorts from single arm studies or cohorts representing one of the arms of an RCT. CUS = compression ultrasound. See Table S1 and S2 legends for expansion of other abbreviations.

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Table S8—*[Sections 3.1-3.5] Methodology of Diagnostic Studies Assessing DD, PTP, and Proximal US for the Diagnosis of Suspected First Lower Extremity DVT: Individual Management Studies With Cohorts*

	Study Details							
Study/Year	Patient Population	Diagnostic Test	Outcome	Methods (Single-Arm Cohort vs Cohort From RCT)	Consecutive Patients	Loss to Follow-up	Received Alternative Tests	Comments
Büller et al[32]/2009	Outpatients in primary care, overall prevalence 13%	Clinical decision rule including moderately sensitive DD	3 mo symptomatic VTE	Single-arm cohort	Invited	3 of 1,002	No	Negative assessment meant negative DD and ≤ 3 points on 8-point scale (likely low-moderate PTP)
Kraijenhagen et al[13]/2002	Patients referred to thrombosis center, prevalence 22%	Moderately sensitive DD and proximal US	3 mo symptomatic VTE	Single-arm cohort	Yes	17 of 1,756 excluded from analysis because DD not performed with knowledge of US result	No	PTP assessed but only used in scenario analysis.
Bernardi et al[33]/1998	University center, likely referred, overall prevalence 27.5%	If normal US → highly sensitive DD	3 mo symptomatic VTE	Single-arm cohort	Yes	2 of 686	No	
Wells et al[12]/1997	Outpatients, referral, overall prevalence 16%	Wells score, DD alone for low PTP, or with US (for moderate and high PTP)	3 mo symptomatic VTE	Single-arm cohort	Yes	?	No	Low PTP and positive CUS was followed by venography. Negative CUS and high PTP led to venography
Anderson et al[17]/2003	ED patients, overall prevalence 18.1%	Combination of Wells score, US, mixed highly sensitive and moderately sensitive DD	3 mo symptomatic VTE	Single-arm cohorts	Yes	?	No	
Tick et al[20]/2002	Outpatients referred to center by family doctor, overall prevalence 42.5%	Low PTP underwent CUS. Moderate to high PTP underwent US and if positive DD. If DD positive, US was repeated at day 8	3 mo symptomatic VTE	Single-arm cohort	Yes	Not reported	2 patients were asymptomatic DVT diagnosed on CT scan performed for other reason	

(Continued)

Table S8—*Continued*

Study/Year	Study Details: Patient Population	Study Details: Diagnostic Test	Study Details: Outcome	Study Details: Methods (Single-Arm Cohort vs Cohort From RCT)	Consecutive Patients	Loss to Follow-up	Received Alternative Tests	Comments
Cogo et al[34]/1998	Outpatients referred	2-Point US, with repeat	6 mo symptomatic VTE	Single-arm cohort	Yes	0	No	
Aguilar et al[35]/2002	ED patients with moderate pretest probability	If negative highly sensitive DD, no further testing	3 mo	Single-arm cohort	Yes	?	No	
Bates et al[15]/2003	Patients referred to thrombosis service	Highly sensitive DD, if negative and low or moderate PTP, no further investigation	3 mo symptomatic VTE	Single-arm cohort	Yes	1 of 90	No	
Schutgens et al[16]/2003	Referred to thrombosis service	Highly sensitive DD, if negative and low or moderate PTP, no further investigation	3 mo symptomatic VTE	Cohorts	Yes	1 of 812	No	
Anderson et al[10]/1999	ED patients	Wells score and proximal US. If pretest low and US negative, no further testing. Patients with a moderate pretest and negative US and a repeat US in 1 wk. High PTP patients with a negative US underwent venography	3 mo symptomatic VTE	Single-arm cohort	Yes	3 of 344	Venogram if low pretest and positive US or if high pretest and negative US	
Ruiz-Gimenes et al[36]/2004	ED patients		3 mo symptomatic VTE	Single-arm cohort	Yes	?		
Oudega et al[37]/2005	Primary care, overall prevalence 22%, 1,295 patients	Modified Wells score plus highly sensitive DD	Serial US	Single-arm cohort	Yes	N/A	No	

(Continued)

Table S8—*Continued*

Study/Year	Study Details							Comments
	Patient Population	Diagnostic Test	Outcome	Methods (Single-Arm Cohort vs Cohort From RCT)	Consecutive Patients	Loss to Follow-up	Received Alternative Tests	
Kearon et al[35]/2001	Low pretest probability and negative moderate sensitivity DD. Referred to thrombosis service, pretest prevalence 14%, for low PTP 2%	Low pretest and negative moderately sensitive DD	3 mo symptomatic VTE	Single-arm cohort	Yes	0 of 177	No	

Cohorts from single-arm studies or cohorts representing one of the arms of an RCT. See Table S1, S3, and S5 legends for expansion of abbreviations.

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Table S9—*[Sections 3.1-3.5] Methodology of Diagnostic Studies Assessing DD, PTP, and Proximal US for the Diagnosis of Suspected First Lower Extremity DVT: Individual RCT With Direct Comparison of Diagnostic Strategies*

	Study Details								
Study/Year	Patient Population	Test 1/Strategy 1	Test 2/Strategy 2	Outcome	Concealment of Randomization	Blinding	Follow-up	Intention to Treat	Comments
Wells et al[21]/2003	Outpatients (thrombosis units, ED), Wells score applied (unlikely or likely)	Pretest unlikely: DD with clinical follow-up if negative and US if positive Pretest likely: US, if negative, DD and repeat US if DD positive	Unlikely: US with clinical follow-up if negative. Likely: Serial US in all	3 mo symptomatic VTE	Yes	N/A	Strategy 1: 7 of 601 lost Strategy 2: 7 of 495 lost	N/A	Mixed DD: SimpliRED (moderately sensitive) and IL DD (sensitive)
Kearon et al[39]/2005	Referral centers of 4 university hospitals, prevalence 7.5%, randomized after first negative US	Moderately sensitive DD with no testing if negative and venogram if positive	Repeat US	3 mo symptomatic VTE	Yes	N/A	9 of 810 lost	N/A	

See Table 1 legend for expansion of abbreviation.

Table S10—*[Sections 3.1-3.5] Description and Results of Diagnostic Studies Assessing DD, PTP, and Proximal US for the Diagnosis of Suspected First Lower Extremity DVT: Results of Cross-sectional Accuracy and Cohort Management Studies*

Question From Structured Clinical Question Table	Study/Year	Clinical Situation/ Question	Meta-analysis vs Primary Study	Accuracy vs Management Cohort (Indicate if Cohort[s] is From an RCT)	Patient Population	Outcome Measure[a]	Result	Comments
What are the consequences of using US to diagnose proximal DVT?	Goodacre et al[23]/2005	Suspected DVT	Meta-analysis	Accuracy	Mixed	Sensitivity/ specificity	Estimates of sensitivity and specificity differ only slightly among different US techniques. Sensitivity for detection of proximal DVT from 93.8% for CUS (95% CI, 92%-95.3%) to 96.5% for duplex US (95% CI, 95.1%-97.6%). Specificity of CUS was 97.8% (95% CI, 97%-98.4%), numerically slightly higher than for duplex (94%; 95% CI, 92.8%-95.1%) or triplex US (94.3%; 95% CI, 92.5–95.8).	
	Wells et al[12]/1997	Low pretest and positive US	Primary	Cohort	3% prevalence	Post-TP (reference standard: venography)	9 of 11, 82% (48-98)	
	Anderson et al[10]/1999	Low pretest and positive US	Primary	Cohort	3.2% prevalence	Post-TP (reference standard: venography)	5 of 5 (100%, proximal)	
	Model Goodacre et al[23]/2005; Jaeschke et al[40]/2009		Meta-analysis of accuracy studies		Assuming sensitivity of 94% and specificity of 98% for US:			
					5% PTP negative post-TP positive 71% (lower 95% CI, 63), negative 0.3 (0.4%)			
					10% PTP negative post-TP positive 84% (77%); negative 0.7% (0.9%)			
					13% PTP negative post-TP positive 88% (lower 95% CI, 82), negative 0.9 (1.2%)			
					20% PTP negative post-TP positive 92% (87%); negative 1.5% (1.3%-2%)			
					38% PTP negative post-TP positive 97% (lower 95% CI, 95), negative 4.8 (lower 3%)			
					50% PTP negative post-TP positive 98% (98%); negative 8% (lower 5%)			
What are the consequences of using PTP with a single negative proximal US to exclude DVT?	Tick et al[20]/2002	Low pretest and negative US	Primary	Management	Outpatients (prevalence in low pretest = 11%)	3 mo follow-up	5 of 250, 2%	Prevalence in low pretest = 11%
	Wells et al[12]/1997	Low pretest and negative US	Primary	Management	3% prevalence	3 mo follow-up	1 of 320, (0.3%)	
	Kraaijenhagen et al[13]/2002	Low pretest and negative US	Primary	Management according to US and DD; results according to PTP via scenario analysis	6.9% prevalence	3 mo follow-up	13 of 834, 1.6%	Scenario analysis

(Continued)

Table S10—*Continued*

Question From Structured Clinical Question Table	Study/Year	Clinical Situation/ Question	Meta-analysis vs Primary Study	Accuracy vs Management Cohort (Indicate if Cohort[s] is From an RCT)	Patient Population	Outcome Measure[a]	Result	Comments
	Anderson et al[10]/1999	Low pretest and negative US	Primary	Management	3.2% prevalence	3 mo follow-up	1 of 185 (calf DVT)	
	Wells et al[21]/2003	Unlikely Wells score and negative US	Primary	Management, RCT	4.4% prevalence	3 mo follow-up	4 of 272, 1.4% (0.4-3.8%)	
	Anderson et al[10]/1999	Moderate pretest and negative US	Primary	Management	13 of 105 initial US	3 mo follow-up	2 of 92 (1 at 1 wk US, 1 calf during follow-up) 2.2%	
	Wells et al[12]/1997	Moderate pretest and negative US	Primary	Management	16.6% prevalence	3 mo follow-up	5 of 166 (3 at 1 wk and 2 during follow-up) 3.0%	
	Tick et al[20]/2002	Moderate-high pretest and negative US	Primary	Cohort	56.5% on initial US	3 mo follow-up	Would miss 13 of 231 5.6%	Second US performed due to positive SimpliRED DD detected 13 of 15, 2 still missed
	Wells et al[21]/2003	Likely Wells score and negative US	Primary	Cohort from RCT	27.4% prevalence	3 mo follow-up	1 of 182 on 1 wk repeat, 2 during follow-up; total = 3 of 182 1.6%	
	Wells et al[12]/1997	High pretest and negative US	Primary	Single cohort	75% prevalence	3 mo follow-up	4 of 22, 18.2%	
	Anderson et al[10]/1999	High pretest and negative US	Primary	Single cohort	20 of 49 on original CUS	Venography	4 of 29 (2 proximal, 2 calf) = 13.2%	
	Ruiz-Gimenez et al[36]/2004	High pretest and negative US	Primary	Cohort	49% prevalence	Repeat US	5 of 62 8.1%	4 detected on repeat US
What are the consequences of using serial proximal US to exclude DVT (regardless of pretest)?	Righini et al[31]/2008	Prevalence of 16%-28% in different studies	Meta-analysis	6 studies, 1 looked at single US	Mixed	3 mo follow-up	0.6% (0.4-0.9%)	

(Continued)

Table S10—*Continued*

Question From Structured Clinical Question Table	Study/Year	Clinical Situation/ Question	Meta-analysis vs Primary Study	Accuracy vs Management Cohort (Indicate if Cohort[s] is From an RCT)	Patient Population	Outcome Measure[a]	Result	Comments
	Wells et al[12]/1997	Moderate pretest, negative serial (2) proximal US	Primary	Management	Outpatients, 16% prevalence	3 mo follow-up	2 of 163 (1.2%)	Included in Righini et al[31] meta-analysis
	Anderson et al[10]/1999	Moderate pretest, negative serial (2) proximal US	Primary	Management	Outpatients, ED, 14.3% prevalence	3 mo follow-up	1 of 91 (3.2%)	
	Kearon et al[39]/2005	7.5% Prevalence	Primary	Management, cohort from RCT	3 of 350 detected on repeat US	6 mo follow-up	2 of 347 (0.6%)	
	Wells et al[21]/2003	Likely Wells score plus serial (2) negative proximal US	Primary	Management, RCT cohort	27.4% prevalence	3 mo follow-up	2 of 181 (1.1%)	
	Cogo et al[34]/1998	24% Pretest, 2 negative proximal US	Primary	Management	24% prevalence	3 mo follow-up	8 of 1301 (0.6%)	Included in Righini et al[31] meta-analysis
	Ruiz-Gimenes et al[36]/2004	Overall prevalence 22.6%	Primary	Management	44.6% among high pretest	3 mo follow-up	0 of 41	
What are the consequences of using a highly sensitive DD as a stand-alone test to exclude DVT?	Geersing et al[24]/2009	Suspected DVT, point of care testing	Meta-analysis	Accuracy and management studies included	ED or office or home (point of care)	Sensitivity/specificity	Highest sensitivity of 96% and 93%, within the range of previous meta-analysis	Results for moderately sensitive tests: 85%; 95% CI, 62%-74% (within range of Goodacre et al[25] 2005 meta-analysis); for 50% pretest, 18% posttest; for 5% pretest, 1.1% posttest
	Goodacre et al[25]/2005	Suspected DVT	Meta-analysis	Accuracy studies	Mixed	Sensitivity/specificity	Highest sensitivity 94%	For moderately sensitive assays, sensitivity 85%-87%
	Stein et al[27]/2004	Suspected DVT	Meta-analysis	Prospective accuracy		Sensitivity/specificity	Highest sensitivity for ELISA 96% (95% CI, 91%-100%)	Authors claim as good as US (but serial US needed if PTP high)

(Continued)

Table S10—*Continued*

Question From Structured Clinical Question Table	Study/Year	Clinical Situation/ Question	Meta-analysis vs Primary Study	Accuracy vs Management Cohort (Indicate if Cohort[s] is From an RCT)	Patient Population	Outcome Measure[a]	Result	Comments
	Di Nisio et al[26]/2007	Suspected DVT	Meta-analysis	Prospective accuracy	Mixed	Sensitivity/specificity	Range consistent with other meta-analyses; highest sensitivity of 97%	Assuming 50% prevalence (high pretest) and 50% specificity, the test would miss 15 of 500 cases, and posttest negative is 15 of 265 or 0.6%
	Fancher et al[29]/2004	Suspected DVT	Meta-analysis	Accuracy and management studies	Mixed	Sensitivity/specificity	Overall sensitivity 98% (95% CI, 96%-99%), specificity 46% (95% CI, 28%-67%) If pretest 5% → posttest 0.3% If pretest 10% → posttest 0.6% If pretest 20% → posttest 1.2% If pretest 30% → posttest 2.1%	
What are the consequences of using PTP and DD to exclude DVT?	Fancher et al[29]/2004	Low pretest and negative moderately sensitive DD	Meta-analysis	Cohorts from management and accuracy studies	Frequency of DVT at presentation, 10.1%-43.2%	3 mo follow-up	0.5% (95% CI, 0.1%-1.1%)	Likely includes people with previous DVT
	Kearon et al[38]/2001	Low pretest and negative moderately sensitive DD	Primary	Management	Referred to thrombosis service, pretest prevalence 14%, for low pretest 2%	3 mo follow-up	1 of 171 (0.6%; 95% CI, 0-2.9%)	Included in Fancher et al[29] meta-analysis
	Wells et al[30]/2006	Low pretest and negative moderately sensitive DD	Meta-analysis	Cohorts from management and accuracy studies	5% prevalence	3 mo follow-up	0.9% LR negative, 0.20 (0.12-0.31)	

(Continued)

Table S10—*Continued*

Question From Structured Clinical Question Table	Study/Year	Clinical Situation/ Question	Meta-analysis vs Primary Study	Accuracy vs Management Cohort (Indicate if Cohort[s] is From an RCT)	Patient Population	Outcome Measure[a]	Result	Comments
	Geersing et al[24]/2009	Low PTP and negative moderately sensitive DD	Meta-analysis	Cohorts from management and accuracy studies		Posttest calculated	SimpliRED: 1.1% (95% CI, 0.8%-1.5%); Clearview Simplify: 1.1% (0.9%-1.5%)	Calculated assuming 5% pretest
	Anderson et al[17]/2003	Low pretest and negative DD	Primary	Management	ED patients, overall prevalence 3.7%	3 mo follow-up	3 of 316 (0.95%)	Mixed DD; SimpliRED and IL DD; included in Fancher et al[29] meta-analysis
	Subraminian et al[28]/2006	Low Hamilton score and negative moderately sensitive DD	Primary	Accuracy with 3-mo follow-up	ED	3 mo follow-up	1 of 103 (1.0%) by low Hamilton, 1 of 81 (1.2%) by low Wells	Calf thrombosis
	Büller et al[32]/2009	Primary care, lower score on unique prediction rule, and negative moderately sensitive DD,	Primary	Management	Outpatients, primary practice, prevalence 13%	3 mo follow-up	7 of 500, 1.4% (95% CI, 0.6%-2.9%)	Two-level CDR incorporating negative SimpliRED DD and unique prediction rule
	Wells et al[21]/2003	Unlikely Wells score and negative moderately sensitive DD	Primary	Cohort from RCT	Outpatients, primary practice, prevalence 4.4%	3 mo follow-up	2 of 218, 0.9% (95% CI, 0.1%-3.3%)	
	Fancher et al[29]/2004	Moderate pretest and negative moderately sensitive DD	Meta-analysis	Cohorts from management and accuracy studies	Frequency of DVT at presentation, 10.1%-43.2%	3 mo follow-up	3.5% (95% CI, 1.4%-6.9%)	
	Wells et al[30]/2006	Moderate pretest and negative moderately sensitive DD	Meta-analysis	Cohorts from management and accuracy studies	Frequency of DVT at presentation, 17%	3 mo follow-up	4.4% LR negative 0.23 (0.13-0.39)	

(Continued)

Table S10—*Continued*

Question From Structured Clinical Question Table	Study/Year	Clinical Situation/ Question	Meta-analysis vs Primary Study	Accuracy vs Management Cohort (Indicate if Cohort[s] is From an RCT)	Patient Population	Outcome Measure[a]	Result	Comments
	Geersing et al[24]/2009	Moderate pretest and negative moderately sensitive DD, point of care	Meta-analysis	Cohorts from management and accuracy studies		Posttest calculated	SimpliRED: 4.9% (95% CI, 3.6%-6.8%) or Clearview Simplify 5.2% (4.1%-6.5%)	Calculated assuming 20% pretest
	Büller et al[32]/2009	Higher score on unique prediction rule and negative moderately sensitive DD	Primary	Cohort	Approximately 26% prevalence	Positive or negative US	12 of 63, 19%	
	Fancher et al[29]/2004	High pretest and negative moderately sensitive DD	Meta-analysis	Cohorts from management and accuracy studies	Frequency of DVT at presentation,n 10.1%-43.2%	3 mo follow-up	21.4% (95% CI, 8.5%-37.9%)	
	Wells et al[30]/2006	High pretest and negative moderately sensitive DD	Meta-analysis	Cohorts from management and accuracy studies	Frequency of DVT at presentation, 53%	3 mo follow-up	19% LR negative 0.20 (0.10-0.38)	
	Geersing et al[24]/2009	High pretest and negative moderately sensitive DD	Meta-analysis	Cohorts from management and accuracy studies		Posttest calculated	> 10 for lower end of CI	Calculated assuming 50% pretest
	Wells et al[30]/2006	Low pretest and negative highly sensitive DD	Meta-analysis	Cohorts from management and accuracy studies	Frequency of DVT at presentation, 10.1%-43.2%	3 mo follow-up	NPV, 99 (97-100); LR negative, 0.1 (0.03-0.37); estimated posttest 0.5%	Low only
	Geersing et al[24]/2009	Low pretest and negative highly sensitive DD, point of care	Meta-analysis	Cohorts from management and accuracy studies		Post-TP calculated	Cardiac: 0.4% (95% CI, 0.2%-0.8%) or Triage: 0.9 (95% CI, 0.4%-2.2%)	Calculated assuming 5% pretest

(Continued)

Table S10—*Continued*

Question From Structured Clinical Question Table	Study/Year	Clinical Situation/ Question	Meta-analysis vs Primary Study	Accuracy vs Management Cohort (Indicate if Cohort[s] is From an RCT)	Patient Population	Outcome Measure[a]	Result	Comments
	Oudega et al[37]/2005	Lowest pretest and negative highly sensitive DD	Single cohort (repeat US as reference standard)	Accuracy	12% Prevalence	Posttest on repeat CUS	5 of 222, 2.3%	
	Fancher et al[29]/2004	Low and moderate pretest; highly sensitive DD	Meta-analysis	Cohorts from management and accuracy studies	Frequency of DVT at presentation 10.1%-43.2%	3 mo follow-up	0.4% (95% CI, 0.04%-1.1%)	
	Wells et al[30]/2006	Moderate pretest and negative highly sensitive DD	Meta-analysis	Cohorts from management and accuracy	17% Prevalence	3 mo follow-up	NPV, 99% (95% CI, 96%-100%); LR negative, 0.05 (0.01-0.21); estimated posttest 1%	
	Aguilar et al[35]/2002	Moderate pretest and negative highly sensitive DD	Primary	Cohort of moderate pretest, accuracy	19.4% Prevalence	3 mo follow-up also performed	0 of 35	
	Bates et al[15]/2003	Moderate pretest and negative highly sensitive DD	Primary	Cohort	9.0% Prevalence	3 mo follow-up	1 of 90, 1.1%	
	Schutgens et al[16]/2003	Moderate pretest and negative sensitive DD	Primary	Cohort	37.7% Prevalence	3 mo follow-up	0 of 89	
	Geersing et al[24]/2009	Moderate pretest and negative highly sensitive DD, point of care	Meta-analysis	Cohorts from management and accuracy studies		Posttest calculated	Cardiac: 1.7% (95% CI, 1.0%-3.8%) or Triage: 4.3% (95% CI, 2.0%-9.7%)	Calculated assuming 20% pretest
	Fancher et al[29]/2004	High pretest and negative highly sensitive DD	Meta-analysis	Cohorts from management and accuracy studies	Frequency of DVT at presentation 10.1%-43.2%	3 mo follow-up	6.4% (95% CI, 1.7%-14.5%)	

(Continued)

Table S10—*Continued*

Question From Structured Clinical Question Table	Study/Year	Clinical Situation/ Question	Meta-analysis vs Primary Study	Accuracy vs Management Cohort (Indicate if Cohort[s] is From an RCT)	Patient Population	Outcome Measure[a]	Result	Comments
	Wells et al[30]/2006	High pretest and negative highly sensitive DD	Meta-analysis	Cohorts from management and accuracy studies	Frequency of DVT at presentation 53%	3 mo follow-up	NPV, 92% (95% CI, 81%-97%); LR negative, 0.07 (95% CI, 0.03-0.18); estimated posttest 8.6%	
	Geersing et al[24]/2009	High PTP and negative highly sensitive DD, point of care	Meta-analysis	Cohorts from management and accuracy studies		Posttest calculated	Cardiac: 6.5% (95% CI, 3.8%-13.7%) or Triage: 15.3% (95% CI, 7.4%-30.1%)	Calculated assuming 50% pretest
What are the consequences of using single proximal US to rule out DVT among those with low pretest and positive moderately sensitive DD	Anderson et al[17]/2003	ED, low pretest, positive DD, negative US	Primary	ED cohort	ED, 18.1% overall, low pretest, prevalence 3.8% to start	Posttest	0 of 113, 0%	Mixed DD: SimpliRED and IL DD; both events confined to calf veins
	Wells et al[21]/2003	Unlikely Wells score and positive DD and negative US	Primary	Cohort (from RCT)	Outpatients, prevalence 4.4%,	Posttest	0 of 85	Mixed DD: SimpliRED and IL DD
What are the consequences of using US to rule out DVT among those with moderate pretest and positive moderately sensitive DD?	Tick et al[20]/2002	Negative US and positive moderately sensitive DD and combination of moderate-high pretest	Primary	Cohort management	11% Prevalence	Posttest	15 of 83, 18.1% (95% CI, 10.5%-28.1%)	18.1% in mixed moderate to high. Unable to determine results for moderate alone

(Continued)

Table S10—*Continued*

Question From Structured Clinical Question Table	Study/Year	Clinical Situation/ Question	Meta-analysis vs Primary Study	Accuracy vs Management Cohort (Indicate if Cohort[s] is From an RCT)	Patient Population	Outcome Measure[a]	Result	Comments
What are the consequences of using US to rule out DVT among those with moderate pretest and a positive highly sensitive DD?	Aguilar et al[35]/2002	Moderate PTP and positive sensitive DD, followed by negative proximal US	Primary	Cohort management	Referral to ED, 19.4%	3 mo follow-up	0 of 73, 0%	Highly sensitive DD
What are the consequences of using serial proximal US to exclude DVT in patients with a positive DD?	Tick et al[20]/2002	Moderate to high pretest, positive moderately sensitive DD, first US negative	Primary	Management	Referral practice, 56.5% prevalence	3 mo follow-up	2 of 64 missed on second US (3.1%)	Overall 15 of 83 with abnormal SimpliRED DD had VTE (18%), 13 detected on second US, 2 of 64 missed, 3.1%
	Bernardi et al[33]/1998	PTP not specified; positive highly sensitive DD and first US negative	Primary	Management	University practice, 27.5% prevalence	3 mo follow-up	2 of 83 missed on second US (2.4%)	Overall 7 of 88 (8%) had VTE, 5 detected on repeat US at 1 wk
	Schutgens et al[16]/2003	Irrespective of pretest, positive highly sensitive DD, first US negative	Primary	Management	Referral practice, 39% prevalence	3 mo follow-up	6 of 291 missed on second US (2.1%)	
What are the consequences of using a negative DD to obviate the need for serial testing in patients with a negative proximal US and moderate or high pretest at presentation?	Tick et al[20]/2002	Moderate to high pretest, negative US, negative moderately sensitive DD	Primary	Management	56.5% prevalence	3 mo follow-up	0 of 148	

(Continued)

Table S10—*Continued*

Question From Structured Clinical Question Table	Study/Year	Clinical Situation/ Question	Meta-analysis vs Primary Study	Accuracy vs Management Cohort (Indicate if Cohort[s] is From an RCT)	Patient Population	Outcome Measure[a]	Result	Comments
	Kraaijenagen et al[13]/2002	22% Original prevalence	Primary	Accuracy plus follow-up	22% prevalence	3 mo follow-up	6 of 828, 0.7%; (95% CI, 0.3%-1.6%)	
	Kearon et al[39]/2005	No pretest established, but 7.5% prevalence, likely low to moderate and negative US and negative moderately sensitive DD	Primary	Management	7.5%	Posttest, 6 mo follow-up	3 of 309, 1%	
	Anderson et al[17]/2003	Moderate pretest, negative US, negative DD (mixed)	Primary	Management	18.1% prevalence	33 mo follow-up	0 of 244	Mixed DD: SimpliRED and IL DD
	Wells et al[21]/2003	Likely Wells score, negative US, negative DD	Primary	Management cohort from RCT	27.3% prevalence	3 mo follow-up	0 of 81	Mixed DD: SimpliRED and IL DD
	Schutgens et al[16]/2003	Consecutive referred, high pretest plus negative highly sensitive DD and negative US	Primary	Management	At least 39%	Posttest	1 of 37, 2.7%	
	Bates et al[15]/2003	Consecutive outpatients, high pretest, negative highly sensitive DD and negative US	Primary	Management	29.6%	Posttest	0 of 20	

CDR = clinical decision rule; LR = likelihood ratio. See Tables S1-S3 legends for expansion of abbreviations.

[a]eg, Post-TP during 3-mo follow-up sensitivity or specificity, and so forth.

Table S11—*[Sections 3.1-3.5] Evidence Profiles for Diagnostic Studies Assessing DD, PTP, and Proximal US for the Diagnosis of Suspected First Lower Extremity DVT: Among Patients With Low PTP, What Is the 3-mo Post-TP of VTE Following Exclusion of DVT With a Given Diagnostic Strategy?*

Quality Assessment							Summary of Findings				
							No. of Patients		Effect		
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Starting Strategy/ For Follow-up After Strategy Negative for DVT	Control Risk	Relative	Absolute, % (95% CI)	Quality
Low PTP and negative moderately sensitive DD											
3 meta-analyses	Management and accuracy studies	…	…	Some (−1) (calculated in one meta-analysis; accuracy studies included)	…	…	…	Assumed 0	N/A	0.5 (0.07-1.1), 0.9 (LR, 0.2; 95% CI, 0.12-0.31), 1.1 (0.8-1.5)	Moderate
Low PTP and negative highly sensitive DD											
5	Management	…	…	…	…	…	1,270/824	Assumed 0	N/A	1.0 (0.5-1.7)	High
3 meta-analyses	Management and accuracy studies	…	…	Some (−1), includes accuracy studies	Upper limit of CI in one meta-analysis > 2%	…	…	Assumed 0	N/A	0.4 (0.04-1.1), 0.4 (0.2-0.8); 0.9 (0.4-2.2)	Moderate

(Continued)

Table S11—*Continued*

Quality Assessment							Summary of Findings				
							No. of Patients		Effect		
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Starting Strategy/ For Follow-up After Strategy Negative for DVT	Control Risk	Relative	Absolute, % (95% CI)	Quality
Low PTP and single negative proximal US											
4	Management cohorts	…	…	Some were calf vein thrombosis	…	…	944/885	Assumed 0	N/A	0.9 (0.5-1.6)	High
Low PTP and positive DD (moderately or highly sensitive) followed by negative proximal US											
2	Management cohorts	…	…	…	…	Mixed DD tests; number of patients tested with each assay not clear	765/198	Assumed 0	N/A	0 (0-1.5)	High

Bibliography: Wells PS, Anderson DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. *N Engl J Med*. 2003;349(13):1227-1235. Geersing GJ, Janssen KJ, Oudega R, et al. Excluding venous thromboembolism using point of care D-dimer tests in outpatients: a diagnostic meta-analysis. *BMJ*. 2009:339:2990. Fancher TL, White RH, Kravitz RL. Combined use of rapid D-dimer testing and estimation of clinical probability in the diagnosis of deep vein thrombosis: a systematic review. *BMJ*. 2004;329(7470):821. Anderson DR, Kovacs MJ, Kovacs G, et al. Combined use of clinical assessment and d-dimer to improve the management of patients presenting to the emergency department with suspected deep vein thrombosis (the EDITED Study). *J Thromb Haemost*. 2003;1(4):645-651. Bates SM, Kearon C, Crowther M, et al. A diagnostic strategy involving a quantitative latex d-dimer assay reliably excludes deep venous thrombosis. *Ann Intern Med*. 2003;138(10): 787-794. Schutgens REG, Ackermark P, Haas FJLM, et al. Combination of a normal D-dimer concentration and a non-high pretest clinical probability score is a safe strategy to exclude deep venous thrombosis. *Circulation*. 2003;107(4):593-659. Elf JL, Strandberg K, Nilsson C, et al. Clinical probability assessment and D-dimer determination in patients with suspected deep vein thrombosis, a prospective multicenter management study. *Thromb Res*. 2009;123:612-616. Dewar C, Selby C, Jamieson K, et al. Emergency department nurse-based outpatient diagnosis of DVT using an evidence-based protocol. *Emerg Med J*. 2008;25:411-416. Anderson DR, Wells PS, Stiell I, et al. Thrombosis in the emergency department: use of a clinical diagnosis model to safely avoid the need for urgent radiological investigation. *Arch Intern Med*. 1999;159(5):477-482. Tick LW, Ton E, ven Voorthuizen R, et al. Practical diagnostic management of paitents with clinically suspected deep vein thrombosis by clinical probability test, compression ultrasonography and D-dimer test. *Am J Med*. 2002;113(8):630-635. Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pre-test probability of deep vein thrombosis in clinical management. *Lancet*. 1997;350(9094):1795-1798. Ruiz-Gimenez N, Friera A, Artieda P, et al. Rapid D-dimer test combined a clinical model for deep vein thrombosis. Validation with ultrasonography and clinical follow-up in 383 patients. *Thromb Haemost*. 2004;91(6):1237-1246. Wells PS, Owen C, Doucette S, Fergusson D, Tran H. Does this patient have deep vein thrombosis? *JAMA*. 2006;295(2):199-207. ceR *Am J Roetgenol*. 2007;189(5):1071-1076. Consequences of presenting with VTE when specified strategies are used to rule out suspected first lower extremity DVT in patient with a low PTP. Settings: outpatients. See Table S1, S3, and S10 legends for expansion of abbreviations.

Table S12—*[Sections 3.1-3.5] Evidence Profiles for Diagnostic Studies Assessing DD, PTP, and Proximal US for the Diagnosis of Suspected First Lower Extremity DVT: Among Patients With Low to Moderate PTP, What Is the 3-mo Post-TP of VTE Following Exclusion of Proximal DVT with a Given Diagnostic Strategy?*

Quality Assessment							Summary of Findings				
							No. of Patients		Effect		
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Starting Strategy/ For Follow-up After Negative for DVT	Control Risk	Relative	Absolute, % (95% CI)	Quality
Low to moderate PTP and negative moderately sensitive DD											
1	Management cohort	…	…	…	Some (−1), upper limit of CI >2%	…	852/500	Assumed 0	N/A	1.4 (0.7-2.6)	Moderate
Low to moderate PTP and negative moderately or highly sensitive DD											
1	Management cohort	…	…	…	Some (−1), upper limit of CI >2%	Number of patients tested with each assay not clear	317/218	Assumed 0	N/A	0.9 (0.2-2.9)	Moderate
Low to moderate PTP and negative highly sensitive DD											
1	Management cohort	…	…	…	…	…	1,169/718	Assumed 0	N/A	0.4 (0.1-1.5)	Moderate
1	Meta-analysis of management and accuracy studies	…	…	Some (−1) accuracy studies included	…	…	…	Assumed 0	N/A	0.4 (0.1-1.1)	Moderate
Low to moderate PTP and single negative proximal US											
1	Management cohort	…	…	…	Some (−1), upper limit of CI >2%	…	284/272	Assumed 0	N/A	1.5 (0.5-3.5)	Moderate
Low to moderate PTP and positive DD (highly or moderately sensitive) followed by negative proximal US											
1	Management cohort	…	…	…	Some (−1), upper limit of CI >2%	Mixed DD tests used in the study; number of patients tested with each assay not clear	317/85	Assumed 0	N/A	0 (0-3.5)	Moderate

Bibliography: Buller HR, Ten Cate-Hoek AJ, Hoes AW, et al. AMUSE (Amsterdam Maastricht Utrecht Study on thromboEmbolism in primary care. *Ann Intern Med*. 2009;150(4):229-235. Wells PS, Anderson DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. *N Engl J Med*. 2003;349(13):1227-1235. Gibson NS, Schellong WM, Kheir DY, et al. Safety and sensitivity of two ultrasound strategies in patients with clinically suspected deep venous thrombosis: a prospective management study. *J Thromb Haemost*. 2009;7(12):2035-2041. Fancher TL, White RH, Kravitz RL. Combined use of rapid D-dimer testing and estimation of clinical probability in the diagnosis of deep vein thrombosis: systematic review. *BMJ*. 2004;239(7590):821.
Consequences of presenting with VTE when specified strategies are used to rule suspected first lower extremity DVT in patients with a low to moderate PTP. Settings: outpatients. See Table S1 and S3 legends for expansion of abbreviation.

Table S13—*[Sections 3.1-3.5] Evidence Profiles for Diagnostic Studies Assessing DD, PTP, and Proximal US for the Diagnosis of Suspected First Lower Extremity DVT: Among Patients With Moderate PTP, What Is the 3-mo Post-TP of VTE Following Exclusion of DVT With a Given Diagnostic Strategy?*

Quality Assessment							Summary of Findings				
							No. of Patients		Effect		
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Starting Strategy/ For Follow-up After Negative for DVT	Control Risk	Relative	Absolute, % (95% CI)	Quality
Moderate PTP and negative moderately sensitive DD											
3	Meta-analyses of management and cohort studies	…	…	Some (−1), accuracy studies included	…	…	…	Assumed 0	N/A	4.4; 3.5 (1.4-6.9), 4.9, or 5.2 (depending on DD, SimpliRED or Simplify), lower limit of CI > 3%	Moderate
Moderate PTP and negative highly sensitive DD											
3	Management cohort	…	…	…	Some (−1), upper limit of CI > 2%	…	655/214	Assumed 0	N/A	0.6 (0.1-2.2)	Moderate
2	Management and accuracy	…	…	Some (−1), accuracy studies included	Some (−1), upper limit of CI > 2%		…	Assumed 0	N/A	NPV, 99 (96-100); estimated post-TP 1% Point-of-care meta-analysis: 1.7 (1.0-3.8) or 4.3 (2.0-9.7) for Cardiac and Triage test	Low
Moderate PTP and single negative proximal US											
1	Management cohort	…	…	…	Some (−1), upper limit of CI > 2%	-	144/114	Assumed 0	N/A	0.9 (0.1-4.1)	Moderate
Moderate PTP with negative US and negative DD (either moderately or highly sensitive)											
2	Management cohort	…	…	…	…	Number of patients tested with each assay not clear	675/325	Assumed 0	N/A	0 (0-0.9)	High
Moderate PTP and negative serial proximal US											
3	Management cohort	…	…	…	Some (−1), upper limit of CI > 2%		?/365	Assumed 0	N/A	1.1 (0.4-2.5)	Moderate

(Continued)

Table S13—*Continued*

Quality Assessment							Summary of Findings				
							No. of Patients		Effect		
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Starting Strategy/ For Follow-up After Negative for DVT	Control Risk	Relative	Absolute, % (95% CI)	Quality
1	Meta-analysis	…	…	Some (−1), includes accuracy and management studies	…	…	…	Assumed 0	N/A	0.6 (0.4-0.9)	Moderate
Moderate PTP and positive highly sensitive DD followed by single negative US											
1	Management cohort	…	…	…	Some (−1), upper limit of CI > 2%	…	134/73	Assumed 0	N/A	0 (0-4.0)	Moderate
Moderate PTP with negative initial US and positive DD (either moderately or highly sensitive) followed by negative US											
1	Management cohort	…	…	…	Some (−1), upper limit of CI > 2%	Number of patients tested with each assay not clear	426/94	Assumed 0	N/A	0 (0-0.3.1)	Moderate

Bibliography: Wells PS, Owen C, Doucette S, Fergusson D, Tran H. Does this patient have deep vein thrombosis? *JAMA*. 2006;295(2):1997-2207. Geersing GJ, Janssen KJ, Oudega R, et al. Excluding venous thromboembolism using point of care D-dimer tests in outpatients: a diagnostic meta-analysis. *BMJ*. 2009;339:2990. Fancher TL, White RH, Kravitz RL. Combined use of rapid D-dimer testing and estimation of clinical probability in the diagnosis of deep vein thrombosis: a systematic review. *BMJ*. 2004;329(7470):821. Bates SM, Kearon C, Crowther M, et al. A diagnostic strategy involving a quantitative latex d-dimer assay reliably excludes deep venous thrombosis. *Ann Intern Med*. 2003;138(10):787-794. Schutgens REG, Ackermark P, Haas FJLM, et al. Combination of a normal D-dimer concentration and a non-high pretest clinical probability score is a safe strategy to exclude deep venous thrombosis. *Circulation*. 2003;107(4):593-597. Aguilar C, Martinez A, Artinez A, Del rio C, Vasquez M, Rodriguez FJ. Diagnostic value of D-dimer in patients with a moderate pre-test probability of deep venous thormbosis. *Br J Haematol*. 2002;118(1):275-277. Ruiz-Gimenez N, Friera A, Artieda P, et al. Rapid D-dimer test combined a clinical model for deep vein thrombosis. Validation with ultrasonography and clinical follow-up in 383 patients. *Thromb Haemost*. 2004;91(6):1237-1246. Anderson DR, Kovacs MJ, Kovacs G, et al. Combined use of clinical assessment and d-dimer to improve the management of patients presenting to the emergency department with suspected deep vein thrombosis (the EDITED Study). *J Thromb Haemost*. 2003;1(4):645-651. Wells PS, Anderson DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. *N Engl J Med*. 2003;349(13):1227-1235. Anderson DR, Wells PS, Stiell I, et al. Thrombosis in the emergency department: use of a clinical diagnosis model to safely avoid the need for urgent radiological investigation. *Arch Intern Med*. 1999;159(5):477-482. Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pre-test probability of deep vein thrombosis in clinical management. *Lancet*. 1997;350(9094):1795-1798. Kearon C, Ginsberg JS, Douketix J, et al. A randomized trial of diagnostic strategies after normal proximal vein ultrasonography for suspected deep venous thrombosis: D-dimer testing compared with repeated ultrasonography. *Ann Intern Med*. 2005;142(7):490-496. Righini M, Perrier A, De Moerloose P, et al. D-dimer for venous thromboembolism diagnosis: 20 years later. *J Thromb Haemost*. 2008;6:1059-1071. Consequences of presenting with VTE when specified strategies are used to rule out suspected first lower extremity DVT in patients with a moderate PTP. Settings: outpatients. See Table S1 and S3 legends for expansion of abbreviations.

Table S14—*[Sections 3.1-3.5] Evidence Profiles for Diagnostic Studies Assessing DD, PTP, and Proximal US for the Diagnosis of Suspected First Lower Extremity DVT: Among Patients With Moderate to High PTP, What Is the 3-mo Post-TP of VTE Following Exclusion of Proximal DVT With a Given Diagnostic Strategy?*

Quality Assessment							Summary of Findings				
							No. of Patients		Effect		
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Starting Strategy/ For Follow-up After Negative for DVT	Control Risk	Relative	Absolute, % (95% CI)	Quality
Moderate to high PTP and negative single proximal US and moderately sensitive DD											
1	Management cohort	…	…	…	Some (−1) with upper limit of CI reaching 2%	…	531/148	Assumed 0	N/A	0 (0-2.0)	Moderate
Moderate to high PTP and negative single proximal US and DD (moderately or highly sensitive)											
1	Management cohort	…	…	…	Some (−1), upper limit of CI > 2%	Number of patients tested with each assay not clear	249/81	Assumed 0	N/A	0 (0-3.6)	Moderate
Pooling of above two studies	Management cohort	…	…	…	…	Number of patients tested with each assay not clear	780/229	Assumed 0	N/A	0 (0-1.3)	High
Moderate to high PTP and negative serial proximal US											
1	Management cohort	…	…	…	Some (−1), upper limit of CU > 2%	…	246/181	Assumed 0	N/A	1.1 (0.2-3.4)	Moderate
Moderate to high PTP with negative proximal US and positive moderately sensitive DD followed by negative proximal US											
1	Management cohort	…	…	…	Some (lower limit of CI < 2%), major if we want to use it to exclude (upper CI > 5)	…	531/83	Assumed 0	N/A	3.6 (1-9.1)	Moderate not to use, low to use

(Continued)

Table S14—*Continued*

Quality Assessment							Summary of Findings				
							No. of Patients		Effect		
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Starting Strategy/ For Follow-up After Negative for DVT	Control Risk	Relative	Absolute, % (95% CI)	Quality
Moderate to high PTP with negative proximal US and positive DD (either moderately or highly sensitive) followed by negative proximal US											
1	Management cohort	…	…	…	Some (−1), upper limit of CI >2%	Not sure how many patients had which DD	249/97	Assumed 0	N/A	0 (0-3.0)	Moderate
Moderate to high PTP with negative proximal US and positive DD (either moderately or highly sensitive) followed by negative proximal US; above two studies pooled											
2	Management cohort	…	…	…	Some (−1), upper limit of CI >2%	Not sure how many patients had which DD	780/180	Assumed 0	N/A	1.7 (0.5-4.2)	Moderate

Bibliography: Tick LW, Ton E, van Voorthuizen T, et al. Practical diagnostic management of patients with clinically suspected deep vein thrombosis by clinical probability test, compression ultrasonography and D-dimer test. *Am J Med*. 2002;113(8):630-635. Wells PS, Anderson DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep vein thrombosis. *N Engl J Med*. 2003;349(13): 1227-1235. Consequences of presenting with VTE when specified strategies are used to rule out suspected first lower extremity DVT in patients with moderate to high PTP. Settings: outpatients. See Table S1 legend for expansion of abbreviation.

Table S15—*[Sections 3.1-3.5] Evidence Profiles for Diagnostic Studies Assessing DD, PTP, and Proximal US for the Diagnosis of Suspected First Lower Extremity DVT: Among Patients With High PTP, What Is the 3-mo Post-TP of VTE Following Exclusion of DVT With a Given Diagnostic Strategy?*

Quality Assessment							Summary of Findings				
							No. of Patients		Effect		
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Starting Strategy/ For Follow-up After Negative for DVT	Control Risk	Relative	Absolute, % (95% CI)	Quality
High PTP and negative moderately sensitive DD											
2	Meta-analysis of management and cohort studies	…	…	Some (−1), accuracy studies	…	…	…	Assumed 0	N/A	In each case point estimate >10%	Moderate
High PTP and negative highly sensitive DD											
3	Meta-analysis of management and cohort studies	…	…	Some (−1), accuracy studies	Minimal, in one case lower limit of CI <2%	…	…	Assumed 0	N/A	In each case point estimate >5%	Moderate
High PTP and negative single proximal US and highly sensitive DD											
2	Management cohort	…	…	…	Large, upper limit of CI 7.8%	…	350/59	Assumed 0	N/A	1.7 (0.1-7.8)	Low
High PTP and negative serial (×2) proximal US											
4	Management cohort	…	…	…	Some (−1), upper limit of CI >2%	…	291/221	Assumed 0	N/A	0.9 (0.2-2.8)	Moderate

(Continued)

Table S15—*Continued*

Quality Assessment							Summary of Findings				
							No. of Patients		Effect		
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Starting Strategy/ For Follow-up After Negative for DVT	Control Risk	Relative	Absolute, % (95% CI)	Quality
High PTP and negative proximal US and positive highly sensitive DD followed by negative proximal US											
1	Management cohort	…	…	…	Major (−2), CI from 0.1% to 12.5%	Scant data	279/36	Assumed 0	N/A	2.8 (0.1-12.5)	Low
High PTP and negative proximal US followed by negative venography											
3	Management cohort	…	…	…	Major (−2), upper limit of CI over 5	Scant data	168/43	Assumed 0	N/A	0 (0-6.7)	Low

Bibliography: Wells PS, Owen C, Doucette S, Fergusson D, Tran H. Does this patient have deep vein thrombosis? *JAMA*. 2006;295(2):1997-2207. Fancher TL, White RH, Kravitz RL. Combined use of rapid D-dimer testing and estimation of clinical probability in the diagnosis of deep vein thrombosis: a systematic review. *BMJ*. 2004;329(7470):821. Geersing GJ, Janssen KJ, Oudega R, et al. Excluding venous thromboembolism using point of care D-dimer tests in outpatients: a diagnostic meta-analysis. *BMJ*. 2009;339:2990. Bates SM, Kearon C, Crowther M, et al. A diagnostic strategy involving a quantitative latex d-dimer assay reliably excludes deep venous thrombosis. *Ann Intern Med*. 2003;138(10):787-794. Schutgens REG, Ackermark P, Haas FJLM, et al. Combination of a normal D-dimer concentration and a non-high pretest clinical probability score is a safe strategy to exclude deep venous thrombosis. *Circulation*. 2003;107(4):593-597. Dewar C, Selby C, Jamieson K, et al. Emergency department nurse-based outpatient diagnosis of DVT using an evidence-based protocol. *Emergency Med*. 2008;25:411-416. Ruiz-Gimenez N, Friera A, Artieda P, et al. Rapid D-dimer test combined a clinical model for deep vein thrombosis. Validation with ultrasonography and clinical follow-up in 383 patients. *Thromb Haemost*. 2004;91(6):1237-1246. Kearon C, Ginsberg JS, Douketis J, et al. A randomized trial of diagnostic strategies after normal proximal vein ultrasonography for suspected deep venous thrombosis: D-dimer testing compared with repeated ultrasonography. *Ann Intern Med*. 2005;142(7):490-496. Anderson DR, Wells PS, Stiell I, et al. Thrombosis in the emergency department: use of a clinical diagnosis model to safely avoid the need for urgent radiological investigation. *Arch Intern Med*. 1999;59(5):477-482. Perrier A, Desmarais S, Miron MJ, et al. Non-invasive diagnosis of venous thromboembolism in outpatients. *Lancet*. 1999;353(9148):190-195. Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pre-test probability of deep vein thrombosis in clinical management. *Lancet*. 1997;350(9094):1795-1798. Consequences of presenting with VTE when specified strategies are used to rule out suspected first lower extremity DVT in patients with a high PTP. Settings: outpatients. See Table S1 legend for expansion of abbreviation.

Table S16—*[Sections 3.1-3.5] Evidence Profiles for Diagnostic Studies Assessing DD, PTP, and Proximal US for the Diagnosis of Suspected First Lower Extremity DVT: Among Patients With an Unspecified PTP, What Is the 3-mo Post-TP of VTE Following Exclusion of Proximal DVT With a Given Diagnostic Strategy?*

Quality Assessment							Summary of Findings				
							No. of Patients		Effect		
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Starting Strategy/ For Follow-up After Negative for DVT	Control Risk	Relative	Absolute, % (95% CI)	Quality
Unspecified PTP and negative highly sensitive DD											
5 meta-analyses	Meta-analysis of accuracy studies	…	Some inconsistency (−1)	Some (−1), accuracy studies	Some (−1)	…	…	…	…	Sensitivity from 93%-96% (point of care) to 97.7%, in modeling assuming best sensitivity (97.7%), post-TP > 2% for PTP of 30%	Moderate
Unspecified PTP and negative single proximal US and moderately sensitive DD											
2	Management and cohort studies	…	…	…	…	Prevalence 22.1%	2,209/1,137	Assumed 0	N/A	0.8 (0.4-1.4)	High
Unspecified PTP and negative single proximal US followed by negative moderately sensitive DD or positive moderately sensitive DD and then negative second proximal US											
1	Management cohort	…	…	…	…	Prevalence 23.3%	1,045/828	Assumed 0	N/A	1.1 (0.6-1.9)	High
Unspecified PTP and negative single proximal US followed by negative highly sensitive DD											
1	Management cohort	…	…	…	…	Prevalence 39.1%	686/598	Assumed 0	N/A	0.2 (0.2-0.8)	High
Unspecified PTP and negative serial proximal US											
3	Management cohort	…	…	…	…	Prevalence 20.9%	2,662/2071	Assumed 0	N/A	1.0 (0.7-1.5)	High
1	Meta-analysis	…	…	Some (−1), both accuracy and management studies	…	…	…	Assumed 0	N/A	0.6 (0.4-0.9)	Moderate
Unspecified PTP and negative proximal US plus positive moderately sensitive DD followed by negative proximal US											
1	Management cohort	…	…	…	Some (−1), lower limit of CI < 2%	Prevalence 24.4%	1,739/520	Assumed 0	N/A	2.1 (1.2-3.5)	Moderate

(Continued)

Table S16—*Continued*

Quality Assessment							Summary of Findings				
							No. of Patients		Effect		
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Starting Strategy/ For Follow-up After Negative for DVT	Control Risk	Relative	Absolute, % (95% CI)	Quality
Unspecified PTP with negative proximal US and positive highly sensitive DD (done in all or in those with a negative US) followed by a negative proximal US											
3	Management cohort	…	…	…	Some (−1), lower limit of CI <2%	Prevalence 31.6%	2,011/577	Assumed 0	N/A	2.2 (1.3-3.5)	Moderate
Unspecified PTP with negative proximal US and positive moderately sensitive DD followed by venography											
1[8]	Management cohort	…	…	…	Major (−2), only 2 events with wide CI	Prevalence 13.2%	470/58	Assumed 0	N/A	3.5 (0.6-10.5)	Low
Unspecified PTP with negative proximal US followed by venography among those with a high PTP											
1[2]	Management cohort	…	…	…	Some (−1), lower limit of CI <2%	Prevalence 25.3%	474/343	Assumed 0	N/A	2.6 (1.4-4.5)	Moderate

Bibliography: Di Nisio M, Squizzato A, Rutjes AWS, et al. Diagnostic accuracy of D-dimer test for exclusion of venous thromboembolism: a systematic review. *J Thromb Haemost*. 2007;5:296-304. Geersing GJ, Janssen KJ, Oudega R, et al. Excluding venous thromboembolism using point of care D-dimer tests in outpatients: a diagnostic meta-analysis. *BMJ*. 2009;339:b2990. Goodacre S, Sampson FC, Sutton AJ, et al. Variation in the diagnostic performance of D-dimer for suspected deep vein thrombosis. *QJM*. 2005;98(7):513-527. Stein PD, Hull RD, Patel KC, et al. D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review. *Ann Intern Med*. 2004;140:589-602. Fancher TL, White RH, Kravitz RL. Combined use of rapid D-dimer testing and estimation of clinical probability in the diagnosis of deep vein thrombosis: a systematic review. *BMJ*. 2004;329(7470):821. Kraaijenhagen RA, Piovella F, Bernardi E, et al. Simplification of the diagnostic management of suspected deep vein thrombosis. *Arch Intern Med*. 2002;162(8):907-911. Kearon C, Ginsberg JS, Douketis J, et al. A randomized trial of diagnostic strategies after normal proximal vein ultrasonography for suspected deep venous thrombosis: D-dimer testing compared with repeated ultrasonography. *Ann Intern Med*. 2005;142(7):490-496. Bernardi E, Camporese G, Buller HR, et al. Serial 2-point ultrasonography plus D-dimer vs whole-leg color-coded Doppler ultrasonography for diagnosing suspected symptomatic deep vein thrombosis: a randomized controlled trial. *JAMA*. 2008;300:1653-1659. Bernardi E, Prandoni P, Lensing AW, et al. D-dimer testing as an adjunct to ultrasonography in patients with clinically suspected deep vein thrombosis: prospective cohort study. The Multicentre Italian D-dimer Ultrasound Study Investigators Group. *BMJ*. 1998;317(7165):1037-1040. Heijboer H, Buller HR, Lensing AW, et al. A comparison of real-time compression ultrasonography with impedance plethysmography for the diagnosis of deep-vein thrombosis in symptomatic outpatients. *N Engl J Med*. 1993;329:1365-1369. Cogo A, Lensing AW, Koopman MM, et al. Compression ultrasonography for diagnostic management of patients with clinically suspected deep vein thrombosis: prospective cohort study. *BMJ*. 1998;316(7124):17-20. Righini M, Perrier A, De Moerloose P, et al. D-Dimer for venous thromboembolism diagnosis: 20 years later. *J Thromb Haemost*. 2008;6:1059-1071. Bates SM, Kearon C, Crowther M, et al. A diagnostic strategy involving a quantitative latex d-dimer assay reliably excludes deep venous thrombosis. *Ann Intern Med*. 2003;138(10):787-794. Schutgens REG, Ackermark P, Haas FJLM, et al. Combination of a normal D-dimer concentration and a non-high pretest clinical probability score is a safe strategy to exclude deep venous thrombosis. *Circulation*. 2003;107(4):593-559. Perrier A, Desmarais S, Miron MJ, et al. Non-invasive diagnosis of venous thromboembolism in outpatients. *Lancet*. 1999;353(9148):190-195. Consequences of presenting with VTE when specified strategies are used to rule suspected first lower extremity DVT in patients with an unspecified PTP. Settings: outpatients.
See Table S1 legend for expansion of abbreviation.

Table S17—*[Sections 3.2-3.5] Methodology of Diagnostic Studies Evaluating Whole-Leg US in First Suspected Lower Extremity DVT: Meta-analysis of Accuracy Studies*

	Study Eligibility				
Study/Year	Patient Population	Diagnostic Test	Outcome (Criterion Standard)	Exploration of Heterogeneity	Comments
Goodacre et al[41]/2006	Broad population, analyzed subgroup with symptoms of DVT	Tested 31 possible diagnostic algorithms using meta-analysis and modeling; whole-leg US, repeat if distal DVT imaged	All strategies compared against venography for all patients and no diagnostic testing at all	Varied with strategy	The modeling provided reporting for specificity of US for all DVT
Kearon et al[42]/1998	Symptomatic inpatients and outpatients	Whole-leg US	Venography	χ^2 comparison derived from fixed-effects model	Included 11 studies, 9 reporting specificity for distal DVT, which met methodologic criteria

All studies are cross-sectional unless otherwise indicated under Comments. IPD = individual patient data. See Table S1 legend for expansion of other abbreviation.

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Table S18—*[Sections 3.2-3.5] Methodology of Diagnostic Studies Evaluating Whole-Leg US in First Suspected Lower Extremity DVT: Individual Accuracy Studies*

	Study Details					
Study/Year	Patient Population	Diagnostic Test	Outcome (Criterion Standard)	Consecutive Patients	Independent Test Assessment	Comments
Atri et al[43]/1996	Symptomatic for DVT	US of calf veins	Venography	Yes	No	
Baxter et al[44]/1990	Symptomatic for DVT	US of calf veins	Venography	No	Yes	
Baxter et al[45]/1992	Symptomatic for DVT	US of calf veins	Venography	No	Yes	
Belcaro et al[46]/1992	Symptomatic for DVT	US of calf veins	Venography	Yes	No	
Bendick et al[47]/1983	Symptomatic for DVT	US of calf veins	Venography	No	No	
Biondetti et al[48]/1990	Symptomatic for DVT	US of calf veins	Venography	Yes	No	
Bradley et al[49]/1993	Symptomatic for DVT	US of calf veins	Venography	Yes	No	
Burke et al[50]/1994	Symptomatic for DVT	US of calf veins	Venography	Yes	Yes	
Cogo et al[51]/1993	Symptomatic for DVT	US of calf veins	Venography	Yes	No	
De Laveaucoup et al[52]/1989	Symptomatic for DVT	US of calf veins	Venography	No	Yes	
Elias[53]/1987	Symptomatic for DVT	US of calf veins	Venography	Yes	Yes	
Forbes et al[54]/1998	Symptomatic for DVT	US of calf veins	Venography	Yes	No	
Grobety et al[55]/1996	Symptomatic for DVT	US of calf veins	Venography	Yes	No	
Guazzaloca et al[56]/1997	Symptomatic for DVT	US of calf veins	Venography	Yes	Yes	
Habscheid et al[57]/1990	Symptomatic for DVT	US of calf veins	Venography	No	Yes	
Kalodiki et al[58]/1993	Symptomatic for DVT	US of calf veins	Venography	No	No	
Labropoulos et al[59]/1995	Symptomatic for DVT	US of calf veins	Venography	No	Yes	
Lensing et al[60]/1989	Symptomatic for DVT	US of calf veins	Venography	Yes	Yes	
Leven and Hassan[61]/1990	Symptomatic for DVT	US of calf veins	Venography	No	No	
Lindqvist[62]/1977	Symptomatic for DVT	US of calf veins	Venography	No	No	
Mattos et al[63]/1992	Symptomatic for DVT	US of calf veins	Venography	Yes	Yes	
McCandless et al[64]/1985	Symptomatic for DVT	US of calf veins	Venography	Yes	No	
Miller et al[65]/1996	Symptomatic for DVT	US of calf veins	Venography	Yes	Yes	
Mitchell et al[66]/1991	Symptomatic for DVT	US of calf veins	Venography	Yes	Yes	
Monreal et al[67]/1989	Symptomatic for DVT	US of calf veins	Venography	Yes	Yes	
Puls et al[68]/1999	Symptomatic for DVT	US of calf veins	Venography	No	No	
Quintavalla et al[69]/1992	Symptomatic for DVT	US of calf veins	Venography	Yes	No	
Robertson et al[70]/1995	Symptomatic for DVT	US of calf veins	Venography	No	Yes	
Robertson et al[71]/1994	Symptomatic for DVT	US of calf veins	Venography	No	Yes	
Rose et al[72]/1990	Symptomatic for DVT	US of calf veins	Venography	Yes	Yes	
Rosier et al[73]/1992	Symptomatic for DVT	US of calf veins	Venography	No	No	

(Continued)

Table S18—*Continued*

Study/Year	Study Details: Patient Population	Study Details: Diagnostic Test	Study Details: Outcome (Criterion Standard)	Consecutive Patients	Independent Test Assessment	Comments
Savy-Stortz et al[74]/1995	Symptomatic for DVT	US of calf veins	Venography	No	No	
Simons et al[75]/1995	Symptomatic for DVT	US of calf veins	Venography	No	No	
Size et al[76]/1993	Symptomatic for DVT	US of calf veins	Venography	No	Yes	
Yucel et al[77]/1991	Symptomatic for DVT	US of calf veins	Venography	No	No	
Zhou et al[78]/1990	Symptomatic for DVT	US of calf veins	Venography	No	No	
Palareti et al[79]/2010	Suspected DVT, ambulatory patients. No proximal DVT seen on proximal CUS, "DVT likely" PTP or positive highly sensitive DD	Single whole-leg US	Results of serial proximal US and 3-mo follow-up	?	Yes, patients received alternate tests as management driven by proximal US results; whole-leg US results blinded and not used for management. Patients with isolated calf DVT on whole-leg US not anticoagulated but followed with serial proximal US and if negative followed for outcome	Single-arm cohort study

In addition to meta-analysis, all studies are cross-sectional unless otherwise indicated under Comments. See Table S1 legend for expansion of abbreviation.

Table S19—*[Sections 3.2-3.5] Methodology of Diagnostic Studies Evaluating Whole-Leg US in First Suspected Lower Extremity DVT: Meta-analysis of Management Cohort Studies*

	Study Eligibility					
Study/Year	Patient Population	Diagnostic Test	Outcome	Methods (Single-Arm Cohort vs Cohort From RCT)	Exploration of Heterogeneity	Comments
Johnson et al[3]/2010	Clinically suspected DVT	Single whole-leg US	≥ 90 d probability of VTE	Single-arm cohort (6 trials) one arm of RCT (1 trial)	Random effects model	Included IPD met-analysis from 2 included studies to assess PTP groups

Cohorts from single-arm studies or cohorts representing one of the arms of an RCT. See Table S1 and S2 legends for expansion of abbreviations.

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Table S20—*[Sections 3.2-3.5] Methodology of Diagnostic Studies Evaluating Whole-Leg US in First Suspected Lower Extremity DVT: Individual Management Studies With Cohorts*

	Study Details							
Study/Year	Patient Population	Diagnostic Test	Outcome	Methods (Single-Arm Cohort vs Cohort From RCT)	Consecutive Patients	Follow-up	Received Alternative Tests	Comments
Bernardi et al[3]/2008	Clinically suspected, first episode DVT (ambulatory patients)	Single whole-leg US	3-mo probability of VTE	Arm of RCT	Yes (1,053)	Telephone or in person	No	DVT diagnosed by noncompressibility and lack of augmentation in muscular calf veins
Gibson et al[1]/2009	Clinically suspected, first episode DVT, likely Wells score or positive highly sensitive DD (Tina-quant)	Single whole-leg US	3-mo probability of VTE	Arm of RCT	Yes (1,002)	Telephone or in person	No	DVT diagnosed by noncompressibility
Elias et al[4]/2003	Clinically suspected, first episode DVT (ambulatory patients)	Single whole-leg US	3-mo probability of VTE	Single-arm cohort	Yes (623)	Telephone or in person	No	Excluded patients with high pretest by the original Wells criteria DVT diagnosed by noncompressibility and intraluminal thrombus
Schellong et al[5]/2003	Clinically suspected DVT (ambulatory and inpatients)	Single whole-leg US	90-d probability of VTE	Single-arm cohort	Yes (1,646)	Telephone, mail, in person	No	DVT diagnosed by noncompressibility
Sevestre et al[6]/2009	Clinically suspected DVT (ambulatory patients)	Single whole-leg US	3-mo probability of VTE	Single-arm cohort	No	Telephone interview and record review, vital status	No	A priori random selection of population to complete follow-up DVT diagnosed by noncompressibility and lack of augmentation in muscular calf veins
Sevestre et al[7]/2010	Clinically suspected DVT (inpatients)	Single whole-leg US	3-mo probability of VTE	Single-arm cohort	No	Telephone interview and record review, vital status	No	A priori random selection of population to complete follow-up

(Continued)

Table S20—*Continued*

Study/Year	Study Details: Patient Population	Diagnostic Test	Outcome	Methods (Single-Arm Cohort vs Cohort From RCT)	Consecutive Patients	Follow-up	Received Alternative Tests	Comments
								DVT diagnosed by noncompressibility and lack of augmentation in muscular calf veins
Stevens et al[8]/2004	Clinically suspected, first episode DVT (ambulatory and inpatients)	Single whole-leg US	3-mo probability of VTE	Single-arm cohort	Yes (445)	Telephone or in person, record review	No	DVT diagnosed by noncompressibility
Subramaniam et al[9]/2005	Clinically suspected DVT (ambulatory patients)	Single whole-leg US	3-mo probability of VTE	Single-arm cohort	Yes (526)	Telephone or in person, record review	No	DVT diagnosed by noncompressibility

Cohorts from single-arm studies or cohorts representing one of the arms of an RCT. See Table S1 and S2 legends for expansion of abbreviations.

Table S21—*[Sections 3.2-3.5] Methodology of Diagnostic Studies Evaluating Whole-Leg US in First Suspected Lower Extremity DVT: Individual RCTs With Direct Comparison Of Diagnostic Strategies*

Study/Year	Study Details				Concealment of Randomization	Blinding	Follow-up	Intention to Treat
	Patient Population	Test 1/ Strategy 1	Test 2/ Strategy 2	Outcome				
Bernardi et al[2]/2008	Clinically suspected DVT	Single whole-leg US	Serial proximal US; single proximal US if DD	VTE during 3-mo follow-up	Not concealed	Not blinded	Telephone or in person	N/A (no crossover occurred)
Gibson et al[1]/2009	Clinically suspected DVT; likely Wells score and/or positive highly sensitive DD (Tina-quant)	Single whole-leg US	Serial proximal US	VTE during 3-mo follow-up	Not concealed	Not blinded	Telephone or in person	N/A (no crossover occurred)

See Table S1 and S2 legends for expansion of abbreviations.

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Table S22—*[3.2-3.5] Description and Results of Diagnostic Studies Evaluating Whole-Leg US in First Suspected Lower Extremity DVT: Cross-sectional Accuracy and Cohort Management Studies*

Question from Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Accuracy vs Management Cohort (Indicate if Cohort Is From an RCT)	Patient Population	Outcome Measure[a]	Result, % (95% CI)	Comments	Reference
What are the consequences of using whole-leg CUS to diagnose distal DVT?	All patients	Primary	Accuracy	Symptomatic	Specificity (vs venography)	96 (86.3-99.5)		Atri et al[43]/1996
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	100 (86.8-100)		Baxter et al[44]/1990
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	100 (83.2-100)		Baxter et al[45]/1992
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	100 (79.4-100)		Belcaro et al[46]/1992
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	96.6 (90.4-99.3)		Bendick et al[47]/1983
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	100 (96.9-100)		Biondetti et al[48]/1990
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	100 (92.9-100)		Bradley et al[49]/1993
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	100 (95.4-100)		Burke et al[50]/1994
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	100 (63.1-100)		Cogo et al[51]/1993
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	97.9 (92.5-99.7)		De Laveaucoup et al[52]/1989
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	96.4 (94.4-97.9)		Elias et al[53]/1987
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	79.3 (60.3-92.0)		Forbes et al[54]/1998
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	95.5 (84.5-99.4)		Grobety et al[55]/1996
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	100 (96.0-100)		Habscheid et al[57]/1990
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	94.3 (84.3-98.8)		Kalodiki et al[58]/1993
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	98.1 (90.1-100)		Labropoulos et al[59]/1995

(Continued)

Table S22—*Continued*

Question from Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Accuracy vs Management Cohort (Indicate if Cohort Is From an RCT)	Patient Population	Outcome Measure[a]	Result, % (95% CI)	Comments	Reference
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	99.3 (96.2-100)		Lensing et al[60]/1989
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	100 (59.0-100)		Leven et al[61]/1990
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	100 (85.2-100)		Lindqvist et al[62]/1977
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	75.0 (58.8-87.3)		Mattos et al[63]/1992
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	100 (90.3-100)		McCandless et al[64]/1985
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	99.2 (95.9-100)		Miller et al[65]/1996
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	89.3 (71.8-97.7)		Mitchell et al[66]/1991
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	100 (81.5-100)		Monreal et al[67]/1989
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	72.7 (39.0-94.0)		Puls et al[68]/1999
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	42.1 (20.3-66.5)		Robertson et al[70]/1995
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	60.6 (42.1-77.1)		Robertson et al[71]/1994
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	73.3 (54.1-87.7)		Rose et al[72]/1990
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	89.5 (80.3-95.3)		Rosier et al[73]/1992
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	76.2 (52.8-91.8)		Savy-Stortz et al[74]/1995
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	100 (59.0-100)		Simons et al[75]1995
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	84.6 (54.6-98.1)		Size et al[76]/1993
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	88.2 (63.6-98.5)		Yucel et al[77]/1991
		Primary	Accuracy	Symptomatic	Specificity (vs venography)	100 (47.8-100)		Zhou et al[78]/1990

(Continued)

Table S22—*Continued*

Question from Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Accuracy vs Management Cohort (Indicate if Cohort Is From an RCT)	Patient Population	Outcome Measure[a]	Result, % (95% CI)	Comments	Reference
	Patients without proximal DVT by proximal CUS, "DVT-likely" pretest, or positive highly sensitive DD	Primary	Accuracy	Symptomatic	Result of serial proximal US and ≥ 90-d follow-up	All: 1.2 (0.4-2.7) No calf DVT: 0.8 (0-2) Calf DVT: 7.8 (3-17)		Palareti et al[79]/2010
	If low pretest	N/A	N/A	N/A	N/A	N/A		
	If moderate pretest	N/A	N/A	N/A	N/A	N/A		
	If high pretest	N/A	N/A	N/A	N/A	N/A		
	If positive highly sensitive DD	N/A	N/A	N/A	N/A	N/A		
	If positive moderately sensitive DD	N/A	N/A	N/A	N/A	N/A		
	If negative highly sensitive DD	N/A	N/A	N/A	N/A	N/A		
	If negative moderately sensitive DD	N/A	N/A	N/A	N/A	N/A		
What are the consequences of using a single whole-leg CUS to exclude DVT?	Negative single whole-leg US on day of presentation – all patients	Meta-analysis	Management cohort (6 trials) arm of RCT (1 trial)	Clinically suspected DVT (Analyzed studies included inpatients, ambulatory patients, or both. Some restricted to first-episode DVT)	≥ 90-d probability of VTE	0.57 (0.25-0.89) pooled event rate		Johnson et al[3]/2010
		Primary	Management	Symptomatic first episode	≥ 90-d probability of VTE	0.5 (0.1-1.8)	Excluded patients with high pretest by the original Wells criteria DVT diagnosed by noncompressibility plus intraluminal thrombus	Elias et al[4]/2003

(Continued)

Table S22—*Continued*

Question from Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Accuracy vs Management Cohort (Indicate if Cohort Is From an RCT)	Patient Population	Outcome Measure[a]	Result, % (95% CI)	Comments	Reference
		Primary	Management	Symptomatic	≥ 90-d probability of VTE	0.3 (0.1-0.8)	DVT diagnosed by noncompressibility	Schellong et al[5]/2003
		Primary	Management	Symptomatic outpatients	≥ 90-d probability of VTE	0.4 (0.1-0.9)	DVT diagnosed by noncompressibility plus lack of augmentation in muscular calf veins	Sevestre et al[6]/2009
		Primary	Management	Symptomatic inpatients	≥ 90-d probability of VTE	1.9 (0.9-3.5)	DVT diagnosed by noncompressibility plus lack of augmentation in muscular calf veins	Sevestre et al[7]/2010
		Primary	Management	Symptomatic inpatients	≥ 90-d probability of VTE	0.80 (0.16-2.33)	DVT diagnosed by noncompressibility	Stevens et al[8]/2004
		Primary	Management	Symptomatic inpatients	≥ 90-d probability of VTE	0.24 (0.01-1.3)	DVT diagnosed by noncompressibility	Subramaniam et al[9]/2005
	Negative single whole-leg US on day of presentation – if low pretest	Meta-analysis	IPD meta-analysis from 2 management cohort studies	Clinically suspected DVT. (Analyzed studies included inpatients, ambulatory patients, or both. Some restricted to first-episode DVT)	3-mo probability of VTE	0.29 pooled event rate		Johnson et al[3]/2010
	Negative single whole-leg US on day of presentation – if moderate pretest	Meta-analysis	IPD meta-analysis from 2 management cohort studies	Clinically suspected DVT. (Analyzed studies included inpatients, ambulatory patients, or both. Some restricted to first-episode DVT)	3-mo probability of VTE	0.82 pooled event rate		Johnson et al[3]/2010

(Continued)

Table S22—*Continued*

Question from Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Accuracy vs Management Cohort (Indicate if Cohort Is From an RCT)	Patient Population	Outcome Measure[a]	Result, % (95% CI)	Comments	Reference
	Negative single whole-leg US on day of presentation – if high pretest	Meta-analysis	IPD meta-analysis from 2 management cohort studies	Clinically suspected DVT. (Analyzed studies included inpatients, ambulatory patients, or both. Some restricted to first-episode DVT)	3-mo probability of VTE	2.49 pooled event rate		Johnson et al[3]/2010

See Table S1-S3, S7, and S19 legends for expansion of abbreviations.

[a]eg, Post-TP during 3 mo follow-up, sensitivity or specificity, and so forth.

Table S23—*[Sections 3.2-3.5] Description and Results of Diagnostic Studies Evaluating Whole-Leg US in First Suspected Lower Extremity DVT: RCTs*

Question from Structured Clinical Question Table	Study/Year	Patients	Intervention 1	Intervention 2	Outcomes	Results	Comments
Comparison of 2-point US based strategy vs whole-leg US	Bernardi et al et al[2]/2008	Symptomatic outpatients	2-point proximal US followed by moderately sensitive DD (and repeat US if positive DD)	Whole-leg US, no further tests if negative	VTE in 3-mo follow-up	0.9% vs 1.2%; absolute difference, − 0.3% (95% CI, − 1.4 to 0.8)	DVT diagnosed by noncompressibility and lack of augmentation (lack of increase in venous flow by Doppler with manual squeeze) in muscular calf veins
	Gibson et al et al[1]/2009	Symptomatic patients with likely Wells score and/or positive highly sensitive DD (Tina-quant)	Serial 2-point proximal US	Whole-leg US, no further tests if negative	VTE in 3-mo follow-up	2.0% vs 1.2%; absolute difference, − 0.8% (95% CI, − 1.8 to 3.4)	DVT diagnosed by noncompressibility

See Table S1 and S2 legends for expansion of abbreviations.

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Table S24—*[Sections 3.1-3.5] Outcome Events for Various Diagnostic Strategies According to Decision Analytic Modeling*

Intervention (All Patients/1,000 Cohort)	Average No. of Outcome Events Per 1,000 Patients (95% Credible Interval)							
	No. Treated	Fatal PE	Nonfatal PE	Nonfatal Intracranial Bleeding Event	Fatal Bleeding Event	Nonfatal Nonintracranial Bleeding Event	No Bleeding	Venographic Mortality
No testing or treatment	0	3.77 (1.27-8.17)	19.44 (11.90-28.39)	0	0	0	1,000	0
Venography for all patients	209	0.65 (0.41-0.96)	3.12 (2.42-4.15)	0.25 (0.13-0.42)	0.71 (0.48-0.99)	4.38 (3.54-5.38)	994.65 (993.53-995.60)	0.03 (0.01-0.14)
Proximal US; repeat if negative	245	0.76 (0.49-1.09)	3.68 (2.91-4.70)	0.30 (0.15-0.49)	0.84 (0.58-1.15)	5.14 (4.26-6.24)	993.72 (992.49-994.76)	0
Whole-leg US; repeat if distal DVT found	240	0.83 (0.51-1.31)	4.06 (3.07-5.72)	0.29 (0.15-0.48)	0.82 (0.57-1.12)	5.03 (4.19-5.99)	993.86 (992.71-994.82)	0
Whole-leg US; treat if distal DVT found	265	0.82 (0.51-1.28)	401 (3.04-5.59)	0.32 (0.16-0.54)	0.91 (0.62-1.27)	5.50 (4.48-6.94)	993.18 (991.57-994.43)	0
Proximal US. No repeat.	229	1.00 (0.56-1.85)	4.94 (3.26-8.43)	0.28 (0.15-0.46)	0.78 (0.54-1.06)	4.81 (4.01-5.61)	994.13 (993.18-995.00)	0
Wells score and proximal US. If PTP low, discharge if US negative, venogram if positive. If PTP moderate, repeat US if negative, treat if positive. If high PTP, venogram if US negative, treat if US positive.	228	0.71 (0.45-1.06)	3.43 (2.64-4.68)	0.28 (0.14-0.46)	0.78 (0.54-1.08)	4.79 (3.92-5.77)	994.15 (993.00-995.12)	0.004 (0.00-0.02)
SimpliRED DD and proximal US. If US positive then treat. If both are negative then discharge. If DD positive and US negative repeat US.	239	0.85 (0.51-1.35)	4.14 (3.08-6.05)	0.29 (0.15-0.48)	0.82 (0.56-1.12)	5.02 (4.18-5.98)	993.88 (992.76-994.83)	0
Wells score and proximal US. If PTP high or moderate, perform proximal US. If positive treat, venogram if negative. If TP low, perform US. If positive treat, discharge if negative.	249	0.68 (0.43-1.00)	3.26 (2.50-4.47)	0.30 (0.16-0.49)	0.85 (0.59-1.17)	5.22 (4.36-6.26)	993.62 (992.41-994.63)	0.01 (0.00-0.06)
Wells score and full-leg US. If PTP high or moderate, perform full-leg US, treat if positive, venogram if negative. If PTP low, full-leg US, treat if positive, discharge if negative.	251	0.65 (0.42-0.94)	3.11 (2.44-4.08)	0.30 (0.15-0.50)	0.86 (0.60-1.18)	5.27 (4.37-6.36)	993.57 (992.34-994.62)	0.01 (0.00-0.06)

(Continued)

Table S24—*Continued*

Intervention (All Patients/1,000 Cohort)	Average No. of Outcome Events Per 1,000 Patients (95% Credible Interval)							
	No. Treated	Fatal PE	Nonfatal PE	Nonfatal Intracranial Bleeding Event	Fatal Bleeding Event	Nonfatal Nonintracranial Bleeding Event	No Bleeding	Venographic Mortality
Quantitative latex DD; if positive, perform proximal US and repeat. If DD negative, perform Wells score. If high, perform proximal US and repeat if negative. If PTP moderate or low, discharge.	214	0.85 (0.53-1.26)	4.13 (3.17-5.45)	0.26 (0.13-0.43)	0.73 (0.51-1.01)	4.50 (3.66-5.50)	994.50 (993.37-995.45)	0
Quantitative latex DD; if positive, perform above-knee US and repeat. If DD negative perform Wells score. If PTP high perform proximal US. If PTP low or moderate, discharge.	213	0.86 (0.53-1.32)	4.22 (3.20-5.70)	0.26 (0.13-0.43)	0.73 (0.51-1.01)	4.49 (3.66-5.46)	994.53 (993.40-995.47	0
Wells score. If PTP high, proximal US, treat if positive, SimpliRED DD if negative. If DD positive, venogram; if negative, repeat US. If PTP moderate, US; treat if positive, SimpliRED DD if negative. If DD positive, repeat US. If DD negative, discharge. If PTP low, SimpliRED. If DD positive, proximal US. Discharge if DD negative.	225	0.80 (0.49-1.27)	3.90 (2.88-5.65)	0.27 (0.14-0.44)	0.77 (0.53-1.05)	4.72 (3.90-5.65)	994.24 (993.17-995.20)	0.0017 (0.00-0.01)
Wells score and SimpliRED DD. If PTP high or moderate, or DD positive, perform full-leg US. If PTP low and DD negative, then discharge.	220	0.88 (0.53-1.40)	4.29 (3.18-6.08)	0.27 (0.14-0.44)	0.75 (0.52-1.04)	4.61 (3.80-5.55)	994.36 (993.33-995.29)	0
ELISA DD. If negative, discharge. If DD positive, perform proximal US. Treat if US positive. If US negative, perform Wells score. If PTP high, perform venogram. If PTP moderate or low, discharge.	214	0.90 (0.53-1.57)	4.44 (3.07-7.18)	0.26 (0.13-0.42)	0.73 (0.51-0.99)	4.47 (3.71-5.31)	994.53 (993.57-995.40)	0.002 (0.00-0.01)

(Continued)

Table S24—*Continued*

Intervention (All Patients/1,000 Cohort)	Average No. of Outcome Events Per 1,000 Patients (95% Credible Interval)							
	No. Treated	Fatal PE	Nonfatal PE	Nonfatal Intracranial Bleeding Event	Fatal Bleeding Event	Nonfatal Nonintracranial Bleeding Event	No Bleeding	Venographic Mortality
Wells score. If PTP high or moderate, perform proximal US. If positive treat, if negative perform SimpliRED DD. Repeat US if DD positive, discharge if DD negative. If PTP low, perform US. Discharge if negative, treat if positive.	240	0.82 (0.51-1.30)	4.04 (3.04-5.67)	0.29 (0.15-0.48)	0.82 (0.57-1.13)	5.08 (4.21-5.99)	993.85 (992.71-994.82)	0
Wells score. If PTP high or moderate, perform proximal US. If positive treat, if negative perform SimpliRED DD. Repeat US if DD positive and discharge if DD negative. If PTP low perform SimpliRED DD, discharge if negative, perform proximal US if positive.	218	0.91 (0.54-1.49)	4.65 (3.20-6.63)	0.26 (0.14-0.43)	0.73 (0.52-1.02)	4.57 (3.79-5.47)	994.42 (993.39-995.32)	0
Wells score. If PTP high, perform proximal US. If positive treat, if negative perform SimpliRED DD. Repeat US if DD positive, discharge if negative. If PTP low or moderate, perform SimpliRED DD. Discharge if negative, perform proximal US if positive.	195	1.06 (0.60-1.87)	5.26 (3.67-8.08)	0.24 (0.12-0.38)	0.67 (0.46-0.91)	4.09 (3.34-4.88)	995.12 (994.10-995.84)	0
Wells score. If PTP high or moderate, perform proximal US. If positive treat, if negative repeat US. If PTP low, perform proximal US, treat if positive, discharge if negative.	242	0.80 (0.50-1.18)	3.90 (2.99-5.27)	0.29 (0.15-0.48)	0.83 (0.57-1.14)	5.08 (4.23-6.09)	993.80 (992.62-994.81)	0

(Continued)

Table S24—*Continued*

Intervention (All Patients/1,000 Cohort)	Average No. of Outcome Events Per 1,000 Patients (95% Credible Interval)							
	No. Treated	Fatal PE	Nonfatal PE	Nonfatal Intracranial Bleeding Event	Fatal Bleeding Event	Nonfatal Nonintracranial Bleeding Event	No Bleeding	Venographic Mortality
Wells score. If PTP high or moderate, perform proximal US. If positive treat, if negative repeat US. If PTP low, perform proximal US; treat if positive, discharge if negative.	234	0.92 (0.54-1.57)	4.50 (3.17-7.02)	0.28 (0.15-0.47)	0.80 (0.56-1.09)	4.92 (4.09-5.79)	993.99 (992.99-994.89)	0
Wells score. If PTP high or moderate, perform proximal US. Treat if positive; if negative discharge. If PTP low, discharge.	194	1.19 (0.63-2.21)	5.94 (3.89-9.49)	0.24 (0.12-0.38)	0.66 (0.46-0.90)	4.08 (3.34-4.84)	995.02 (994-12-995.78)	0
Perform SimpliRED DD. Discharge if negative, perform proximal US if positive. Treat if US positive, repeat US if initial US is negative	176	1.30 (0.69-2.25)	6.49 (4.58-9.13)	0.21 (0.11-0.35)	0.60 (0.41-0.83)	3.70 (2.99-4.84)	995.48 (994.55-996.27)	0

The model applies each strategy to a population with 19% prevalence of proximal DVT and 5% prevalence of distal DVT, using sensitivities and specificities derived from meta-analyses, to determine what proportion of patients with proximal, distal, and no DVT are treated with anticoagulant therapy. Untreated distal DVT are assumed to have a 21.4% probability of subsequent propagation to form proximal DVT, but do not directly cause PE. Patients with treated proximal DVT have a 0.3% probability of fatal PE and a 1.4% probability of nonfatal PE over the following 3 mo. The respective probabilities for untreated proximal DVT are 1.9% and 9.3%. Bleeding outcomes are assumed to be entirely due to anticoagulant therapy. Patients receiving treatment have a 0.3% probability of fatal bleeding, a 0.1% probability of nonfatal intracranial bleeding, and a 2.1% probability of major nonfatal non-intracranial bleeding. All parameters are modeled with a probability distribution to generate a credible range for the outcomes. See Table S1, S5, and S19 legends for expansion of abbreviations.

Table S25—*[Sections 3.1-3.5] Additional Outcome Events for Various Diagnostic Strategies Compared With Serial CUSs According to Decision Analytic Modeling*

Intervention (All Patients/1,000 Cohort)	Additional Number of Outcome Events Per 1,000 Patients Compared With Serial CUS					
	Fatal PE	Nonfatal PE	Nonfatal Intracranial Bleeding Event	Fatal Bleeding Event	Nonfatal Nonintracranial Bleeding Event	No Bleeding
No testing or treatment	3.02	15.76	−0.30	−0.84	−5.14	6.27
Venography for all patients	−0.11	−0.55	−0.04	−0.12	−0.75	−0.92
Proximal US; repeat if negative	0	0	0	0	0	0
Whole-leg US; repeat if distal DVT found	0.07	0.39	−0.01	−0.02	−0.10	0.12
Whole-leg US; treat if distal DVT found	0.06	0.34	0.03	0.07	0.45	−0.55
Proximal US. No repeat.	0.24	1.26	−0.02	−0.05	−0.33	0.40
Wells score and proximal US. If PTP low, discharge if US negative; venogram if positive. If PTP moderate, repeat US if negative, treat if positive. If high PTP, venogram if US negative, treat if US positive.	−0.05	−0.24	−0.02	−0.06	−0.34	0.42
SimpliRED DD and proximal US. If US positive then treat. If both are negative then discharge. If DD positive and US negative, repeat US.	0.09	0.46	−0.01	−0.02	−0.12	0.15
Wells score and proximal US. If PTP high or moderate, perform proximal US. If positive treat, venogram if negative. If PTP low, perform proximal US. If positive treat, discharge if negative.	−0.08	−0.41	0.01	0.01	0.09	−0.11
Wells score and full leg US. If PTP high or moderate perform proximal US. If positive treat, venogram if negative. If PTP, low, full-leg US, treat if positive, discharge if negative.	−0.11	−0.57	0.01	0.02	0.13	−0.16
Quantitative latex DD. If positive perform proximal US and repeat. If DD negative, perform Wells score. If high, perform proximal US and repeat if negative. If PTP moderate or low, discharge.	0.09	0.46	−0.04	−0.10	−0.63	0.78
Quantitative latex DD: if positive perform above-knee US and repeat. If DD negative, perform Wells score. If high perform proximal US. If PTP low or moderate, then discharge.	0.10	0.55	−0.04	−0.11	−0.65	0.80
Wells score. If PTP high, proximal US; treat if positive, SimpliRED DD if negative. If DD positive, venogram, if negative, repeat US. If PTP moderate, US; treat if positive, SimpliRED if negative. If DD positive, repeat US; if DD negative, discharge. If PTP low, SimpliRED DD. If DD positive, proximal US.	0.04	0.21	−0.02	−0.07	−0.42	0.51

(Continued)

Table S25—*Continued*

Intervention (All Patients/1,000 Cohort)	Additional Number of Outcome Events Per 1,000 Patients Compared With Serial CUS					
	Fatal PE	Nonfatal PE	Nonfatal Intracranial Bleeding Event	Fatal Bleeding Event	Nonfatal Nonintracranial Bleeding Event	No Bleeding
Wells score and SimpliRED DD. If PTP high or moderate, or DD positive, perform full-leg US. If PTP low and DD negative, then discharge.	0.12	0.61	−0.03	−0.08	−0.52	0.63
ELISA DD. If negative, discharge. If DD positive, perform proximal US. Treat if US positive. If US negative, perform Wells score. If PTP high, perform venogram. If PTP moderate or low, discharge.	0.15	0.77	−0.04	−0.11	−0.65	0.79
Wells score. If PTP high or moderate, perform proximal US. If positive treat, if negative perform SimpliRED DD. Repeat US if DD positive, discharge if negative. If PTP low, perform US. Discharge if negative, treat if positive.	0.07	0.37	−0.005	−0.02	−0.10	0.12
Wells score. If PTP high or moderate, perform proximal US. If positive treat, if negative perform SimpliRED DD. Repeat US if DD positive, and discharge if DD negative. If PTP low, perform SimpliRED DD, discharge if negative and perform US if positive.	0.15	0.77	−0.03	−0.09	−0.56	0.69
Wells score. If PTP high, perform proximal US. If positive treat, if negative, perform SimpliRED DD. Repeat US if DD positive, discharge if DD negative. If PTP moderate or low, perform SimpliRED DD. Discharge if negative, perform proximal US if positive.	0.30	1.59	−0.06	−0.17	−1.05	1.28
Wells score. If PTP high or moderate, perform proximal US. If positive treat, if negative repeat US. If PTP low, perform proximal US, treat if positive, discharge if negative.	0.04	0.23	−0.003	−0.01	−0.06	0.07
Wells score. If PTP high, perform proximal US. If positive treat, if negative repeat US. If PTP moderate or low perform proximal US, if positive treat, if negative then discharge.	0.16	0.83	−0.012	3.67	−0.21	0.26
Wells score. If PTP high or moderate, perform proximal US. Treat if positive, if negative discharge. If PTP low, discharge.	0.43	2.27	−0.06	−0.17	−1.05	1.28
Perform SimpliRED DD. Discharge if negative, perform proximal US if positive. Treat if US positive, repeat US if initial US is negative	0.54	2.81	−0.08	−0.23	−1.43	1.74

The model applies each strategy to a population with 19% prevalence of proximal DVT and 5% prevalence of distal DVT, using sensitivities and specificities derived from meta-analyses, to determine what proportion of patients with proximal, distal, and no DVT are treated with anticoagulant therapy. Untreated distal DVT are assumed to have a 21.4% probability of subsequent propagation to form proximal DVT, but do not directly cause PE. Patients with treated proximal DVT have a 0.3% probability of fatal PE and a 1.4% probability of nonfatal PE over the following 3 mo. The respective probabilities for untreated proximal DVT are 1.9% and 9.3%. Bleeding outcomes are assumed to be entirely due to anticoagulant therapy. Patients receiving treatment have a 0.3% probability of fatal bleeding, a 0.1% probability of nonfatal intracranial bleeding, and a 2.1% probability of major nonfatal non-intracranial bleeding. All parameters are modeled with a probability distribution to generate a credible range for the outcomes. See Table S1, S5, S7, and S19 legends for expansion of abbreviations.

Table S26—*[Sections 3.1-3.5] Additional Testing Maneuvers Compared With a Strategy Involving Serial CUSs According to Decision Analytic Modeling*

Intervention (All Patients/1,000 Cohort)	Number of Testing Maneuvers Per 1,000 Patients					Additional Tests Per 1,000 Patients		
	Wells Score	Proximal CUS	Whole-Leg US	DD Tests	Venogram	Proximal CUS	Wells Score	DD Tests
No testing or treatment	0	0	0	0	0	−1,771	0	0
Venography for all patients	0	0	0	0	1,000	−1,771	0	0
Proximal US. Repeat if negative.	0	1,771	0	0	0	0	0	0
Whole-leg US. Repeat if distal found.	0	39	1,000	0	0	−1,732	0	0
Whole-leg US. Treat if distal DVT found.	0	0	1,000	0	0	−1,771	0	0
Proximal US. No repeat.	0	1,000	0	0	0	−771	0	0
Wells score and proximal US. If PTP low, discharge if US negative; venogram if positive. If PTP moderate, repeat US if negative. If high PTP, venogram if negative, treat if positive.	1,000	1,347	0	0	138	−424	1,000	0
SimpliRED DD and proximal US. If US positive, then treat. If both are negative, then discharge. If DD positive and US negative, repeat US.	0	1,244	0	1,000	0	−527	0	1,000
Wells score and proximal US. If PTP high or moderate, perform proximal US. If positive treat, venogram if negative. If PTP low, perform proximal US, if positive treat, if negative discharge.	1,000	1,081	0	0	422	−690	1,000	0
Wells score and full-leg US. If PTP high or moderate, perform full-leg US; treat if positive, venogram if negative. If PTP low, full-leg US; treat if positive, discharge if negative.	1,000	91	1,000	0	390	−680	1,000	0
Quantitative latex DD. If positive, perform proximal US and repeat. If DD negative, perform Wells score. If high, perform proximal US and repeat if negative. If PTP moderate or low, then discharge.	458	975	0	1,000	0	−796	458	1,000
Quantitative latex DD. If positive perform above-knee US and repeat. If DD negative, perform Wells score. If PTP high, perform proximal US. If PTP low or moderate, then discharge.	458	938	0	1,000	0	−833	458	1,000
Wells score. If PTP high, proximal US; treat if positive, SimpliRED DD if negative. If DD positive, venogram if negative, repeat US; if DD negative, discharge. If PTP low, SimpliRED. If PTP moderate, US treat if positive, SimpliRED DD if negative. If DD positive, repeat US; if negative, then discharge. If PTP low, SimpliRED DD.	1,000	890	0	806	55	−881	1,000	806
Wells score and SimpliRED DD. If PTP high or moderate, or DD positive, perform full-leg US. If PTP low and DD negative, then discharge.	1,000	36	709	1,000	0	−1,026	1,000	1,000
ELISA DD. If negative, discharge. If positive, perform proximal US. Treat if US positive; if US negative, perform Wells score. If PTP high, perform venogram. If PTP low or moderate, then discharge.	429	654	0	1,000	74	−1,117	429	1,000

(Continued)

Table S26—*Continued*

Intervention (All Patients/1,000 Cohort)	Number of Testing Maneuvers Per 1,000 Patients					Additional Tests Per 1,000 Patients		
	Wells Score	Proximal CUS	Whole-Leg US	DD Tests	Venogram	Proximal CUS	Wells Score	DD Tests
Wells score. If PTP high or moderate, perform proximal US. If positive treat, if negative perform SimpliRED DD. Repeat US if DD negative, discharge if negative. If PTP low, perform US; discharge if negative, treat if positive.	1,000	1,258	0	422	0	−513	1,000	422
Wells score. If PTP high or moderate, perform proximal US. If positive treat, if negative perform SimpliRED DD. Repeat US if DD negative, discharge if DD negative. If PTP low, perform SimpliRED DD, discharge if negative, perform proximal US if positive.	1,000	876	0	806	0	−895	1,000	806
Wells score. If PTP high, perform proximal US. If positive treat, if negative perform SimpliRED DD. Repeat US if DD positive, discharge if negative, perform proximal US if negative.	1,000	537	0	871	0	−1,234	1,000	871
Wells score. If PTP high or moderate, perform proximal US. If positive treat, if negative, repeat US. If PTP low, perform proximal US; treat if positive, discharge if negative.	1,000	1,422	0	0	0	−349	1,000	0
Wells score. If PTP high, perform proximal US. If positive treat, if negative repeat US. If PTP low, perform proximal US; treat if positive, discharge if negative	1,000	1,103	0	0	0	−668	1,000	0
Wells score. If PTP high or moderate, perform proximal US. Treat if positive, if negative, discharge. If PTP low discharge.	1,000	616	0	0	0	−1,155	1,000	0
Perform SimpliRED DD. Discharge if negative, perform proximal US if positive. Treat if US positive, repeat US if initial US is negative	0	656	0	1,000	0	−1,115	0	1,000

See Table S1 and S7 legends for expansion of abbreviations.

Table S27—*[Sections 3.2-3.6] Methodology of Diagnostic Studies Evaluating CT Scan Venography in Patients With Suspected First Lower Extremity DVT: Meta-analysis of Accuracy Studies of CT Scan Venography*

Study Eligibility					
Patient Population	Diagnostic Test	Outcome (Criterion Standard)	Exploration of Heterogeneity	Comments	Source
Suspected DVT or suspected PE	CT scan venography	US or contrast venography	χ^2 test for heterogeneity. No formal analysis for sources of heterogeneity	Most of the primary studies were of patients with suspected PE and used US as a reference standard. Summary estimates were calculated despite significant unexplained heterogeneity	Thomas et al et al[80]/2008

See Table S1 and S5 legends for expansion of abbreviations.

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Table S28—*[Sections 3.2-3.6] Methodology of Diagnostic Studies Evaluating CT Scan Venography in Patients With Suspected First Lower Extremity DVT: Individual Accuracy Studies of CT Scan Venography*

	Study Details					
Study/Year	Patient Population	Diagnostic Test	Outcome (Criterion Standard)	Consecutive Patients	Independent Test Assessment	Comments
Byun et al[81]/2008	Asymptomatic, Post-arthroplasty	CT scan venography	US	No	Yes	
Rhee et al[82]/2007	Suspected PE	CT scan venography	US	No	Yes	
Goodman et al[83]/2007	Suspected PE	CT scan venography	US	Yes	Yes	
Garcia-Bolado et al[84]/2007	Suspected PE	CT scan venography	US	Yes	Yes	
Kim et al[85]/2004	Suspected PE and DVT	CT scan venography	US	Unclear	Yes	Included in Thomas et al[80]
Lim et al[86]/2004	Suspected PE	CT scan venography	US	Yes	Yes	Included in Thomas et al[80]
Lim et al[86]/2004	Suspected PE	CT scan venography	US	Yes	Yes	Included in Thomas et al[80]
Begeman et al[88]/2003	Suspected PE	CT scan venography	US	No	Yes	
Loud et al[89]/2001	Suspected PE	CT scan venography	US	Yes	Yes	Included in Thomas et al[80]
Peterson et al[90]/2001	Suspected PE	CT scan venography	US	No	Yes	Included in Thomas et al[80]
Yoshida et al[91]/2001	Suspected DVT	CT scan venography	US	Yes	Yes	Included in Thomas et al[80]
Ghaye et al[92]/2000	Suspected PE	CT scan venography	US	No	Yes	Included in Thomas et al[80]
Cham et al[93]/2000	Suspected PE	CT scan venography	US	Yes	Unclear	Included in Thomas et al[80]
Garg et al[94]/2000	Suspected PE	CT scan venography	US	Yes	Yes	Included in Thomas et al[80]
Coche et al[95]/2000	Suspected PE	CT scan venography	US	Yes	Yes	Included in Thomas et al[80]
Duwe et al[96]/2000	Suspected PE	CT scan venography	US	Unclear	Unclear	Included in Thomas et al[80]
Shah et al[97]/1999	Suspected PE and DVT	CT scan venography	US	Unclear	Unclear	Included in Thomas et al[80]
Baldt et al[98]/1996	Suspected DVT	CT scan venography	Contrast venography	Yes	Yes	Included in Thomas et al[80]

See Table S1 and S5 legends for expansion of abbreviations.

Table S29—*[Sections 3.2-3.6] Description and Results of Diagnostic Studies Evaluating CT Scan Venography in Patients With Suspected First Lower Extremity DVT: Meta-Analyses and Cross-sectional Accuracy Studies of CT Scan Venography*

Question from Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Accuracy vs Management Cohort	Patient Population	Outcome Measure	Result, % (95% CI)	Comments	Reference
What are the consequences of using CT scan venography to diagnose DVT?	Suspected DVT	Meta-analysis	Accuracy	Mixed, but mostly suspected PE	Specificity	Summary estimate: 95.2 (93.6-96.5) Range, 93-100		Thomas et al[80]/2008
	Suspected DVT	Primary study	Accuracy	Asymptomatic	Specificity	96.9 (84.3-99.4)		Byun et al[81]/2008
	Suspected DVT			Suspected PE	Specificity	95.0 (90.8-97.5)		Garcia-Bolado et al[84]/2007
	Suspected DVT	Primary study	Accuracy	Suspected PE	Specificity	97.2 (95.6-98.3)	Results were reported as agreement between CT scan and US, rather than US as reference	Goodman et al[83]/2007
	Suspected DVT	Primary study	Accuracy	Suspected PE	Specificity	92.6 (85.6-96.4)	Results were reported as agreement between CT scan and US, rather than US as reference	Rhee et al[82]/2007
	Suspected DVT	Primary study	Accuracy	Suspected PE	Specificity	96.7 (83.3-99.4)		Begeman et al[88]/2003
What are the consequences of using CT scan venography to exclude DVT?	Suspected DVT	Meta-analysis	Accuracy	Mixed, but mostly suspected PE	Sensitivity	Summary estimate: 95.9 (93.0-97.8) Range: 71-100		Thomas et al[80]/2008
	Suspected DVT	Primary study	Accuracy	Asymptomatic	Sensitivity	90.0 (74.4-96.5)		Byun et al[81]/2008
	Suspected DVT	Primary study	Accuracy	Suspected PE	Sensitivity	58.8 (40.8-74.9)		Garcia-Bolado et al[84]/2007
	Suspected DVT	Primary study	Accuracy	Suspected PE	Sensitivity	84.4 (75.8-90.3)	Results were reported as agreement between CT scan and US, rather than US as reference	Goodman et al[83]/2007
	Suspected DVT	Primary study	Accuracy	Suspected PE	Sensitivity	72.3 (43.4-90.3)	Results were reported as agreement between CT scan and US, rather than US as reference	Rhee et al[82]/2007
	Suspected DVT	Primary study	Accuracy	Suspected PE	Sensitivity	100 (74.1-100)		Begeman et al[88]/2003

See Table S1 and S5 legends for expansion of abbreviations.

Table S30—*[Sections 3.2-3.6] Evidence Profile: Should CT Scan Venography Be Used for the Diagnosis of First Suspected DVT?*

Outcome	No. of Studies	Study Design	Limitations[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Final Quality	Effect/1,000[e]
True positive (patients with DVT)	Meta-analysis of 13, plus 5 additional primary studies[125-129,133]	Accuracy cohort	Serious	Moderate	Serious	Moderate	Low	Prev 53%: 508 Prev 17%: 163 Prev 5%: 48
True negative (patients without DVT)								Prev 53%: 447 Prev 17%: 790 Prev 5%: 904
False negative (patients incorrectly classified DVT negative)								Prev 53%: 22 Prev 17%: 7 Prev 5%: 2
False positive (patients incorrectly classified DVT positive)								Prev 53%: 23 Prev 17%: 40 Prev 5%: 46

Bibliography: Thomas SM, Goodacre SW, Sampson FC, et al. Diagnostic value of CT for deep vein thrombosis: results of a systematic review and meta-analysis. *Clin Radiol*. 2008;63(3):299-304. Byun SS, Kim JH, Kim YJ, et al. Evaluation of deep vein thrombosis with multidetector row CT after orthopedic arthroplasty: a prospective study for comparison with Doppler sonography. *Korean J Radiol*. 2008;9(1):59-66. Rhee KH, Iyer RS, Cha S, et al. Benefit of CT venography for the diagnosis of thromboembolic disease. *Clin Imaging*. 2007;31(4):253-258. Goodman LR, Stein PD, Matta F, et al. CT venography and compression sonography are diagnostically equivalent: data from PIOPED II. *AJR Am J Roentgenol*. 2007;189(5):1071-1076. Garcia-Bolado A, Del Cura JL. CT venography vs ultrasound in the diagnosis of thromboembolic disease in patients with clinical suspicion of pulmonary embolism. *Emerg Radiol*. 2007;14(6):403-409. Begemann PG, Bonacker M, Kemper J, et al. Evaluation of the deep venous system in patients with suspected pulmonary embolism with multi-detector CT: a prospective study in comparison to Doppler sonography. *J Comput Assist Tomogr*. 2003;27(3):399-409. Setting: predominantly suspected PE. Reference test: predominantly single US. See Table S1 and S5 legends for expansion of abbreviations.

[a] Most used a single US as a reference standard.

[b] Significant heterogeneity between studies.

[c] Few studies in suspected DVT; most in suspected PE. No management studies.

[d] Reported specificities range from 93%-100%; reported sensitivities range from 59%-100%.

[e] Based on a combined summary specificity of 95.2% (95% CI, 93.6%-96.5%) and sensitivity of 95.9% (95% CI, 93.0%-97.8%). Prevalences for high (53%), moderate (17%), and low (5%) taken from Wells et al.[30]

Table S31—*[Sections 3.2-3.6] Methodology of Diagnostic Studies Evaluating MR Venography in Patients With Suspected First DVT: Meta-analysis of Accuracy Studies of MR Venography or Direct Thrombus Imaging*

Study Eligibility					
Patient Population	Diagnostic Test	Outcome (Criterion Standard)	Exploration of Heterogeneity	Comments	Source
Suspected DVT, suspected PE, or high-risk asymptomatic patients	MR venography and direct MRI	US or contrast venography	χ^2 test for heterogeneity. No formal analysis for sources of heterogeneity.	Summary estimates were calculated despite significant unexplained heterogeneity. Prevalence of DVT was high in primary studies.	Sampson et al[99]/2007

See Table S1 and S5 legends for expansion of abbreviations.

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Table S32—*[Sections 3.2-3.6] Methodology of Diagnostic Studies Evaluating MR Venography in Patients With Suspected First DVT: Individual Accuracy Studies of MR Venography*

	Study Details					
Study/Year	Patient Population	Diagnostic Test	Outcome (Criterion Standard)	Consecutive Patients	Independent Test Assessment	Comments
Cantwell et al[100]/2006	Suspected DVT	MR venography	Contrast venography	No	Yes	
Fraser et al[101]/2003	Suspected DVT	MR venography	Contrast venography	No	Yes	Included in Sampson et al[99]
Sica et al[102]/2001	Suspected DVT, with negative above-knee US	MR venography	Contrast venography	No	Yes	Included in Sampson et al[99]
Jensen et al[103]/2001	Asymptomatic, lower limb injuries	MR venography	Contrast venography	Yes	Yes	Included in Sampson et al[99]
Catalano et al[104]/1997	Suspected DVT	MR venography	Contrast venography	Unclear	Yes	Included in Sampson et al[99]
Laissy et al[105]/1996	Suspected DVT/PE	MR venography	Contrast venography	Unclear	Yes	Included in Sampson et al[99]
Larcom et al[106]/1996	Asymptomatic, post-arthroplasty	MR venography	Contrast venography	Yes	Yes	Included in Sampson et al[99]
Evans et al[107]/1996	Suspected DVT	MR venography	US	No	Yes	Included in Sampson et al[99]
Evans et al[108]/1993	Suspected DVT	MR venography	Contrast venography	Unclear	Yes	Included in Sampson et al[99]
Carpenter et al[109]/1993	Suspected DVT	MR venography	Contrast venography	Unclear	Yes	Included in Sampson et al[99]
Spritzer et al[110]/1993	Suspected DVT	MR venography	Contrast venography	Yes	Yes	Included in Sampson et al[99]
Pope et al[111]/1991	Suspected DVT	MR venography	Contrast venography	Unclear	Yes	Included in Sampson et al[99]
Vukov et al[112]/1991	Suspected DVT	MR venography	Contrast venography	Yes	Yes	Included in Sampson et al[99]
Erdman et al[113]/1990	Suspected DVT	MR venography	Contrast venography	Yes	Yes	Included in Sampson et al[99]

See Table S1 and S5 legends for expansion of abbreviations.

Table S33—*[Sections 3.2-3.6] Description and Summary of Results of Diagnostic Studies Evaluating MR Venography in Patients With Suspected First DVT: Results: Meta-analyses and Cross-Sectional Accuracy Studies of MR Venography*

Question from Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Accuracy vs Management Cohort	Patient Population	Outcome Measure	Result, %	Comments	Reference
What are the consequences of using contrast MR venography to diagnose DVT?	Suspected DVT	Meta-analysis	Accuracy	Mixed, but mostly suspected DVT	Specificity	Summary estimate: 94.8 (95% CI, 92.6-96.5) Range: 43-100	Technique not always clear in primary studies. Included one study of direct MRI	Sampson et al[99]/2007
	Suspected DVT	Primary study	Accuracy	Suspected DVT	Specificity	77.8 (95% CI, 54.8-91.0)	Results were reported as agreement between MR venography and contrast venography, rather than contrast venography as reference	Cantwell et al[100]/2006
What are the consequences of using contrast MR venography to exclude DVT?	Suspected DVT	Meta-analysis	Accuracy	Mixed, but mostly suspected DVT	Sensitivity	Summary estimate: 91.5 (95% CI, 87.5-94.5) Range: 0 to 100	Technique not always clear in primary studies. Included one study of direct MRI. Sensitivity was lower in two studies of asymptomatic patients. When these were excluded, summary sensitivity was 95.7%. Pooled sensitivities for proximal and distal DVT were 93.9% (95% CI: 88.8%-97.2%) and 62.1% (95% CI: 42.3%-79.3%)	Sampson et al[99]/2007
	Suspected DVT	Primary study	Accuracy	Suspected DVT	Sensitivity	100% (95% CI, 61.0-100)	Results were reported as agreement between MR venography and contrast venography, rather than contrast venography as reference	Cantwell et al[100]/2006

Table S34—*[Sections 3.2-3.6] Evidence Profile: Should MR Venography Be Used for the Diagnosis of First Suspected DVT?*

Outcome	No. of Studies	Study Design	Limitations[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Final Quality	Effect/1,000[e]
True positive (patients with DVT)	Meta-analysis of 13 plus 1 additional primary study[144,145]	Accuracy cohort	…	Moderate	Moderate	Serious	Low	Prev 53%: 486 Prev 17%: 158 Prev 5%: 46
True negative (patients without DVT)								Prev 53%: 446 Prev 17%: 787 Prev 5%: 901
False negative (patients incorrectly classified DVT negative)								Prev 53%: 45 Prev 17%: 14 Prev 5%: 4
False positive (patients incorrectly classified DVT positive)								Prev 53%: 24 Prev 17%: 43 Prev 5%: 49

Bibliography: Sampson FC, Goodacre SW, Thomas SM, et al. The accuracy of MRI in diagnosis of suspected deep vein thrombosis: systematic review and meta-analysis. *Eur Radiol*. 2007;17(1):175-181. Cantwell CP, Cradock A, Bruzzi J, et al. MR venography with true fast imaging with steady-state precession for suspected lower-limb deep vein thrombosis. *J Vasc Interv Radiol*. 2006;17(11 pt 1):1763-1769.
Setting: predominantly suspected DVT. Reference test: predominantly contrast venography.

[a] No major limitations.

[b] Significant heterogeneity between studies.

[c] No management studies.

[d] Reported specificities range from 43%-100%; reported sensitivities range from 0-100%.

[e] Based on a combined summary specificity of 94.8% (95% CI, 92.6%-96.5%) and sensitivity of 91.5% (95% CI, 87.5%-94.5%). Prevalences for high (53%), moderate (17%), and low (5%) taken from Wells et al.[10]

Table S35—*[Sections 3.2-3.6] Methodology of Diagnostic Studies Evaluating MR Direct Thrombus Imaging in Patients with Suspected First DVT: Individual Accuracy Studies of MR Direct Thrombus Imaging*

	Study Details					
Study/Year	Patient Population	Diagnostic Test	Outcome (Criterion Standard)	Consecutive Patients	Independent Test Assessment	Comments
Fraser et al[114]/2002	Suspected DVT	Direct MRI	Contrast venography	No	Yes	Included in Sampson et al[99]/2007

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Table S36—*[Sections 3.2-3.6] Description and Results of Diagnostic Studies Evaluating MR Direct Thrombus Imaging in Patients With Suspected First DVT: Cross-Sectional Accuracy Studies of MR Direct Thrombus Imaging*

Question From Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Accuracy vs Management Cohort (Indicate if Cohort is From an RCT)	Patient Population	Outcome Measure[a]	Result, % (95% CI)	Comments	Reference
What are the consequences of using MR direct thrombus imaging to diagnose DVT?	Suspected DVT	Primary study	Accuracy	Suspected DVT	Specificity	92 (80-98)	Included in Sampson et al[99] meta-analysis	Fraser et al[114]/2002
What are the consequences of using MR direct thrombus imaging to exclude DVT?	Suspected DVT	Primary study	Accuracy	Suspected DVT	Sensitivity	94 (84-97)	Included in Sampson et al[99] meta-analysis	Fraser et al[99]/2002

See Table S2 legend for expansion of abbreviation.

[a]eg, Post-TP during 3 mo follow-up; sensitivity or specificity, and so forth.

Table S37—*[Sections 3.2-3.6] Evidence Profile: Should Direct MRI Be Used for the Diagnosis of First Suspected DVT?*

Outcome	No. of Studies	Study Design	Limitations[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Final Quality	Effect/1,000[e]
True positive (patients with DVT)	1 Primary study[159]	Accuracy cohort	…	Not applicable	Moderate	Moderate	Low	Prev 53%: 498 Prev 17%: 160 Prev 5%: 47
True negative (patients without DVT)								Prev 53%: 432 Prev 17%: 764 Prev 5%: 874
False negative (patients incorrectly classified DVT negative)								Prev 53%: 32 Prev 17%: 10 Prev 5%: 3
False positive (patients incorrectly classified DVT positive)								Prev 53%: 38 Prev 17%: 66 Prev 5%: 76

Bibliography: Fraser DG, Moody AR, Morgan PS, Martel AL, Davidson I. Diagnosis of lower-limb deep venous thrombosis: a prospective blinded study of magnetic resonance direct thrombus imaging. *Ann Intern Med*. 2002;136(2)89-98. Setting: suspected DVT. Reference test: venography.

[a] No significant limitations

[b] Only one study

[c] No management studies.

[d] Reported specificities range from 93%-100%; reported sensitivities range from 59%-100%.

[e] Based on a specificity of 92% (95% CI, 80%-98%) and sensitivity of 94.9% (95% CI, 84%-97%). Prevalences for high (53%), moderate (17%), and low (5%) taken from Wells et al.[30]

Table S38—*[Sections 4.1-4.3] Methodology of Diagnostic Studies in Patients With Suspected Recurrent Lower Extremity DVT: Individual Accuracy Studies*

Study Details						
Patient Population	Diagnostic Test	Outcome (Criterion Standard)	Consecutive Patients	Independent Test Assessment	Comments	Source
Suspected recurrent DVT	CUS with measurement of residual venous diameter in abnormal venous segments	Venography	Yes	Yes	N = 29 patients with suspected recurrent DVT; 12 with confirmed recurrence (1 with isolated distal DVT)	Prandoni P, Cogo A, Bernardi E, et al. A simple ultrasound approach for detection of recurrent proximal-vein thrombosis. *Circulation*. 1993;88:1730-1735
		Venography	Yes	Not stated	N = 86 patients with suspected recurrent DVT; 16 patients with confirmed recurrence	Villalta S, Rossi L, Bernardi E, Bagatella P, Marchiori A, Scudellar A. Serial compression ultrasonography in the diagnostic approach of patients with clinically suspected recurrent deep vein thrombosis. Interim report of an ongoing study [abstract]. *Thromb Haemost*. 1997;78(Suppl):588.
		Venography	Not stated	Not stated	N = 16 patients with suspected recurrent DVT; 7 with confirmed recurrence	Koopman MM, Jongbloets L, Lensing AW, Buller H, ten Cate JW. Clinical utility of a quantitative B-mode ultrasonography method in patients with suspected recurrent deep vein thrombosis (DVT) [abstract]. *Thromb Haemost*. 1993;69:623.
		Venography	Yes	Yes	N = 205 patients with suspected recurrent DVT; 10 of 52 patients with initially abnormal CUS either could not undergo venography or had inadequate venography	Prandoni P, Lensing AWA, Bernardi E, Villalta S, Bagatella P, Girolami A for the DERECUS Investigators Group. The diagnostic value of compression ultrasonography in patients with suspected recurrent deep vein thrombosis. *Thromb Haemost*. 2002;88:402-406.

All studies are cross-sectional unless otherwise indicated under Comments. See Table S7 legend for expansion of abbreviation.

Table S39—*[Sections 4.1-4.3] Methodology of Diagnostic Studies in Patients With Suspected Recurrent Lower Extremity DVT: Individual Management Studies with Cohorts*

Study Details								
Patient Population	Diagnostic Test	Outcome	Methods (Single-Arm Cohort vs Cohort From RCT)	Consecutive Patients	Follow-up	Received Alternative Tests	Comments	Source
Suspected recurrent DVT	Normal serial CUS (day of presentation, day 2 [± 1], and day 7 [± 1])	Probability of VTE during follow-up	Single-arm cohort	Yes	6 mo	No	N = 150 patients with normal serial CUS; recurrence confirmed by venography	Prandoni P, Lensing AWA, Bernardi E, Villalta S, Bagatella P, Girolami A for the DERECUS Investigators Group. The diagnostic value of compression ultrasonography in patients with suspected recurrent deep vein thrombosis. *Thromb Haemost*. 2002;88:402-406.
	Normal serial CUS (day of presentation, day 1-3, and day 6-10)	Probability of VTE during follow-up	Single-arm cohort	Yes	3 mo	No	N = 488 patients with suspected recurrence; 129 patients with normal serial CUS	Bates SM, Kearon C, Kahn SR, et al. A negative DD excludes recurrent deep vein thrombosis: results of a multicentre management trial. *Blood*. 2007;110:214a (abstract #698).
	Negative (normal or unchanged/decreased residual venous diameter) on serial CUS (day of presentation, day 2 [± 1], and day 7 [± 1])	Probability of VTE during follow-up	Single-arm cohort	Yes	6 mo	No	N = 65 patients with negative serial CUS; recurrence confirmed by venography	Villalta S, Rossi L, Bernardi E, Bagatella P, Marchiori A, Scudellar A. Serial compression ultrasonography in the diagnostic approach of patients with clinically suspected recurrent deep vein thrombosis. Interim report of an ongoing study [abstract]. *Thromb Haemost*. 1997;78(suppl):588.
	Unchanged residual venous diameter (< 4-mm increase in residual venous diameter) on serial CUS (day of presentation and day 7)	Probability of VTE during follow-up	Single-arm cohort	Yes	3 mo	No	N = 42 patients with unchanged residual venous diameter on serial CUS	Le Gal G, Kovacs MJ, Carrier M, et al. Validation of a diagnostic approach to exclude recurrent venous thromboembolism. *J Thromb Haemost*. 2009;7:752-759.

(Continued)

Table S39—Continued

Study Details								
Patient Population	Diagnostic Test	Outcome	Methods (Single-Arm Cohort vs Cohort From RCT)	Consecutive Patients	Follow-up	Received Alternative Tests	Comments	Source
	Unchanged residual venous diameter (< 4-mm increase) at presentation and negative sensitive DD (Biopool Autodimer, threshold level not specified)	Probability of VTE during follow-up	Single-arm cohort	Yes	3 mo	No	N = 146 patients with suspected recurrence, all of whom underwent CUS; 38 patients diagnosed at presentation with recurrence (new noncompressible segment or increased residual venous diameter of > 4 mm); 75 of 108 remaining patients had a negative DD and were followed for recurrence	Prandoni P, Tormene D, Dalla Valle F, Concolator A, Pesavento R. D-Dimer as an adjunct to compression ultrasonography in patients with suspected recurrent deep vein thrombosis. *J Thromb Haemost*. 2007;5:1076-1077.
	Unlikely PTP according to Wells model and negative sensitive (STA Liatest, < 0.4 μg/mL) DD	Probability of VTE during follow-up	Single-arm cohort	Yes	3 mo	No	N = 105 patients with suspected recurrent DVT; 61 had an "unlikely" PTP for DVT using the Wells model; 16 had a negative DD and were followed for recurrence	Aguilar C, del Villar V. Combined D-dimer and clinical probability are useful for exclusion of recurrent deep venous thrombosis. *Am J Hematol*. 2007;82:41-44.
	Negative sensitive (STA Liatest, 0.4 μg/mL) DD	Probability of VTE during follow-up	Single-arm cohort	Yes	3 mo	No	N = 300 patients with suspected recurrent DVT; 134 had a negative DD – recurrence confirmed in 1 patient; however, recurrence could not be excluded in an additional 6 patients	Rathbun SW, Whitsett TL, Raskob GE. Negative D-dimer result to exclude recurrent deep vein thrombosis: a management trial. *Ann Intern Med*. 2004;141:839-845.
	Negative sensitive (MDA, < 0.5 μg/mL) DD	Probability of VTE during follow-up	Single-arm cohort	Yes	3 mo	No	N = 488 patients with suspected recurrent DVT; 229 had a negative DD – recurrence confirmed in 4 patients	Bates SM, Kearon C, Kahn SR, et al. A negative D-dimer excludes recurrent deep vein thrombosis: results of a multicentre management trial. *Blood*. 2007;110:214a (abstract # 698).

Cohorts from single-arm studies or cohorts representing one of the arms of an RCT. See Table S1, S2, and S7 legends for expansion of abbreviations.

Table S40—*[Sections 4.1-4.3] Description and Results for Diagnostic Studies in Patients With Suspected Recurrent Lower Extremity DVT*

Question From Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Reference Standard	Patient Population	Outcome Measure[a]	Result, % (95% CI)	Comments	Reference
Suspected recurrent lower extremity DVT (Section 4.0)	What are the consequences of using venography to diagnose recurrent lower extremity DVT?	N/A	N/A	Patients with suspected recurrent DVT	N/A	N/A	Implied reference standard	N/A
	What are the consequences of using venography to rule out recurrent lower extremity DVT?	N/A	N/A	Patients with suspected recurrent DVT	N/A	N/A	Implied reference standard	N/A
	What are the consequences of using CUS (new noncompressible segment or increased residual venous diameter compared with previous CUS) to diagnose recurrent DVT?	Primary study	Venography	Patients with suspected recurrent DVT	Specificity: new noncompressible segment or increased residual venous diameter ≥ 2 mm compared with previous CUS	100 (81-100)	N = 29 patients with suspected recurrent DVT; 12 with confirmed recurrence (1 with isolated distal DVT)	Prandoni P, Cogo A, Bernardi E, et al. A simple ultrasound approach for detection of recurrent proximal-vein thrombosis. *Circulation*. 1993;88:1730-1735.
		Primary study	Venography	Patients with suspected recurrent DVT	Specificity: new noncompressible segment or increased residual venous diameter ≥ 2 mm compared with previous CUS	97 (90-99)	N = 86 patients with suspected recurrence; 16 patients with confirmed recurrence	Villalta S, Rossi L, Bernardi E, Bagatella P, Marchiori A, Scudellar A. Serial compression ultrasonography in the diagnostic approach of patients with clinically suspected recurrent deep vein thrombosis. Interim report of an ongoing study [abstract]. *Thromb Haemost*. 1997;78(Suppl):588.

(Continued)

Table S40—*Continued*

Question From Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Reference Standard	Patient Population	Outcome Measure[a]	Result, % (95% CI)	Comments	Reference
		Primary study	Venography	Patients with suspected recurrent DVT	Specificity (a) New noncompressible segment or increased residual venous diameter 1-2 mm compared with previous CUS	(a) 78 (45-94)	N = 16 patients with suspected recurrence; 7 with confirmed recurrence	Koopman MM, Jongbloets L, Lensing AW, Buller H, ten Cate JW. Clinical utility of a quantitative B-mode ultrasonography method in patients with suspected recurrent deep vein thrombosis (DVT) [abstract]. *Thromb Haemost*. 1993;69:623.
					Specificity (b) New noncompressible segment or increased residual venous diameter ≥ 4 mm compared with previous CUS	(b) 100 (70-100)		
		Primary study	Venography	Patients with suspected recurrent DVT	Positive predictive value (a) New noncompressible segment	(a) 100 (72-100)	N = 205 patients with suspected recurrent DVT; 10 of 52 patients with initially abnormal CUS either could not undergo venography or had inadequate venography; results of 42 patients used to calculate positive predictive value	Prandoni P, Lensing AWA, Bernardi E, Villalta S, Bagatella P, Girolami A for the DERECUS Investigators Group. The diagnostic value of compression ultrasonography in patients with suspected recurrent deep vein thrombosis. *Thromb Haemost*. 2002;88:402-406.
					Positive predictive value (b) New noncompressible segment and/or increased residual venous diameter ≥ 2 mm compared with previous compression US	(b) 86 (69-94)		
					Positive predictive value (c) New noncompressible segment and/or increased residual venous diameter ≥ 2 but < 4 mm compared with previous CUS	(c) 50 (22-79)		
					Positive predictive value (d) Increased residual venous diameter > 4 mm compared with previous CUS	(d) 100 (84-100)		

(Continued)

Table S40—*Continued*

Question From Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Reference Standard	Patient Population	Outcome Measure[a]	Result, % (95% CI)	Comments	Reference
	What are the consequences of using a single CUS (full compressibility, unchanged or improved residual venous diameter) to exclude recurrent DVT?	Primary study	Venography	Patients with suspected recurrent DVT	Sensitivity: Full compressibility, unchanged (< 2 mm) or improved residual venous diameter compared with previous CUS	Overall: 91 (59-100) Proximal only: 100 (69-100)	N = 29 patients with suspected recurrent DVT; 12 with confirmed recurrence (1 with isolated distal DVT)	Prandoni P, Cogo A, Bernardi E, et al. A simple ultrasound approach for detection of recurrent proximal-vein thrombosis. *Circulation*. 1993;88:1730-1735.
		Primary study	Venography	Patients with suspected recurrent DVT	Sensitivity: Full compressibility, unchanged (< 2 mm) or improved residual venous diameter compared with previous CUS	100 (81-100)	N = 86 patients with suspected recurrence; 16 patients with confirmed recurrence	Villalta S, Rossi L, Bernardi E, Bagatella P, Marchiori A, Scudellar A. Serial compression ultrasonography in the diagnostic approach of patients with clinically suspected recurrent deep vein thrombosis. Interim report of an ongoing study [abstract]. *Thromb Haemost*. 1997;78(suppl):588.
		Primary study	Venography	Patients with suspected recurrent DVT	Sensitivity (a) New noncompressible segment or increased residual venous diameter 1-2 mm compared with previous CUS	(a) 29 (8-64)	N = 16 patients with suspected recurrence; 7 with confirmed recurrence	Koopman MM, Jongbloets L, Lensing AW, Buller H, ten Cate JW. Clinical utility of a quantitative B-mode ultrasonography method in patients with suspected recurrent deep vein thrombosis (DVT) [abstract]. *Thromb Haemost*. 1993;69:623.
					Sensitivity (b) New noncompressible segment or increased residual venous diameter ≥ 4 mm compared with previous CUS	(b) 71 (36-92)		

(Continued)

Table S40—*Continued*

Question From Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Reference Standard	Patient Population	Outcome Measure[a]	Result, % (95% CI)	Comments	Reference
	What are the consequences of using serial CUS to exclude recurrent DVT?	Primary	Confirmed VTE during 6 mo of follow-up	Patients with suspected recurrent DVT and normal serial CUS (day of presentation, day 2 [± 1] and day 7 [± 1])	NPV	99 (95-100)	N = 150 patients with normal serial CUS; 1 patient died of confirmed myocardial infarction during follow-up and analysis based on 149 remaining patients; recurrence confirmed by venography	Prandoni P, Lensing AWA, Bernardi E, Villalta S, Bagatella P, Girolami A for the DERECUS Investigators Group. The diagnostic value of compression ultrasonography in patients with suspected recurrent deep vein thrombosis. *Thromb Haemost*. 2002;88:402-406.
		Primary	Confirmed VTE during 3 mo of follow-up	Patients with suspected recurrent DVT and normal serial CUS (day of presentation, day 1-3, and day 6-10)	NPV	98 (92-99)	N = 488 patients with suspected recurrence; 129 with normal serial CUS	Bates SM, Kearon C, Kahn SR, et al. A negative DD excludes recurrent deep vein thrombosis: results of a multicentre management trial. *Blood*. 2007;110:214a (abstract #698).
		Primary	Confirmed VTE during 6 mo of follow-up	Patients with suspected recurrent DVT and negative (normal or unchanged/ improved residual venous diameter) serial CUS (day of presentation, day 2 [± 1] and day 7 [± 1])	NPV	97 (90-99)	N = 65 patients with negative serial CUS; recurrence confirmed by venography	Villalta S, Rossi L, Bernardi E, Bagatella P, Marchiori A, Scudellar A. Serial compression ultrasonography in the diagnostic approach of patients with clinically suspected recurrent deep vein thrombosis. Interim report of an ongoing study [abstract]. *Thromb Haemost*. 1997;78(*Suppl*):588.
		Primary	Confirmed thromboembolism during 3 mo of follow-up	Patients with unchanged residual venous diameter (< 4-mm increase in residual venous diameter) on serial CUS (day of presentation and day 7)	NPV	95 (84-99)	N = 42 patients with unchanged residual venous diameter on serial CUS	Le Gal G, Kovacs MJ, Carrier M, et al. Validation of a diagnostic approach to exclude recurrent venous thromboembolism. *J Thromb Haemost*. 2009;7:752-759.

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Table S40—*Continued*

Question From Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Reference Standard	Patient Population	Outcome Measure[a]	Result, % (95% CI)	Comments	Reference
	What are the consequences of using an unchanged CUS at presentation and negative sensitive DD to exclude recurrent DVT?	Primary	Confirmed thromboembolism during 3 mo of follow-up	Patients with unchanged residual venous diameter (< 4-mm increase) at presentation and negative sensitive DD (Biopool Autodimer)	NPV	100 (95-100)	N = 146 patients with suspected recurrence, all of whom underwent CUS; 38 patients diagnosed at presentation with recurrence (new noncompressible segment or increased residual venous diameter of > 4 mm; 75 of 108 remaining patients had a negative DD and were followed for recurrence	Prandoni P, Tormene D, Dalla Valle F, Concolator A, Pesavento R. D-Dimer as an adjunct to compression ultrasonography in patients with suspected recurrent deep vein thrombosis. *J Thromb Haemost*. 2007;5:1076-1077.
	What are the consequences of using an unchanged CUS at presentation and a negative SimpliRED DD to exclude recurrent DVT?	N/A	N/A	N/A	N/A	N/A	There are no accuracy or management studies of the SimpliRED DD in combination with CUS in this patient population	N/A
	What are the consequences of using an unlikely PTP with the Wells model in combination with a negative sensitive DD to exclude recurrent DVT?	Primary study	Confirmed thromboembolism during 3 mo of follow-up	Patients with unlikely PTP and negative sensitive DD (STA Liatest, < 0.4 ug/mL)	NPV	100 (81-100)	N = 105 patients with suspected recurrent DVT; 61 had an "unlikely" PTP for DVT using the Wells model; 16 had a negative DD and were followed for recurrence	Aguilar C, del Villar V. Combined D-dimer and clinical probability are useful for exclusion of recurrent deep venous thrombosis. *Am J Hematol*. 2007;82:41-44.

(Continued)

Table S40—*Continued*

Question From Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Reference Standard	Patient Population	Outcome Measure[a]	Result, % (95% CI)	Comments	Reference
	What are the consequences of using a low PTP with the Wells model with a negative sensitive DD to exclude recurrent DVT?	N/A	N/A	N/A	N/A	N/A	There are no accuracy or management studies of the combination of sensitive DD and PTP in this patient population	N/A
	What are the consequences of using a low or moderate PTP with the Wells model with a negative sensitive DD to exclude recurrent DVT?	N/A	N/A	N/A	N/A	N/A	There are no accuracy or management studies of the combination of sensitive DD and PTP in this patient population	N/A
	What are the consequences of using a sensitive DD as a stand-alone test to exclude recurrent DVT?	Primary	Confirmed recurrence during 3 mo of follow-up	Patients with suspected recurrent DVT	NPV of the STA Liatest DD	Confirmed recurrence: 99 (96-100) Confirmed or possible recurrence: 95 (90-97)	N = 300 patients with suspected recurrent DVT; 134 had a negative DD, recurrence confirmed in 1 patient; however, recurrence could not be excluded in an additional 6 patients	Rathbun SW, Whitsett TL, Raskob GE. Negative D-dimer result to exclude recurrent deep vein thrombosis: a management trial. *Ann Intern Med*. 2004;141:839-845.
		Primary	Confirmed recurrence during 3 mo of follow-up	Patients with suspected recurrent DVT	NPV of the MDA DD	98 (96-100)	N = 488 patients with suspected recurrent DVT; 229 had a negative DD, recurrence confirmed in 4 patients	Bates SM, Kearon C, Kahn SR, et al. A negative D-dimer excludes recurrent deep vein thrombosis: results of a multicentre management trial. *Blood*. 2007;110:214a (abstract #698).

(Continued)

Table S40—*Continued*

Question From Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Reference Standard	Patient Population	Outcome Measure[a]	Result, % (95% CI)	Comments	Reference
	What are the consequences of using a SimpliRED DD as a stand-alone test to recurrent DVT?	N/A	N/A	N/A	N/A	N/A	There are no accuracy or management studies of the SimpliRED DD alone in this patient population	N/A
	What are the consequences of using CT scan venography to diagnose recurrent DVT?	N/A	N/A	Patients with suspected recurrent DVT	N/A	N/A	There are no accuracy or management studies of CT scan venography in this population	N/A
	What are the consequences of using CT scan venography to exclude recurrent DVT?	N/A	N/A	Patients with suspected recurrent DVT	N/A	N/A	There are no accuracy or management studies of CT scan venography in this population	N/A
	What are the consequences of using MRI to diagnose recurrent DVT?	N/A	N/A	Patients with suspected recurrent DVT	N/A	N/A	There are no accuracy or management studies of MR venography or direct MR imaging in this population	N/A
	What are the consequences of using MRI to exclude recurrent DVT?	N/A	N/A	Patients with suspected recurrent DVT	N/A	N/A	There are no accuracy or management studies of MR venography or direct MR imaging in this population	N/A

[a]eg, Post-TP during 3 month follow-up; sensitivity or specificity, and so forth. See Table S1, S3, and S7 legends for expansion of abbreviations.

Table S41—*[Sections 4.1-4.3] Evidence Profile: Should Serial Normal Proximal CUS Be Used to Rule Out Recurrent DVT?*

Quality Assessment							Summary of Findings	
							Accuracy Indices, %	Quality
No. of Studies (Patients)	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Normal Serial CUS	
Negative predictive value of serial normal CUS (day of presentation, day 2 [± 1], day 7 [± 1]) for recurrent DVT during 6-mo follow-up								
2 Studies Study 1 = 150 Study 2 = 129	Single-arm prospective management cohort studies	Moderate[a]	None	N/A	Study 1: 95% CI, 95%-100% Study 2: 95% CI, 92%-99%	3- (Study 2) or 6-(Study 1) mo follow-up as reference standard. Confined to patients with a positive DD in Study 2	Study 1: 99 Study 2: 98	Moderate

Bibliography: Prandoni P, Lensing AWA, Bernardi E, Villalta S, Bagatella P, Girolami A for the DERECUS Investigators Group. The diagnostic value of compression ultrasonography in patients with suspected deep vein thrombosis. *Thromb Haemost*. 2002;88(3):402-406. Bates SM, Kearon C, Kahn SR, et al. A negative DD excludes recurrent deep vein thrombosis: results of a multicentre management trial. *Blood*. 2007;110:214a (abstract #698). Settings: predominantly outpatients. See Table S7 legend for expansion of abbreviation.

[a]Study by Bates et al only in abstract form.

Table S42—*[Sections 4.1-4.3] Evidence Profile: Should the Criterion of New Noncompressible Segment or Increased Residual Venous Diameter of 1-2 mm on CUS Be Used to Rule Out or Diagnose Recurrent DVT?*

Outcome	No. of Studies	Study Design	Limitations[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Final Quality	Effect/1,000[e]
True positive (patients with DVT)	1 (16 participants)	Accuracy cohort	Serious	N/A	Serious	Very serious	Low	Prev 53%: 154 Prev 17%: 49 Prev 5%: 14
True negative (patients without DVT)								Prev 53%: 367 Prev 17%: 647 Prev 5%: 741
False negative (patients incorrectly classified DVT negative)								Prev 53%: 376 Prev 17%: 121 Prev 5%: 36
False positive (patients incorrectly classified DVT positive)								Prev 53%: 103 Prev 17%: 183 Prev 5%: 209

Bibliography: Koopman MM, Jongbloets L, Lensing AWA, Buller H, ten Cate JW. Clinical utility of a quantitative B-mode ultrasonography method in patients with suspected recurrent deep vein thrombosis (DVT) [abstract]. *Thromb Haemost*. 1993;69:623. Settings: not stated. Reference standard: venography. See Table S7 legend for expansion of abbreviation.

[a] Setting not stated, published only in abstract form, unclear if consecutive or selected patients used; technique requires local expertise and previous CUS for comparison.

[b] Single study.

[c] Accuracy study.

[d] Wide 95% CIs.

[e] Based on a specificity of 78% (95% CI, 45%-94%) and sensitivity of 29% (95% CI, 8%-64%). Prevalences taken from Wells et al.[30]

Table S43—*[Sections 4.1-4.3] Evidence Profile: Should the Criterion of New Noncompressible Segment or Increased Residual Venous Diameter of ≥ 2 mm on Proximal CUS Be Used to Rule Out or Diagnose Recurrent DVT?*

Outcome	No. of Studies	Study Design	Limitations[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Final Quality	Effect/1,000[e]
True positive (patients with DVT)	2 (115 Participants)	Accuracy cohorts	Serious	No	Serious	Serious	Low	Prev 53%: 482 Prev 17%: 456 Prev 5%: 49
True negative (patients without DVT)								Prev 53%: 155 Prev 17%: 805 Prev 5%: 921
False negative (patients incorrectly classified DVT negative)								Prev 53%: 49 Prev 17%: 15 Prev 5%: 5
False positive (patients incorrectly classified DVT positive)								Prev 53%: 14 Prev 17%: 25 Prev 5%: 29

Bibliography: Prandoni P, Cogo A, Bernardi E, et al. A simple ultrasound approach for detection of recurrent proximal-vein thrombosis. *Circulation.* 1993;88:1730-1735. Villalta S, Rossi L, Bernardi E, Bagatella P, Marchiori A, Sculdellar A. Serial compression ultrasonography in the diagnostic approach of patients with clinically suspected recurrent deep vein thrombosis. Interim report of an ongoing study [abstract]. *Thromb Haemost.* 1997;78 (suppl):588. Setting: suspected recurrent DVT. Reference test: venography. See Table S7 legend for expansion of abbreviation.

[a] Villalta et al published only in abstract form, unclear if consecutive or selected patients used; technique requires local expertise and previous CUS for comparison.

[b] Two studies only.

[c] Accuracy study.

[d] Wide 95% CIs.

[e] Based on a specificity of 97% and sensitivity of 91%. Prevalences taken from Wells et al.[30]

Table S44—*[Sections 4.1-4.3] Evidence Profile: Should the Criterion of New Noncompressible Segment or Increased Residual Venous Diameter of > 4 mm on Proximal CUS Be Used to Rule Out or Diagnose Recurrent DVT?*

Outcome	No. of Studies	Study Design	Limitations[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Final Quality	Effect/1,000[e]
True positive (patients with DVT)	2, but estimates of both sensitivity and specificity only in 1 (16 participants; Koopman et al)	Accuracy cohort	Serious	N/A	Serious	Very serious	Moderate	Prev 53%: 376 Prev 17%: 121 Prev 5%: 36
True negative (patients without DVT)								Prev 53%: 470 Prev 17%: 830 Prev 5%: 950
False negative (patients incorrectly classified DVT negative)								Prev 53%: 154 Prev 17%: 50 Prev 5%: 14
False positive (patients incorrectly classified DVT positive)								Prev 53%: 0 Prev 17%: 0 Prev 5%: 0

Bibliography: Koopman MM, Jongbloets L, Lensing AWA, Buller H, ten Cate JW. Clinical utility of a quantitative B-mode ultrasonography method in patients with suspected recurrent deep vein thrombosis (DVT) [abstract]. *Thromb Haemost*. 1993;69:623. Prandoni P, Lensing AWA, Bernardi E, Villalta S, Bagatella P, Girolami A for the DERECUS Investigators Group. The diagnostic value of compression ultrasonography in patients with suspected deep vein thrombosis. *Thromb Haemost*. 2002;88:402-406. Setting: suspected recurrent DVT. Reference test: venography. See Table S3 and S7 legends for expansion of abbreviations.

[a] Setting not stated, published only in abstract form, unclear if consecutive or selected patients used; technique requires local expertise and previous CUS for comparison (Koopman et al); positive predictive value only of 100% (95% CI, 84%-100%) (Prandoni et al).

[b] Single study only for sensitivity and specificity.

[c] Accuracy studies.

[d] Wide 95% CIs.

[e] Based on a specificity of 100% (95% CI, 70%-100%) and sensitivity of 71% (95% CI, 36%-92%) (Koopman et al); positive predictive value of 100% (95% CI, 84%-100%); sensitivity and specificity not provided (Prandoni et al). Prevalences taken from Wells et al.[30]

Table S45—*[Sections 4.1-4.3] Evidence Profile: Should the Combination of an Unchanged CUS (Change in Residual Venous Diameter of < 4 mm) and a Negative Highly Sensitive DD (Biopool Autodimer) Be Used to Exclude Recurrent DVT?*

	Quality Assessment						Summary of Findings	
							NPV	
No. of Studies (Patients)	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Sensitive DD and Unchanged (4-mm Increase) Residual Venous Diameter	Quality
NPV of an unchanged proximal CUS (change in residual venous diameter of < 4 mm) and a sensitive DD during 3-mo follow-up								
1 (145; 75 patients had an unchanged CUS and negative Biopool Autodimer)	Prospective single-arm cohort study	Serious[a]	Single study	N/A	95% CI, 95%-100%	…	100%	Moderate

Bibliography: Prandoni P, Tormeni D, Dalla Valle, A Concolato, Pesaventao R. DD as an adjunct to compression ultrasonography in patients with suspected recurrent deep vein thrombosis. *J Thromb Haemost*. 2007;5:1076-1077. Settings: not stated. See Table S1, S3, and S7 legends for expansion of abbreviations.

[a]Single-center study; setting not specified; unclear if patients receiving long-term warfarin included; technique requires local expertise and previous CUS for comparison

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Table S46—*[Sections 4.1-4.3] Evidence Profile: Should the Combination of an Unlikely PTP and Negative Highly Sensitive DD (STA Liatest) Be Used to Exclude Recurrent DVT?*

	Quality Assessment						Summary of Findings	
No. of Studies (Patients)	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	NPV Sensitive DD and Unlikely PTP	Quality
NPV compared with confirmed recurrent VTE during 3-mo follow-up								
1 (105; 16 with unlikely PTP and negative STA Liatest DD (<0.4 μg/mL)	Prospective single-arm cohort study	Very serious[a]	Single study	N/A	Very serious; 95% CI, 81%-100%	Study excluded patients receiving long-term warfarin therapy	100%	Low

Bibliography: Aguilar C, del Villar V. Combined D-dimer and clinical probability are useful for exclusion of recurrent deep venous thrombosis. *Am J Hematol*. 2007;82:41-44. Settings: ED. See Table S1, S3, and S7 legends for expansion of abbreviations.

[a] Only outpatients presenting to the ED were enrolled; patients receiving long-term warfarin were excluded; only 15% of patients could be managed with this approach.

 DOI: 10.1378/chest.11-2299

Table S47—*[Sections 4.1-4.3] Evidence Profile: Should a Highly Sensitive DD Be Used to Exclude Recurrent DVT?*

Quality Assessment							Summary of Findings	
							NPV, % (95% CI)	
No. of Studies (Patients)	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sensitive DD	Quality
NPV of a sensitive DD for recurrent VTE during 3-mo follow-up								
2 Studies	Prospective single-arm cohort studies	Serious[a]	None	N/A	Serious; in both studies 95% CI, 96%-100%	Both studies included patients receiving long-term warfarin		Moderate
Study 1 (300; 134 with negative DD)							Study 1: STA Liatest DD: 99, 96-100	
Study 2 (488; 229 with negative DD, 82 with confirmed VTE)							Study 2: MDA DD: 98 (96-100)	

Bibliography: Rathbun SW, Whitsett TL, Raskob GE. Negative D-dimer result to exclude recurrent deep vein thrombosis: a management trial. *Ann Intern Med*. 2004;141:839-845. Bates SM, Kearon C, Kahn SR, et al. A negative D-dimer excludes recurrent deep vein thrombosis: results of a multicentre management trial. *Blood.* 2007;110:214a (abstract 698). Settings: Predominantly outpatient; includes patients receiving long-term warfarin. See Table S1 and S3 legends for expansion of abbreviation.

[a] Study by Bates et al only in abstract form; Rathbun et al enrolled only outpatients and 97% of patients in study by Bates et al were outpatients; studies used different sensitive DD assays; in Rathbun et al, NPV could have been as low as 95% (95% CI, 90%-97%) if possible recurrences included; no data provided on proportion of patients with various PTPs; unable to determine exact overall prevalence of recurrent DVT in Rathbun et al study.

Table S48—*[Sections 5.1-5.3] Methodology of Diagnostic Studies in Patients with Suspected Pregnancy-Related DVT: Individual Accuracy Studies*

Study Details						
Patient Population	Diagnostic Test	Outcome (Criterion Standard)	Consecutive Patients	Independent Test Assessment	Comments	Source
Pregnant and postpartum women with suspected DVT	Single complete US extending from the inferior vena cava to the soleal veins	VTE during 3 mo of follow-up	No	No	Retrospective cohort study of 162 women; 82 women were postpartum. Twenty-five women were diagnosed with DVT at presentation; the proportion of patients with calf vein thrombosis only not specified. Nineteen women received anticoagulant therapy despite US that demonstrated no DVT (muscular or superficial thrombosis present only); 3 additional women received who extended (≥6 wk) postpartum prophylaxis were excluded from analysis; 11 women discharged without anticoagulant therapy (9%) were lost to follow-up	Le Gal, Prins A-M, Righini M, et al. Diagnostic value of a negative single complete compression ultrasound of the lower limbs to exclude the diagnosis of deep venous thrombosis in pregnant or postpartum women: a retrospective hospital based study. *Thromb Res*. 2006;118:691-697
Suspected pregnancy-related DVT	Clinical model	CUS at presentation; some patients had follow-up testing on day 3 and 7; all patients were followed for 3 mo	Not stated; "unselected patients"	Clinical assessment performed prior to performance of diagnostic testing; however, diagnostic test results not blinded	Failure to use accepted reference standard (venography); small number of events (n = 17; prevalence 8.8%); internal validation only	Chan WS, Lee A, Spencer FA, et al. Predicting deep venous thrombosis in pregnancy: out in "LEFt" field? *Ann Intern Med*. 2009;151:85-92
	VIDAS DD (bioMerieux) Asserachrome DD (Stago) IL Test DD (Instrumentation Laboratories) Sta-Lia Test (Stago) Innovance DD (Siemens)	CUS at presentation (including examination of the iliac vein in patients with suspicious symptoms), an unspecified proportion underwent serial US on day 3 and 7; all patients with negative testing were followed for 3 mo	Not stated; "unselected patients"	Yes	Frozen samples, failure to use accepted reference standard (venography); small number of events (n-15; prevalence 6.6%)	Chan WS, Lee A, Spencer FA, et al. D-Dimer testing in pregnant patients: toward determining the next "level" in the diagnosis of deep vein thrombosis. *J Thromb Haemost*. 2010;8:1004-1011

(Continued)

Table S48—*Continued*

Study Details						
Patient Population	Diagnostic Test	Outcome (Criterion Standard)	Consecutive Patients	Independent Test Assessment	Comments	Source
	SimpliRED DD	CUS at presentation (including examination of the iliac vein in patients with suspicious symptoms), an unspecified proportion underwent serial US on day 3 and 7; all patients with negative testing were followed for 3 mo	Yes	Yes	Frozen samples, failure to use accepted reference standard (venography); small number of events (n = 13; prevalence 8.7%);	Chan WS, Chunilal SD, Lee AYY, Crowther M, Rodger M, Ginsberg JS. A red blood cell agglutination D-dimer test to exclude deep venous thrombosis in pregnancy. *Ann Intern Med.* 2007;147:165-170

In addition to meta-analysis, all studies are cross-sectional unless otherwise indicated under Comments. See Table S1 and S7 legends for expansion of abbreviations.

Table S49—*[Sections 5.1-5.3] Methodology of Diagnostic Studies in Patients With Suspected Pregnancy-Related DVT: Individual Management Studies With Cohorts*

Study Details								
Patient Population	Diagnostic Test	Outcome	Methods (Single-Arm Cohort vs Cohort From RCT)	Consecutive Patients	Follow-up	Received Alternative Tests	Comments	Source
Suspected pregnancy-related DVT	CUS of the proximal veins and calf trifurcation at presentation (including examination of the iliac vein in patients with suspicious symptoms); an unspecified proportion underwent serial US on day 3 and 7	Confirmed VTE at 3-mo follow-up	Single-arm cohort	Yes	3 mo	No	The proportion of patients who underwent single vs serial CUS not specified. Prevalence of DVT 8.7% (12 patients at presentation and 1 during follow-up)	Chan WS, Chunilal SD, Lee AYY, Crowther M, Rodger M, Ginsberg JS. A red blood cell agglutination D-dimer test to exclude deep venous thrombosis in pregnancy. *Ann Intern Med.* 2007;147:165-170
	Single complete US extending from the inferior vena cava to the soleal veins	VTE during 3 mo of follow-up	Single-arm cohort	Yes	3 mo	No	Patient population included an unspecified number of postpartum women. Prevalence of DVT was 9.3%; proportion of calf thrombosis not specified. Three patients received full-dose anticoagulants despite negative US results.	Le Gal G, Righini M, Kercret L, et al. Diagnosis of deep vein thrombosis by compression ultrasonography during pregnancy and the postpartum period: a management study [abstract]. *J Thromb Haemost.* 2009; 7 (2):abstract PP-TH-508

Cohorts from single-arm studies or cohorts representing one of the arms of an RCT. See Table S1, S2, and S7 legends for expansion of abbreviations.

Table S50—*[Sections 5.1-5.3] Description and Results of Diagnostic Studies in Patients with Suspected Pregnancy-Related DVT*

Question from Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Reference Standard	Patient Population	Outcome Measure[a]	Result	Comments	Reference
Suspected Pregnancy-Related DVT (Section 5.0)	What are the consequences of using venography to diagnose pregnancy-related DVT?	N/A	N/A	Pregnant patients with suspected DVT	N/A	N/A	Implied reference standard	N/A
	What are the consequences of using venography to rule out pregnancy-related DVT?	N/A	N/A	Pregnant patients with suspected DVT	N/A	N/A	Implied reference standard	N/A
	What are the consequences of using CUS to diagnose pregnancy-related DVT?	N/A	N/A	Pregnant patients with suspected DVT	N/A	N/A	N/A	N/A
	What are the consequences of using CUS of the proximal veins and calf trifurcation (with imaging of the iliac veins in symptomatic women) to exclude pregnancy-related DVT	Primary, cohort management	3-mo follow-up	Pregnant patients with suspected DVT	NPV	NPV, 99.3% (95% CI, 96.0%-99.9%)	N = 149 (prevalence 8.7%); CUS of the proximal veins and calf trifurcation at presentation (including examination of the iliac vein in patients with suspicious symptoms), an unspecified proportion underwent serial US on day 3 and 7; proportion of inpatients and outpatients not specified	Chan WS, Chunilal SD, Lee AYY, Crowther M, Rodger M, Ginsberg JS. A red blood cell agglutination D-dimer test to exclude deep venous thrombosis in pregnancy. *Ann Intern Med*. 2007;147:165-170

(Continued)

Table S50—*Continued*

Question from Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Reference Standard	Patient Population	Outcome Measure[a]	Result	Comments	Reference
	What are the consequences of using a single complete US to exclude pregnancy-related DVT?	Primary, cohort management	3-mo follow-up	Pregnant and postpartum patients with suspected DVT	NPV	NPV, 100% (95% CI, 96.4%-100%)	N = 162; retrospective cohort study. Eighty-two women were postpartum; 25 women were diagnosed with DVT at presentation; 19 women received anticoagulant therapy despite US that demonstrated no DVT (muscular or superficial thrombosis); 3 additional women received extended (≥6 wk) postpartum prophylaxis were excluded from analysis; 11 women discharged without anticoagulant therapy (9%) were lost to follow-up	Le Gal, Prins A-M, Righini M, et al. Diagnostic value of a negative single complete compression ultrasound of the lower limbs to exclude the diagnosis of deep venous thrombosis in pregnant or postpartum women: a retrospective hospital based study. *Thromb Res*. 2006;118:691-697
		Primary, cohort management	3-mo follow-up	Pregnant and postpartum patients with suspected DVT	NPV	NPV, 98.2 (95% CI, 94.9%-99.4%)	N = 194; prospective cohort study. Patient population included an unspecified number of postpartum women. Prevalence of DVT was 9.3%; proportion of calf thrombosis not specified. Three patients received full-dose anticoagulants despite negative US results.	Le Gal G, Righini M, Kercret L, et al. Diagnosis of deep vein thrombosis by compression ultrasonography during pregnancy and the postpartum period: a management study [abstract]. *J Thromb Haemost*. 2009; 7 (2): abstract PP-TH-508

(Continued)

Table S50—*Continued*

Question from Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Reference Standard	Patient Population	Outcome Measure[a]	Result	Comments	Reference
	What are the consequences of using a clinical score to diagnose pregnancy-related DVT?	Primary, cohort accuracy	CUS and 3-mo follow-up	Pregnant patients with suspected DVT	Specificity	Specificity (for one or more variables) 50% (43%-58%)	N = 194 (prevalence 8.8%)	Chan WS, Lee A, Spencer FA, et al. Predicting deep venous thrombosis in pregnancy: out in "LEFt" field? *Ann Intern Med.* 2009;151:85-92
					Positive LR	LR positive, 2.0 (1.7-2.3)	Clinical score based on presence of left leg symptoms, difference in calf circumference of ≥ 2 cm, and first trimester presentation. Proportion of inpatients and outpatients not specified.	
	What are the consequences of using a clinical score to exclude pregnancy- DVT?	Primary, cohort accuracy	CUS and 3-mo follow-up	Pregnant patients with suspected DVT	Sensitivity	Sensitivity 100% (81%-100%)	N = 194 (prevalence 8.8%)	Chan WS, Lee A, Spencer FA, et al. Predicting deep venous thrombosis in pregnancy: out in "LEFt" field? *Ann Intern Med.* 2009;151:85-92
					Negative LR	LR negative, 0 (0-0)	Clinical score based on presence of left leg symptoms, difference in calf circumference of ≥ 2 cm, and first trimester presentation. Proportion of inpatients and outpatients not specified.	
	What are the consequences of using a highly sensitive DD to diagnose pregnancy-related DVT?	Primary, cohort accuracy	CUS and 3-mo follow-up	Pregnant patients with suspected DVT	Specificity	VIDAS DD, μg FEU/mL Traditional (0.5) 10.3 (6.6-15.5) Pregnancy (1.89) 78.8 (72.7-84.1)	N = 228 (prevalence 6.6%, n = 15). Five highly sensitive DD assays evaluated. Frozen samples. Cut-point based on ROC analysis. Proportion of inpatients and outpatients not specified.	Chan WS, Lee A, Spencer FA, et al. D-Dimer testing in pregnant patients: toward determining the next "level" in the diagnosis of deep vein thrombosis. *J Thromb Haemost.* 2010;8:1004-1011

(Continued)

Table S50—*Continued*

Question from Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Reference Standard	Patient Population	Outcome Measure[a]	Result	Comments	Reference
						Asserachrome, μg FEU/mL		
						Traditional (0.5) 12.3 (8.3-17.8)		
						Pregnancy (1.51) 73.9 (67.5-79.7)		
						IL Test, μg DD/mL		
						Traditional (0.23) 17.8 (13.0-24.0)		
						Pregnancy (0.57) 74.8 (68.3-80.5)		
						STA-Lia, μg FEU/mL		
						Traditional (0.5) 22.9 (17.5-29.4)		
						Pregnancy (1.38) 75.6 (69.3-81.2)		
						Innovance, μg FEU/mL		
						Traditional (0.5) 6.2 (3.5-10.6)		
						Pregnancy (1.5) 61.2 (54.3-67.8)		

(Continued)

Table S50—*Continued*

Question from Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Reference Standard	Patient Population	Outcome Measure[a]	Result	Comments	Reference
	What are the consequences of using a highly sensitive DD to exclude pregnancy-related DVT?	Primary, cohort accuracy	CUS and 3-mo follow-up	Pregnant patients with suspected DVT	Sensitivity	VIDAS DD, μg FEU/mL Traditional (0.5) 100 (74.7-100) Pregnancy (1.89) 93.3 (68.1-99.8) Asserachrome, μg FEU/mL Traditional (0.5) 100 (74.7-100) Pregnancy (1.51) 100 (78.2-100) IL Test, μg DD/mL Traditional (0.23) 100 (74.7-100) Pregnancy (0.57) 80.0 (51.9-95.7) STA-Lia, μg FEU/mL Traditional (0.5) 100 (74.7-100) Pregnancy (1.38) 93.3 (68.1-99.8) Innovance, μg FEU/mL Traditional (0.5) 100 (74.7-100) Pregnancy (1.5) 100 (74.7-100)	N = 228 (prevalence 6.6%, n = 15). Five highly sensitive DD assays evaluated. Frozen samples. Cut-point based on ROC analysis. Proportion of inpatients and outpatients not specified.	Chan WS, Lee A, Spencer FA, et al. D-Dimer testing in pregnant patients: toward determining the next "level" in the diagnosis of deep vein thrombosis. *J Thromb Haemost*. 2010;8:1004-1011

(Continued)

Table S50—*Continued*

Question from Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Reference Standard	Patient Population	Outcome Measure[a]	Result	Comments	Reference
					Negative LR	VIDAS DD, μg FEU/mL		
						Traditional (0.5) 0.09 (0.01-0.56)		
						Asserachrome, μg FEU/mL		
						Traditional (0.5) 0 (Not calculable)		
						IL Test, μg DD/mL		
						Traditional (0.23) 0.27 (0.1-0.74)		
						STA-Lia, μg FEU/mL		
						Traditional (0.5) 0.09 (0.01-0.59)		
						Pregnancy (1.38) 75.6 (69.3-81.2)		
						Innovance, μg FEU/mL		
						Traditional (0.5) 0 (Not calculable)		
	What are the consequences of using a moderately sensitive DD to diagnose pregnancy-related DVT?	Primary, cohort accuracy	CUS and 3-mo follow-up	Pregnant patients with suspected DVT	Specificity	Specificity 60% (52%-68%)	N = 149 (prevalence 8.7%, n = 13) SimpliRED DD used. Frozen samples. Proportion of inpatients and outpatients not specified.	Chan WS, Chunilal SD, Lee AYY, Crowther M, Rodger M, Ginsberg JS. A red blood cell agglutination D-dimer test to exclude deep venous thrombosis in pregnancy. *Ann Intern Med*. 2007;147:165-170
					Positive LR	LR positive, 2.5 (2.0-3.1)		

(Continued)

Table S50—*Continued*

Question from Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Reference Standard	Patient Population	Outcome Measure[a]	Result	Comments	Reference
	What are the consequences of using a moderately sensitive DD to exclude pregnancy-related DVT?	Primary, cohort accuracy	CUS and 3-mo follow-up	Pregnant patients with suspected DVT	Sensitivity	Sensitivity 100% (77%-100%)	N = 149 (prevalence 8.7%, n = 13) SimpliRED DD used. Frozen samples. Proportion of inpatients and outpatients not specified.	Chan WS, Chunilal SD, Lee AYY, Crowther M, Rodger M, Ginsberg JS. A red blood cell agglutination D-dimer test to exclude deep venous thrombosis in pregnancy. *Ann Intern Med.* 2007;147:165-170
					Negative LR	LR negative, 0 (0-0.9)		
	What are the consequences of using CT scan venography to diagnose DVT during pregnancy?	N/A	N/A	Pregnant patients with suspected DVT	N/A	N/A	N/A	N/A
	What are the consequences of using CT scan venography to exclude DVT during pregnancy?	N/A	N/A	Pregnant patients with suspected DVT	N/A	N/A	N/A	N/A
	What are the consequences of using contrast MR venography to diagnose DVT during pregnancy?	N/A	N/A	Pregnant patients with suspected DVT	N/A	N/A	N/A	N/A
	What are the consequences of using MR venography to exclude DVT during pregnancy?	N/A	N/A	Pregnant patients with suspected DVT	N/A	N/A	N/A	N/A

ROC = receiver operator curve. See Table S1-S3, S7, and S10 legends for expansion of other abbreviations.

[a]eg, Post-TP during 3 mo follow-up; sensitivity or specificity, and so forth.

Table S51—*[Sections 5.1-5.3] Evidence Profile: Should Serial Negative CUSs of the Proximal Veins and Calf Trifurcation (With Imaging of the Iliac Veins in Symptomatic Women) Be Used to Exclude DVT During Pregnancy.*[3]

No. of Studies (Patients)	Quality Assessment						Summary of Findings	
	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Accuracy Indices, % (95% CI) CUS of Proximal Veins and Calf Trifurcation (± Iliac Veins)	Quality
NPV for pregnancy-related DVT compared with 3 mo of clinical follow-up								
1 (149)	Single-arm prospective cohort	Serious[a]	Single study	N/A	Serious	Prevalence of DVT, 8.7%	99.3 (96.0-99.9)	Moderate

Bibliography: Chan WS, Chunilal SD, Lee AYY, Crowther M, Rodger M, Ginsberg JS. A red blood cell agglutination D-dimer test to exclude deep venous thrombosis in pregnancy. *Ann Intern Med.* 2007;147:165-170. Settings: not stated. See Table S3 and S7 legends for expansion of abbreviations.

[a]The proportion of patients who underwent single CUS vs those who underwent serial testing on days 3 and 7 not specified.

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Table S52—*[Sections 5.1-5.3] Evidence Profile: Should a Negative Complete US Be Used to Exclude DVT During Pregnancy?*

Quality Assessment							Summary of Findings	
							Accuracy Indices, % (95% CI)	
No. of Studies (Patients)	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Complete US	Quality
NPV for DVT during pregnancy as compared with 3 mo of clinical follow-up								
2 Studies		Very serious[a]	None	Serious[b]	Serious	Prevalence of DVT in retrospective study 15.4%; in prospective study 9.3%.		Low
Study 1 (162)	Study 1: retrospective cohort						Study 1: NPV, 100 (96.4-100)	
Study 2 (194)	Study 2: prospective cohort						Study 2: NPV, 98.2 (94.9-99.4)	

Bibliography: Le Gal, Prins A-M, Righini M, et al. Diagnostic value of a negative single complete compression ultrasound of the lower limbs to exclude the diagnosis of deep venous thrombosis in pregnant or postpartum women: a retrospective hospital based study. *Thromb Res*. 2006;118:691-697. Le Gal G, Righini M, Kercret L, et al. Diagnosis of deep vein thrombosis by compression ultrasonography during pregnancy and the postpartum period: a management study [abstract]. *J Thromb Haemost*. 2009;7 (2):abstract PP-TH-508. Settings: not stated. See Table S1 and S3 legends for expansion of abbreviations.

[a] In retrospective study, 51% of women were postpartum. Of 137 women without DVT at presentation, 19 women received anticoagulant therapy on the basis of USs that demonstrated muscular or superficial thrombosis; three additional women who received extended (≥ 6 wk) postpartum prophylaxis were excluded from analysis; 11 women discharged without anticoagulant therapy (9%) were lost to follow-up. Prospective study published only in abstract. An unspecified number of women in this study were postpartum. Of 176 women without DVT at presentation, three patients received full-dose anticoagulants despite negative US results. Follow-up only available on 167 women.

[b] A substantial proportion of the study population was postpartum.

Table S53—*[Sections 5.1-5.3] Evidence Profile: Should a Clinical Model Be Used to Evaluate Pregnant Patients With Suspected DVT?*

Outcome	No. of Studies	Study Design	Limitations[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Final Quality	Effect/1,000[e]
True positive (patients with DVT)	1 (195 patients)	Accuracy cohort	Very serious	N/A	Serious	Very serious	Low	Prev 24.6%: 246 Prev 8.7%: 87 Prev 1.5%: 15
True negative (patients without DVT)								Prev 24.6%: 377 Prev 8.7%: 457 Prev 1.5%: 493
False negative (patients incorrectly classified DVT negative)								Prev 24.6%: 0 Prev 8.7%: 0 Prev 1.5%: 0
False positive (patients incorrectly classified DVT positive)								Prev 24.6%: 377 Prev 8.7%: 456 Prev 1.5%: 492

Bibliography: Chan WS, Lee A, Spencer FA, et al. Predicting deep venous thrombosis in pregnancy: out in "LEFt" field? *Ann Intern Med*. 2009;151:85-92. Setting: Suspected pregnancy-related DVT. Reference test: proximal CUS and 3 mo follow-up. See Table S3 and S7 legends for expansion of abbreviations.

[a] Setting not stated, not clearly a sample of consecutive patients, accepted reference standard not used, reference standard results no blinded, internal validation only, small number of events (17).

[b] Single study.

[c] Accuracy study.

[d] Wide 95% CIs.

[e] Based on a specificity of 50% (95% CI, 43%-58%) for absence of left leg symptoms, difference in calf circumference of at least 2 cm, and first trimester presentation and sensitivity of 100% (95% CI, 71%-100%) for at least one of these characteristics. Prevalences taken from Chan et al.

Table S54—*[Sections 5.1-5.3] Evidence Profile: Should a High Sensitivity DD (Standard Threshold) Be Used to Evaluate Pregnant Patients With Suspected DVT?*

Outcome	No. of Studies	Study Design	Limitations[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Final Quality	Effect/1,000[e]
True positive (patients with DVT)	1 (249 patients)	Accuracy cohort	Very serious	N/A	Serious	Very serious	Low	Prev 24.6%: 246 Prev 8.7%: 87 Prev 1.5%: 15
True negative (patients without DVT)								Prev 24.6%: 78 Prev 8.7%: 94 Prev 1.5%: 101
False negative (patients incorrectly classified DVT negative)								Prev 24.6%: 0 Prev 8.7%: 0 Prev 1.5%: 0
False positive (patients incorrectly classified DVT positive)								Prev 24.6%: 676 Prev 8.7%: 819 Prev 1.5%: 884

Bibliography: Chan WS, Lee A, Spencer FA, et al. D-Dimer testing in pregnant patients: toward determining the next "level" in the diagnosis of deep vein thrombosis. *J Thromb Haemost*. 2010;8:1004-1011.

Setting: suspected pregnancy-related DVT. Reference test: proximal CUS and 3 mo follow-up. See Table S1, S3, and S7 legends for expansion of abbreviations.

[a]Setting not stated, not clearly a sample of consecutive patients, accepted reference standard not used, frozen samples, small number of events (15).

[b]Single study.

[c]Accuracy study.

[d]Wide 95% CIs.

[e]Based on a specificity of 10.3% (95% CI, 6.6%-15.5%) and sensitivity of 100% (95% CI, 74.7%-100%) for the VIDAS DD using the standard cut-point of 0.5 μg FEU/mL. Prevalences taken from Chan et al.

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Table S55—*[Sections 5.1-5.3] Evidence Profile: Should a Moderately Sensitive DD Be Used to Evaluate Pregnant Patients With Suspected DVT?*

Outcome	No. of Studies	Study Design	Limitations[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Final Quality	Effect/1,000[e]
True positive (patients with DVT)	1 (149 patients)	Accuracy cohort	Serious	N/A	Serious	Very serious	Low	Prev 24.6%: 247 Prev 8.7%: 87 Prev 1.5%: 15
True negative (patients without DVT)								Prev 24.6%: 452 Prev 8.7%: 548 Prev 1.5%: 591
False negative (patients incorrectly classified DVT negative)								Prev 24.6%: 0 Prev 8.7%: 0 Prev 1.5%: 0
False positive (patients incorrectly classified DVT positive)								Prev 24.6%: 302 Prev 8.7%: 306 Prev 1.5%: 394

Bibliography: Chan WS, Chunilal SD, Lee AYY, Crowther M, Rodger M, Ginsberg JS. A red blood cell agglutination D-dimer test to exclude deep venous thrombosis in pregnancy. *Ann Intern Med*. 2007;147:165-170. Setting: Suspected pregnancy-related DVT. Reference test: proximal CUS and 3-mo follow-up. See Table S1, S3, and S7 legends for expansion of abbreviations.

[a] Accepted reference standard not used, frozen samples, small number of events (13).

[b] Single study.

[c] Accuracy study.

[d] Wide 95% CIs.

[e] Based on a specificity of 60% (95% CI, 52%-68%) and sensitivity of 100% (95% CI, 77%-100%) for the SimpliRED DD. Prevalences taken from Chan et al.

Table S56—*[Section 6.2] Methodology of Diagnostic Studies in Patients With Suspected Upper Extremity DVT: Meta-analysis of Accuracy Studies*

Study Eligibility				
Patient Population	Diagnostic Test	Outcome (Criterion Standard)	Exploration of Heterogeneity	Source
Suspected upper extremity DVT	CUS	Venography	Could not test for influence of study design characteristics given limited number of studies available for each specific test	Di Nisio M, van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. 2010;8: 684-692
	Doppler US	Venography		
	Doppler US and CUS	Venography		

All studies are cross-sectional. See Table S1 and S7 for expansion of abbreviations.

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Table S57—*[Section 6.2] Methodology of Diagnostic Studies in Patients With Suspected Upper Extremity DVT: Individual Accuracy Studies*

Study Details						
Patient Population	Diagnostic Test	Outcome (Criterion Standard)	Consecutive Patients	Independent Test Assessment	Comments	Source
Suspected upper extremity DVT	Clinical model	Duplex US	Not stated	Reference standard results not blinded	Failure to use accepted reference standard (venography)	Constans J, Salmi L-R, Sevestre-Pietri M-A, et al. A clinical prediction score for upper extremity deep venous thrombosis. *Thromb Haemost*. 2008;99:202-207
Suspected upper extremity DVT	VIDAS DD	CT scan; Duplex US	Yes	Blinding of criterion and diagnostic test unclear	Failure to use accepted reference standard (venography)	Merminod T, Pellicciotta S, Bounameaux H. Limited usefulness of D-dimer in suspected deep vein thrombosis of the upper extremities. *Blood Coagul Fibrinolysis*. 2006;17:225-227
Suspected upper extremity DVT	MRI	Venography	Yes	Yes	10 of 31 Patients unable to undergo diagnostic tests	Baarslag H-J, van Beek EJR, Reekers JA. Magnetic resonance venography in consecutive patients with suspected deep vein thrombosis of the upper extremity: initial experience. *Acta Radiol*. 2004;45:38-43

In addition to meta-analysis, all studies are cross-sectional unless otherwise indicated under Comments.

Table S58—*[Sections 6.1, 6.2] Description and Results of Diagnostic Studies in Patients with Suspected Upper Extremity DVT*

Question from Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Reference Standard	Patient Population	Outcome Measure[a]	Result	Comments	Reference
Suspected upper extremity DVT (Section 6.0)	What are the consequences of using venography to diagnose upper extremity DVT?	N/A	N/A	Patients with suspected upper extremity DVT	N/A	N/A	Implied reference standard	Di Nisio M, van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. 2010;8:684-692
	What are the consequences of using venography to rule out upper extremity DVT?	N/A	N/A	Patients with suspected upper extremity DVT	N/A	N/A	Implied reference standard	
	What are the consequences of using CUS to diagnose upper extremity DVT?	Meta-analysis	Venography	Patients with suspected upper extremity DVT	Specificity	Specificity 96% (87%-100%)	2 studies; N = 65 patients	Prandoni P, Polistena P, Bernardi E, et al. Upper extremity deep vein thrombosis. Risk factors, diagnosis, and complications. *Arch Intern Med*. 1997; 157:57-62. Sullivan ED, Peter DJ, Cranley JJ. Real-time B-mode venous ultrasound. *J Vasc Surg*. 1984;1:365-571.
	What are the consequences of using a single CUS to exclude upper extremity DVT?	Meta-analysis	Venography	Patients with suspected upper extremity DVT	Sensitivity	Sensitivity 97% (90%-100%)	2 studies; N = 65 patients	Prandoni P, Polistena P, Bernardi E, et al. Upper extremity deep vein thrombosis. Risk factors, diagnosis, and complications. *Arch Intern Med*. 1997;157: 57-62. Sullivan ED, Peter DJ, Cranley JJ. Real-time B-mode venous ultrasound. *J Vasc Surg*. 1984;1:365-571.
	What are the consequences of using serial CUS to exclude upper extremity DVT?	N/A	N/A	Patients with suspected upper extremity DVT	N/A	N/A	No studies with serial USs	Di Nisio M, van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. 2010;8:684-692.

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Table S58—Continued

Question from Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Reference Standard	Patient Population	Outcome Measure[a]	Result	Comments	Reference
	What are the consequences of using Doppler US to diagnose upper extremity DVT?	Meta-analysis	Venography	Patients with suspected upper extremity DVT	Specificity	Specificity 94% (86%-100%)	3 studies; N = 101 patients	Di Nisio M, van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. 2010;8:684-692.
	What are the consequences of using a single Doppler US to exclude upper extremity DVT?	Meta-analysis	Venography	Patients with suspected upper extremity DVT	Sensitivity	Sensitivity 84% (72%-97%)	3 studies; N = 101 patients	Di Nisio M, van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. 2010;8:684-692.
	What are the consequences of using serial Doppler US to exclude upper extremity DVT?	N/A	N/A	Patients with suspected upper extremity DVT	N/A	N/A	No studies with serial Doppler US	Di Nisio M, van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. 2010;8:684-692.
	What are the consequences of using CUS plus Doppler to diagnose upper extremity DVT?	Meta-analysis	Venography	Patients with suspected upper extremity DVT	Specificity	Specificity 93% (80%-100%)	6 studies; N = 320 patients	Di Nisio M, van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. 2010;8:684-692.
	What are the consequences of using a single CUS plus Doppler to exclude upper extremity DVT?	Meta-analysis	Venography	Patients with suspected upper extremity DVT	Sensitivity	Sensitivity 91% (85%-97%)	6 studies; N = 320 patients	Di Nisio M, van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. 2010;8:684-692.

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Table S58—Continued

Question from Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Reference Standard	Patient Population	Outcome Measure[a]	Result	Comments	Reference
	What are the consequences of using a serial CUS plus Doppler to exclude upper extremity DVT?	N/A	N/A	Patients with suspected upper extremity DVT	N/A	N/A	No studies with serial duplex US	Di Nisio M, van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. 2010;8:684-692.
	What are the consequences of using a negative CUS and negative DD to exclude upper extremity DVT	N/A	N/A	Patients with suspected upper extremity DVT	N/A	N/A	No studies using a combination of US and DD	Di Nisio M, van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. 2010;8:684-692.
	What are the consequences of using a negative Doppler US and negative DD to exclude upper extremity DVT?	N/A	N/A	Patients with suspected upper extremity DVT	N/A	N/A	No studies using a combination of US and DD	Di Nisio M, van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. 2010;8:684-692.
	What are the consequences of using a negative CUS plus Doppler and negative DD to exclude upper extremity DVT?	N/A	N/A	Patients with suspected upper extremity DVT	N/A	N/A	No studies using a combination of US and DD	Di Nisio M, van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. 2010;8:684-692.
	What are the consequences of using low PTP with a negative CUS to exclude upper extremity DVT?	N/A	N/A	Patients with suspected upper extremity DVT	N/A	N/A	No studies using a combination of PTP and US	Di Nisio M, van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. 2010;8:684-692.

(Continued)

Table S58—Continued

Question from Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Reference Standard	Patient Population	Outcome Measure[a]	Result	Comments	Reference
	What are the consequences of using low PTP with a negative Doppler US to exclude upper extremity DVT?	N/A	N/A	Patients with suspected upper extremity DVT	N/A	N/A	No studies using a combination of PTP and US	Di Nisio M, van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. 2010;8:684-692.
	What are the consequences of using low pretest with a negative CUS plus Doppler to exclude upper extremity DVT	N/A	N/A	Patients with suspected upper extremity DVT	N/A	N/A	No studies using a combination of PTP and US	Di Nisio M, van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. 2010;8:684-692.
	What are the consequences of using serial CUS to exclude DVT in patients with a low, moderate, or high PTP of upper extremity DVT?	N/A	N/A	Patients with suspected upper extremity DVT	N/A	N/A	No studies using a combination of PTP and US	Di Nisio M, van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. 2010;8:684-692.
	What are the consequences of using serial Doppler US to exclude DVT in patients with a low, moderate, or high PTP of upper extremity DVT?	Meta-analysis	N/A	Patients with suspected upper extremity DVT	N/A	N/A	No studies using a combination of PTP and US	Di Nisio M, van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. 2010;8:684-692.
	What are the consequences of using serial CUS plus Doppler to exclude DVT in patients with a low, moderate, or high PTP of upper extremity DVT?	Meta-analysis	N/A	Patients with suspected upper extremity DVT	N/A	N/A	No studies using a combination of PTP and US	Di Nisio M, van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. 2010;8:684-692.

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Table S58—Continued

Question from Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Reference Standard	Patient Population	Outcome Measure[a]	Result	Comments	Reference
	What are the consequences of using serial CUS to exclude upper extremity DVT in patients with a positive DD and either a low, moderate, or high PTP?	Meta-analysis	N/A	Patients with suspected upper extremity DVT	N/A	N/A	No studies using a combination of DD, PTP and US	Di Nisio M, van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. 2010;8:684-692.
	What are the consequences of using serial Doppler US to exclude upper extremity DVT in patients with a positive DD and either a low, moderate, or high PTP?	Meta-analysis	N/A	Patients with suspected upper extremity DVT	N/A	N/A	No studies using a combination of DD, PTP, and US	Di Nisio M, van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. 2010;8:684-692.
	What are the consequences of using serial CUS plus Doppler to exclude upper extremity DVT in patients with a positive DD and either a low, moderate, or high PTP?	Meta-analysis	N/A	Patients with suspected upper extremity DVT	N/A	N/A	No studies using a combination of DD, PTP, and US	Di Nisio M, van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. 2010;8:684-692.

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Table S58—Continued

Question from Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Reference Standard	Patient Population	Outcome Measure[a]	Result	Comments	Reference
	What are the consequences of using a negative DD to obviate the need for serial testing in patients with suspected upper extremity DVT and a negative CUS and either a low, moderate, or high PTP?	Meta-analysis	N/A	Patients with suspected upper extremity DVT	N/A	N/A	No studies using a combination of DD, PTP, and US	Di Nisio M, van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. 2010;8:684-692.
	What are the consequences of using a negative DD to obviate the need for serial testing in patients with suspected upper extremity DVT and a negative Doppler US and either a low, moderate, or high PTP?	Meta-analysis	N/A	Patients with suspected upper extremity DVT	N/A	N/A	No studies using a combination of DD, PTP, and US	Di Nisio M, van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. 2010;8:684-692.
	What are the consequences of using a negative DD to obviate the need for serial testing in patients with suspected upper extremity DVT and a negative CUS plus Doppler and either a low, moderate, or high PTP?	Meta-analysis	NA	Patients with suspected upper extremity DVT	N/A	N/A	No studies using a combination of DD, PTP, and US	Di Nisio M, van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. 2010;8:684-692.

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Table S58—Continued

Question from Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Reference Standard	Patient Population	Outcome Measure[a]	Result	Comments	Reference
	What are the consequences of using a sensitive DD as a stand-alone test to exclude upper extremity DVT?	Primary	Venography	Patients with suspected upper extremity DVT	Sensitivity	Sensitivity 100% (78%-100%) Specificity, 14% (4%-29%)	N = 52 patients; 23 had cancer; Vidas DD. Mixed inpatient and outpatient population	Merminod T, Pellicciotta S, Bounameaux H. Limited usefulness of D-dimer in suspected deep vein thrombosis of the upper extremities. *Blood Coagul Fibrinolysis*. 2006;17:225-227.
	What are the consequences of using a SimpliRED DD as a stand-alone test to exclude upper extremity DVT?	Meta-analysis	N/A	Patients with suspected upper extremity DVT	N/A	N/A	No studies using the SimpliRED DD alone	Di Nisio M, van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. 2010;8:684-692.
	What are the consequences of using MRI to diagnose upper extremity DVT?	Primary	Venography	Patients with suspected upper extremity DVT	Specificity	Time of flight MRI; specificity, 89% (52%-100%) Gadolinium-enhanced; specificity, 80% (44%-97%)	N = 31; 10 patients unable to undergo MRI. Mixed inpatient and outpatient population	Baarslag H-J, van Beek EJR, Reekers JA. Magnetic resonance venography in consecutive patients with suspected deep vein thrombosis of the upper extremity: initial experience. *Acta Radiol*. 2004;45:38-43.

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Table S58—Continued

Question from Structured Clinical Question Table	Clinical Situation/ Question	Meta-analysis vs Primary Study	Reference Standard	Patient Population	Outcome Measure[a]	Result	Comments	Reference
	What are the consequences of using MRI to exclude upper extremity DVT?	Primary	Venography	Patients with suspected upper extremity DVT	Sensitivity	Time of flight MRI; sensitivity, 71% (26%-96%) Gadolinium-enhanced; sensitivity, 50% (12%-88%)	N = 31; 10 patients unable to undergo MRI. Mixed inpatient and outpatient population	Baarslag H-J, van Beek EJR, Reekers JA. Magnetic resonance venography in consecutive patients with suspected deep vein thrombosis of the upper extremity: initial experience. *Acta Radiol*. 2004;45:38-43.
	What are the consequences of using a clinical score to diagnose upper extremity DVT?	Primary	Duplex US	Patients with suspected upper extremity DVT	Specificity	Specificity, 64% (57%-72%)	N = 214; clinical score based on presence of localized pain, unilateral pitting edema, presence of central line or pacemaker, and presence of an alternative diagnosis. Mixed inpatient and outpatient population. Duplex US used as reference standard	Constans J, Salmi L-R, Sevestre-Pietri M-A, et al. A clinical prediction score for upper extremity deep venous thrombosis. *Thromb Haemost*. 2008;99:202-207.
	What are the consequences of using a clinical score to exclude upper extremity DVT?	Primary	Duplex US	Patients with suspected upper extremity DVT	Sensitivity	Sensitivity, 78% (68%-88%)	N = 214; Clinical score based on presence of localized pain, unilateral pitting edema, presence of central line or pacemaker, and presence of an alternative diagnosis. Mixed inpatient and outpatient population. Duplex US used as reference standard	Constans J, Salmi L-R, Sevestre-Pietri M-A, et al. A clinical prediction score for upper extremity deep venous thrombosis. *Thromb Haemost*. 2008;99:202-207.

See Table S1, S3, and S7 legends for expansion of abbreviations.

Table S59—*[Sections 6.1, 6.2] Evidence Profile: Should a Clinical Model Be Used to Evaluate Patients With Suspected Upper Extremity DVT?*

Outcome	No. of Studies	Study Design	Limitations[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Final Quality	Effect/1,000[e]
True positive (patients with DVT)	1 (214 Patients)	Accuracy cohort	Very serious	N/A	Serious	Serious	Low	Prev 53%: 413 Prev 17%: 133 Prev 5%: 39
True negative (patients without DVT)								Prev 53%: 301 Prev 17%: 531 Prev 5%: 608
False negative (patients incorrectly classified DVT negative)								Prev 53%: 117 Prev 17%: 37 Prev 5%: 11
False positive (patients incorrectly classified DVT positive)								Prev 53%: 169 Prev 17%: 299 Prev 5%: 342

Bibliography: Constans J, Salmi L-R, Sevestre-Pietri M-A, et al. A clinical prediction score for upper extremity deep venous thrombosis. *Thromb Haemost.* 2008;99:202-207. Setting: Suspected upper extremity DVT. Reference test: single US.

[a] Not clearly a representative sample, accepted reference standard not used, reference standard results not blinded, no data on withdrawals

[b] Single study.

[c] Accuracy study.

[d] Wide 95% CIs.

[e] Based on a specificity of 64% (95% CI, 57%-72%) and a sensitivity of 78% (95% CI, 68%-88%). Prevalences taken from Wells et al.[30]

Table S60—*[Sections 6.1, 6.2] Evidence Profile: Should a Highly Sensitive DD Be Used to Evaluate Suspected Upper Extremity DVT?*

Outcome	No. of Studies	Study Design	Limitations[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Final Quality	Effect/1,000[e]
True positive (patients with DVT)	1 (52 patients)	Accuracy cohort	Very serious	N/A	Serious	Very serious	Low	Prev 53%: 530 Prev 17%: 170 Prev 5%: 50
True negative (patients without DVT)								Prev 53%: 66 Prev 17%: 116 Prev 5%: 133
False negative (patients incorrectly classified DVT negative)								Prev 53%: 0 Prev 17%: 0 Prev 5%: 0
False positive (patients incorrectly classified DVT positive)								Prev 53%: 404 Prev 17%: 714 Prev 5%: 817

Bibliography: Merminod T, Pellicciotta S, Bounameaux H. Limited usefulness of D-dimer in suspected deep vein thrombosis of the upper extremities. *Blood Coagul Fibrinolysis.* 2006;17:225-227. Setting: Suspected upper extremity DVT. Reference test: single US. See Table 1 legend for expansion of abbreviation.

[a] Differential verification, accepted reference standard not used, no data on withdrawals

[b] Single study

[c] Accuracy study

[d] Wide 95% CIs.

[e] Based on a specificity of 14% (95% CI, 4%-29%) and a sensitivity of 100% (95% CI, 78%-100%). Prevalences taken from Wells et al.[30]

Table S61—*[Sections 6.1, 6.2] Evidence Profile: Should CUS Be Used to Evaluate Patients With Suspected Upper Extremity DVT?*

Outcome	No. of Studies	Study Design	Limitations[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Final Quality	Effect/1,000[e]
True positive (patients with DVT)	2 (65 Patients)	Accuracy cohort	Very serious	None	Serious	Serious	Low	Prev 53%: 514 Prev 17%: 165 Prev 5%: 49
True negative (patients without DVT)								Prev 53%: 442 Prev 17%: 780 Prev 5%: 893
False negative (patients incorrectly classified DVT negative)								Prev 53%:16 Prev 17%: 5 Prev 5%: 1
False positive (patients incorrectly classified DVT positive)								Prev 53%: 28 Prev 17%: 50 Prev 5%: 57

Bibliography: Prandoni P, Polistena P, Bernardi E, et al. Upper-extremity deep vein thrombosis. Risk factors, diagnosis, and complications. *Arch Intern Med*. 1997;157:57-62. Sullivan ED, Peter DJ, Cranley JJ. Real-time B-mode venous ultrasound. *J Vasc Surg*. 1984;1:465-471. Setting: suspected upper extremity DVT. Reference test: venography. See Table S7 legend for expansion of abbreviation.

[a] In one study, CUS results unverified against reference standard in 26 of 33 patients; unclear if representative sample; unclear if reference standard results blinded, withdrawals not reported.

[b] Two studies

[c] No management studies.

[d] Wide 95% CIs.

Based on a specificity of 94% (95% CI, 80%-99%) and a sensitivity of 97% (95% CI, 90%-100%). Prevalences taken from Wells et al.[30]

Table S62—*[Sections 6.1, 6.2] Evidence Profile: Should Doppler US Be Used to Evaluate Patients With Suspected Upper Extremity DVT?*

Outcome	No. of Studies	Study Design	Limitations[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Final Quality	Effect/1,000[e]
True positive (patients with DVT)	3 (101 Patients)	Accuracy cohort	Very serious	None	Serious	Serious for specificity, very serious for sensitivity	Low	Prev 53%: 445 Prev 17%: 143 Prev 5%: 42
True negative (patients without DVT)								Prev 53%: 451 Prev 17%: 797 Prev 5%: 912
False negative (patients incorrectly classified DVT negative)								Prev 53%: 85 Prev 17%: 27 Prev 5%: 8
False positive (patients incorrectly classified DVT positive)								Prev 53%: 19 Prev 17%: 33 Prev 5%: 38

Bibliography: Di Nisio M, van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. 2010;8:684-692. Setting: suspected upper extremity DVT. Reference test: venography.

[a] In one study, three of 21 Doppler US results unverified against reference standard and four of 18 patients verified against CT scan, rather than venography; in another study, CUS also performed with potential for bias.

[b] Three studies.

[c] No management studies.

[d] Wide 95% CIs.

[e] Based on a specificity of 96% (95% CI, 86%-100%) and a sensitivity of 84% (95% CI, 72%-87%). Prevalences taken from Wells et al.[10]

Table S63—*[Sections 6.1, 6.2] Evidence Profile Should Doppler US Plus CUS Be Used to Evaluate Patients With Suspected Upper Extremity DVT?*

Outcome	No. of Studies	Study Design	Limitations[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Final Quality	Effect/1,000[e]
True positive (patients with DVT)	6 (320 Patients)	Accuracy cohort	Very serious	None	Serious	Serious	Low	Prev 53%: 482 Prev 17%: 155 Prev 5%: 45
True negative (patients without DVT)								Prev 53%: 437 Prev 17%: 772 Prev 5%: 883
False negative (patients incorrectly classified DVT negative)								Prev 53%: 48 Prev 17%: 15 Prev 5%: 5
False positive (patients incorrectly classified DVT positive)								Prev 53%: 33 Prev 17%: 58 Prev 5%: 67

Bibliography: Di Nisio M, van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. 2010;8:684-692. Setting: suspected upper extremity DVT. Reference test: venography. See Table S1 and S7 legends for expansion of abbreviations.

[a] In one study, 19 of 42 duplex US results unverified against reference standard; in another nine of 130 results unverified against reference standard and 22 of 121 duplex results verified against venography with remainder against CT scan, MRI, and clinical follow-up; four of six studies unclear if representative patient spectrum; two of six studies unclear if blinding of reference standard and index test results.

[b] Six studies

[c] No management studies.

[d] Wide 95% CIs.

[e] Based on a specificity of 93% (95% CI, 80%-100%) and a sensitivity of 91% (95% CI, 85%-97%). Prevalences taken from Wells et al.[30]

Table S64—*[Sections 6.1 and 6.2] Evidence Profile: Should MRI (Time of Flight) Be Used to Evaluate Patients With Suspected Upper Extremity DVT?*

Outcome	No. of Studies	Study Design	Limitations[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Final Quality	Effect/1,000[e]
True positive (patients with DVT)	1 (31 Patients)	Accuracy cohort	Very serious	N/A	Serious	Very serious	Low	Prev 53%: 376 Prev 17%: 121 Prev 5%: 35
True negative (patients without DVT)								Prev 53%: 418 Prev 17%: 739 Prev 5%: 845
False negative (patients incorrectly classified DVT negative)								Prev 53%: 154 Prev 17%: 49 Prev 5%: 15
False positive (patients incorrectly classified DVT positive)								Prev 53%: 52 Prev 17%: 91 Prev 5%: 105

Bibliography: Baarslag HJ, van Beek EJR, Reekers JA. Magnetic resonance venography in consecutive patients with suspected deep vein thrombosis of the upper extremity: initial experience. *Acta Radiol*. 2004;45:38-43. Setting: suspected upper extremity DVT. Reference test: venography.

[a] Twenty-three of initial 44 patients were lost and not available for follow-up.

[b] Single study.

[c] No management studies.

[d] Wide 95% CIs.

[e] Based on a specificity of 89% (95% CI, 52%-100%) and a sensitivity of 71% (95% CI, 26%-96%). Prevalences taken from Wells et al.[10]

Table S65—*[Sections 6.1 and 6.2] Evidence Profile: Should MRI (Gadolinium) Be Used to Evaluate Patients With Suspected Upper Extremity DVT?*

Outcome	No. of Studies	Study Design	Limitations[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Final Quality	Effect/1,000 [e]
True positive (patients with DVT)	1 (31 Patients)	Accuracy cohort	Very serious	N/A	Serious	Very serious	Low	Prev 53%: 265 Prev 17%: 85 Prev 5%: 25
True negative (patients without DVT)								Prev 53%: 376 Prev 17%: 664 Prev 5%: 760
False negative (patients incorrectly classified DVT negative)								Prev 53%: 265 Prev 17%: 85 Prev 5%: 25
False positive (patients incorrectly classified DVT positive)								Prev 53%: 94 Prev 17%: 166 Prev 5%: 190

Bibliography: Baarslag HJ, van Beek EJR, Reekers JA. Magnetic resonance venography in consecutive patients with suspected deep vein thrombosis of the upper extremity: initial experience. *Acta Radiol*. 2004;45:38-43. Setting: suspected upper extremity DVT. Reference test: venography.

[a] Twenty-three of initial 44 patients were lost and not available for follow-up.

[b] Single study.

[c] No management studies.

[d] Wide 95% CIs.

[e] Based on a specificity of 80% (95% CI, 44%-97%) and a sensitivity of 50% (95% CI, 12%-88%). Prevalences taken from Wells et al.[30]

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