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The Saudi Center for
Evidence Based Health Care

Deep Vein Thrombosis

Clinical Practice Guideline on the Diagnosis of Suspected First Deep Vein Thrombosis of Lower Extremity

April 2014

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Executive summary

Introduction

Deep vein thrombosis (DVT) is a common condition and its diagnosis may be challenging due to the diversity of the available diagnostic tests and the inaccuracy of clinical assessment. If not diagnosed and treated correctly, DVT may result in life-threatening conditions, such as pulmonary embolism. On the other hand, unnecessary treatment may result in serious bleeding events. Given the importance of this topic, the Ministry of Health of the Kingdom of Saudi Arabia with the methodological support of the McMaster University working group produced clinical practice guidelines to assist health care providers in evidence-based clinical decision-making.

Methodology

This clinical practice guideline is a part of the larger initiative of the Ministry of Health of the Kingdom of Saudi Arabia (KSA) to establish a program of rigorous adaptation and de novo development of guidelines. The ultimate goals are to provide guidance for clinicians and reduce variability in clinical practice across the Kingdom.

The KSA guideline panel selected the topic of this guideline and all clinical questions addressed herein using a formal prioritization process. For all selected questions we updated existing systematic reviews that were used for the "Diagnosis of DVT" chapter of the 2012 Antithrombotic Therapy and Prevention of Thrombosis guidelines, 9th edition (see **Appendix 1**).[1] We also conducted systematic searches for information that was required to develop full guidelines for the KSA, including searches for information about patients' values and preferences and cost (resource use) specific to the Saudi context. Based on the updated systematic reviews we prepared summaries of available evidence supporting each recommendation following the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach.[2] We used this information to prepare the evidence to recommendation tables that served the guideline panel to follow the structured consensus process and transparently document all decisions made during the meeting (see **Appendix 2**). The guideline panel met in Riyadh on December 3, 2013 and formulated all recommendations during this meeting. Potential conflicts of interests of all panel members were managed according to the World Health Organization (WHO) rules.[3]

How to use these guidelines

The guideline working group developed and graded the recommendations and assessed the quality of the supporting evidence according to the GRADE approach. Quality of evidence (confidence in the available estimates of treatment effects) is categorized as: high, moderate, low, or very low based on consideration of risk of bias, directness, consistency and precision of the estimates. High quality evidence indicates that we are very confident that the *true* effect lies close to that of the estimate of the effect. Moderate quality evidence indicates moderate confidence, and that the *true* effect is likely close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality evidence indicates that our confidence in the effect estimate is limited, and that the *true* effect may be substantially different. Finally, very low quality evidence indicates that the estimate of effect of interventions is very uncertain, the *true* effect is likely to be substantially different from the effect estimate and further research is likely to have important potential for reducing the uncertainty.

The strength of recommendations is expressed as either strong ('guideline panel recommends…') or conditional ('guideline panel suggests…') and has explicit implications (see **Table 1**). Understanding the interpretation of these two grades is essential for sagacious clinical decision making.

Table 1: Interpretation of strong and conditional (weak) recommendations

Implications	Strong recommendation	Conditional (weak) recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences.
For policy makers	The recommendation can be adapted as policy in most situations	Policy making will require substantial debate and involvement of various stakeholders.

Key questions

1. What are the consequences of using venography to diagnose first DVT?
2. What are the consequences of using venography to rule out first DVT?
3. What are the consequences of using compression ultrasonography (CUS) to diagnose proximal DVT?
4. What are the consequences of using serial proximal CUS to exclude DVT?
5. What are the consequences of using a highly sensitive D-dimer as a stand-alone test to exclude DVT?
6. What are the consequences of using D-dimer and pretest probability to exclude DVT?
7. What are the consequences of using a negative proximal CUS and negative D-dimer to exclude DVT?
8. What are the consequences of using pretest probability with a negative proximal CUS to exclude DVT?
9. What are the consequences of using serial proximal CUS to exclude DVT in patients with a low/moderate/high pretest probability?
10. What are the consequences of using serial proximal CUS to exclude DVT in patients with a positive D-dimer?
11. What are the consequences of using a negative D-dimer to obviate the need for serial testing in patients with a negative proximal CUS and moderate or high pretest probability at presentation? (1) Negative proximal CUS plus moderate pretest probability. (2) Negative proximal CUS plus high pretest probability.

Recommendations

Recommendation 1:
The Ministry of Health of Saudi Arabia guideline panel recommends the use of a clinical strategy to assess the pretest probability based on Wells criteria compared to not using a strategy, for the diagnosis of suspected first lower extremity DVT. (Strong recommendation, Moderate quality of evidence)

Recommendation 2:
The Ministry of Health of Saudi Arabia panel recommends the use of highly sensitivity D-dimer (ELISA) as an initial test for the diagnosis of DVT in patients with low pretest probability of first lower extremity DVT. (Strong recommendation, Moderate quality of evidence)

Recommendation 3:
The Ministry of Health of Saudi Arabia guideline panel recommends the use of proximal CUS as an initial test for the diagnosis of DVT in patients with low pretest probability of first lower extremity DVT. (Strong recommendation, Low quality of evidence)

Recommendation 4:
The Ministry of Health of Saudi Arabia guideline panel suggests the use of highly sensitive D-dimer (ELISA) rather than proximal CUS as an initial test for the diagnosis of DVT in patients with low pretest probability of first lower extremity DVT. (Weak recommendation, Low quality of evidence)

Recommendation 5:
The Ministry of Health of Saudi Arabia guideline panel recommends no further testing over further investigation with proximal CUS in patients with low pretest probability of first lower extremity DVT and negative highly sensitive D-dimer test (ELISA). (Strong recommendation, Low quality of evidence)

Recommendation 6:
The Ministry of Health of Saudi Arabia guideline panel recommends no further investigation rather than venography in patients with low pretest probability of first lower extremity DVT, after negative initial proximal CUS. (Strong recommendation, Moderate-level quality)

Recommendation 7:
The Ministry of Health of Saudi Arabia guideline panel recommends performing proximal CUS rather than venography in patients with low pretest probability of first lower extremity DVT and positive highly sensitive D-dimer test (ELISA). (Strong recommendation, Low quality of evidence)

Recommendation 8:
The Ministry of Health of Saudi Arabia panel recommends no further investigation, rather than confirmatory venography, in patients with low pretest probability of first lower extremity DVT and positive proximal CUS. (Strong recommendation, Low quality of evidence)

Recommendation 9:
The Ministry of Health of Saudi Arabia panel recommends the use of highly sensitivity D-dimer (ELISA) as an initial test for the diagnosis of DVT in patients with moderate pretest probability of first lower extremity DVT. (Strong recommendation, Moderate quality of evidence)

Recommendation 10:
The Ministry of Health of Saudi Arabia guideline panel recommends the use of proximal CUS as an initial test for the diagnosis of DVT in patients with moderate pretest probability of first lower extremity DVT. (Strong recommendation, Low quality of evidence)

Recommendation 11:
The Ministry of Health of Saudi Arabia guideline panel suggests the use of highly sensitive D-dimer (ELISA) rather than proximal CUS as an initial test for the diagnosis of DVT in patients with moderate pretest probability of first lower extremity DVT. (Weak recommendation, Low quality of evidence)

Recommendation 12:
The Ministry of Health of Saudi Arabia guideline panel recommends no further testing over further investigation with proximal CUS in patients with moderate pretest probability of first lower extremity DVT and negative highly sensitive D-dimer test (ELISA). (Strong recommendation. Low quality of evidence)

Recommendation 13:
The Ministry of Health of Saudi Arabia guideline panel recommends performing proximal CUS rather than venography in patients with moderate pretest probability of first lower extremity DVT and positive highly sensitive D-dimer test (ELISA). (Strong recommendation, Low quality of evidence)

Recommendation 14:
The Ministry of Health of Saudi Arabia guideline panel suggests no further testing rather than repeat proximal CUS in patients with a moderate pretest probability of first lower extremity DVT and negative initial proximal CUS. (Weak recommendation, Low quality of evidence)

Recommendation 15:
The Ministry of Health of Saudi Arabia guideline suggests repeating proximal CUS in one week over no further testing in patients with moderate pretest probability of first lower extremity DVT and initial negative proximal CUS and positive highly sensitive D-dimer test (ELISA). (Weak recommendation, Low quality of evidence)

Recommendation 16:
The Ministry of Health of Saudi Arabia panel recommends no further investigation, rather than confirmatory venography, in patients with moderate pretest probability of first lower extremity DVT and positive proximal CUS. (Strong recommendation, Low quality of evidence)

Recommendation 17:
The Ministry of Health of Saudi Arabia panel recommends against the use of highly sensitivity D-dimer (ELISA) as a standalone test to rule out DVT in patients with high pretest probability of first lower extremity DVT. (Strong recommendation, Moderate quality of evidence

Recommendation 18:
The Ministry of Health of Saudi Arabia panel recommends against the use of proximal CUS as a standalone test to rule out DVT in patients with high pretest probability of first lower extremity DVT. (Strong recommendation, Moderate quality of evidence)

Recommendation 19:
The Ministry of Health of Saudi Arabia panel recommends no further investigation, rather than confirmatory venography, in patients with high pretest probability of first lower extremity DVT and positive proximal CUS. (Strong recommendation, Moderate quality of evidence)

Recommendation 20:
The Ministry of Health of Saudi Arabia guideline panel recommends repeating proximal CUS in one week rather than no further testing in patients with a high pretest probability of first lower extremity DVT and negative initial proximal CUS. (Strong recommendation, Moderate quality of evidence)

Recommendation 21:
The Ministry of Health of Saudi Arabia panel recommends additional testing with highly sensitive D-dimer (ELISA) rather than no further testing in patients with high pretest probability of first lower extremity DVT and initial negative proximal CUS. (Strong recommendation, Low quality of evidence)

Recommendation 22:
The Ministry of Health of Saudi Arabia panel recommends repeating proximal CUS in one week over performing venography in patients with high pretest probability of first lower extremity DVT, negative initial proximal CUS negative and positive highly sensitive D-dimer test (ELISA). (Strong recommendation, Low quality of evidence)

Recommendation 23:
The Ministry of Health of Saudi Arabia panel recommends no further testing rather than venography in patients with high pretest probability of first lower extremity DVT and negative serial proximal CUS. (Strong recommendation, Moderate quality of evidence)

Recommendation 24:
The Ministry of Health of Saudi Arabia panel recommends no further testing rather than venography in patients with high pretest probability of first lower extremity DVT, negative highly sensitive D-dimer test (ELISA) and negative proximal CUS. (Strong recommendation, Low quality of evidence)

Scope and purpose

The purpose of this document is to provide guidance for the diagnosis of suspected first deep vein thrombosis (DVT) of the lower extremity. Recommendations are applicable for the ambulatory setting (i.e., outpatient or emergency department). The target audience of these guidelines includes primary care physicians, specialists in internal medicine and in emergency medicine in the Kingdom of Saudi Arabia. Other health care professionals and policy makers may also benefit from these guidelines.

Given the importance of this topic, the Ministry of Health (MoH) of Saudi Arabia with the methodological support of the McMaster University working group produced clinical practice guidelines to assist health care providers in evidence-based clinical decision-making. This clinical practice guideline is a part of the larger initiative of the Ministry of Health of Saudi Arabia to establish a program of rigorous adaptation and de novo development of guidelines in the Kingdom; the ultimate goal being to provide guidance for clinicians and reduce variability in clinical practice across the Kingdom.

Introduction

DVT is a common condition, affecting approximately 100 in 100,000 persons per year.[1,4,5] Incidence increases with age, rising exponentially from less than 5 per 100,000 per year in those aged under 15 to over 500 per 100,000 per year in those aged over 80 years in the West.[6,7] The true incidence of DVT in KSA is unknown. Clinical assessment is inaccurate for diagnosing DVT. Misdiagnosis is an important concern. While not treating DVT may result in serious complications such as pulmonary embolism, the overtreatment is associated with higher bleeding rates, including intracranial and gastrointestinal hemorrhages.[8-11]

Usually, diagnostic strategies for DVT consist of sequential testing in order to improve diagnostic accuracy, thus, minimizing the health consequences of misdiagnosis and overtreatment. Three categories of tests are typically used to determine the probability of DVT: (1)clinical pretest probability assessment, (2) D-dimer assay, and (3) imaging studies, most commonly proximal venous compression ultrasound (CUS), however other tests may be occasionally used, such as contrast venography, that is still considered the reference standard for DVT diagnosis, CT scan and MRI.[1,6]

Methodology

To facilitate the interpretation of these guidelines; we briefly describe the methodology we used to develop and grade recommendations and quality of the supporting evidence. We present the detailed methodology in a separate publication.[12]

The KSA guideline panel selected the topic of this guideline and all clinical questions addressed herein using a formal prioritization process. For all selected questions we updated existing systematic reviews that were used for the "Diagnosis of DVT" chapter of the 2012 Antithrombotic Therapy and Prevention of Thrombosis guidelines, 9th edition (see **Appendix 1**).[1] We also conducted systematic searches for information that was required to develop full guidelines for the KSA, including searches for information about patients' values and preferences and cost (resource use) specific to the Saudi context. Based on the updated systematic reviews we prepared summaries of available evidence supporting each recommendation following the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach.[2]
Results of diagnostic accuracy studies were presented as sensitivity, specificity and post-test probabilities of having DVT during the follow-up period. In order to estimate the impact on patient-important outcomes, when possible, simulations of crude rate of events were provided for the panel members to support the clinical judgment. We used the baseline risks for undesirable events presented in

the systematic review. The assumed rates of fatal and non-fatal pulmonary embolism were respectively 0.3% and 1.4% for treated patients and 1.9% and 9.3% for untreated patients. Assumed risk for fatal bleeding, non-fatal intracranial bleeding and non-fatal non-intracranial bleeding were respectively 0.3%, 2.1% and 0.1% for patients using antithrombotic therapy.[1,6] The link between the diagnosis/treatment of DVT and the occurrence of adverse outcomes was considered strong, thus, the quality of evidence was not downgraded due to indirectness in these circumstances.

We assessed the quality of evidence using the system described by the GRADE working group.[13] Quality of evidence is classified as "high", "moderate", "low", or "very low" based on decisions about methodological characteristics of the available evidence for a specific health care problem. The definition of each category is as follows:

- *High*: We are very confident that the true effect lies close to that of the estimate of the effect.
- *Moderate*: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- *Low*: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- *Very low*: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

According to the GRADE approach, the strength of a recommendation is either strong or conditional (weak) and has explicit implications (see **Table 1**). Understanding the interpretation of these two grades – either strong or conditional – of the strength of recommendations is essential for sagacious clinical decision-making.

Based on this information and the input of KSA MoH panel members we prepared the evidence-to-recommendation tables that served the guideline panel to follow the structured consensus process and transparently document all decisions made during the meeting (see **Appendix 2**). The guideline panel met in Riyadh on December 3, 2013 and formulated all recommendations during this meeting. Potential conflicts of interests of all panel members were managed according to the World Health Organization (WHO) rules.[3]

How to use these guidelines

The Ministry of Health of Saudi Arabia and McMaster University Clinical Practice Guidelines provide clinicians and their patients with a basis for rational decisions in the diagnosis of DVT. Clinicians, patients, third-party payers, institutional review committees, other stakeholders, or the courts should never view these recommendations as dictates. No guidelines and recommendations can take into account all of the often-compelling unique features of individual clinical circumstances. Therefore, no one charged with evaluating clinicians' actions should attempt to apply the recommendations from these guidelines by rote or in a blanket fashion.

Statements about the underlying values and preferences as well as qualifying remarks accompanying each recommendation are its integral parts and serve to facilitate an accurate interpretation. They should never be omitted when quoting or translating recommendations from these guidelines.

Key questions

The following is a list of the clinical questions selected by the KSA guideline panel and addressed in this guideline. For details on the process by which the questions were selected please refer to the separate methodology publication.[12]

1. What are the consequences of using venography to diagnose first DVT?
2. What are the consequences of using venography to rule out first DVT?
3. What are the consequences of using compression ultrasonography (CUS) to diagnose proximal DVT?
4. What are the consequences of using serial proximal CUS to exclude DVT?
5. What are the consequences of using a highly sensitive D-dimer as a stand-alone test to exclude DVT?
6. What are the consequences of using D-dimer and pretest probability to exclude DVT?
7. What are the consequences of using a negative proximal CUS and negative D-dimer to exclude DVT?
8. What are the consequences of using pretest probability with a negative proximal CUS to exclude DVT?
9. What are the consequences of using serial proximal CUS to exclude DVT in patients with a low/moderate/high pretest probability?
10. What are the consequences of using serial proximal CUS to exclude DVT in patients with a positive D-dimer?
11. What are the consequences of using a negative D-dimer to obviate the need for serial testing in patients with a negative proximal CUS and moderate or high pretest probability at presentation? (1) Negative proximal CUS plus moderate pretest probability. (2) Negative proximal CUS plus high pretest probability.

Questions were structured as presented below in order to allow the development of the diagnostic algorithms. The reason was the codependency of the questions, since the strategies evaluated mainly consisted of sequential testing.

The diagnostic tests evaluated were clinical assessment of pretest probability, highly sensitive D-dimer (ELISA), CUS and contrast venography.

I - Clinical assessment of pretest probability of first lower extremity DVT

1. In patients with a suspected first lower extremity DVT, should the choice of diagnostic tests process be guided by the clinical assessment of pretest probability rather than by performing the same diagnostic tests in all patients?

II - Patients with low pretest probability of first lower extremity DVT

2. In patients with low pretest probability of first lower extremity DVT, should we use highly sensitive D-dimer (ELISA) as an initial test for the diagnosis of DVT?
3. In patients with low pretest probability of first lower extremity DVT, should we use proximal CUS as an initial test for the diagnosis of DVT?
4. In patients with low pretest probability of first lower extremity DVT, should we use highly sensitive D-dimer (ELISA) instead of proximal CUS as initial test for the diagnosis of DVT?
5. In patients with low pretest probability of first lower extremity DVT and negative highly sensitive D-dimer test (ELISA), should we perform proximal CUS instead of discharge with no further evaluation?
6. In patients with low pretest probability of first lower extremity DVT and negative proximal CUS, should we perform venography instead of discharge with no further evaluation?
7. In patients with low pretest probability of first lower extremity DVT and positive highly sensitive D-dimer test (ELISA), should we perform proximal CUS instead of venography?
8. In patients with low pretest probability of first lower extremity DVT and positive proximal CUS, should we perform contrast venography instead of treatment, without further investigation?

III - Patients with moderate pretest probability of first lower extremity DVT

9. In patients with a moderate pretest probability of first lower extremity DVT, should we use highly sensitive D-dimer (ELISA) as an initial test for the diagnosis of DVT?
10. In patients with moderate pretest probability of first lower extremity DVT, should we use proximal CUS as an initial test for the diagnosis of DVT?
11. In patients with moderate pretest probability of first lower extremity DVT, should we use highly sensitive D-dimer (ELISA) instead of proximal CUS as the initial test for the diagnosis of DVT?
12. In patients with moderate pretest probability of first lower extremity DVT and negative highly sensitive D-dimer test (ELISA), should we perform proximal CUS instead of discharge with no further evaluation?
13. In patients with moderate pretest probability of first lower extremity DVT and positive highly sensitive D-dimer test (ELISA), should we perform proximal CUS instead of venography?
14. In patients with moderate pretest probability of first lower extremity DVT, negative proximal CUS and positive highly sensitive D-dimer test (ELISA), should we repeat proximal CUS in 1 week instead of rule out without further investigation?
15. In patients with moderate pretest probability of first lower extremity DVT, negative proximal CUS and negative highly sensitive D-dimer test (ELISA), should we repeat proximal CUS in 1 week instead of rule out without further investigation?
16. In patients with moderate pretest probability of first lower extremity DVT and positive proximal CUS, should we perform venography instead of treatment, without further investigation?

IV - Patients with high pretest probability of first lower extremity DVT

17. In patients with high pretest probability of first lower extremity DVT, should we use highly sensitive D-dimer (ELISA) as an initial test to rule out the diagnosis of DVT?
18. In patients with high pretest probability of first lower extremity DVT, should we use proximal CUS as an initial test to rule out the diagnosis of DVT?
19. In patients with high pretest probability of first lower extremity DVT and positive proximal CUS, should we perform proximal venography instead of treatment without further investigation?
20. In patients with high pretest probability of first lower extremity DVT and negative initial proximal CUS, should we repeat proximal CUS instead of rule out without further investigation?
21. In patients with high pretest probability of first lower extremity DVT and negative initial proximal CUS, should we use highly sensitive D-dimer test (ELISA) instead of rule out without further investigation?
22. In patients with high pretest probability of first lower extremity DVT, positive highly sensitive D-dimer test (ELISA) and negative CUS , should we repeat proximal CUS instead of venography?
23. In patients with high pretest probability of first lower extremity DVT and negative serial CUS, should we perform venography instead of rule out without further investigation?
24. In patients with high pretest probability of first lower extremity DVT, negative highly sensitive D-dimer test (ELISA) and negative proximal CUS, should we perform venography instead of rule out without further investigation?

Recommendations

Implications of Values and Preferences in the Diagnostic Process

Patient-important outcomes:

No evidence specific for the Middle East context was identified. A recent systematic review was identified evaluating values and preferences of patients considering antithrombotic therapy.[14] Utility values for outcomes considered critical for decision making are summarized in **Table 2**.

The panel members assumed that the values on outcomes of the people in the Middle East are probably similar to those in other populations. Based on the presented evidence, the panel concluded that there might be some degree of variability in values and preferences, the importance of major bleeding is equivalent to pulmonary embolism, intracranial bleeding is 2 to 3 times worse than non-intracranial major bleeding or pulmonary embolism, and the DVT treatment is generally well accepted.

Table 2: Values and preferences of patients considering antithrombotic therapy

Outcome	Utility (range)
Death	0
Nonfatal Intracranial Bleed (severe)	0.1 – 0.51
Nonfatal Intracranial Bleed (moderate)	0.29 – 0.77
Nonfatal Intracranial Bleed (mild)	0.47 – 0.94
Nonfatal Pulmonary Embolism	0.63
Major bleed	0.44 – 0.84

Utility values range from 0 to 1. Zero is attributed to death while 1 represents perfect state of health.

Diagnostic tests:
No evidence was identified. The panel members concluded that the acceptability of D-dimer testing and of CUS may be considered similar in the KSA setting, however some women may refuse US performed by a man. Patients would prefer D-dimer testing and proximal CUS over contrast venography due to the discomfort and potential adverse events.

I - Clinical assessment of pretest probability of first lower extremity DVT

Question 1: In patients with a suspected first lower extremity DVT, should the choice of diagnostic tests process be guided by the clinical assessment of pretest probability rather than by performing the same diagnostic tests in all patients?

Summary of findings:
Pretest probability assessment is commonly used in practice associated to proximal CUS and D-dimer testing. Several structured scoring systems have been developed for this purpose, the most studied system is the Wells score (see **Table 3**).[15,16] This system categorizes patients as having low (5.0%, 95%CI, 4.0% - 8.0%), moderate (17%, 95%CI, 13% - 23%), or high probability of having DVT (53%, 95%CI, 44% - 61%).[16]

Table 3: Simplified Clinical Model for Assessment of Deep Vein Thrombosis*

Clinical Variable	Score
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swelling	1
Calf swelling at least 3 cm larger than that on the asymptomatic leg (measured 10 cm below the tibial tuberosity)†	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Previously documented DVT	1
Alternative diagnosis at least as likely as DVT	-2
Abbreviation: DVT, deep vein thrombosis. *Scoring method indicates high probability if score is 3 or more; moderate if score is 1 or 2; and low if score is 0 or less. †In patients with symptoms in both legs, the more symptomatic leg was used.	

Adapted from Wells PS, Owen C, Doucette S, Fergusson D, Tran H. Does this patient have deep vein thrombosis? JAMA. 2006 Jan 11;295(2):199-207.

We identified only one recent randomized controlled trial (RCT) comparing the clinical assessment of the pretest probability of having DVT (followed by a diagnostic strategy) with a uniform diagnostic strategy without clinical assessment of the pretest probability.[17] This study was identified in our update of the systematic review; no other RCTs had been identified. We based our judgments on this study.

The trial randomized 1723 patients (89% outpatients). Of note, study personnel were not blinded and the trial was stopped prematurely. During the three months of follow-up, no differences were observed in the risk of venous thromboembolism (VTE) (0%, 95%CI -0.8% to 0.8%), major bleeding events (0.1%, 95%CI -0.5% to 0.7%) or death (0%, 95%CI -1.3% to 1.3%) with the strategy based on the clinical assessment of pretest probability compared to the uniform strategy.[17] (Moderate quality of evidence)

Resource use:
Clinical pretest probability assessment does not add costs, since the clinical variables considered are usually part of the anamnesis and physical exam of a patient with suspected DVT. Number of tests required was lower for the strategy based on clinical assessment of pretest probability (-21.8%, 95%CI -19.1% to -24.8% and -7.6%, 95%CI -2.9% to -12.2% for D-dimer testing and ultrasound respectively).[17] (Moderate quality of evidence)

Although there was no formal economic assessment, the strategy was considered cost-saving, once the number of tests required was lower and the rate of events was similar.

Other considerations:
Although the recommendation was considered an acceptable option to stakeholders, there may be resistance on its use by some physicians.

Implementation considerations:
Administrative empowerment and educational interventions may be needed to overcome potential expected initial resistance. When applicable, the use of new technologies may be helpful for the implementation (e.g. inclusion of the criteria in computerized patient data entry)

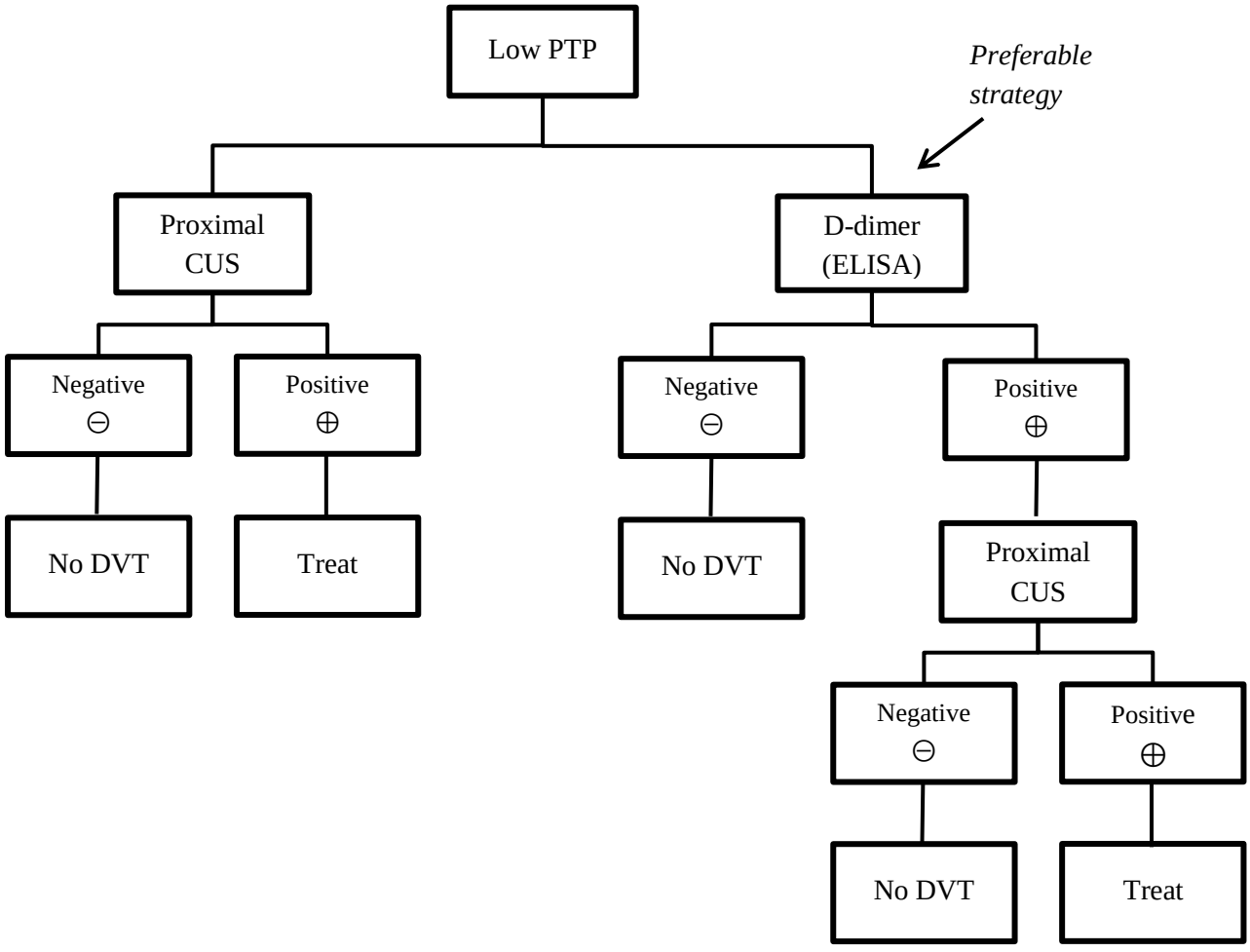
Recommendation 1:

The Ministry of Health of Saudi Arabia guideline panel recommends the use of a clinical strategy to assess the pretest probability based on Wells criteria compared to not using a strategy, for the diagnosis of suspected first lower extremity DVT. (Strong recommendation, Moderate quality of evidence)

II – Diagnostic strategy in patients with low pretest probability of first lower extremity DVT

Questions 2 to 8 are related to the diagnostic strategy of DVT in patients with low clinical pretest probability of first lower extremity DVT. Figure 1 summarizes the diagnostic recommendations.

Figure 1: Recommendations for evaluation of suspected first lower extremity DVT in patients with low pretest probability.



PTP – Pretest probability; CUS – Compression ultrasound; DVT: Deep vein thrombosis

Question 2: In patients with low pretest probability of first lower extremity DVT, should we use highly sensitive D-dimer (ELISA) as an initial test for the diagnosis of DVT?

Summary of findings:
Our judgments were based on a systematic review published in 2006, including 217 management cohorts and accuracy studies evaluating diagnostic properties of D-dimer in patients with suspected VTE.[6] We identified seven additional studies, that could not be pooled with the systematic review.[18-24] For ELISA D-dimer assays, the pooled sensitivity and specificity for DVT were 94% (95%CI 93% to 95%) and 45% (95%CI 44% to 46%) respectively. (Moderate quality of evidence) These data will be used for the assessment of all questions related to D-dimer testing as a standalone test or combined with a single proximal CUS.

Only 3 patients per 1000 tested would be incorrectly classified as not having DVT (false negatives). On the other hand, 523 patients would be incorrectly classified as having DVT (false positives), requiring further investigation. The probability of having DVT after a negative test is 0.70% and after a positive test is 8.25%. With no testing or treatment, we would have respectively 0.8 and 3.6 additional cases of fatal and non-fatal pulmonary per 1000 patients initially tested. (Moderate quality of evidence)

Resource use:
The cost of ELISA D-dimer assay was considered low for the Saudi context by the panel members.

Recommendation 2:

The Ministry of Health of Saudi Arabia panel recommends the use of highly sensitivity D-dimer (ELISA) as an initial test for the diagnosis of DVT in patients with low pretest probability of first lower extremity DVT. (Strong recommendation, Moderate quality of evidence)

Question 3: In patients with low pretest probability of first lower extremity DVT, should we use proximal CUS as an initial test for the diagnosis of DVT?

Summary of findings:
Our judgments were based on a systematic review published in 2006 including 100 management cohorts and accuracy studies evaluating diagnostic properties of ultrasound in patients with suspected DVT. The meta-analysis pooled 22 studies specifically evaluating proximal CUS.[6] We identified four additional studies, which could not be pooled with the systematic review.[25-28] The pooled sensitivity and specificity for DVT was 90.3% (95%CI 88.4% to 92%) and 97.8% (95%CI 97% to 98.4%) respectively. (Low quality of evidence) Quality of evidence was downgraded due to inconsistency specifically for patients with low and moderate pretest probability because the sensitivity of the test tends to be higher in patients with higher pretest probability of DVT. These data will be used for the assessment of all questions related to proximal CUS as a standalone test or combined with D-dimer testing.

Only 5 patients per 1000 tested would be incorrectly classified as not having DVT (false negatives). On the other hand, 21 patients would be incorrectly classified as having DVT (false positives). The probability of having DVT after a negative test is 0.52% and after a positive test is 68.4%. Treating those patients with a positive test and discharging those with negative test, would result on 0.14 deaths, 0.36 cases of non-fatal pulmonary embolism and 0.35 major bleeding episodes (0.02 intracranial) per 1000 patients. With no testing or treatment, we would have respectively 0.8 and 3.6 additional cases of fatal and non-fatal pulmonary per 1000 patients. (Low quality of evidence)

Resource use:
The cost of proximal CUS was considered low for the Saudi context by the panel members.

Recommendation 3:

The Ministry of Health of Saudi Arabia guideline panel recommends the use of proximal CUS as an initial test for the diagnosis of DVT in patients with low pretest probability of first lower extremity DVT. (Strong recommendation, Low quality of evidence)

Question 4: In patients with low pretest probability of first lower extremity DVT, should we use highly sensitive D-dimer (ELISA) instead of proximal CUS as initial test for the diagnosis of DVT?

Summary of findings:
No evidence directly combining these two interventions was identified. To make judgments, we indirectly combined data available from questions 2 and 3. For proximal CUS, the pooled sensitivity and specificity for DVT were 90.3% (95%CI 88.4% to 92%) and 97.8% (95%CI 97% to 98.4%) respectively.[6] (Low quality of evidence) For D-dimer testing, the pooled sensitivity and specificity for DVT was 94% (95%CI 93% to 95%) and 45% (95%CI 44% to 46%) respectively. (Moderate quality of evidence)

With proximal CUS, only 5 patients per 1000 tested would be incorrectly classified as not having DVT (false negatives). On the other hand, 21 patients would be incorrectly classified as having DVT (false positives). Similarly with D-dimer (ELISA), only 3 patients per 1000 tested would be incorrectly classified as not having DVT. However, 428 patients would be discharged with no need of a further test (D-dimer negative).

Resource use:
The cost of D-dimer is lower than the cost of proximal CUS. Using D-dimer as an initial test probably would be cost-saving in the Saudi setting.

Recommendation 4:

The Ministry of Health of Saudi Arabia guideline panel suggests the use of highly sensitive D-dimer (ELISA) rather than proximal CUS as an initial test for the diagnosis of DVT in patients with low pretest probability of first lower extremity DVT. (Weak recommendation, Low quality of evidence)

Question 5: In patients with low pretest probability of first lower extremity DVT and negative highly sensitive D-dimer test (ELISA), should we perform proximal CUS instead of discharge with no further evaluation?

Summary of findings:
As reported in question 2, using D-dimer as initial test, 3 patients per 1000 tested would be incorrectly classified as not having DVT. The probability of having DVT after a negative test is 0.70%. If patients with D-dimer negative be discharged with no further testing, we would have 0.05 and 0.22 additional cases of fatal and non-fatal pulmonary among the false negatives per 1000 patients tested.[6] (Moderate quality of evidence)

In patients with sequential D-dimer and proximal CUS negatives, the posttest probability would be negligible (0.07%). Otherwise, the number of false positives would increase 9 per 1000 initially tested. Thus, we would expect an increase of 0.03 deaths and 0.2 non-fatal major bleeding events per 1000 patients tested.[6] (Low quality of evidence)

Resource use:
Performing proximal CUS in patients with low clinical pretest probability and D-Dimer negative would increase costs: 428 additional ultrasounds would be needed per 1000 patients initially tested.

Recommendation 5:

The Ministry of Health of Saudi Arabia guideline panel recommends no further testing over further investigation with proximal CUS in patients with low pretest probability of first lower extremity DVT and negative highly sensitive D-dimer test (ELISA). (Strong recommendation, Low quality of evidence)

Question 6: In patients with low pretest probability of first lower extremity DVT and negative proximal CUS, should we perform venography instead of discharge with no further evaluation?

Summary of findings:
For contrast venography, only a single-arm prospective cohort study, evaluating 160 patients with unknown clinical pretest probability, was identified. The prevalence of DVT in the study population was not described. Post a negative test, the probability of having recurrent VTE during 3 months of follow of up is 1.2% (95%CI 0.2% to 4.4%).[29] (Moderate quality of evidence)

Similarly, after proximal CUS, only 5 patients per 1000 tested would be incorrectly classified as not having DVT (0.52% probability of having DVT after a negative test). (Low quality of evidence)

Resource use:
Contrast venography is an expensive diagnostic test compared to proximal CUS.

Other considerations:
Venography is considered the reference standard for DVT, however, it is subject to a considerably variation. Although often considered as 100%, the posttest probability of a positive test cannot be estimated with confidence. There are no studies evaluating contrast venography in patients with low risk for DVT. Additionally, venography is associated with 1 to 4% of incidence of adverse reactions to contrast media, including dizziness and nausea, severe allergic reaction in 0 to 0.4% and post-venography DVT in 0 to 2% of patients.[1]

Implementation considerations:
The required technology for performing contrast venography is not widely available in the Kingdom of Saudi Arabia.

Recommendation 6:

The Ministry of Health of Saudi Arabia guideline panel recommends no further investigation rather than venography in patients with low pretest probability of first lower extremity DVT, after negative initial proximal CUS (Strong recommendation, Low quality of evidence)

Question 7: In patients with low pretest probability of first lower extremity DVT and positive highly sensitive D-dimer test (ELISA), should we perform proximal CUS instead of venography?

Summary of findings:
As described in question 6, after a negative contrast venography, the probability of having recurrent VTE during 3 months of follow of up is 1.2% (95%CI 0.2% to 4.4%).[29] (Moderate quality of evidence)

In patients with low pretest clinical probability and positive D-Dimer test, the probability of having DVT after a negative proximal CUS is 0.88% and the probability after a positive CUS is 78.69%. Per 1000 patients initially tested, 11 patients without DVT would be treated and 5 patients with DVT and D-dimer positive would be discharged. Due to misdiagnosing, we would have additionally 0.11 deaths, 0.36 cases of non-fatal pulmonary embolism and 0.23 major bleeding episodes (0.01 intracranial) per 1000 patients. (Low quality of evidence)
Resource use:
Contrast venography is an expensive diagnostic test compared to proximal CUS.

Other considerations:
Venography is considered the reference standard for DVT, however it is subject to a considerably variation. Although often considered as 100%, the posttest probability of a positive test cannot be estimated with confidence. There are no studies evaluating contrast venography in patients with low risk for DVT. Additionally, venography is associated with 1 to 4% of incidence of adverse reactions to contrast media, including dizziness and nausea, severe allergic reaction in 0 to 0.4% and post-venography DVT in 0 to 2% of patients.[1]

Implementation considerations:
The required technology for performing contrast venography is not widely available in the Kingdom of Saudi Arabia.

Recommendation 7:

The Ministry of Health of Saudi Arabia guideline panel recommends performing proximal CUS rather than venography in patients with low pretest probability of first lower extremity DVT and positive highly sensitive D-dimer test (ELISA) (Strong recommendation, Low quality of evidence)

Question 8: In patients with low pretest probability of first lower extremity DVT and positive proximal CUS, should we perform contrast venography instead of treatment, without further investigation?

Summary of findings:
As described in question 6, after a negative contrast venography, the probability of having recurrent VTE during 3 months of follow of up is 1.2% (95%CI 0.2% to 4.4%).[29] (Moderate quality of evidence)

As reported in question 3, 21 patients per 1000 tested with proximal CUS would be incorrectly classified as not having DVT. Treating unnecessary this patients we would result in 0.06 deaths and 0.46 major bleeding

episodes (0.02 intracranial). (Moderate quality of evidence)

Resource use:
Contrast venography is an expensive diagnostic test compared to proximal CUS.

Other considerations:
Venography is considered the reference standard for DVT, however it is subject to a considerably variation. Although often considered as 100%, the posttest probability of a positive test cannot be estimated with confidence. There are no studies evaluating contrast venography in patients with low risk for DVT. Additionally, venography is associated with 1 to 4% of incidence of adverse reactions to contrast media, including dizziness and nausea, severe allergic reaction in 0 to 0.4% and post-venography DVT in 0 to 2% of patients.[1]

Implementation considerations:
The required technology for performing contrast venography is not widely available in the Kingdom of Saudi Arabia.

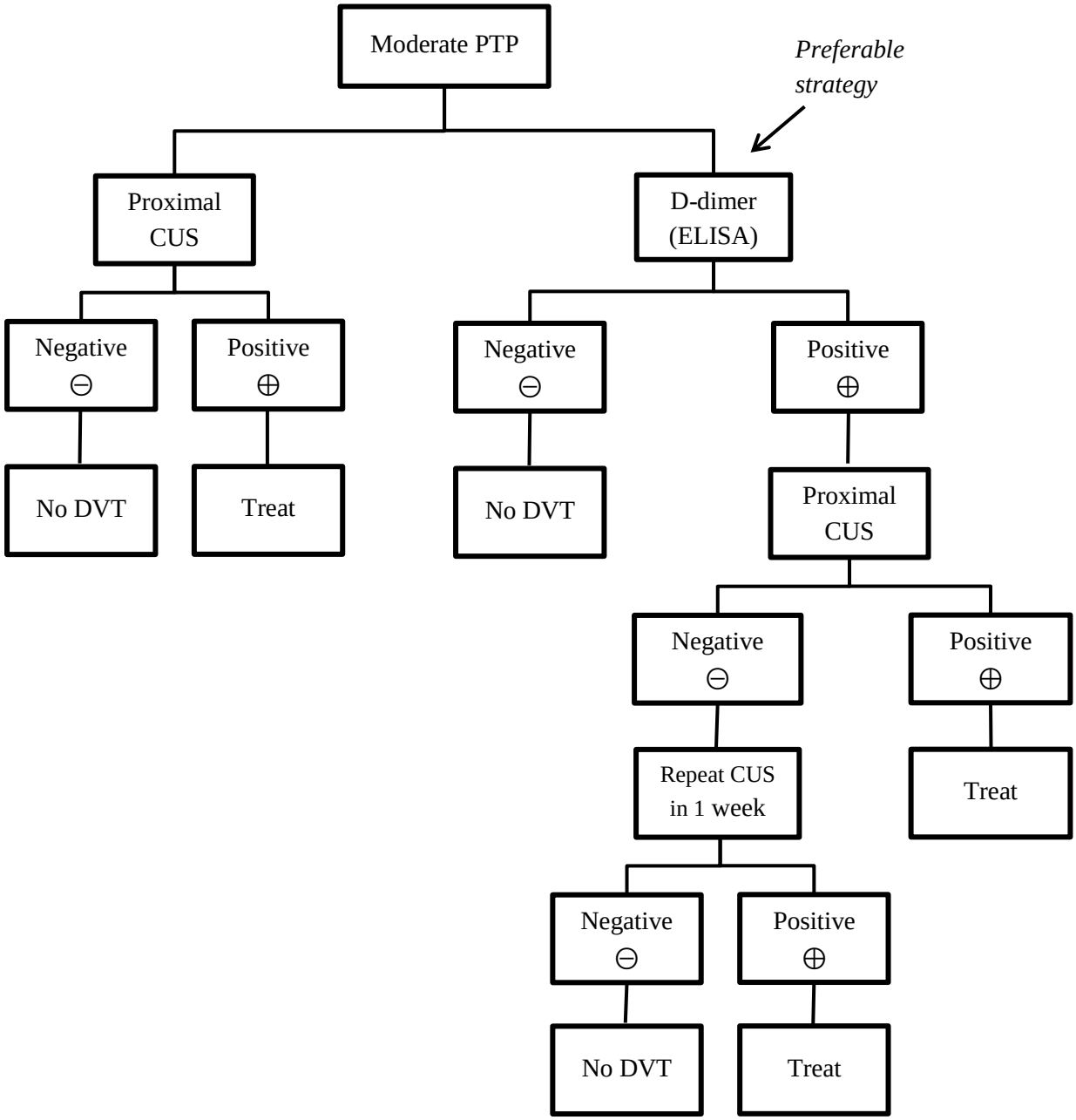
Recommendation 8

The Ministry of Health of Saudi Arabia panel recommends no further investigation, rather than confirmatory venography, in patients with low pretest probability of first lower extremity DVT and positive proximal CUS. (Strong recommendation, Low quality of evidence)

III – Diagnostic strategy in patients with moderate pretest probability of first lower extremity DVT

Questions 9 to 16 are related to the diagnostic strategy of DVT in patients with moderate clinical pretest probability of first lower extremity DVT. Figure 2 summarizes the diagnostic recommendations.

Figure 2: Recommendations for evaluation of suspected first lower extremity DVT in patients with moderate pretest probability.



PTP – Pretest probability; CUS – Compression ultrasound; DVT: Deep vein thrombosis

Question 9: In patients with moderate pre-test probability of first lower extremity DVT, should we use D-dimer (ELISA) as an initial test for the diagnosis of DVT?

Summary of findings:
As reported in question 2, for D-dimer, the estimates of sensitivity and specificity are 94% (95%CI 93% to 95%) and 45% (95%CI 44% to 46%) respectively.[6] (Moderate quality of evidence)

With this strategy, only 10 patients per 1000 tested would be incorrectly classified as not having DVT (false negatives). On the other hand, 457 patients would be incorrectly classified as having DVT (false positives). The probability of having DVT after a negative test is 2.7% and after a positive test is 25.9%. With no testing or treatment, we would have respectively 2.7 and 12.2 additional cases of fatal and non-fatal pulmonary per 1000 patients.

Resource use:
The cost of ELISA D-dimer assay was considered low for the Saudi context by the panel members.

Recommendation 9:

The Ministry of Health of Saudi Arabia panel recommends the use of highly sensitivity D-dimer (ELISA) as an initial test for the diagnosis of DVT in patients with moderate pretest probability of first lower extremity DVT. (Strong recommendation, Moderate quality of evidence)

Question 10: In patients with moderate pre-test probability of first lower extremity DVT, should we use proximal CUS as an initial test for the diagnosis of DVT?

Summary of findings:
As reported in question 3, for proximal CUS the estimates for sensitivity and specificity for DVT are 90.3% (95%CI 88.4% to 92%) and 97.8% (95%CI 97% to 98.4%) respectively.[6] (Low quality of evidence)

Sixteen patients per 1000 tested would be incorrectly classified as not having DVT (false negatives). On the other hand, 18 patients would be incorrectly classified as having DVT (false positives). The probability of having DVT after a negative test is 2% and after a positive test is 89.4%. Treating those patients with a positive test and discharging those with negative test, would result on 0.26 deaths, 1.15 cases of non-fatal pulmonary embolism and 0.04 major bleeding episodes (0.002 intracranial) per 1000 patients. With no testing or treatment, we would have respectively 2.7 and 12.2 additional cases of fatal and non-fatal pulmonary per 1000 patients.

Resource use:
The cost of proximal CUS was considered low for the Saudi context by the panel members.

Recommendation 10:

The Ministry of Health of Saudi Arabia guideline panel recommends the use of proximal CUS as an initial test for the diagnosis of DVT in patients with moderate pretest probability of first lower extremity DVT. (Strong recommendation, Low quality of evidence)

Question 11: In patients with moderate pre-test probability of first lower extremity DVT, should we use highly sensitive D-dimer (ELISA) instead of proximal CUS as the initial test for the diagnosis of DVT?

Summary of findings:
As reported in question 2, for D-dimer, the estimates of sensitivity and specificity are 94% (95%CI 93% to 95%) and 45% (95%CI 44% to 46%) respectively.[6] (Moderate quality of evidence) Ruling out patients with negative D-dimer, only 10 patients per 1000 tested would be incorrectly classified as not having DVT. However, 374 patients would be discharged with no need of a further test.

As reported in question 3, for proximal CUS, the estimates for sensitivity and specificity for DVT are 90.3% (95%CI 88.4% to 92%) and

97.8% (95%CI 97% to 98.4%) respectively.[6] (Low quality of evidence) With proximal CUS, 16 patients per 1000 tested would be incorrectly classified as not having DVT. On the other hand, 18 patients would be incorrectly classified as having DVT.

Resource use:
The cost of D-dimer is lower than the cost of proximal CUS. Using D-dimer ELISA as an initial test would probably be cost-saving in the Saudi setting.

Recommendation 11:

The Ministry of Health of Saudi Arabia guideline panel suggests the use of highly sensitive D-dimer (ELISA) rather than proximal CUS as an initial test for the diagnosis of DVT in patients with moderate pretest probability of first lower extremity DVT. (Weak recommendation, Low quality of evidence)

Question 12: In patients with moderate pretest probability of first lower extremity DVT and negative highly sensitive D-dimer test (ELISA), should we perform proximal CUS instead of discharge with no further evaluation?

Summary of findings:
As reported in question 2, for D-dimer, the estimates of sensitivity and specificity are 94% (95%CI 93% to 95%) and 45% (95%CI 44% to 46%) respectively.[6] (Moderate quality of evidence) As reported in question 3, for proximal CUS, the estimates for sensitivity and specificity for DVT are 90.3% (95%CI 88.4% to 92%) and 97.8% (95%CI 97% to 98.4%) respectively.[6] (Low quality of evidence)

Ruling out patients with negative D-dimer, 10 patients per 1000 tested would be incorrectly classified as not having DVT. The probability of having DVT after a negative test is 2.7%. If patients with negative D-dimer are discharged with no further testing, we would have 0.16 and 0.72 additional cases of fatal and non-fatal pulmonary among the false negatives per 1000 patients tested. (Moderate quality of evidence)

Ruling out patients with sequential D-dimer (ELISA) and proximal CUS negatives, only 1 per

1000 patients tested would be the false negative (posttest probability = 0.27%). Otherwise, the number of false positives would increase 8 per 1000 initially tested. Thus, we would expect an increase of 0.02 deaths and 0.2 non-fatal major bleeding events per 1000 patients tested. (Low quality of evidence)

Resource use:
Performing proximal CUS in patients with moderate clinical pretest probability and D-dimer negative would increase costs: 374 additional ultrasounds would be needed per 1000 patients initially tested.

Recommendation 12:

The Ministry of Health of Saudi Arabia guideline panel recommends no further testing over further investigation with proximal CUS in patients with moderate pretest probability of first lower extremity DVT and negative highly sensitive D-dimer test (ELISA). (Strong recommendation. Low quality of evidence)

Question 13: In patients with moderate pretest probability of first lower extremity DVT and positive highly sensitive D-dimer test (ELISA), should we perform proximal CUS instead of venography?

Summary of findings:
As described in question 6, after a contrast venography negative, the probability of having recurrent VTE during 3 months of follow up is 1.2% (95%CI 0.2% to 4.4%).[29] (Moderate quality of evidence)

In patients with moderate pretest clinical probability and positive D-dimer test (ELISA), the probability of having DVT after a negative CUS is 3.36% and the probability after a positive CUS is 93.49%. Per 1000 patients initially tested, 10 patients without DVT would be treated and 15 patients with DVT and D-dimer positive would be discharged. Due to misdiagnosing, we would have additional 0.23

deaths, 1.08 cases of non-fatal pulmonary embolism and fewer 0.11 major bleeding episodes per 1000 patients. (Low level of evidence)

Resource use:

Contrast venography is an expensive diagnostic test compared to proximal CUS.

Other considerations:

Venography is considered the reference standard for DVT, however it is subject to a considerably variation. Although often considered as 100%, the posttest probability of a positive test cannot be estimated with confidence. There are no studies evaluating contrast venography in patients with low risk for DVT. Additionally, venography is associated with 1 to 4% of incidence of adverse reactions to contrast media, including dizziness and nausea, severe allergic reaction in 0 to 0.4% and post-venography DVT in 0 to 2% of patients.[1]

Implementation considerations:

The required technology for performing contrast venography is not widely available in the Kingdom of Saudi Arabia.

Recommendation 13:

The Ministry of Health of Saudi Arabia guideline panel recommends performing proximal CUS rather than venography in patients with moderate pretest probability of first lower extremity DVT and positive highly sensitive D-dimer test (ELISA). (Strong recommendation, Low quality of evidence)

Question 14: In patients with moderate pretest probability of first lower extremity DVT, negative proximal CUS and positive highly sensitive D-dimer test (ELISA), should we repeat proximal CUS in 1 week instead of rule out without further investigation?

Summary of findings:

For single proximal CUS testing, as described in question 10, 16 per 1000 patients tested would be incorrectly classified as not having DVT. The probability of having DVT after a negative test is 2%. Discharging those patients with negative test would result on 0.26 deaths, 1.15 cases of non-fatal pulmonary embolism per 1000 patients initially tested. (Low quality of evidence)

For serial CUS in patients with moderate clinical pretest probability, three observational studies were identified. In these studies, the pooled prevalence of DVT was 15.8% and the probability of DVT post-negative serial CUS were 1.1% (95%CI 0.4% to 2.5%) and 0.6% (95%CI 0.4% to 0.9%).[30-32] (Moderate quality of evidence) It would represent 1 to 2 false negatives per 1000 patients, resulting on additional 0.02 to 0.04 and 0.07 to 0.14 fatal and nonfatal pulmonary embolism respectively.

Resource use:

Repeating proximal CUS in patients with moderate clinical pretest probability and negative initial CUS would increase costs: 831 additional ultrasounds would be needed per 1000 patients initially tested.

Other considerations:

Repeating the proximal CUS would reduce the rate of false negatives, however it may increase the number of false positives, resulting in higher bleeding rates.

Recommendation 14:

The Ministry of Health of Saudi Arabia guideline panel suggests no further testing rather than repeat proximal CUS in patients with a moderate pretest probability of first lower extremity DVT and negative initial proximal CUS. (Weak recommendation, Low quality of evidence)

Question 15: In patients with moderate pretest probability of first lower extremity DVT, negative proximal CUS and negative highly sensitive D-dimer test (ELISA), should we repeat proximal CUS in 1 week instead of rule out without further investigation?

Summary of findings:

As reported in question 13, in patients with moderate pretest clinical probability and positive D-dimer test, the probability of having

DVT after a negative CUS is 3.36%. Per 1000 patients initially tested, 16 patients with DVT and D-dimer positive will be discharged. Due to misdiagnosing, we would have additionally 0.25 deaths due to pulmonary embolism and 1.15 cases of non-fatal pulmonary embolism 1000 patients. (Low quality of evidence)

For repeated proximal CUS in patients with positive D-dimer test and negative initial proximal CUS, one study with 426 patients was identified. The prevalence of DVT was 18.8% and the probability of DVT after a D-dimer positive and serial CUS negative was 0% (95%CI 0 to 3.1%).[30] (Moderate quality of evidence)

Resource use:
Performing proximal CUS in patients with moderate clinical pretest probability and D-Dimer negative would increase costs: 616 additional ultrasounds would be needed per 1000 patients initially tested.

Other considerations:
Repeating the proximal CUS would reduce the rate of false negatives, however it may increase the number of false positives, resulting in higher bleeding rates.

Recommendation 15:

The Ministry of Health of Saudi Arabia guideline suggests repeating proximal CUS in one week over no further testing in patients with moderate pretest probability of first lower extremity DVT and initial negative proximal CUS and positive highly sensitive D-dimer test (ELISA) (Weak recommendation, Low quality of evidence)

Question 16: In patients with moderate pretest probability of first lower extremity DVT and positive proximal CUS, should we perform venography instead of treatment, without further investigation?

Summary of findings:
As described in question 6, after a negative contrast venography, the probability of having recurrent VTE during 3 months of follow up is 1.2% (95%CI 0.2% to 4.4%).[29] (Moderate quality of evidence)

Among patients with tested initially with proximal CUS positive, 16 patients per 1000 would be incorrectly classified as not having DVT. Treating unnecessary this patients we would result in 0.05 deaths and 0.34 major bleeding episodes (0.02 intracranial) per 1000 individuals tested. (Low quality of evidence).

Resource use:
Contrast venography is an expensive diagnostic test compared to proximal CUS.

Other considerations:
Venography is considered the reference standard for DVT, however it is subject to a considerably variation. Although often considered as 100%, the posttest probability of a positive test cannot be estimated with confidence. There are no studies evaluating contrast venography in patients with low risk for DVT. Additionally, venography is associated with 1 to 4% of incidence of adverse reactions to contrast media, including dizziness and nausea, severe allergic reaction in 0 to 0.4% and post-venography DVT in 0 to 2% of patients.[1]

Implementation considerations:
The required technology for performing contrast venography is not widely available in the Kingdom of Saudi Arabia.

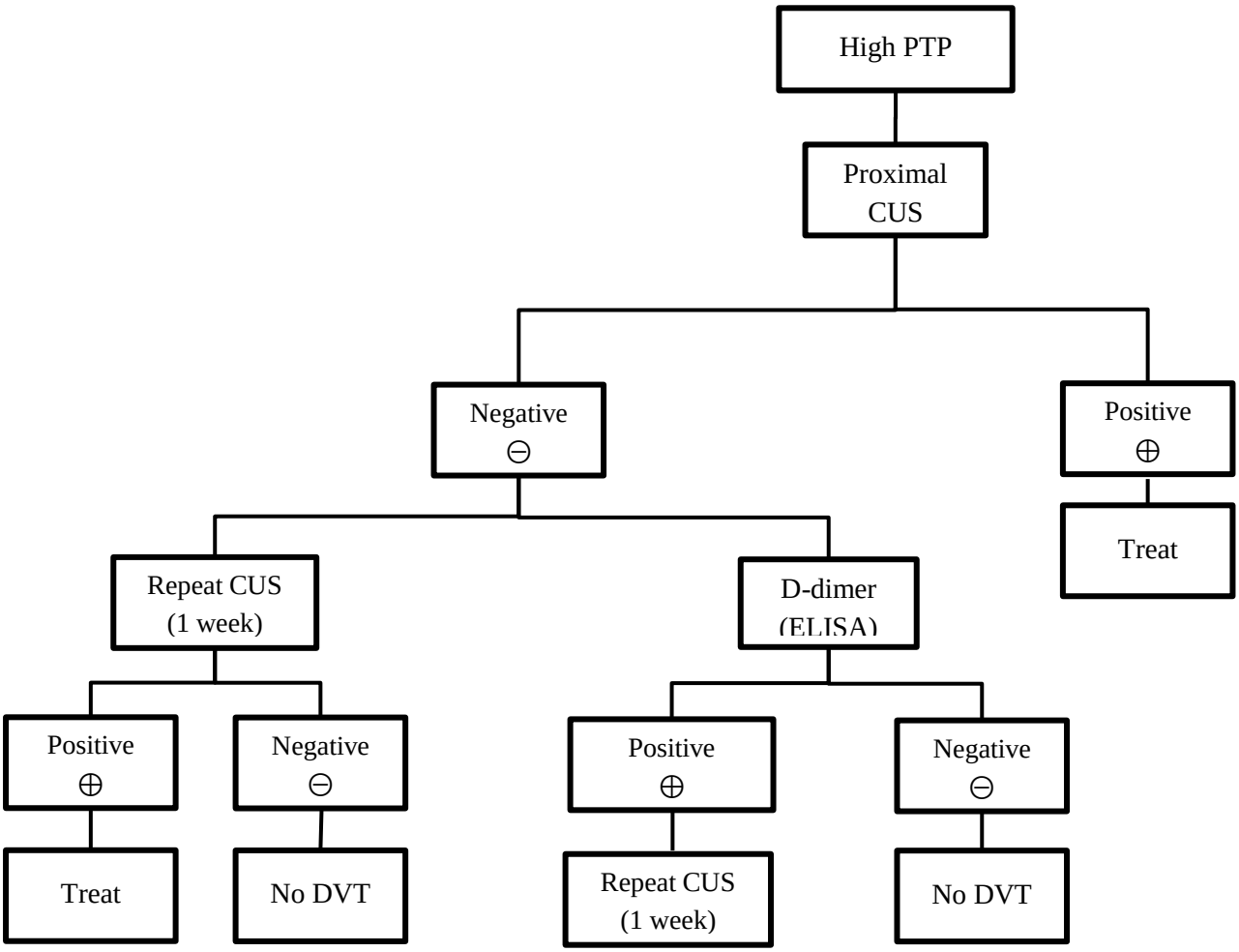
Recommendation 16:

The Ministry of Health of Saudi Arabia panel recommends no further investigation, rather than confirmatory venography, in patients with moderate pretest probability of first lower extremity DVT and positive proximal CUS. (Strong recommendation, Low quality of evidence)

IV – Diagnostic strategy in patients with high pretest probability of first lower extremity DVT

Questions 17 to 24 are related to the diagnostic strategy of DVT in patients with high clinical pretest probability of first lower extremity DVT. Figure 3 summarizes the diagnostic recommendations.

Figure 3: Recommendations for evaluation of suspected first lower extremity DVT in patients with high pretest probability.



PTP – Pretest probability; CUS – Compression ultrasound; DVT: Deep vein thrombosis

Question 17: In patients with high pretest probability of first lower extremity DVT, should we use highly sensitive D-dimer (ELISA) as an initial test to rule out the diagnosis of DVT?

Summary of findings:
As reported in question 2, for D-dimer, the estimates of sensitivity and specificity are 94% (95%CI 93% to 95%) and 45% (95%CI 44% to 46%) respectively (Moderate quality of evidence)

Thirty two patients per 1000 tested would be incorrectly classified as not having DVT. The probability of having DVT after a negative test is 13.1%. Not treating these individuals would result in additional 0.51 and 2.3 fatal and non-fatal pulmonary embolism per 1000 patients tested. (Moderate quality of evidence)

Resource use:
The cost of ELISA D-dimer assay was considered low for the Saudi context by the panel members.

Recommendation 17:

The Ministry of Health of Saudi Arabia panel recommends against the use of highly sensitivity D-dimer (ELISA) as a standalone test to rule out DVT in patients with high pretest probability of first lower extremity DVT. (Strong recommendation, Moderate quality of evidence)

Question 18: In patients with high pretest probability of first lower extremity DVT, should we use proximal CUS as initial test to rule out the diagnosis of DVT?

Summary of findings:
As reported in question 3, for proximal CUS the estimates for sensitivity and specificity for DVT are 90.3% (95%CI 88.4% to 92%) and 97.8% (95%CI 97% to 98.4%) respectively. (Moderate quality of evidence) Once sensitivity tends to be higher in individual with higher pretest probability of DVT, level of evidence was not downgraded due to inconsistency for the group patients with high clinical pretest probability.

Fifty one patients per 1000 tested would be incorrectly classified as not having DVT. The probability of having DVT after a negative test is 10.1%. Not treating these individuals would result in additional 0.82 and 3.67 fatal and non-fatal pulmonary embolism per 1000 patients tested. (Moderate quality of evidence)

Resource use:
The cost of proximal CUS was considered low for the Saudi context by the panel members.

Recommendation 18:

The Ministry of Health of Saudi Arabia panel recommends against the use of proximal CUS as a standalone test to rule out DVT in patients with high pretest probability of first lower extremity DVT. (Strong recommendation, Moderate quality of evidence)

Question 19: In patients with high pretest probability of first lower extremity DVT, should we use proximal CUS as an initial test to rule out the diagnosis of DVT?

Summary of findings:
As described in question 6, after a negative contrast venography, the probability of having recurrent VTE during 3 months of follow up is 1.2% (95%CI 0.2% to 4.4%).[29] (Moderate quality of evidence)

Among individuals with high pretest probability, 10 patients per 1000 tested with proximal CUS would be incorrectly classified as having DVT. Treating these patients unnecessarily would result in 0.03 deaths and 0.22 major bleeding episodes (0.01 intracranial) per 1000 individuals initially tested. (Moderate quality of evidence)

Resource use:
Contrast venography is an expensive diagnostic test compared to proximal CUS.
Other considerations:

Venography is considered the reference standard for DVT, however it is subject to a considerably variation. Although often considered as 100%, the posttest probability of a positive test cannot be estimated with confidence. There are no studies evaluating contrast venography in patients with low risk for DVT. Additionally, venography is associated with 1 to 4% of incidence of adverse reactions to contrast media, including dizziness and nausea, severe allergic reaction in 0 to 0.4% and post-venography DVT in 0 to 2% of patients.[1]

Implementation considerations:
The required technology for performing contrast venography is not widely available in the Kingdom of Saudi Arabia.

Recommendation 19:

The Ministry of Health of Saudi Arabia panel recommends no further investigation, rather than confirmatory venography, in patients with high pretest probability of first lower extremity DVT and positive proximal CUS. (Strong recommendation, Moderate quality of evidence)

Question 20: In patients with high pretest probability of first lower extremity DVT and positive proximal CUS, should we perform proximal venography instead of treatment without further investigation?

Summary of findings:
For single proximal CUS testing, as described in question 18, 51 patients per 1000 tested would be incorrectly classified as not having DVT (false negatives). The probability of having DVT after a negative test is 10.1%. Not treating these individuals would result in additional 0.82 fatal and 3.67 non-fatal pulmonary embolisms per 1000 patients tested.

For serial CUS in patients with high clinical pretest probability, four studies were identified in the systematic review. In these studies, the pooled prevalence of DVT was 36.4% and the probability of DVT post-negative serial CUS was 0.9% (95%CI 0.2% to 2.8%).[32-35] It would represent 3 patients per 1000 tested; not treating these individuals would result in additional 0.05 fatal and 0.22 and non-fatal pulmonary embolism episodes. (Moderate quality of evidence)

Resource use:
Repeating proximal CUS in patients with high clinical pretest probability and initial CUS negative would increase costs: 511 additional ultrasounds would be needed per 1000 patients initially tested.

Recommendation 20:

The Ministry of Health of Saudi Arabia guideline panel recommends repeating proximal CUS in one week rather than no further testing in patients with a high pretest probability of first lower extremity DVT and negative initial proximal CUS. (Strong recommendation, Moderate quality of evidence)

Question 21: In patients with high pretest probability of first lower extremity DVT and negative initial proximal CUS, should we repeat proximal CUS instead of rule out without further investigation?

Summary of findings:
For single proximal CUS testing, as described in question 18, 51 patients per 1000 tested would be incorrectly classified as not having DVT. The probability of having DVT after a negative test is 10.1%. Not treating these individuals would result in additional 0.82 and 3.67 fatal and non-fatal pulmonary embolism per 1000 patients tested. (Moderate quality of evidence)

Among those individuals with negative initial proximal CUS and negative D-dimer (ELISA), only 3 patients per 1000 initially tested in the population would be classified as false negatives. The probability of having DVT after proximal CUS and D-dimer negatives is 1.47%. Not treating these individuals would result in additional 0.05 and 0.22 fatal and non-fatal pulmonary embolism per 1000 patients tested. However, 301 patients would present a

positive D-dimer test, requiring further evaluation. (Low quality of evidence)

Resource use:
With this strategy, 511 D-dimer tests would be required per 1000 patients. The cost of D-dimer and proximal CUS was considered low for the Saudi context by the panel members.

Recommendation 21:

The Ministry of Health of Saudi Arabia panel recommends additional testing with highly sensitive D-dimer (ELISA) rather than no further testing in patients with high pretest probability of first lower extremity DVT and initial negative proximal CUS. (Strong recommendation, Low quality of evidence)

Question 22: In patients with high pretest probability of first lower extremity DVT, positive highly sensitive D-dimer test (ELISA) and negative CUS , should we repeat proximal CUS instead of venography?

Summary of findings:
As described in question 6, after a negative contrast venography, the probability of having recurrent VTE during 3 months of follow up is 1.2% (95%CI 0.2% to 4.4%).[29] (Moderate quality of evidence)

For repeating proximal CUS in patients with high clinical pretest probability, negative initial CUS and positive D-dimer, only one study was identified. In this study, the prevalence of DVT was 59.5% and the post-test probability was 2.8% (95%CI 0.1% to 12.5%).[36] (Low quality of evidence) It would represent 17 patients per 1000 tested; not treating these individuals would result in additional 0.27 fatal and 1.22 and non-fatal pulmonary embolism episodes. (Low quality of evidence)

Resource use:
Contrast venography is an expensive diagnostic test compared to proximal CUS.

Other considerations:
Venography is considered the reference standard for DVT, however it is subject to a considerably variation. Although often considered as 100%, the posttest probability of a positive test cannot be estimated with confidence. There are no studies evaluating contrast venography in patients with low risk for DVT. Additionally, venography is associated with 1 to 4% of incidence of adverse reactions to contrast media, including dizziness and nausea, severe allergic reaction in 0 to 0.4% and post-venography DVT in 0 to 2% of patients.[1]

Implementation considerations:
The required technology for performing contrast venography is not widely available in the Kingdom of Saudi Arabia.

Recommendation 22:

The Ministry of Health of Saudi Arabia panel recommends repeating proximal CUS in one week over performing venography in patients with a high pretest probability of first lower extremity DVT, negative initial proximal CUS and positive highly sensitive D-dimer test (ELISA). (Strong recommendation, Low quality of evidence)

Question 23: In patients with high pretest probability of first lower extremity DVT and negative serial CUS, should we perform venography instead of rule out without further investigation?

Summary of findings:
As described in question 6, after a negative contrast venography, the probability of having recurrent VTE during 3 months of follow up is 1.2% (95%CI 0.2% to 4.4%).[29] (Moderate quality of evidence)

As reported in question 20, for serial CUS in patients with high clinical pretest probability, the estimate probability of DVT post-negative serial CUS is 0.9% (95%CI 0.2% to 2.8%)[32-35] (Moderate quality of evidence)

Resource use:
Contrast venography is an expensive diagnostic test compared to proximal CUS.
Other considerations:

Venography is considered the reference standard for DVT, however it is subject to a considerably variation. Although often considered as 100%, the post-test probability of a positive test cannot be estimated with confidence. There are no studies evaluating contrast venography in patients with low risk for DVT. Additionally, venography is associated with 1 to 4% of incidence of adverse reactions to contrast media, including dizziness and nausea, severe allergic reaction in 0 to 0.4% and post-venography DVT in 0 to 2% of patients.[1]

Implementation considerations:
The required technology for performing contrast venography is not widely available in the Kingdom of Saudi Arabia.

Recommendation 23:

The Ministry of Health of Saudi Arabia panel recommends no further testing rather than venography in patients with high pretest probability of first lower extremity DVT and negative serial proximal CUS. (Strong recommendation, Moderate quality of evidence)

Question 24: In patients with high pretest probability of first lower extremity DVT, negative highly sensitive D-dimer test (ELISA) and negative proximal CUS, should we perform venography instead of rule out without further investigation?

Summary of findings:
As described in question 6, after a negative contrast venography, the probability of having recurrent VTE during 3 months follow of up is 1.2% (95%CI 0.2% to 4.4%).[29] (Moderate quality of evidence)
As reported in question 21, among those individuals with negative initial proximal CUS and negative D-dimer (ELISA), only 3 patients per 1000 initially tested in the population would be classified as false negatives. The probability of having DVT after proximal CUS and D-dimer negatives is 1.47%. Not treating these individuals would result in additional 0.05 and 2.16 fatal and non-fatal pulmonary embolism per 1000 patients tested. (Low quality of evidence)
Resource use:
Contrast venography is an expensive diagnostic test compared to proximal CUS.

Other considerations:
Venography is considered the reference standard for DVT, however it is subject to a considerably variation. Although often considered as 100%, the posttest probability of a positive test cannot be estimated with confidence. There are no studies evaluating contrast venography in patients with low risk for DVT. Additionally, venography is associated with 1 to 4% of incidence of adverse reactions to contrast media, including dizziness and nausea, severe allergic reaction in 0 to 0.4% and post-venography DVT in 0 to 2% of patients.[1]

Implementation considerations:
The required technology for performing contrast venography is not widely available in the Kingdom of Saudi Arabia.

Recommendation 24:

The Ministry of Health of Saudi Arabia panel recommends no further testing rather than venography in patients with high pretest probability of first lower extremity DVT, negative D-dimer test (ELISA) and negative proximal CUS. (Strong recommendation, Low quality of evidence)

Table 4: Number of events due to lack of treatment in patients with deep vein thrombosis according to the ruling out strategy adopted.

Ruling out strategy for DVI	Clinical pretest probability of DVT (prevalence)	Posttest probability of DVT	Events per 1000 patients tested[1]				Quality of evidence
			Patients ruled out	False negatives	Fatal pulmonary embolism	Nonfatal pulmonary embolism	
No test and treatment	Low (5%)	-	-	-	0.8	3.6	-
D-dimer negative	Low (5%)	0.7%	431	5	0.08	0.36	Moderate
Proximal CUS negative	Low (5%)	0.5%	934	3	0.05	0.22	Low
D-dimer negative + proximal CUS negative	Low (5%)	<0.1%	418	0	0	0	Low
(1) D-dimer negative or (2) D-dimer positive and proximal CUS negative	Low (5%)	(1) 0.7% (2) 0,88%	947	10	0.16	0.72	Low
No test and treatment	Moderate (17%)	-	-	-	2.72	12.24	-
D-dimer negative	Moderate (17%)	2.7%	384	10	0.16	0.72	Moderate
Proximal CUS negative	Moderate (17%)	2%	828	16	0.26	1.15	Low
D-dimer negative + proximal CUS negative	Moderate (17%)	0.3%	366	1	0.02	0.07	Low
(1) D-dimer negative or (2) D-dimer positive and proximal CUS negative	Moderate (17%)	(1) 2.7% (2) 3.4%	846	26	0.42	1.87	Low
Serial proximal CUS negative[2]	Moderate (15.8%)	(1) 0.6% (2) 1.1%	-	(1) 1 (2) 2	(1) 0.02 (2) 0.04	(1) 0.07 (2) 0.14	Moderate
No test and treatment	High (53%)	-	-	-	8.64	38.88	-
D-dimer negative	High (53%)	13.1%	242	32	0.51	2.3	Moderate
Proximal CUS negative	High (53%)	10.1%	511	51	0.82	3.67	Moderate
D-dimer negative + proximal CUS negative	High (53%)	1.5%	210	3	0.05	0.22	Moderate
(1) D-dimer negative or (2) D-dimer positive and proximal CUS negative	High (53%)	(1) 13.1% (2) 16.5%)	543	80	1.28	5.76	Moderate
Serial proximal CUS negative	High (36.4%)	0.9%	-	3	0.05	0.22	Moderate
Proximal CUS negative → D-dimer positive → proximal CUS negative	High (59.5%)	2.8%	-	17	0.27	1.22	Low

DVT: deep vein thrombosis; CUS: compression ultrasound

[1] Is not accounted the number of bleeding events prevented for not providing anti-thrombotic treatment for patients with DVT.

[2] Data from two different studies

Table 5: Number of adverse events due to overtreatment in patients without deep vein thrombosis according to the diagnostic strategy adopted.

Diagnostic strategy	Clinical pretest probability of DVT (prevalence)	Events per 1000 patients tested[1]				Quality of evidence
		False positives	Fatal Bleeding	Non-fatal intracranial bleeding	Non-fatal non-intracranial major bleeding	
Proximal CUS positive	Low (5%)	21	0.06	0.02	0.44	Low
D-dimer positive + proximal CUS positive (D-dimer negative ruled out)	Low (5%)	11	0.03	0.01	0.23	Low
Proximal CUS positive	Moderate (17%)	18	0.05	0.02	0.38	Low
D-dimer positive + proximal CUS positive (D-dimer negative ruled out)	Moderate (17%)	10	0.03	0.01	0.21	Low
Proximal CUS positive	High (53%)	10	0.03	0.01	0.21	Moderate

DVT: deep vein thrombosis; CUS: compression ultrasound

[1] Is accounted only the number of bleeding events among patients without DVT (false positives)

Final considerations

Implementation considerations

An adequate diagnostic process is crucial to reduce the incidence of pulmonary embolism and to minimize the risk associated with over-treatment. The adoption of a standardized diagnostic strategy for DVT is expected to reduce health inequities in Saudi Arabia. The Ministry of Health should make efforts in order to make available the resources needed for the diagnostic strategies proposed here (CUS and highly sensitive D-dimer by ELISA).

Monitoring and evaluation

The Ministry of Health of Saudi Arabia guideline panel suggests periodic and formal evaluations of the adherence to the recommendations of this guideline according to their strength:

- Strong recommendations should be applied to the large majority of patients. Therefore, the adherence to the course of action proposed by strong recommendations could be used as a quality criterion or performance indicator.
- For weak recommendations, however, it is important to recognize that different choices could be appropriate for different patients. Therefore, measuring the adherence to the course of action proposed by weak recommendations is not appropriate for quality criteria or performance indicators.

The Ministry of Health of Saudi Arabia guideline panel suggests periodic updates of this guideline every 2-3 years. Early updates could be considered in case of the emergence of new evidence relevant to the interventions covered in the guideline.

Additional considerations

Novel diagnostic strategies, such as CT scan and MRI, had not been evaluated for this guideline. They may constitute diagnostic alternatives for select cases.

Research priorities

The Ministry of Health of Saudi Arabia guideline panel suggests local research in the following topic areas:

- Values and preferences of the Saudi population regarding the relative value (utility) of preventing DVT versus bleeds; and also regarding the burden of treatment with antithrombotics
- Economic evaluations of diagnostic strategies for DVT.

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Appendices

1. Search Strategies and Results
2. Evidence-to-Recommendation Tables and Evidence Profiles

Appendix 1: Search Strategies and Results

Properties of diagnostic tests for DVT

Database: **Medline (OVID), EMBASE (OVID)**	
Search strategy:	**Date of search: 11/2013**
1. exp "Sensitivity and Specificity"/ 2. sensitivity.tw. 3. specificity.tw. 4. ((pre-test or pretest) adj probability).tw. 5. post-test probability.tw. 6. predictive value$.tw. 7. likelihood ratio$.tw. 8. venous thromboembolism.mp. or Venous Thromboembolism/ 9. Venous Thrombosis.mp. or Venous Thrombosis/ 10. venous thromb$.mp. 11. ((vein or venous) adj3 (Emboli$ or thrombo$)).mp. 12. deep venous thromb$.mp. 13. 8 or 9 or 10 or 11 or 12 14. 1 or 2 or 3 or 4 or 5 or 6 or 7 15. 13 and 14 Date limit: 2009- 11/2013 Study Types: Screening and diagnostic test accuracy studies	
Records Retrieved	2461

Note: original search strategy from systematic review not available. New search strategy developed for this guideline.

Summary of Searches

Total No. Retrieved: 2461
Screening (Title and Abstract Review)
No. Excluded: **2416**
Included for Full Text review: **45**
Selection (Full Text Review)
No. Excluded: **23**
No. Included: **22**
4 – Compression ultrasound; 7 – clinical decision rules; 11 – D-dimer

List of included studies:

1. Boeer K. Siegmund R. Schmidt D. Deufel T. Kiehntopf M. Comparison of six D-dimer assays for the detection of clinically suspected deep venous thrombosis of the lower extremities. Blood Coagulation & Fibrinolysis. 20(2):141-5, 2009 Mar.
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List of excluded studies:

Study	Reason
Canan 2012	Etiology of VTE
Carrier 2010	Risk of bleeding assessment
Deng 2012	Animal model
Douketis 2012	Evaluation of radiomarkers
Douma 2011	Non systematic review
Enden 2010	Evaluation of MRI
Guanella 2012	Non systematic review
Haas 2013	Evaluation of other serum markers than D-dimer
Hansch 2011	Evaluation of MRI
Hippisley-Cox 2011	Etiology of VTE
Huisman 2013	Non systematic review
Ingber 2013	Implementation of a clinical practice protocol
Janczak 2011	Evaluation of radiomarkers
Krishan 2011	Evaluation of CT scan
Kulkarni 2012	Evaluation of CT scan
Le Gal 2012	Pregnant women only
McQueen 2009	Non systematic review
Nieto 2013	Risk of bleeding assessment
Sharif-Kashani 2009	Evaluation of photoplethysmography
Scherz 2013	Risk of bleeding assessment
Shiver 2010	Evaluation of CT scan
Slater 2012	Evaluation of CT scan
Stevens 2013	Evaluation of Whole-leg ultrasound

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Values and Preferences

Database: **Medline (OVID) (1964-2013), EMBASE (OVID) (1980-2013)**	
Search strategy:	**Date of search: 11/2013**
1. venous thromboembolism.mp. or Venous Thromboembolism/ 2. Venous Thrombosis.mp. or Venous Thrombosis/ 3. venous thromb$.mp. 4. ((vein or venous) adj3 (Emboli$ or thrombo$)).mp. 5. deep venous thromb$.mp. 6. 1 or 2 or 3 or 4 or 5 7. patient$ participation.mp. or exp patient participation/ 8. patient$ satisfaction.mp. or exp patient satisfaction/ 9. attitude to health.mp. or exp Attitude to health/ 10. (patient$ preference$ or patient$ perception$ or patient$ decision$ or patient$ perspective$ or user$ view$ or patient$ view$ or patient$ value$).mp. 11. (patient$ utilit$ or health utilit$).mp. 12. health related quality of life.mp. or exp "quality of life"/ 13. (health stat$ utilit$ or health stat$ indicator$ or (health stat$ adj 2 valu$)).mp. or exp Health Status Indicators/ 14. 7 or 8 or 9 or 10 or 11 or 12 or 13 15. Saudi Arab$.mp,in. or Saudi Arabia/ 16. Riyadh.mp,in.	

17. Jeddah.mp,in. 18. Kh*bar.mp,in. 19. Dammam.mp,in. 20. 15 or 16 or 17 or 18 or 19 21. Kuwait$.mp,in. or Kuwait/ 22. United Arab Emirates.mp,in. or United Arab Emirates/ 23. Qatar$.mp,in. or Qatar/ 24. Oman$.mp,in. or Oman/ 25. Yemen$.mp,in. or Yemen/ 26. Bahr*in$.mp,in. or Bahrain/ 27. 20 or 21 or 22 or 23 or 24 or 25 or 26 28. Middle East$.mp,in. or Middle East/ 29. Jordan$.mp,in. or Jordan/ 30. Libya$.mp,in. or Libya/ 31. Egypt$.mp,in. or Egypt/ 32. Syria$.mp,in. or Syria/ 33. Iraq$/ or Iraq.mp,in. 34. Morocc$.mp,in. or Morocco/ 35. Tunisia$.mp,in. or Tunisia/ 36. Leban$.mp,in. or Lebanon/ 37. West Bank.mp,in. 38. Iran$.mp,in. or Iran/ 39. Turkey/ or (Turkey or Turkish).mp,in. 40. Algeria$.mp,in. or Algeria/ 41. Arab$.mp,in. or Arabs/ 42. 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 43. 20 or 27 or 42 44. "journal of epidemiology and global health".jn. 45. "journal of infection and public health".jn. 46. "saudi journal of kidney diseases & transplantation".jn. 47. saudi medical journal.jn. 48. saudi pharmaceutical journal.jn. 49. "annals of saudi medicine".jn. 50. "saudi journal of gastroenterology".jn. 51. 44 or 45 or 46 or 47 or 48 or 49 or 50 52. 43 or 51 53. 6 and 14 and 52	
Records Retrieved	127

Summary of Searches

Total No. Retrieved: 127
Screening (Title and Abstract Review)
No. Excluded: **124**
Included for Full Text review: **3**
Selection (Full Text Review)
No. Excluded: **3**
No. Included: **0**

List of excluded studies:

Study	Reason
Al-Otair 2012	Not assessing patients values and preferences
Chamsi Pasha 2013	Editorial, not related to VTE
Bozkurt 2011	Not assessing patients values and preferences

References:

1. Al-Otair HA, Khurshid SM, Alzeer AH. Venous thromboembolism in a medical intensive care unit. The effect of implementing clinical practice guidelines. Saudi Med J. 2012 Jan;33(1):55-60.
2. Chamsi-Pasha H. Islam and the cardiovascular patient – pragmatism in practice. Br J Cardiol 2013;20:90–1
3. M. Bozkurt, K. Okutur, K. Aydin, E. Namal, A. Öztürk, C. Tecimer, Z. Akcali, G. Demir. The impact of early thromboembolic event on prognosis in cancer patients: A single-center analysis of 1838 patients. J Clin Oncol 29: 2011 (suppl; abstr e19694)

Costs Related to Diagnostic Strategies

Database: **Medline (OVID), EMBASE (OVID)**	
Search strategy:	**Date of search: 11/2013**
1. "costs and cost analysis"/ 2. Cost allocation/ 3. Cost-benefit analysis/ 4. Cost savings/ 5. Health care costs/ 6. Health care costs/ 7. Direct service costs/ 8. Drug costs/ 9. Health expenditures/ 10. Capital expenditures/ 11. Value of life/ 12. (health?care adj cost$).mp. 13. (cost adj estimate$).mp. 14. (cost adj variable).mp. 15. (economic$ or pharmacoeconomic$ or price$ or pricing).tw. 16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 17. diagnos:.mp. 18. exp "Sensitivity and Specificity"/ 19. sensitivity.tw. 20. specificity.tw. 21. ((pre-test or pretest) adj probability).tw. 22. post-test probability.tw. 23. predictive value$.tw. 24. likelihood ratio$.tw. 25. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 26. venous thromboembolism.mp. or Venous Thromboembolism/ 27. Venous Thrombosis.mp. or Venous Thrombosis/ 28. venous thromb$.mp. 29. ((vein or venous) adj3 (Emboli$ or thrombo$)).mp. 30. deep venous thromb$.mp. 31. 26 or 27 or 28 or 29 or 30 32. 16 and 25 and 31 33. limit 32 to yr="2009 - 2014" Date limit: 2009-11/2013	
Records Retrieved	117

Summary of Searches

Total No. Retrieved: 117
Screening (Title and Abstract Review)
No. Excluded: **108**
Included for Full Text review: **9**
Selection (Full Text Review)
No. Excluded: **4**
No. Included: **5**

Summary of findings for costs

Direct costs related to the diagnostic test

Test / strategy (setting)	Country (year)	Cost	Source
D-dimer (ER)	Serbia (2011)	€ 17.00- 47.11 [1]	Bogavac-Stanojevic 2013
CUS (ER)	Serbia (2011)	€ 84.67	
D-dimer (ER)	Sweden (2008)	€ 16	Norlin 2010
CUS (ER)	Sweden (2008)	€ 157	
Contrast venography (ER)	Sweden (2008)	€ 461	
"AMUSE strategy": D-dimer (primary care) + CUS if needed (hospital)	Holland (2004)	€ 168	Cate-Hoek 2009
D-dimer + CUS if needed (hospital)	Holland (2004)	€ 227	
CUS for all patients (hospital)	Holland (2004)	€ 251	

CUS - Compressive ultrasonography. ER – Emergency Room

[1] Dependent of the numbers of tests performed and type of D-Dimer technique. High sensitive D-dimer methods

Direct costs related to the undesirable events

Event	Country / year	Cost	Source
DVT event (acute + 2 years follow up)	Canada (2010)	CAD 5,180	Guanella
Inpatient DVT event	USA (2010)	USD 12,393	Mahan 2012
Outpatient DVTevent	USA (2010)	USD 14,963	
Minor bleed	USA (2010)	USD 137	
Major bleed	USA (2010)	USD 7,199	
Annual cost of post-thrombotic syndrome	USA (2010)	USD 5,018	
DVT	Holland (2004)	€ 1,322	Cate-Hoek 2009
Pulmonary Embolism	Holland (2004)	€ 4,210	
Major bleed	Holland (2004)	€ 4,211	
CNS bleed	Holland (2004)	€ 11,281	
Incident post-thrombotic syndrome	Holland (2004)	€ 3,367	

List of included studies:

1. Bogavac-Stanojević N, Dopsaj V, Jelić-Ivanović Z, Lakić D, Vasić D, Petrova G. Economic evaluation of different screening alternatives for patients with clinically suspected acute deep vein thrombosis. Biochem Med (Zagreb). 2013;23(1):96-106.
2. Cate-Hoek AJT, Toll DB, Büller HR, Hoes AW, Moons KG, Oudega R, Stoffers HE, van der Velde EF, van Weert HC, Prins MH, Joore MA. Cost-effectiveness of ruling out deep venous thrombosis in primary care versus care as usual. J Thromb Haemost. 2009 Dec;7(12):2042-9.
3. Guanella R, Ducruet T, Johri M, Miron MJ, Roussin A, Desmarais S, Joyal F, Kassis J, Solymoss S, Ginsberg JS, Lamping DL, Shrier I, Kahn SR. Economic burden and cost determinants of deep vein thrombosis during 2 years following diagnosis: a prospective evaluation. J Thromb Haemost. 2011 Dec;9(12):2397-405.
4. Norlin JM, Elf JL, Svensson PJ, Carlsson KS. A cost-effectiveness analysis of diagnostic algorithms of deep vein thrombosis at the emergency department. Thromb Res. 2010 Sep;126(3):195-9.
5. Mahan CE, Holdsworth MT, Welch SM, Borrego M, Spyropoulos AC. Deep-vein thrombosis: a United States cost model for a preventable and costly adverse event. Thromb Haemost. 2011 Sep;106(3):405-15.

List of excluded studies:

Study	Reason
Kachroo 2013	No data about costs of diagnostic strategies or its direct complications
Novielli 2012	No data about costs of diagnostic strategies or its direct complications
Pendergraft 2013	No data about costs of diagnostic strategies or its direct complications
Vera Arroyo 2013	No data about costs of diagnostic strategies or its direct complications

References:

1. Kachroo S, Boyd D, Bookhart BK, LaMori J, Schein JR, Rosenberg DJ, Reynolds MW. Quality of life and economic costs associated with postthrombotic syndrome. Am J Health Syst Pharm. 2012 Apr 1;69(7):567-72.
2. Novielli N, Cooper NJ, Sutton AJ. Evaluating the cost-effectiveness of diagnostic tests in combination: is it important to allow for performance dependency? Value Health. 2013 Jun;16(4):536-41.
3. Pendergraft T, Atwood M, Liu X, Phatak H, Liu LZ, Oster G. Cost of venous thromboembolism in hospitalized medically ill patients. Am J Health Syst Pharm. 2013 Oct 1;70(19):1681-7.
4. Vera-Arroyo B1, Linares-Palomino JP, Lozano-Alonso S, Moreno-Villalonga JJ, Bravo-Molina A, Ros-Die E. Clinical and health costs impact of progress in diagnosis and treatment in venous thromboembolic disease: evolution in 15 years. Ann Vasc Surg. 2013 Nov;27(8):1162-8.

Appendix 2: Evidence-to-Recommendation Tables and Evidence Profiles

Evidence to recommendation framework 1

Question 1: In patients with a suspected first lower extremity DVT, should the choice of diagnostic tests process be guided by the clinical assessment of pretest probability rather than by performing the same diagnostic tests in all patients?

Population: Patients with suspected first lower extremity DVT
Diagnostic test: clinical assessment of the pretest probability of having DVT, followed by a diagnostic strategy
Comparison: diagnostic strategy without clinical assessment of the pretest probability of having DVT.
Setting: Outpatients
Perspective: Public health

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐	**Estimate incidence:** - Overall: 0.1% (per year) **Estimate pre-test probability of prevalence of proximal lower extremity DVT in individuals with suspected DVT:** - Overall: 19% (95%CI 16 – 23%) - Low pre-test clinical probability: 5% (95%CI 4 – 8%) - Moderate pre-test clinical probability: 17% (95% 13 – 23%) - High pre-test clinical probability: 53% (95%CI 44 – 61%) No evidence specific for the KSA setting found.	The panel considered adequate the use of Wells criteria in the Saudi population. The panel agreed that the estimates of risk presented also could apply for the Saudi population.

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Moderate* ☒ | *High* ☐	No evidence specific for the Middle East setting identified. Importance and estimate utility values for outcomes **Outcome** | **Utility (range)** | **Importance** Death | 0 | Critical Nonfatal Intracranial Bleed (severe) | 0.1 – 0.51 | Critical Nonfatal Intracranial Bleed (moderate) | 0.29 – 0.77 | Critical Nonfatal Intracranial Bleed (mild) | 0.47 – 0.94 | Critical Nonfatal Pulmonary Embolism | 0.63 | Critical Major bleed | 0.44 – 0.84 | Critical Source: *MacLean 2012* Assumptions (outcomes): - Major bleeding equivalent to pulmonary embolism - Intracranial bleed (overall): 2 to 3 times worse than major bleed or pulmonary embolism - DVT treatment generally well accepted See evidence profile below for the summary of findings.	Since there are no evidence specific for the KSA, panel members assumed that the values on outcomes should be probably similar than in other populations. The panel highlighted that there are a need for studies of values and preferences in the KSA setting. There might be some variability and we don't have direct evidence from the KSA setting No impact was observed on patient important outcomes
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☐ | *Probably no important uncertainty or variability* ☒ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐		
Are the desirable anticipated effects large?	*No* ☐ | *Probably No* ☒ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		
Are the undesirable anticipated effects small?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | ***Varies*** ☐		
Are the desirable effects large relative to undesirable effects?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☒ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	Clinical pre-test probability assessment does not add costs, since the clinical variables considered are usually part of the anamnesis and physical exam of a patient with suspected DVT.
	Is the incremental cost small relative to the net benefits?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	The strategy was considered cost-saving, since the number of tests required was lower. (see evidence profile below for the summary of findings)
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☒ / Varies ☐	No evidence found	Standardize judgement regardless of the size of center or location
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☒ / Yes ☐ / Varies ☐	No evidence found	There may be resistance on its use by some physicians.
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	Administrative empowerment and educational interventions to overcome potential expected initial resistance. When applicable, the use of new technologies may be helpful for the implementation (e.g. inclusion of the criteria in computerized patient data entry)

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	☒

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☐	☒

Recommendation (text)	The Ministry of Health of Saudi Arabia guideline panel recommends the use of a clinical strategy to assess the pretest probability based on Wells criteria compared to not using a strategy, for the diagnosis of suspected firs lower extremity DVT. (Strong recommendation, Moderate-quality of evidence)
Justification	Despite the impact on clinical important outcomes seem to be inexistent compared to uniform strategies, the proposed curse of action recommended is a cost-saving strategy, since the number of exams required is expected to be small.
Subgroup considerations	-
Implementation considerations	Administrative empowerment and educational interventions may be needed to overcome potential expected initial resistance. When applicable, the use of new technologies may be helpful for the implementation (e.g. inclusion of the criteria in computerized patient data entry)
Monitoring and evaluation	-
Research priorities	-

Should the Choice of Diagnostic Test Process be Guided by the Clinical Assessment of Pretest Probability rather than by Performing the Same Diagnostic Tests in All Patients?

Population: Patients with suspected first lower extremity DVT
Intervention: Selective testing (D-dimer testing for outpatients with low or moderate pretest probability; venous ultrasonography without D-dimer testing for outpatients with high pretest probability and inpatients)
Comparison: Uniform testing (D-dimer testing for all participants)
Setting: Outpatients

No. of studies (No. of patients)	Study design	Factors that may decrease quality of evidence					Study event rates (%)		Absolute effect per 1000 patients	Quality of Evidence	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Selective testing	Uniform testing			
Venous thromboembolism during follow-up (3 months)											
1 Study (1723 patients)	Randomized controlled trial	Serious [1]	None [2]	None [3]	None	Undetected [2]	4 / 798 [4] (0.5%)	4 / 798 [4] (0.5%)	0 (8 fewer to 8 more)	⊕⊕⊕⊖ moderate	CRITICAL
Death (3 months)											
1 Study (1723 patients)	Randomized controlled trial	Serious [1]	None [2]	None [3]	None	Undetected [2]	15 / 860	15 / 863	0 (13 fewer to 13 more)	⊕⊕⊕⊖ moderate	CRITICAL
Major bleeding											
1 Study (1723 patients)	Randomized controlled trial	Serious [1]	None [2]	None [3]	None	Undetected [2]	2 / 860	1 / 863	1 more (5 fewer to 7 more)	⊕⊕⊕⊖ moderate	CRITICAL
D-dimer testing											
1 Study (1723 patients)	Randomized controlled trial	Serious [1]	None [2]	None	None	Undetected [2]	668 / 860 (77.7%)	859 / 863 (99.5%)	218 fewer (248 fewer to 191 fewer)	⊕⊕⊕⊖ moderate	CRITICAL
Ultrasonography											
1 Study (1723 patients)	Randomized controlled trial	Serious [1]	None [2]	None	None	Undetected [2]	438 / 860 (50.9%)	505 / 863 (58.5%)	76 fewer (122 fewer to 29 fewer)	⊕⊕⊕⊖ moderate	IMPORTANT
Ultrasonography in outpatients with a low clinical pre-test probability											
1 Study (694 patients)	Randomized controlled trial	Serious [1]	None [2]	None	None	Undetected [2]	72 / 360 (20%)	137 / 334 (41%)	210 fewer (276 fewer to 142 fewer)	⊕⊕⊕⊖ moderate	IMPORTANT

Footnotes:

[1] Study personnel were not blinded. The trial was stopped prematurely

[2] Only one study identified, not allowing adequate assessment of inconsistency and publication bias.

[3] Outpatients: 89%

[4] Exclude patients lost to follow-up (n=20) and with DVT on initial testing

Reference:

1. Linkins LA. Bates SM. Lang E. Kahn SR. Douketis JD. Julian J. Parpia S. Gross P. Weitz JI. Spencer FA. Lee AY. O'Donnell MJ. Crowther MA. Chan HH. Lim W. Schulman S. Ginsberg JS. Kearon C. Selective D-dimer testing for diagnosis of a first suspected episode of deep venous thrombosis: a randomized trial. Ann Intern Med. 158(2):93-100, 2013 Jan 15.

Evidence to recommendation framework 2

Question 2: In patients with a low pre-test probability of first lower extremity DVT, should we use D-Dimer (ELISA) as initial test for the diagnosis of DVT?

Population: Patients with suspected first lower extremity DVT, with low clinical pre-test probability.
Diagnostic test: D-dimer (ELISA)
Comparison: No testing
Setting: Outpatients
Perspective: Public health

<table>
<tr><th></th><th>CRITERIA</th><th>JUDGEMENTS</th><th>RESEARCH EVIDENCE</th><th>ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>PROBLEM</td><td>Is the problem a priority?</td><td>No ☐ | Probably No ☐ | Uncertain ☐ | Probably Yes ☐ | Yes ☒ | Varies ☐</td><td>Estimate pre-test probability of prevalence of proximal DVT:
- 5% (95% CI 4 – 8%)

Risk estimates for undesirable outcomes
<table><tr><th>Outcome</th><th>Incidence (treated)</th><th>Incidence (untreated)</th></tr><tr><td>Fatal pulmonary embolism</td><td>0.3%</td><td>1.9%</td></tr><tr><td>Nonfatal pulmonary embolism</td><td>1.4%</td><td>9.3%</td></tr><tr><td>Fatal bleeding</td><td>0.3%</td><td>-</td></tr><tr><td>Nonfatal intracranial bleeding</td><td>2.1%</td><td>-</td></tr><tr><td>Nonfatal non-intracranial bleeding</td><td>0.1%</td><td>-</td></tr><tr><td>Venographic mortality</td><td>0.03%</td><td>-</td></tr><tr><td>Propagation to proximal veins (distal DVT)</td><td>-</td><td>21.4%</td></tr></table>Estimate incidence for 3 months</td><td>The panel agreed that the estimates of risk and prevalence presented also could apply for the Saudi population.</td></tr>
</table>

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Moderate* ☒ | *High* ☐	No evidence specific for the Middle East setting identified. Importance and estimate utility values for outcomes **Outcome** | **Utility (range)** | **Importance** Death | 0 | Critical Nonfatal Intracranial Bleed (severe) | 0.1 – 0.51 | Critical Nonfatal Intracranial Bleed (moderate) | 0.29 – 0.77 | Critical Nonfatal Intracranial Bleed (mild) | 0.47 – 0.94 | Critical Nonfatal Pulmonary Embolism | 0.63 | Critical Major bleed | 0.44 – 0.84 | Critical *MacLean 2012* Assumptions (outcomes): - Major bleeding equivalent to pulmonary embolism - Intracranial bleed (overall): 2 to 3 times worse than major bleed or pulmonary embolism - DVT treatment generally well accepted See evidence profile below for the summary of findings.	Since there are no evidence specific for the KSA, panel members assumed that the values on outcomes should be probably similar than in other populations. The panel highlighted that there are a need for studies of values and preferences in the KSA setting. Only 3 patients per 1000 tested would be incorrectly classified as not having DVT (false negatives). On the other hand, 523 patients would be incorrectly classified as having DVT (false positives), requiring further investigation. The probability of having DVT after a negative test is 0.70% and after a positive test is 8.25%. With no testing or treatment, we would have respectively 0.95 and 4.65 cases of fatal and non-fatal pulmonary per 1000 patients tested.
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☐ | *Probably no important uncertainty or variability* ☒ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐		
Are the desirable anticipated effects large?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☒ | ***Varies*** ☐		
Are the undesirable anticipated effects small?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☒ | ***Varies*** ☐		
Are the desirable effects large relative to undesirable effects?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☒ | ***Varies*** ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	The cost of ELISA D-dimer was considered low for the KSA setting
	Is the incremental cost small relative to the net benefits?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☒ / Yes ☐ / Varies ☐	No evidence found	As the effects are large and the costs are small, the strategy seems to be cost-effective.
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☒ / Varies ☐	No evidence found	MOH would make available in all areas ELISA D-dimer assay, reducing inequities.
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	-
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	In some places, ELISA D-Dimer may not be currently available, however, as it was considered easy to implement

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	☒

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☐	☒

Recommendation (text)	The Ministry of Health of Saudi Arabia panel recommends the use of highly sensitivity D-Dimer (ELISA) as an initial test for the diagnosis of DVT in patients with low pretest probability of first lower extremity DVT. (Strong recommendation, Moderate-quality evidence)
Justification	Advantages of the intervention were considered large compared to undesirable consequences. The rate of false negatives and its impact on patient important outcomes was considered small.
Subgroup considerations	-
Implementation considerations	The KSA MoH would make available in all areas ELISA D-dimer assay
Monitoring and evaluation	-
Research priorities	-

Evidence Profile Table for Studies Assessing Highly Sensitive D-Dimer in Patients with Suspected First Lower Extremity DVT: Should Highly Sensitive D-Dimer Be Used to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT
Intervention: D-Dimer (e ELISA)
Comparison: Recurrent VTE during 3 months follow
Outcome: DVT

Diagnostic test accuracy

Pooled sensitivity	94% (95%CI: 93% to 95%)
Pooled specificity	45% (95%CI: 44% to 46%)

Outcome	Study design	Factors that may decrease quality of evidence					Quality of Evidence	Effect per 1000 patients, according to different clinical pre-test probabilities			Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		5% (low)	17% (moderate)	53% (high)	
True positives (patients with DVT)	Systematic reviews of management cohorts and of accuracy studies	Not Serious	Not Serious[1]	Serious[2]	None	Undetected	⊕⊕⊕⊖ moderate	47 (47 to 48)	160 (158 to 162)	498 (493 to 504)	CRITICAL
False negatives (patients incorrectly classified as not having DVT)								3 (3 to 4)	10 (9 to 12)	32 (27 to 37)	CRITICAL
True negatives (patients without DVT)	Systematic reviews of management cohorts and of accuracy studies	Not Serious	Not Serious[1]	Serious[2]	None	Undetected	⊕⊕⊕⊖ moderate	428 (418 to 437	374 (365 to 382)	212 (207 to 216)	CRITICAL
False positives (patients incorrectly classified as not having DVT)								523 513 to 532)	457 (448 to 465)	259 (254 to 263)	CRITICAL

Footnotes:

[1] Estimates consistent with estimates from similar ELISA methods. Similar estimates for different clinical pretest probability.

[2] Accuracy studies included in the meta-analysis, which may increase the specificity estimate

References:

1. Di Nisio M, Squizzato A, Rutjes AW, Büller HR, Zwinderman AH, Bossuyt PM. Diagnostic accuracy of D-dimer test for exclusion of venous thromboembolism: a systematic review. J Thromb Haemost. 2007 Feb;5(2):296-304.
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.
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Evidence to recommendation framework 3

Question 3: In patients with a low pretest probability of first lower extremity DVT, should we use proximal CUS as initial test for the diagnosis of DVT?

Population: Patients with suspected first lower extremity DVT, with low clinical pretest probability.
Diagnostic test: Proximal CUS
Comparison: No testing
Setting: Outpatients
Perspective: Public health

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐	**Estimate pre-test probability of prevalence of proximal DVT:** - 5% (4 – 8%) **Risk estimates for undesirable outcomes** Outcome / Incidence (treated) / Incidence (untreated) Fatal pulmonary embolism: 0.3% / 1.9% Nonfatal pulmonary embolism: 1.4% / 9.3% Fatal bleeding: 0.3% / - Nonfatal intracranial bleeding: 2.1% / - Nonfatal non-intracranial bleeding: 0.1% / - Venographic mortality: 0.03% / - Propagation to proximal veins (distal DVT): - / 21.4% *Estimate incidence for 3 months*	The panel considered adequate the use of Wells criteria in the Saudi population. The panel agreed that the estimates of risk presented also could apply for the Saudi population.

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ | *Low* ☒ | *Moderate* ☐ | *High* ☐	No evidence specific for the Middle East setting identified. Importance and estimate utility values for outcomes	Since there are no evidence specific for the KSA, panel members assumed that the values on outcomes should be probably similar than in other populations. The panel highlighted that there are a need for studies of values and preferences in the KSA setting. Only 5 patients per 1000 tested would be incorrectly classified as not having DVT (false negatives). On the other hand, 21 patients would be incorrectly classified as having DVT (false positives). The probability of having DVT after a negative test is 0.52% and after a positive test is 68.4%. Treating those patients with a positive test and discharging those with negative test, would result on 0.14 deaths, 0.36 cases of non-fatal pulmonary embolism and 0.35 major bleeding episodes (0.02 intracranial) per 1000 patients. With no testing or treatment, we would have respectively 0.95 and 4.65 cases of fatal and non-fatal pulmonary per 1000 patients.
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☐ | *Probably no important uncertainty or variability* ☒ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐		
Are the desirable anticipated effects large?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☒ | ***Varies*** ☐		
Are the undesirable anticipated effects small?	*No* ☐ | *Probably No* ☒ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		
Are the desirable effects large relative to undesirable effects?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | ***Varies*** ☐		

Outcome	Utility (range)	Importance
Death	0	Critical
Nonfatal Intracranial Bleed (severe)	0.1 – 0.51	Critical
Nonfatal Intracranial Bleed (moderate)	0.29 – 0.77	Critical
Nonfatal Intracranial Bleed (mild)	0.47 – 0.94	Critical
Nonfatal Pulmonary Embolism	0.63	Critical
Major bleed	0.44 – 0.84	Critical

Source: *MacLean 2012*

Assumptions (outcomes):

- Major bleeding equivalent to pulmonary embolism
- Intracranial bleed (overall): 2 to 3 times worse than major bleed or pulmonary embolism
- DVT treatment generally well accepted

See evidence profile below for the summary of findings.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	No evidence found	Cost of proximal CUS was considered low for the KSA setting.
	Is the incremental cost small relative to the net benefits?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	No evidence found	
EQUITY	What would be the impact on health inequities?	Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☒ Reduced ☐ Varies ☐	No evidence found	
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	No evidence found	
FEASIBILITY	Is the option feasible to implement?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	No evidence found	

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	☒

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☐	☒

Recommendation (text)	The Ministry of Health of Saudi Arabia guideline panel recommends the use of proximal CUS as an initial test for the diagnosis of DVT in patients with low pretest probability of first lower extremity DVT. (Strong recommendation, Low-quality evidence)
Justification	Advantages of the intervention were considered large compared to undesirable consequences. The rate of false negatives/positives and its impact on patient important outcomes was considered small.
Subgroup considerations	-
Implementation considerations	-
Monitoring and evaluation	-
Research priorities	-

Evidence Profile Table for Studies Assessing Compression Ultrasound in Patients with Suspected First Lower Extremity DVT: Should Compression Ultrasound Be Used to Diagnose or to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT
Intervention: Compression Ultrasound
Comparison: Recurrent VTE during 3 months follow up
Outcome: DVT

Diagnostic test accuracy [1]

Pooled sensitivity	90.3% (95%CI: 88.4% to 92%)
Pooled specificity	97.8% (95%CI: 97% to 98.4%)

Outcome	Study design	Factors that may decrease quality of evidence					Quality of Evidence	Effect per 1000 patients, according to different clinical pre-test probabilities			Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		5% (low)	17% (mod-erate)	53% (high)	
True positives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	45 (44 to 46)	154 (150 to 156)	479 (469 to 488)	CRITICAL
False negatives (patients incorrectly classified as not having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	5 (6 to 4)	16 (20 to 14)	51 (61 to 42)	CRITICAL
True negatives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	929 (922 to 935)	812 (805 to 817)	460 (456 to 462)	CRITICAL
False positives (patients incorrectly classified as having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	21 (28 to 15)	18 (25 to 13)	10 (14 to 8)	CRITICAL

Footnotes:

[1] Data obtained from a meta-analysis with 22 studies evaluating compression ultrasonography alone (Goodacre 2006)

[2] Higher sensitivity observed in studies with higher prevalence.

[3] Accuracy studies included in the meta-analysis, which may increase the specificity estimate. Median prevalence of DVT: 48%, results tend to be more applicable for high risk individuals

[4] Estimates consistent with estimates from similar studies

References:

1. Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, Locker T, Ryan A. Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis. Health Technol Assess. 2006 May;10(15):1-168, iii-iv
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.
3. Pomero F. Dentali F. Borretta V. Bonzini M. Melchio R. Douketis JD. Fenoglio LM. Accuracy of emergency physician–performed ultrasonography in the diagnosis of deep-vein thrombosis. Thromb Haemost. 109(1):137-45, 2013 Jan.
4. Kory PD. Pellecchia CM. Shiloh AL. Mayo PH. DiBello C. Koenig S. Accuracy of ultrasonography performed by critical care physicians for the diagnosis of DVT. Chest. 139(3):538-42, 2011 Mar.
5. Crisp JG. Lovato LM. Jang TB. Compression ultrasonography of the lower extremity with portable vascular ultrasonography can accurately detect deep venous thrombosis in the emergency department. Ann Emerg Med. 56(6):601-10, 2010 Dec.
6. Gibson NS. Schellong SM. Kheir DY. Beyer-Westendorf J. Gallus AS. McRae S. Schutgens RE. Piovella F. Gerdes VE. Buller HR. Safety and sensitivity of two ultrasound strategies in patients with clinically suspected deep venous thrombosis: a prospective management study. J Thromb Haemost. 7(12):2035-41, 2009 Dec.

Evidence to recommendation framework 4

Question 4: In patients with a low pretest probability of first lower extremity DVT, should we use D-dimer instead of proximal CUS as initial test for the diagnosis of DVT?

Population: Patients with suspected first lower extremity DVT, with low clinical pretest probability.
Diagnostic test: D-Dimer
Comparison: Proximal CUS
Setting: Outpatients
Perspective: Public health

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐	**Estimate pre-test probability of prevalence of proximal DVT:** - 5% (4 – 8%) **Risk estimates for undesirable outcomes** *Estimate incidence for 3 months*	The panel considered adequate the use of Wells criteria in the Saudi population. The panel agreed that the estimates of risk presented also could apply for the Saudi population.

Outcome	Incidence (treated)	Incidence (untreated)
Fatal pulmonary embolism	0.3%	1.9%
Nonfatal pulmonary embolism	1.4%	9.3%
Fatal bleeding	0.3%	-
Nonfatal intracranial bleeding	2.1%	-
Nonfatal non-intracranial bleeding	0.1%	-
Venographic mortality	0.03%	-
Propagation to proximal veins (distal DVT)	-	21.4%

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ | *Low* ☒ | *Moderate* ☐ | *High* ☐		
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☒ | *Probably no important uncertainty or variability* ☐ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐	No evidence specific for the Middle East setting identified. Importance and estimate utility values for outcomes **Outcome** / **Utility (range)** / **Importance** Death / 0 / Critical Nonfatal Intracranial Bleed (severe) / 0.1 – 0.51 / Critical Nonfatal Intracranial Bleed (moderate) / 0.29 – 0.77 / Critical Nonfatal Intracranial Bleed (mild) / 0.47 – 0.94 / Critical Nonfatal Pulmonary Embolism / 0.63 / Critical Major bleed / 0.44 – 0.84 / Critical Assumptions (outcomes): - Major bleeding equivalent to pulmonary embolism - Intracranial bleed (overall): 2 to 3 times worse than major bleed or pulmonary embolism - DVT treatment generally well accepted	Since there are no evidence specific for the KSA, panel members assumed that the values on outcomes should be probably similar than in other populations. The panel highlighted that there are a need for studies of values and preferences in the KSA setting. Some women may refuse US performed by a man With proximal CUS, only 5 patients per 1000 tested would be incorrectly classified as not having DVT (false negatives). On the other hand, 21 patients would be incorrectly classified as having DVT (false positives). Similarly with D-dimer (ELISA), only 3 patients per 1000 tested would be incorrectly classified as not having DVT. However, 428 patients would be discharged with no need of a further test (D-dimer negative).
Are the desirable anticipated effects large?	*No* ☒ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		
Are the undesirable anticipated effects small?	*No* ☐ | *Probably No* ☒ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		
Are the desirable effects large relative to undesirable effects?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☒ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	No evidence found	D-dimer test is less expensive than proximal CUS
	Is the incremental cost small relative to the net benefits?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	No evidence found	
EQUITY	What would be the impact on health inequities?	Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ☒ Varies ☐	No evidence found	
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	No evidence found	
FEASIBILITY	Is the option feasible to implement?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	No evidence found	

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☒	☐

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☒	☐

Recommendation (text)	The Ministry of Health of Saudi Arabia guideline panel suggests the use of highly sensitive D-Dimer (ELISA) rather than proximal CUS as an initial test for the diagnosis of DVT in patients with low pretest probability of first lower extremity DVT. (Weak recommendation, Low-quality evidence)
Justification	The cost of D-dimer is lower than the cost of proximal CUS. Using D-dimer ELISA as an initial test probably would be cost-saving in the Saudi setting.
Subgroup considerations	-
Implementation considerations	-
Monitoring and evaluation	-
Research priorities	-

Evidence Profile Table for Studies Assessing Compression Ultrasound in Patients with Suspected First Lower Extremity DVT: Should Compression Ultrasound Be Used to Diagnose or to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT
Intervention: Proximal Compression Ultrasound
Comparison: Recurrent VTE during 3 months follow up
Outcome: DVT

Diagnostic test accuracy [1]

Pooled sensitivity	90.3% (95%CI: 88.4% to 92%)
Pooled specificity	97.8% (95%CI: 97% to 98.4%)

Outcome	Study design	Factors that may decrease quality of evidence					Quality of Evidence	Effect per 1000 patients, according to different clinical pre-test probabilities			Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		5% (low)	17% (moderate)	53% (high)	
True positives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	45 (44 to 46)	154 (150 to 156)	479 (469 to 488)	CRITICAL
False negatives (patients incorrectly classified as not having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	5 (6 to 4)	16 (20 to 14)	51 (61 to 42)	CRITICAL
True negatives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	929 (922 to 935)	812 (805 to 817)	460 (456 to 462)	CRITICAL
False positives (patients incorrectly classified as having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	21 (28 to 15)	18 (25 to 13)	10 (14 to 8)	CRITICAL

Footnotes:

[1] Data obtained from a meta-analysis with 22 studies evaluating compression ultrasonography alone (Goodacre 2006)

[2] Higher sensitivity observed in studies with higher prevalence.

[3] Accuracy studies included in the meta-analysis, which may increase the specificity estimate. Median prevalence of DVT: 48%, results tend to be more applicable for high risk individuals

[4] Estimates consistent with estimates from similar studies

References:

1. Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, Locker T, Ryan A. Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis. Health Technol Assess. 2006 May;10(15):1-168, iii-iv
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.
3. Pomero F. Dentali F. Borretta V. Bonzini M. Melchio R. Douketis JD. Fenoglio LM. Accuracy of emergency physician–performed ultrasonography in the diagnosis of deep-vein thrombosis. Thromb Haemost. 109(1):137-45, 2013 Jan.
4. Kory PD. Pellecchia CM. Shiloh AL. Mayo PH. DiBello C. Koenig S. Accuracy of ultrasonography performed by critical care physicians for the diagnosis of DVT. Chest. 139(3):538-42, 2011 Mar.
5. Crisp JG. Lovato LM. Jang TB. Compression ultrasonography of the lower extremity with portable vascular ultrasonography can accurately detect deep venous thrombosis in the emergency department. Ann Emerg Med. 56(6):601-10, 2010 Dec.
6. Gibson NS. Schellong SM. Kheir DY. Beyer-Westendorf J. Gallus AS. McRae S. Schutgens RE. Piovella F. Gerdes VE. Buller HR. Safety and sensitivity of two ultrasound strategies in patients with clinically suspected deep venous thrombosis: a prospective management study. J Thromb Haemost. 7(12):2035-41, 2009 Dec.

Evidence to recommendation framework 5

Question 5: In patients with a low pretest probability of first lower extremity DVT and D-Dimer negative, should we perform proximal CUS instead of discharge with no further evaluation?

Population: Patients with suspected first lower extremity DVT, with low clinical pretest probability and D-dimer negative
Diagnostic test: Proximal CUS
Comparison: No testing (rule out)
Setting: Outpatients
Perspective: Public health

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐	**Estimate pre-test probability of prevalence of proximal DVT:** - 5% (4 – 8%) **Risk estimates for undesirable outcomes**	The panel considered adequate the use of Wells criteria in the Saudi population. The panel agreed that the estimates of risk presented also could apply for the Saudi population.

Outcome	Incidence (treated)	Incidence (untreated)
Fatal pulmonary embolism	0.3%	1.9%
Nonfatal pulmonary embolism	1.4%	9.3%
Fatal bleeding	0.3%	-
Nonfatal intracranial bleeding	2.1%	-
Nonfatal non-intracranial bleeding	0.1%	-
Venographic mortality	0.03%	-
Propagation to proximal veins (distal DVT)	-	21.4%

Estimate incidence for 3 months

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Moderate* ☒ | *High* ☐	No evidence specific for the Middle East setting identified. Importance and estimate utility values for outcomes	Since there are no evidence specific for the KSA, panel members assumed that the values on outcomes should be probably similar than in other populations. The panel highlighted that there are a need for studies of values and preferences in the KSA setting.
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☐ | *Probably no important uncertainty or variability* ☒ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐		
Are the desirable anticipated effects large?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | ***Varies*** ☐		
Are the undesirable anticipated effects small?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | ***Varies*** ☐		
Are the desirable effects large relative to undesirable effects?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | ***Varies*** ☐		

Outcome	Utility (range)	Importance
Death	0	Critical
Nonfatal Intracranial Bleed (severe)	0.1 – 0.51	Critical
Nonfatal Intracranial Bleed (moderate)	0.29 – 0.77	Critical
Nonfatal Intracranial Bleed (mild)	0.47 – 0.94	Critical
Nonfatal Pulmonary Embolism	0.63	Critical
Major bleed	0.44 – 0.84	Critical

Assumptions (outcomes):

- Major bleeding equivalent to pulmonary embolism
- Intracranial bleed (overall): 2 to 3 times worse than major bleed or pulmonary embolism
- DVT treatment generally well accepted

Two observational studies, including 765 patients, were identified in the systematic review and considered for their judgment. In these studies, the pooled pre-test probability was 5% and the probability of DVT post-negative D-dimer test (mixed highly and moderately sensitive) and proximal CUS test was 0% (95% CI 0% to 1.5%).
With D-dimer (ELISA), 3 patients per 1000 tested would be incorrectly classified as not having DVT (false negatives). The probability of having DVT after a negative test is 0.70%. If patients with D-dimer negative be discharged with no further testing, we would have 0.05 and 0.22 additional cases of fatal and non-fatal pulmonary among the false negatives per 1000 patients tested.
With sequential D-dimer (ELISA) and proximal CUS negatives, the post-test probability would be negligible (0.07%). Otherwise, the number of false positives would increase 9 per 1000 initially tested. Thus, we would expect an increase of 0.03 deaths and 0.2 non-fatal major bleeding events per 1000 patients tested.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	No evidence found	
	Is the incremental cost small relative to the net benefits?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	No evidence found	Performing proximal CUS in patients with low clinical pre-test probability and D-Dimer negative would increase costs: 428 additional ultrasounds would be needed per 1000 patients initially tested.
EQUITY	What would be the impact on health inequities?	Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ☒ Varies ☐	No evidence found	
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	No evidence found	
FEASIBILITY	Is the option feasible to implement?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	No evidence found	

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	☒

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☐	☒

Recommendation (text)	The Ministry of Health of Saudi Arabia guideline panel recommends no further testing over further investigation with proximal CUS in patients with low pretest probability of first lower extremity DVT and D-dimer negative (ELISA). (Strong recommendation. Low-quality evidence)
Justification	Performing proximal CUS in patients with low clinical pre-test probability and D-Dimer negative would increase costs, without impacting on patient important outcomes. False negative rates in this population were considered low by the panel members
Subgroup considerations	-
Implementation considerations	-
Monitoring and evaluation	-
Research priorities	-

Evidence Profile Table for Studies Assessing Compression Ultrasound in Patients with Suspected First Lower Extremity DVT: Should Compression Ultrasound Be Used to Diagnose or to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT
Intervention: Compression Ultrasound
Comparison: Recurrent VTE during 3 months follow up
Outcome: DVT

Diagnostic test accuracy [1]

Pooled sensitivity	90.3% (95%CI: 88.4% to 92%)
Pooled specificity	97.8% (95%CI: 97% to 98.4%)

Outcome	Study design	Factors that may decrease quality of evidence					Quality of Evidence	Effect per 1000 patients, according to different clinical pre-test probabilities			Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		5% (low)	17% (mod-erate)	53% (high)	
True positives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	45 (44 to 46)	154 (150 to 156)	479 (469 to 488)	CRITICAL
False negatives (patients incorrectly classified as not having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	5 (6 to 4)	16 (20 to 14)	51 (61 to 42)	CRITICAL
True negatives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	929 (922 to 935)	812 (805 to 817)	460 (456 to 462)	CRITICAL
False positives (patients incorrectly classified as having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	21 (28 to 15)	18 (25 to 13)	10 (14 to 8)	CRITICAL

Footnotes:

[1] Data obtained from a meta-analysis with 22 studies evaluating compression ultrasonography alone (Goodacre 2006)

[2] Higher sensitivity observed in studies with higher prevalence.

[3] Accuracy studies included in the meta-analysis, which may increase the specificity estimate. Median prevalence of DVT: 48%, results tend to be more applicable for high risk individuals

[4] Estimates consistent with estimates from similar studies

References:

1. Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, Locker T, Ryan A. Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis. Health Technol Assess. 2006 May;10(15):1-168, iii-iv
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.
3. Pomero F. Dentali F. Borretta V. Bonzini M. Melchio R. Douketis JD. Fenoglio LM. Accuracy of emergency physician–performed ultrasonography in the diagnosis of deep-vein thrombosis. Thromb Haemost. 109(1):137-45, 2013 Jan.
4. Kory PD. Pellecchia CM. Shiloh AL. Mayo PH. DiBello C. Koenig S. Accuracy of ultrasonography performed by critical care physicians for the diagnosis of DVT. Chest. 139(3):538-42, 2011 Mar.
5. Crisp JG. Lovato LM. Jang TB. Compression ultrasonography of the lower extremity with portable vascular ultrasonography can accurately detect deep venous thrombosis in the emergency department. Ann Emerg Med. 56(6):601-10, 2010 Dec.
6. Gibson NS. Schellong SM. Kheir DY. Beyer-Westendorf J. Gallus AS. McRae S. Schutgens RE. Piovella F. Gerdes VE. Buller HR. Safety and sensitivity of two ultrasound strategies in patients with clinically suspected deep venous thrombosis: a prospective management study. J Thromb Haemost. 7(12):2035-41, 2009 Dec.

Evidence Profile Table for Studies Assessing Highly Sensitive D-Dimer in Patients with Suspected First Lower Extremity DVT: Should Highly Sensitive D-Dimer Be Used to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT
Intervention: D-Dimer (e ELISA)
Comparison: Recurrent VTE during 3 months follow
Outcome: DVT

Diagnostic test accuracy

Pooled sensitivity	94% (95%CI: 93% to 95%)
Pooled specificity	45% (95%CI: 44% to 46%)

Outcome	Study design	Factors that may decrease quality of evidence					Quality of Evidence	Effect per 1000 patients, according to different clinical pre-test probabilities			Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		5% (low)	17% (moderate)	53% (high)	
True positives (patients with DVT)	Systematic reviews of management cohorts and of accuracy studies	Not Serious	Not Serious[1]	Serious[2]	None	Undetected	⊕⊕⊕⊖ moderate	47 (47 to 48)	160 (158 to 162)	498 (493 to 504)	CRITICAL
False negatives (patients incorrectly classified as not having DVT)								3 (3 to 4)	10 (9 to 12)	32 (27 to 37)	CRITICAL
True negatives (patients without DVT)	Systematic reviews of management cohorts and of accuracy studies	Not Serious	Not Serious[1]	Serious[2]	None	Undetected	⊕⊕⊕⊖ moderate	428 (418 to 437	374 (365 to 382)	212 (207 to 216)	CRITICAL
False positives (patients incorrectly classified as not having DVT)								523 513 to 532)	457 (448 to 465)	259 (254 to 263)	CRITICAL

Footnotes:

[1] Estimates consistent with estimates from similar ELISA methods. Similar estimates for different clinical pretest probability.

[2] Accuracy studies included in the meta-analysis, which may increase the specificity estimate

References:

1. Di Nisio M, Squizzato A, Rutjes AW, Büller HR, Zwinderman AH, Bossuyt PM. Diagnostic accuracy of D-dimer test for exclusion of venous thromboembolism: a systematic review. J Thromb Haemost. 2007 Feb;5(2):296-304.
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.
3. Schouten HJ. Geersing GJ. Koek HL. Zuithoff NP. Janssen KJ. Douma RA. van Delden JJ. Moons KG. Reitsma JB. Diagnostic accuracy of conventional or age adjusted D-dimer cut-off values in older patients with suspected venous thromboembolism: systematic review and meta-analysis. BMJ. 346:f2492, 2013.
4. Der Sahakian G. Claessens YE. Allo JC. Kansao J. Kierzek G. Pourriat JL. Accuracy of D-Dimers to Rule Out Venous Thromboembolism Events across Age Categories. emerg. med. int.. 2010:185453, 2010
5. Elías-Hernández T, Otero-Candelera R, Fernández-Jiménez D, Jara-Palomares L, Jiménez-Castro V, Barrot-Cortés E. [Clinical usefulness of three quantitative D-dimers tests in outpatients with suspected deep vein thrombosis]. Rev Clin Esp. 2012 May;212(5):235-41.
6. Douma RA. Tan M. Schutgens RE. Bates SM. Perrier A. Legnani C. Biesma DH. Ginsberg JS. Bounameaux H. Palareti G. Carrier M. Mol GC. Le Gal G. Kamphuisen PW. Righini M. Using an age-dependent D-dimer cut-off value increases the number of older patients in whom deep vein thrombosis can be safely excluded. Haematologica. 97(10):1507-13, 2012 Oct.
7. Boeer K. Siegmund R. Schmidt D. Deufel T. Kiehntopf M. Comparison of six D-dimer assays for the detection of clinically suspected deep venous thrombosis of the lower extremities. Blood Coagulation & Fibrinolysis. 20(2):141-5, 2009 Mar.
8. Luxembourg B. Schwonberg J. Hecking C. Schindewolf M. Zgouras D. Lehmeyer S. Lindhoff-Last E. Performance of five D-dimer assays for the exclusion of symptomatic distal leg vein thrombosis. Thromb Haemost. 107(2):369-78, 2012 Feb.

Evidence to recommendation framework 6

Question 6: In patients with a low pretest probability of first lower extremity DVT and proximal CUS negative, should we perform venography instead of discharge with no further evaluation?

Population: Patients with suspected first lower extremity DVT, with low clinical pretest probability and proximal CUS negative
Diagnostic test: Venography
Comparison: No testing
Setting: Outpatients
Perspective: Public health

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐	**Estimate pre-test probability of prevalence of proximal DVT:** - 5% (4 – 8%) **Risk estimates for undesirable outcomes** *Estimate incidence for 3 months*	The panel considered adequate the use of Wells criteria in the Saudi population. The panel agreed that the estimates of risk presented also could apply for the Saudi population.

Outcome	Incidence (treated)	Incidence (untreated)
Fatal pulmonary embolism	0.3%	1.9%
Nonfatal pulmonary embolism	1.4%	9.3%
Fatal bleeding	0.3%	-
Nonfatal intracranial bleeding	2.1%	-
Nonfatal non-intracranial bleeding	0.1%	-
Venographic mortality	0.03%	-
Propagation to proximal veins (distal DVT)	-	21.4%

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	No included studies ☐ | Very low ☐ | Low ☒ | Moderate ☐ | High ☐	No evidence specific for the Middle East setting identified. Importance and estimate utility values for outcomes **Outcome** | **Utility (range)** | **Importance** Death | 0 | Critical Nonfatal Intracranial Bleed (severe) | 0.1 – 0.51 | Critical Nonfatal Intracranial Bleed (moderate) | 0.29 – 0.77 | Critical Nonfatal Intracranial Bleed (mild) | 0.47 – 0.94 | Critical Nonfatal Pulmonary Embolism | 0.63 | Critical Major bleed | 0.44 – 0.84 | Critical Assumptions (outcomes): - Major bleeding equivalent to pulmonary embolism - Intracranial bleed (overall): 2 to 3 times worse than major bleed or pulmonary embolism - DVT treatment generally well accepted	Since there are no evidence specific for the KSA, panel members assumed that the values on outcomes should be probably similar than in other populations. The panel highlighted that there are a need for studies of values and preferences in the KSA setting. Venography is considered reference standard for DVT, however it is subject to a considerably variation. Posttest probability of a positive test cannot be estimated with confidence. Post-test negative, the probability of having recurrent venous thromboembolism during 3 months follow was 1.2% (95%CI 0.2% to 4.4%). Similarly, after proximal CUS, only 5 patients per 1000 tested would be incorrectly classified as not having DVT (0.52% probability of having DVT after a negative test). Venography is associated with 1 to 4% of incidence of adverse reactions to contrast media, including dizziness and nausea, severe alergic reaction in 0 to 0.4% and post-venogrraphy DVT in 0 to 2% of patients.
Is there important uncertainty about how much people value the main outcomes?	Important uncertainty or variability ☐ | Possibly important uncertainty or variability ☐ | Probably no important uncertainty or variability ☒ | No important uncertainty or variability ☐ | No known undesirable outcomes ☐		
Are the desirable anticipated effects large?	No ☐ | Probably No ☐ | Uncertain ☐ | Probably Yes ☐ | Yes ☒ | ***Varies*** ☐		
Are the undesirable anticipated effects small?	No ☐ | Probably No ☐ | Uncertain ☐ | Probably Yes ☐ | Yes ☒ | ***Varies*** ☐		
Are the desirable effects large relative to undesirable effects?	No ☐ | Probably No ☐ | Uncertain ☐ | Probably Yes ☒ | Yes ☐ | ***Varies*** ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
	Is the incremental cost small relative to the net benefits?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	Contrast venography is a costly intervention
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☒ / Varies ☐	No evidence found	
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	Technology is not widely available for contrast venography

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	☒

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☐	☒

Recommendation (text)	The Ministry of Health of Saudi Arabia guideline panel recommends performing proximal CUS rather than venography in patients with low pretest probability of first lower extremity DVT and positive highly sensitive D-dimer (ELISA) (Strong recommendation, Low-quality evidence)
Justification	The panel considered contrast venography an expansive, potentially harmful and difficult to implement alternative for a situations when there are no clear benefit established.
Subgroup considerations	-
Implementation considerations	-
Monitoring and evaluation	-
Research priorities	-

Evidence Profile Table for Studies Assessing Venography in Patients with Suspected First Lower Extremity Deep Vein Thrombosis (DVT):

Should Venography Be Used to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT and negative result for contrast venography
Outcome: Recurrent venous thromboembolism during 3 months follow-up

Diagnostic test accuracy

Pooled sensitivity	Not Available
Pooled specificity	Not Available
Accuracy[1]	98.8% (95% CI: 95.6% to 99.8%)

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease quality of evidence					Quality of Evidence [2]	Post-test probability of negative test	Importance
			Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias			
Venous thrombo-embolism (3 months)	1 Study (160 patients)	Single-arm prospective cohort study	Serious [3]	None [4]	Not Serious	Not Serious	Undetected [4]	⊕⊕⊕⊖ moderate	1.2% (0.2 to 4.4%)	CRITICAL

Footnotes:

[1] Individuals with normal venography and without venous thromboembolism during 3 months follow-up.

[2] Judgement according to the original systematic review; no additional study had been identified.

[3] Prevalence of DVT in original population not specified

[4] Only one study identified, not allowing adequate assessment of inconsistency and publication bias.

References:

1. Hull R, Hirsh J, Sackett DL, Taylor DW, Carter C, Turpie AG, Powers P, Gent M. Clinical validity of a negative venogram in patients with clinically suspected venous thrombosis. Circulation. 1981 Sep;64(3):622-5.
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.

Evidence Profile Table for Studies Assessing Compression Ultrasound in Patients with Suspected First Lower Extremity DVT: Should Compression Ultrasound Be Used to Diagnose or to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT
Intervention: Compression Ultrasound
Comparison: Recurrent VTE during 3 months follow up
Outcome: DVT

Diagnostic test accuracy [1]

Pooled sensitivity	90.3% (95%CI: 88.4% to 92%)
Pooled specificity	97.8% (95%CI: 97% to 98.4%)

Outcome	Study design	Factors that may decrease quality of evidence					Quality of Evidence	Effect per 1000 patients, according to different clinical pre-test probabilities			Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		5% (low)	17% (mod-erate)	53% (high)	
True positives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	45 (44 to 46)	154 (150 to 156)	479 (469 to 488)	CRITICAL
False negatives (patients incorrectly classified as not having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	5 (6 to 4)	16 (20 to 14)	51 (61 to 42)	CRITICAL
True negatives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	929 (922 to 935)	812 (805 to 817)	460 (456 to 462)	CRITICAL
False positives (patients incorrectly classified as having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	21 (28 to 15)	18 (25 to 13)	10 (14 to 8)	CRITICAL

Footnotes:

[1] Data obtained from a meta-analysis with 22 studies evaluating compression ultrasonography alone (Goodacre 2006)

[2] Higher sensitivity observed in studies with higher prevalence.

[3] Accuracy studies included in the meta-analysis, which may increase the specificity estimate. Median prevalence of DVT: 48%, results tend to be more applicable for high risk individuals

[4] Estimates consistent with estimates from similar studies

References:

1. Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, Locker T, Ryan A. Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis. Health Technol Assess. 2006 May;10(15):1-168, iii-iv
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.
3. Pomero F. Dentali F. Borretta V. Bonzini M. Melchio R. Douketis JD. Fenoglio LM. Accuracy of emergency physician–performed ultrasonography in the diagnosis of deep-vein thrombosis. Thromb Haemost. 109(1):137-45, 2013 Jan.
4. Kory PD. Pellecchia CM. Shiloh AL. Mayo PH. DiBello C. Koenig S. Accuracy of ultrasonography performed by critical care physicians for the diagnosis of DVT. Chest. 139(3):538-42, 2011 Mar.
5. Crisp JG. Lovato LM. Jang TB. Compression ultrasonography of the lower extremity with portable vascular ultrasonography can accurately detect deep venous thrombosis in the emergency department. Ann Emerg Med. 56(6):601-10, 2010 Dec.
6. Gibson NS. Schellong SM. Kheir DY. Beyer-Westendorf J. Gallus AS. McRae S. Schutgens RE. Piovella F. Gerdes VE. Buller HR. Safety and sensitivity of two ultrasound strategies in patients with clinically suspected deep venous thrombosis: a prospective management study. J Thromb Haemost. 7(12):2035-41, 2009 Dec.

Evidence to recommendation framework 7

Question 7: In patients with low pretest probability of first lower extremity DVT and D-Dimer positive (ELISA), should we perform proximal CUS instead of venography?

Population: Patients with suspected first lower extremity DVT, with low clinical pretest probability and D-Dimer positive
Diagnostic test: proximal CUS
Comparison: Venography
Setting: Outpatients
Perspective: Public health

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐	**Estimate pre-test probability of prevalence of proximal DVT in patients with D-dimer (ELISA) positive:** - 8.25% **Risk estimates for undesirable outcomes**	The panel considered adequate the use of Wells criteria in the Saudi population. The panel agreed that the estimates of risk presented also could apply for the Saudi population.

Outcome	Incidence (treated)	Incidence (untreated)
Fatal pulmonary embolism	0.3%	1.9%
Nonfatal pulmonary embolism	1.4%	9.3%
Fatal bleeding	0.3%	-
Nonfatal intracranial bleeding	2.1%	-
Nonfatal non-intracranial bleeding	0.1%	-
Venographic mortality	0.03%	-
Propagation to proximal veins (distal DVT)	-	21.4%

Estimate incidence for 3 months

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ *Low* ☒ *Moderate* ☐ *High* ☐		Since there are no evidence specific for the KSA, panel members assumed that the values on outcomes should be probably similar than in other populations. The panel highlighted that there are a need for studies of values and preferences in the KSA setting.
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ *Possibly important uncertainty or variability* ☒ *Probably no important uncertainty or variability* ☐ *No important uncertainty or variability* ☐ *No known undesirable outcomes* ☐	No evidence specific for the Middle East setting identified. Importance and estimate utility values for outcomes	There are no studies evaluating Venography in patients with low risk for DVT. Venography is considered reference standard for DVT, however it is subject to a considerably variation. Although often considered as 100%, post-test probability of a positive test cannot be estimated with confidence. There are no studies evaluating Venography in patients with low risk for DVT. Additionally, venography is associated with 1 to 4% of incidence of adverse reactions to contrast media, including dizziness and nausea, severe allergic reaction in 0 to 0.4% and post-venography DVT in 0 to 2% of patients.
Are the desirable anticipated effects large?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ | ***Varies*** ☐		
Are the undesirable anticipated effects small?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ | ***Varies*** ☐		As described in the question 6, post a negative venography, the probability of having recurrent venous thromboembolism during 3 months follow of up is 1.2% (95%CI 0.2% to 4.4%). (ref) (Moderate-quality evidence).
Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ | ***Varies*** ☐		In patients with low pre-test clinical probability and D-Dimer test positive (ELISA), the probability of having DVT after a negative CUS is 0.88% and the probability after a positive CUS is 78.69%. Per 1000 patients initially tested, 11

Outcome	Utility (range)	Importance
Death	0	Critical
Nonfatal Intracranial Bleed (severe)	0.1 – 0.51	Critical
Nonfatal Intracranial Bleed (moderate)	0.29 – 0.77	Critical
Nonfatal Intracranial Bleed (mild)	0.47 – 0.94	Critical
Nonfatal Pulmonary Embolism	0.63	Critical
Major bleed	0.44 – 0.84	Critical

Assumptions (outcomes):

- Major bleeding equivalent to pulmonary embolism
- Intracranial bleed (overall): 2 to 3 times worse than major bleed or pulmonary embolism
- DVT treatment generally well accepted

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
				patients without DVT will be treated and 5 patients with DVT and D-dimer positive will be discharged. Due to misdiagnosing, we would have additionally 0.11 deaths, 0.36 cases of non-fatal pulmonary embolism and 0.23 major bleeding episodes (0.01 intracranial) per 1000 patients.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
RESOURCE USE	Is the incremental cost small relative to the net benefits?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	Contrast venography is a costly intervention compared to proximal CUS
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☒ / Varies ☐	No evidence found	
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	Technology is not widely available for contrast venography

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	☒

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☐	☒

Recommendation (text)	The Ministry of Health of Saudi Arabia guideline panel recommends performing proximal CUS rather than venography in patients with low pretest probability of first lower extremity DVT and positive highly sensitive D-dimer (ELISA) (Strong recommendation, Low-quality evidence)
Justification	-The panel considered contrast venography an expansive, potentially harmful and difficult to implement alternative for a situations when there are no clear benefit established.
Subgroup considerations	-
Implementation considerations	-
Monitoring and evaluation	-
Research priorities	-

Evidence Profile Table for Studies Assessing Venography in Patients with Suspected First Lower Extremity Deep Vein Thrombosis (DVT):

Should Venography Be Used to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT and negative result for contrast venography
Outcome: Recurrent venous thromboembolism during 3 months follow-up

Diagnostic test accuracy

Pooled sensitivity	Not Available
Pooled specificity	Not Available
Accuracy[1]	98.8% (95% CI: 95.6% to 99.8%)

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease quality of evidence					Quality of Evidence [2]	Post-test probability of negative test	Importance
			Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias			
Venous thromboembolism (3 months)	1 Study (160 patients)	Single-arm prospective cohort study	Serious [3]	None [4]	Not Serious	Not Serious	Undetected [4]	⊕⊕⊕⊖ moderate	1.2% (0.2 to 4.4%)	CRITICAL

Footnotes:

[1] Individuals with normal venography and without venous thromboembolism during 3 months follow-up.

[2] Judgement according to the original systematic review; no additional study had been identified.

[3] Prevalence of DVT in original population not specified

[4] Only one study identified, not allowing adequate assessment of inconsistency and publication bias.

References:

1. Hull R, Hirsh J, Sackett DL, Taylor DW, Carter C, Turpie AG, Powers P, Gent M. Clinical validity of a negative venogram in patients with clinically suspected venous thrombosis. Circulation. 1981 Sep;64(3):622-5.
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.

Evidence Profile Table for Studies Assessing Compression Ultrasound in Patients with Suspected First Lower Extremity DVT and D-dimer (ELISA) positive: Should Compression Ultrasound Be Used to Diagnose or to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT and D-dimer (ELISA) positive
Intervention: Proximal Compression Ultrasound
Comparison: Recurrent VTE during 3 months follow up
Outcome: DVT

Diagnostic test accuracy of proximal CUS [1]

Pooled sensitivity	90.3% (95%CI: 88.4% to 92%)
Pooled specificity	97.8% (95%CI: 97% to 98.4%)

Outcome	Study design	Factors that may decrease quality of evidence					Quality of Evidence	Effect per 570 patients (equivalent to patients with D-dimer positive per 1000) 8.25% (Proportion of patients with low pretest probability and D-dimer positive)	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias			
True positives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	44 (43 to 45)	CRITICAL
False negatives (patients incorrectly classified as not having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	5 (4 to 6)	CRITICAL
True negatives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	510 (506 to 513)	CRITICAL
False positives (patients incorrectly classified as having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	11 (8 to 16)	CRITICAL

Footnotes:

[1] Data obtained from a meta-analysis with 22 studies evaluating compression ultrasonography alone (Goodacre 2006)

[2] Higher sensitivity observed in studies with higher prevalence.

[3] Accuracy studies included in the meta-analysis, which may increase the specificity estimate. Median prevalence of DVT: 48%, results tend to be more applicable for high risk individuals

[4] Estimates consistent with estimates from similar studies

References:

1. Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, Locker T, Ryan A. Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis. Health Technol Assess. 2006 May;10(15):1-168, iii-iv
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.
3. Pomero F. Dentali F. Borretta V. Bonzini M. Melchio R. Douketis JD. Fenoglio LM. Accuracy of emergency physician–performed ultrasonography in the diagnosis of deep-vein thrombosis. Thromb Haemost. 109(1):137-45, 2013 Jan.
4. Kory PD. Pellecchia CM. Shiloh AL. Mayo PH. DiBello C. Koenig S. Accuracy of ultrasonography performed by critical care physicians for the diagnosis of DVT. Chest. 139(3):538-42, 2011 Mar.
5. Crisp JG. Lovato LM. Jang TB. Compression ultrasonography of the lower extremity with portable vascular ultrasonography can accurately detect deep venous thrombosis in the emergency department. Ann Emerg Med. 56(6):601-10, 2010 Dec.
6. Gibson NS. Schellong SM. Kheir DY. Beyer-Westendorf J. Gallus AS. McRae S. Schutgens RE. Piovella F. Gerdes VE. Buller HR. Safety and sensitivity of two ultrasound strategies in patients with clinically suspected deep venous thrombosis: a prospective management study. J Thromb Haemost. 7(12):2035-41, 2009 Dec.

Evidence to recommendation framework 8

Question 8: In patients with low pretest probability of first lower extremity DVT and proximal CUS positive, should we perform proximal venography instead of treating, without further investigation?

Population: Patients with suspected first lower extremity DVT, with low clinical pretest probability and proximal CUS positive
Diagnostic test: venography
Comparison: no testing (treat)
Setting: Outpatients
Perspective: Public health

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐	**Estimate pre-test probability of prevalence of proximal DVT:** - 5% (4 – 8%) **Risk estimates for undesirable outcomes**	The panel considered adequate the use of Wells criteria in the Saudi population. The panel agreed that the estimates of risk presented also could apply for the Saudi population.

Outcome	Incidence (treated)	Incidence (untreated)
Fatal pulmonary embolism	0.3%	1.9%
Nonfatal pulmonary embolism	1.4%	9.3%
Fatal bleeding	0.3%	-
Nonfatal intracranial bleeding	2.1%	-
Nonfatal non-intracranial bleeding	0.1%	-
Venographic mortality	0.03%	-
Propagation to proximal veins (distal DVT)	-	21.4%

Estimate incidence for 3 months

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ | *Low* ☒ | *Moderate* ☐ | *High* ☐		
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☒ | *Probably no important uncertainty or variability* ☐ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐	No evidence specific for the Middle East setting identified. Importance and estimate utility values for outcomes **Outcome** | **Utility (range)** | **Importance** Death | 0 | Critical Nonfatal Intracranial Bleed (severe) | 0.1 – 0.51 | Critical Nonfatal Intracranial Bleed (moderate) | 0.29 – 0.77 | Critical Nonfatal Intracranial Bleed (mild) | 0.47 – 0.94 | Critical Nonfatal Pulmonary Embolism | 0.63 | Critical Major bleed | 0.44 – 0.84 | Critical *Cate-hoek 2009, MacLean 2012* Assumptions (outcomes): - Major bleeding equivalent to pulmonary embolism - Intracranial bleed (overall): 2 to 3 times worse than major bleed or pulmonary embolism - DVT treatment generally well accepted	Since there are no evidence specific for the KSA, panel members assumed that the values on outcomes should be probably similar than in other populations. The panel highlighted that there are a need for studies of values and preferences in the KSA setting.
Are the desirable anticipated effects large?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☒ | ***Varies*** ☐		As described in the question 6, post a negative venography, the probability of having recurrent venous thromboembolism during 3 months follow of up is 1.2% (95%CI 0.2% to 4.4%). (ref) (Moderate-quality evidence). Venography is considered the reference standard for DVT.
Are the undesirable anticipated effects small?	*No* ☐ | *Probably No* ☒ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		As reported in the question 3, 21 patients per 1000 tested with proximal CUS would be incorrectly classified as not having DVT (Moderate-quality evidence). Treating unnecessary this patients we would result in 0.06 deaths and 0.46 major bleeding episodes (0.02 intracranial).
Are the desirable effects large relative to undesirable effects?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | ***Varies*** ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
	Is the incremental cost small relative to the net benefits?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	Contrast venography is a costly intervention compared to proximal CUS
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☒ / Varies ☐	No evidence found	
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	Technology is not widely available for contrast venography

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	☒

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☐	☒

Recommendation (text)	The Ministry of Health of Saudi Arabia panel recommends no further investigation, rather than confirmatory venography, in patients with low pretest probability of first lower extremity DVT and positive proximal CUS. (Strong recommendation, Moderate-quality evidence)
Justification	The panel considered contrast venography an expansive, potentially harmful and difficult to implement alternative for a situations when there are no clear benefit established. The false positive rates of proximal CUS were considered acceptable to proceed with treatment, without confirmatory venography.
Subgroup considerations	-
Implementation considerations	-
Monitoring and evaluation	-
Research priorities	-

Evidence Profile Table for Studies Assessing Venography in Patients with Suspected First Lower Extremity Deep Vein Thrombosis (DVT):

Should Venography Be Used to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT and negative result for contrast venography
Outcome: Recurrent venous thromboembolism during 3 months follow-up

Diagnostic test accuracy

Pooled sensitivity	Not Available
Pooled specificity	Not Available
Accuracy[1]	98.8% (95% CI: 95.6% to 99.8%)

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease quality of evidence					Quality of Evidence [2]	Post-test probability of negative test	Importance
			Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias			
Venous thromboembolism (3 months)	1 Study (160 patients)	Single-arm prospective cohort study	Serious [3]	None [4]	Not Serious	Not Serious	Undetected [4]	⊕⊕⊕⊖ moderate	1.2% (0.2 to 4.4%)	CRITICAL

Footnotes:

[1] Individuals with normal venography and without venous thromboembolism during 3 months follow-up.

[2] Judgement according to the original systematic review; no additional study had been identified.

[3] Prevalence of DVT in original population not specified

[4] Only one study identified, not allowing adequate assessment of inconsistency and publication bias.

References:

1. Hull R, Hirsh J, Sackett DL, Taylor DW, Carter C, Turpie AG, Powers P, Gent M. Clinical validity of a negative venogram in patients with clinically suspected venous thrombosis. Circulation. 1981 Sep;64(3):622-5.
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.

Evidence Profile Table for Studies Assessing Compression Ultrasound in Patients with Suspected First Lower Extremity DVT: Should Compression Ultrasound Be Used to Diagnose or to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT
Intervention: Compression Ultrasound
Comparison: Recurrent VTE during 3 months follow up
Outcome: DVT

Diagnostic test accuracy [1]

Pooled sensitivity	90.3% (95%CI: 88.4% to 92%)
Pooled specificity	97.8% (95%CI: 97% to 98.4%)

Outcome	Study design	Factors that may decrease quality of evidence					Quality of Evidence	Effect per 1000 patients, according to different clinical pre-test probabilities			Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		5% (low)	17% (mod-erate)	53% (high)	
True positives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	45 (44 to 46)	154 (150 to 156)	479 (469 to 488)	CRITICAL
False negatives (patients incorrectly classified as not having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	5 (6 to 4)	16 (20 to 14)	51 (61 to 42)	CRITICAL
True negatives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	929 (922 to 935)	812 (805 to 817)	460 (456 to 462)	CRITICAL
False positives (patients incorrectly classified as having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	21 (28 to 15)	18 (25 to 13)	10 (14 to 8)	CRITICAL

Footnotes:

[1] Data obtained from a meta-analysis with 22 studies evaluating compression ultrasonography alone (Goodacre 2006)

[2] Higher sensitivity observed in studies with higher prevalence.

[3] Accuracy studies included in the meta-analysis, which may increase the specificity estimate. Median prevalence of DVT: 48%, results tend to be more applicable for high risk individuals

[4] Estimates consistent with estimates from similar studies

References:

1. Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, Locker T, Ryan A. Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis. Health Technol Assess. 2006 May;10(15):1-168, iii-iv
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.
3. Pomero F. Dentali F. Borretta V. Bonzini M. Melchio R. Douketis JD. Fenoglio LM. Accuracy of emergency physician–performed ultrasonography in the diagnosis of deep-vein thrombosis. Thromb Haemost. 109(1):137-45, 2013 Jan.
4. Kory PD. Pellecchia CM. Shiloh AL. Mayo PH. DiBello C. Koenig S. Accuracy of ultrasonography performed by critical care physicians for the diagnosis of DVT. Chest. 139(3):538-42, 2011 Mar.
5. Crisp JG. Lovato LM. Jang TB. Compression ultrasonography of the lower extremity with portable vascular ultrasonography can accurately detect deep venous thrombosis in the emergency department. Ann Emerg Med. 56(6):601-10, 2010 Dec.
6. Gibson NS. Schellong SM. Kheir DY. Beyer-Westendorf J. Gallus AS. McRae S. Schutgens RE. Piovella F. Gerdes VE. Buller HR. Safety and sensitivity of two ultrasound strategies in patients with clinically suspected deep venous thrombosis: a prospective management study. J Thromb Haemost. 7(12):2035-41, 2009 Dec.

Evidence to recommendation framework 9

Question 9: In patients with a moderate pretest probability of first lower extremity DVT, should we use D-Dimer (ELISA) as initial test for the diagnosis of DVT?

Population: Patients with suspected first lower extremity DVT, with moderate clinical pretest probability.
Diagnostic test: D-dimer (ELISA)
Comparison: No testing
Setting: Outpatients
Perspective: Public health

<table>
<tr><th></th><th>CRITERIA</th><th>JUDGEMENTS</th><th>RESEARCH EVIDENCE</th><th>ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>PROBLEM</td><td>Is the problem a priority?</td><td>No ☐ | Probably No ☐ | Uncertain ☐ | Probably Yes ☐ | Yes ☒ | Varies ☐</td><td>Estimate pre-test probability of prevalence of proximal DVT:
- 17% (13 – 23%)

Risk estimates for undesirable outcomes
<table><tr><th>Outcome</th><th>Incidence (treated)</th><th>Incidence (untreated)</th></tr><tr><td>Fatal pulmonary embolism</td><td>0.3%</td><td>1.9%</td></tr><tr><td>Nonfatal pulmonary embolism</td><td>1.4%</td><td>9.3%</td></tr><tr><td>Fatal bleeding</td><td>0.3%</td><td>-</td></tr><tr><td>Nonfatal intracranial bleeding</td><td>2.1%</td><td>-</td></tr><tr><td>Nonfatal non-intracranial bleeding</td><td>0.1%</td><td>-</td></tr><tr><td>Venographic mortality</td><td>0.03%</td><td>-</td></tr><tr><td>Propagation to proximal veins (distal DVT)</td><td>-</td><td>21.4%</td></tr></table>Estimate incidence for 3 months</td><td>The panel agreed that the estimates of risk presented also could apply for the Saudi population.</td></tr>
</table>

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Moderate* ☒ | *High* ☐		
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☐ | *Probably no important uncertainty or variability* ☒ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐	No evidence specific for the Middle East setting identified. Importance and estimate utility values for outcomes **Outcome** | **Utility (range)** | **Importance** Death | 0 | Critical Nonfatal Intracranial Bleed (severe) | 0.1 – 0.51 | Critical Nonfatal Intracranial Bleed (moderate) | 0.29 – 0.77 | Critical Nonfatal Intracranial Bleed (mild) | 0.47 – 0.94 | Critical Nonfatal Pulmonary Embolism | 0.63 | Critical Major bleed | 0.44 – 0.84 | Critical *Cate-hoek 2009, MacLean 2012*	Since there are no evidence specific for the KSA, panel members assumed that the values on outcomes should be probably similar than in other populations. The panel highlighted that there are a need for studies of values and preferences in the KSA setting.
Are the desirable anticipated effects large?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☒ | ***Varies*** ☐		
Are the undesirable anticipated effects small?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | ***Varies*** ☐	Assumptions (outcomes): - Major bleeding equivalent to pulmonary embolism - Intracranial bleed (overall): 2 to 3 times worse than major bleed or pulmonary embolism - DVT treatment generally well accepted	Only 10 patients per 1000 tested would be incorrectly classified as not having DVT (false negatives). On the other hand, 457 patients would be incorrectly classified as having DVT (false positives). The probability of having DVT after a negative test is 2.7% and after a positive test is 25.9%. With no testing or treatment, we would have respectively 3.2 and 15.8 cases of fatal and non-fatal pulmonary per 1000 patients.
Are the desirable effects large relative to undesirable effects?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☒ | ***Varies*** ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	The cost of ELISA D-dimer was considered low for the KSA setting
	Is the incremental cost small relative to the net benefits?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☒ / Yes ☐ / Varies ☐	No evidence found	As the effects are large and the costs are small, the strategy seems to be cost-effective.
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☒ / Varies ☐	No evidence found	MOH would make available in all areas ELISA D-dimer assay, reducing inequities.
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	In some places, ELISA D-Dimer may not be currently available, however, as it was considered easy to implement

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	☒

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☐	☒

Recommendation (text)	The Ministry of Health of Saudi Arabia panel recommends the use of highly sensitivity D-Dimer (ELISA) as an initial test for the diagnosis of DVT in patients with moderate pretest probability of first lower extremity DVT. (Strong recommendation, Moderate-quality evidence
Justification	Advantages of the intervention were considered large compared to undesirable consequences. The rate of false negatives and its impact on patient important outcomes was considered small.
Subgroup considerations	-
Implementation considerations	The KSA MoH would make available in all areas ELISA D-dimer assay
Monitoring and evaluation	-
Research priorities	-

Evidence Profile Table for Studies Assessing Highly Sensitive D-Dimer in Patients with Suspected First Lower Extremity DVT: Should Highly Sensitive D-Dimer Be Used to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT
Intervention: D-Dimer (e ELISA)
Comparison: Recurrent VTE during 3 months follow
Outcome: DVT

Diagnostic test accuracy

Pooled sensitivity	94% (95%CI: 93% to 95%)
Pooled specificity	45% (95%CI: 44% to 46%)

Outcome	Study design	Factors that may decrease quality of evidence					Quality of Evidence	Effect per 1000 patients, according to different clinical pre-test probabilities			Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		5% (low)	17% (moderate)	53% (high)	
True positives (patients with DVT)	Systematic reviews of management cohorts and of accuracy studies	Not Serious	Not Serious[1]	Serious[2]	None	Undetected	⊕⊕⊕⊖ moderate	47 (47 to 48)	160 (158 to 162)	498 (493 to 504)	CRITICAL
False negatives (patients incorrectly classified as not having DVT)								3 (3 to 4)	10 (9 to 12)	32 (27 to 37)	CRITICAL
True negatives (patients without DVT)	Systematic reviews of management cohorts and of accuracy studies	Not Serious	Not Serious[1]	Serious[2]	None	Undetected	⊕⊕⊕⊖ moderate	428 (418 to 437	374 (365 to 382)	212 (207 to 216)	CRITICAL
False positives (patients incorrectly classified as not having DVT)								523 513 to 532)	457 (448 to 465)	259 (254 to 263)	CRITICAL

Footnotes:

[1] Estimates consistent with estimates from similar ELISA methods. Similar estimates for different clinical pretest probability.

[2] Accuracy studies included in the meta-analysis, which may increase the specificity estimate

References:

1. Di Nisio M, Squizzato A, Rutjes AW, Büller HR, Zwinderman AH, Bossuyt PM. Diagnostic accuracy of D-dimer test for exclusion of venous thromboembolism: a systematic review. J Thromb Haemost. 2007 Feb;5(2):296-304.
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.
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6. Douma RA. Tan M. Schutgens RE. Bates SM. Perrier A. Legnani C. Biesma DH. Ginsberg JS. Bounameaux H. Palareti G. Carrier M. Mol GC. Le Gal G. Kamphuisen PW. Righini M. Using an age-dependent D-dimer cut-off value increases the number of older patients in whom deep vein thrombosis can be safely excluded. Haematologica. 97(10):1507-13, 2012 Oct.
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8. Luxembourg B. Schwonberg J. Hecking C. Schindewolf M. Zgouras D. Lehmeyer S. Lindhoff-Last E. Performance of five D-dimer assays for the exclusion of symptomatic distal leg vein thrombosis. Thromb Haemost. 107(2):369-78, 2012 Feb.

Evidence to recommendation framework 10

Question 10: In patients with a moderate pretest probability of first lower extremity DVT, should we use proximal CUS as initial test for the diagnosis of DVT?

Population: Patients with suspected first lower extremity DVT, with moderate clinical pretest probability.
Diagnostic test: Proximal CUS
Comparison: No testing
Setting: Outpatients
Perspective: Public health

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐	**Estimate pre-test probability of prevalence of proximal DVT:** - 17% (13 – 23%) **Risk estimates for undesirable outcomes**	The panel considered adequate the use of Wells criteria in the Saudi population. The panel agreed that the estimates of risk presented also could apply for the Saudi population.

Outcome	Incidence (treated)	Incidence (untreated)
Fatal pulmonary embolism	0.3%	1.9%
Nonfatal pulmonary embolism	1.4%	9.3%
Fatal bleeding	0.3%	-
Nonfatal intracranial bleeding	2.1%	-
Nonfatal non-intracranial bleeding	0.1%	-
Venographic mortality	0.03%	-
Propagation to proximal veins (distal DVT)	-	21.4%

Estimate incidence for 3 months

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Moderate* ☒ | *High* ☐	No evidence specific for the Middle East setting identified. Importance and estimate utility values for outcomes **Outcome** / **Utility (range)** / **Importance** Death / 0 / Critical Nonfatal Intracranial Bleed (severe) / 0.1 – 0.51 / Critical Nonfatal Intracranial Bleed (moderate) / 0.29 – 0.77 / Critical Nonfatal Intracranial Bleed (mild) / 0.47 – 0.94 / Critical Nonfatal Pulmonary Embolism / 0.63 / Critical Major bleed / 0.44 – 0.84 / Critical Assumptions (outcomes): - Major bleeding equivalent to pulmonary embolism - Intracranial bleed (overall): 2 to 3 times worse than major bleed or pulmonary embolism - DVT treatment generally well accepted	Since there are no evidence specific for the KSA, panel members assumed that the values on outcomes should be probably similar than in other populations. The panel highlighted that there are a need for studies of values and preferences in the KSA setting. Sixteen patients per 1000 tested would be incorrectly classified as not having DVT (false negatives). On the other hand, 18 patients would be incorrectly classified as having DVT (false positives). The probability of having DVT after a negative test is 2% and after a positive test is 89.4%. Treating those patients with a positive test and discharging those with negative test, would result on 0.26 deaths, 1.15 cases of non-fatal pulmonary embolism and 0.04 major bleeding episodes (0.002 intracranial) per 1000 patients. With no testing or treatment, we would have respectively 3.2 and 15.8 cases of fatal and non-fatal pulmonary per 1000 patients.
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☐ | *Probably no important uncertainty or variability* ☒ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐		
Are the desirable anticipated effects large?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☒ | ***Varies*** ☐		
Are the undesirable anticipated effects small?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☒ | ***Varies*** ☐		
Are the desirable effects large relative to undesirable effects?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☒ | ***Varies*** ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	Cost of proximal CUS was considered low for the KSA setting.
	Is the incremental cost small relative to the net benefits?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☒ / Reduced ☐ / Varies ☐	No evidence found	
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	☒

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☐	☒

Recommendation (text)	The Ministry of Health of Saudi Arabia guideline panel recommends the use of proximal CUS as an initial test for the diagnosis of DVT in patients with moderate pretest probability of first lower extremity DVT. (Strong recommendation, Low-quality evidence)
Justification	Advantages of the intervention were considered large compared to undesirable consequences. The rate of false negatives/positives and its impact on patient important outcomes was considered small.
Subgroup considerations	-
Implementation considerations	-
Monitoring and evaluation	-
Research priorities	-

Evidence Profile Table for Studies Assessing Compression Ultrasound in Patients with Suspected First Lower Extremity DVT: Should Compression Ultrasound Be Used to Diagnose or to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT
Intervention: Proximal Compression Ultrasound
Comparison: Recurrent VTE during 3 months follow up
Outcome: DVT

Diagnostic test accuracy [1]

Pooled sensitivity	90.3% (95%CI: 88.4% to 92%)
Pooled specificity	97.8% (95%CI: 97% to 98.4%)

Outcome	Study design	Factors that may decrease quality of evidence					Quality of Evidence	Effect per 1000 patients, according to different clinical pre-test probabilities			Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		5% (low)	17% (mod-erate)	53% (high)	
True positives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	45 (44 to 46)	154 (150 to 156)	479 (469 to 488)	CRITICAL
False negatives (patients incorrectly classified as not having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	5 (6 to 4)	16 (20 to 14)	51 (61 to 42)	CRITICAL
True negatives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	929 (922 to 935)	812 (805 to 817)	460 (456 to 462)	CRITICAL
False positives (patients incorrectly classified as having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	21 (28 to 15)	18 (25 to 13)	10 (14 to 8)	CRITICAL

Footnotes:

[1] Data obtained from a meta-analysis with 22 studies evaluating compression ultrasonography alone (Goodacre 2006)

[2] Higher sensitivity observed in studies with higher prevalence.

[3] Accuracy studies included in the meta-analysis, which may increase the specificity estimate. Median prevalence of DVT: 48%, results tend to be more applicable for high risk individuals

[4] Estimates consistent with estimates from similar studies

References:

1. Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, Locker T, Ryan A. Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis. Health Technol Assess. 2006 May;10(15):1-168, iii-iv
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.
3. Pomero F. Dentali F. Borretta V. Bonzini M. Melchio R. Douketis JD. Fenoglio LM. Accuracy of emergency physician–performed ultrasonography in the diagnosis of deep-vein thrombosis. Thromb Haemost. 109(1):137-45, 2013 Jan.
4. Kory PD. Pellecchia CM. Shiloh AL. Mayo PH. DiBello C. Koenig S. Accuracy of ultrasonography performed by critical care physicians for the diagnosis of DVT. Chest. 139(3):538-42, 2011 Mar.
5. Crisp JG. Lovato LM. Jang TB. Compression ultrasonography of the lower extremity with portable vascular ultrasonography can accurately detect deep venous thrombosis in the emergency department. Ann Emerg Med. 56(6):601-10, 2010 Dec.
6. Gibson NS. Schellong SM. Kheir DY. Beyer-Westendorf J. Gallus AS. McRae S. Schutgens RE. Piovella F. Gerdes VE. Buller HR. Safety and sensitivity of two ultrasound strategies in patients with clinically suspected deep venous thrombosis: a prospective management study. J Thromb Haemost. 7(12):2035-41, 2009 Dec.

Evidence to recommendation framework 11

Question 11: In patients with moderate pretest probability of first lower extremity DVT, should we use D-dimer instead of proximal CUS as initial test for the diagnosis of DVT?

Population: Patients with suspected first lower extremity DVT, with moderate clinical pretest probability.
Diagnostic test: D-Dimer
Comparison: Proximal CUS
Setting: Outpatients
Perspective: Public health

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐	**Estimate pre-test probability of prevalence of proximal DVT:** - 17% (13 – 23%) **Risk estimates for undesirable outcomes**	The panel considered adequate the use of Wells criteria in the Saudi population. The panel agreed that the estimates of risk presented also could apply for the Saudi population.

Outcome	Incidence (treated)	Incidence (untreated)
Fatal pulmonary embolism	0.3%	1.9%
Nonfatal pulmonary embolism	1.4%	9.3%
Fatal bleeding	0.3%	-
Nonfatal intracranial bleeding	2.1%	-
Nonfatal non-intracranial bleeding	0.1%	-
Venographic mortality	0.03%	-
Propagation to proximal veins (distal DVT)	-	21.4%

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Moderate* ☒ | *High* ☐	No evidence specific for the Middle East setting identified. Importance and estimate utility values for outcomes **Outcome** | **Utility (range)** | **Importance** Death | 0 | Critical Nonfatal Intracranial Bleed (severe) | 0.1 – 0.51 | Critical Nonfatal Intracranial Bleed (moderate) | 0.29 – 0.77 | Critical Nonfatal Intracranial Bleed (mild) | 0.47 – 0.94 | Critical Nonfatal Pulmonary Embolism | 0.63 | Critical Major bleed | 0.44 – 0.84 | Critical Assumptions (outcomes): - Major bleeding equivalent to pulmonary embolism - Intracranial bleed (overall): 2 to 3 times worse than major bleed or pulmonary embolism - DVT treatment generally well accepted	Since there are no evidence specific for the KSA, panel members assumed that the values on outcomes should be probably similar than in other populations. The panel highlighted that there are a need for studies of values and preferences in the KSA setting. With proximal CUS, 16 patients per 1000 tested would be incorrectly classified as not having DVT (false negatives). On the other hand, 18 patients would be incorrectly classified as having DVT (false positives). Similarly with D-dimer (ELISA), only 10 patients per 1000 tested would be incorrectly classified as not having DVT. However, 374 patients would be discharged with no need of a further test (D-dimer negative).
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☐ | *Probably no important uncertainty or variability* ☒ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐		
Are the desirable anticipated effects large?	*No* ☐ | *Probably No* ☒ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		
Are the undesirable anticipated effects small?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | ***Varies*** ☐		
Are the desirable effects large relative to undesirable effects?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | ***Varies*** ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	No evidence found	D-dimer test is less expensive than proximal CUS
	Is the incremental cost small relative to the net benefits?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	No evidence found	
EQUITY	What would be the impact on health inequities?	Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ☒ Varies ☐	No evidence found	
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	No evidence found	
FEASIBILITY	Is the option feasible to implement?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	No evidence found	

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☒	☐

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☒	☐

Recommendation (text)	The Ministry of Health of Saudi Arabia guideline panel suggests the use of highly sensitive D-Dimer (ELISA) rather than proximal CUS as an initial test for the diagnosis of DVT in patients with moderate pretest probability of first lower extremity DVT. (Weak recommendation, Low-quality evidence)
Justification	The cost of D-dimer is lower than the cost of proximal CUS. Using D-dimer ELISA as an initial test probably would be cost-saving in the Saudi setting.
Subgroup considerations	-
Implementation considerations	-
Monitoring and evaluation	
Research priorities	

Evidence Profile Table for Studies Assessing Compression Ultrasound in Patients with Suspected First Lower Extremity DVT: Should Compression Ultrasound Be Used to Diagnose or to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT
Intervention: Proximal Compression Ultrasound
Comparison: Recurrent VTE during 3 months follow up
Outcome: DVT

Diagnostic test accuracy [1]

Pooled sensitivity	90.3% (95%CI: 88.4% to 92%)
Pooled specificity	97.8% (95%CI: 97% to 98.4%)

Outcome	Study design	Factors that may decrease quality of evidence					Quality of Evidence	Effect per 1000 patients, according to different clinical pre-test probabilities			Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		5% (low)	17% (mod-erate)	53% (high)	
True positives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	45 (44 to 46)	154 (150 to 156)	479 (469 to 488)	CRITICAL
False negatives (patients incorrectly classified as not having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	5 (6 to 4)	16 (20 to 14)	51 (61 to 42)	CRITICAL
True negatives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	929 (922 to 935)	812 (805 to 817)	460 (456 to 462)	CRITICAL
False positives (patients incorrectly classified as having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	21 (28 to 15)	18 (25 to 13)	10 (14 to 8)	CRITICAL

Footnotes:

[1] Data obtained from a meta-analysis with 22 studies evaluating compression ultrasonography alone (Goodacre 2006)

[2] Higher sensitivity observed in studies with higher prevalence.

[3] Accuracy studies included in the meta-analysis, which may increase the specificity estimate. Median prevalence of DVT: 48%, results tend to be more applicable for high risk individuals

[4] Estimates consistent with estimates from similar studies

References:

1. Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, Locker T, Ryan A. Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis. Health Technol Assess. 2006 May;10(15):1-168, iii-iv
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.
3. Pomero F. Dentali F. Borretta V. Bonzini M. Melchio R. Douketis JD. Fenoglio LM. Accuracy of emergency physician–performed ultrasonography in the diagnosis of deep-vein thrombosis. Thromb Haemost. 109(1):137-45, 2013 Jan.
4. Kory PD. Pellecchia CM. Shiloh AL. Mayo PH. DiBello C. Koenig S. Accuracy of ultrasonography performed by critical care physicians for the diagnosis of DVT. Chest. 139(3):538-42, 2011 Mar.
5. Crisp JG. Lovato LM. Jang TB. Compression ultrasonography of the lower extremity with portable vascular ultrasonography can accurately detect deep venous thrombosis in the emergency department. Ann Emerg Med. 56(6):601-10, 2010 Dec.
6. Gibson NS. Schellong SM. Kheir DY. Beyer-Westendorf J. Gallus AS. McRae S. Schutgens RE. Piovella F. Gerdes VE. Buller HR. Safety and sensitivity of two ultrasound strategies in patients with clinically suspected deep venous thrombosis: a prospective management study. J Thromb Haemost. 7(12):2035-41, 2009 Dec.

Evidence Profile Table for Studies Assessing Highly Sensitive D-Dimer in Patients with Suspected First Lower Extremity DVT: Should Highly Sensitive D-Dimer Be Used to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT
Intervention: D-Dimer (ELISA)
Comparison: Recurrent VTE during 3 months follow
Outcome: DVT

Diagnostic test accuracy

Pooled sensitivity	94% (95%CI: 93% to 95%)
Pooled specificity	45% (95%CI: 44% to 46%)

Outcome	Study design	Factors that may decrease quality of evidence					Quality of Evidence	Effect per 1000 patients, according to different clinical pre-test probabilities			Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		5% (low)	17% (moderate)	53% (high)	
True positives (patients with DVT)	Systematic reviews of management cohorts and of accuracy studies	Not Serious	Not Serious[1]	Serious[2]	None	Undetected	⊕⊕⊕⊖ moderate	47 (47 to 48)	160 (158 to 162)	498 (493 to 504)	CRITICAL
False negatives (patients incorrectly classified as not having DVT)								3 (3 to 4)	10 (9 to 12)	32 (27 to 37)	CRITICAL
True negatives (patients without DVT)	Systematic reviews of management cohorts and of accuracy studies	Not Serious	Not Serious[1]	Serious[2]	None	Undetected	⊕⊕⊕⊖ moderate	428 (418 to 437	374 (365 to 382)	212 (207 to 216)	CRITICAL
False positives (patients incorrectly classified as not having DVT)								523 513 to 532)	457 (448 to 465)	259 (254 to 263)	CRITICAL

Footnotes:

[1] Estimates consistent with estimates from similar ELISA methods. Similar estimates for different clinical pretest probability.

[2] Accuracy studies included in the meta-analysis, which may increase the specificity estimate

References:

1. Di Nisio M, Squizzato A, Rutjes AW, Büller HR, Zwinderman AH, Bossuyt PM. Diagnostic accuracy of D-dimer test for exclusion of venous thromboembolism: a systematic review. J Thromb Haemost. 2007 Feb;5(2):296-304.
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.
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7. Boeer K. Siegmund R. Schmidt D. Deufel T. Kiehntopf M. Comparison of six D-dimer assays for the detection of clinically suspected deep venous thrombosis of the lower extremities. Blood Coagulation & Fibrinolysis. 20(2):141-5, 2009 Mar.
8. Luxembourg B. Schwonberg J. Hecking C. Schindewolf M. Zgouras D. Lehmeyer S. Lindhoff-Last E. Performance of five D-dimer assays for the exclusion of symptomatic distal leg vein thrombosis. Thromb Haemost. 107(2):369-78, 2012 Feb.

Evidence to recommendation framework 12

Question 12: In patients with a moderate pretest probability of first lower extremity DVT and D-Dimer negative, should we perform proximal CUS instead of discharge with no further evaluation?

Population: Patients with suspected first lower extremity DVT, with moderate clinical pretest probability and D-dimer negative
Diagnostic test: Proximal CUS
Comparison: No testing (rule out)
Setting: Outpatients
Perspective: Public health

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐	**Estimate pre-test probability of prevalence of proximal DVT:** - 17% (13 – 23%) **Risk estimates for undesirable outcomes**	The panel considered adequate the use of Wells criteria in the Saudi population. The panel agreed that the estimates of risk presented also could apply for the Saudi population.

Outcome	Incidence (treated)	Incidence (untreated)
Fatal pulmonary embolism	0.3%	1.9%
Nonfatal pulmonary embolism	1.4%	9.3%
Fatal bleeding	0.3%	-
Nonfatal intracranial bleeding	2.1%	-
Nonfatal non-intracranial bleeding	0.1%	-
Venographic mortality	0.03%	-
Propagation to proximal veins (distal DVT)	-	21.4%

Estimate incidence for 3 months

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ | *Low* ☒ | *Moderate* ☐ | *High* ☐	No evidence specific for the Middle East setting identified. Importance and estimate utility values for outcomes	Since there are no evidence specific for the KSA, panel members assumed that the values on outcomes should be probably similar than in other populations. The panel highlighted that there are a need for studies of values and preferences in the KSA setting. As reported in question 9, using D-dimer as initial test (ELISA), 10 patients per 1000 tested would be incorrectly classified as not having DVT (false negatives). The probability of having DVT after a negative test is 2.7%. If patients with D-dimer negative be discharged with no further testing, we would have 0.16 and 0.72 additional cases of fatal and non-fatal pulmonary among the false negatives per 1000 patients tested. With sequential D-dimer (ELISA) and proximal CUS negatives, only 1 per 1000 patients tested would be the false negative (posttest probability = 0.27%). Otherwise, the number of false positives would increase 8 per 1000 initially tested. Thus, we would expect an increase of 0.02 deaths and 0.2 non-fatal major bleeding events per 1000 patients tested.
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☐ | *Probably no important uncertainty or variability* ☐ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐		
Are the desirable anticipated effects large?	*No* ☐ | *Probably No* ☒ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		
Are the undesirable anticipated effects small?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | ***Varies*** ☐		
Are the desirable effects large relative to undesirable effects?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☒ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		

Outcome	Utility (range)	Importance
Death	0	Critical
Nonfatal Intracranial Bleed (severe)	0.1 – 0.51	Critical
Nonfatal Intracranial Bleed (moderate)	0.29 – 0.77	Critical
Nonfatal Intracranial Bleed (mild)	0.47 – 0.94	Critical
Nonfatal Pulmonary Embolism	0.63	Critical
Major bleed	0.44 – 0.84	Critical

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☒ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐	No evidence found	
	Is the incremental cost small relative to the net benefits?	No ☒ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐	No evidence found	Performing proximal CUS in patients with low clinical pre-test probability and D-Dimer negative would increase costs: 374 additional ultrasounds would be needed per 1000 patients initially tested.
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☒ / Varies ☐	No evidence found	
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☒	☐	☐	☐

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☒	☐	☐

Recommendation (text)	The Ministry of Health of Saudi Arabia guideline panel recommends no further testing over further investigation with proximal CUS in patients with moderate pretest probability of first lower extremity DVT and D-dimer negative (ELISA). (Strong recommendation. Low-quality evidence)
Justification	Performing proximal CUS in patients with low clinical pre-test probability and D-Dimer negative would increase costs, without impacting on patient important outcomes. False negative rates in this population were considered low by the panel member.
Subgroup considerations	-
Implementation considerations	-
Monitoring and evaluation	-
Research priorities	-

Evidence Profile Table for Studies Assessing Compression Ultrasound in Patients with Suspected First Lower Extremity DVT: Should Compression Ultrasound Be Used to Diagnose or to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT
Intervention: Proximal compression Ultrasound
Comparison: Recurrent VTE during 3 months follow up
Outcome: DVT

Diagnostic test accuracy [1]

Pooled sensitivity	90.3% (95%CI: 88.4% to 92%)
Pooled specificity	97.8% (95%CI: 97% to 98.4%)

Outcome	Study design	Factors that may decrease quality of evidence					Quality of Evidence	Effect per 1000 patients, according to different clinical pre-test probabilities			Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		5% (low)	17% (moderate)	53% (high)	
True positives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	45 (44 to 46)	154 (150 to 156)	479 (469 to 488)	CRITICAL
False negatives (patients incorrectly classified as not having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	5 (6 to 4)	16 (20 to 14)	51 (61 to 42)	CRITICAL
True negatives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	929 (922 to 935)	812 (805 to 817)	460 (456 to 462)	CRITICAL
False positives (patients incorrectly classified as having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	21 (28 to 15)	18 (25 to 13)	10 (14 to 8)	CRITICAL

Footnotes:

[1] Data obtained from a meta-analysis with 22 studies evaluating compression ultrasonography alone (Goodacre 2006)

[2] Higher sensitivity observed in studies with higher prevalence.

[3] Accuracy studies included in the meta-analysis, which may increase the specificity estimate. Median prevalence of DVT: 48%, results tend to be more applicable for high risk individuals

[4] Estimates consistent with estimates from similar studies

References:

1. Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, Locker T, Ryan A. Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis. Health Technol Assess. 2006 May;10(15):1-168, iii-iv
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.
3. Pomero F. Dentali F. Borretta V. Bonzini M. Melchio R. Douketis JD. Fenoglio LM. Accuracy of emergency physician–performed ultrasonography in the diagnosis of deep-vein thrombosis. Thromb Haemost. 109(1):137-45, 2013 Jan.
4. Kory PD. Pellecchia CM. Shiloh AL. Mayo PH. DiBello C. Koenig S. Accuracy of ultrasonography performed by critical care physicians for the diagnosis of DVT. Chest. 139(3):538-42, 2011 Mar.
5. Crisp JG. Lovato LM. Jang TB. Compression ultrasonography of the lower extremity with portable vascular ultrasonography can accurately detect deep venous thrombosis in the emergency department. Ann Emerg Med. 56(6):601-10, 2010 Dec.
6. Gibson NS. Schellong SM. Kheir DY. Beyer-Westendorf J. Gallus AS. McRae S. Schutgens RE. Piovella F. Gerdes VE. Buller HR. Safety and sensitivity of two ultrasound strategies in patients with clinically suspected deep venous thrombosis: a prospective management study. J Thromb Haemost. 7(12):2035-41, 2009 Dec.

Evidence Profile Table for Studies Assessing Highly Sensitive D-Dimer in Patients with Suspected First Lower Extremity DVT: Should Highly Sensitive D-Dimer Be Used to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT
Intervention: D-Dimer (e ELISA)
Comparison: Recurrent VTE during 3 months follow
Outcome: DVT

Diagnostic test accuracy

Pooled sensitivity	94% (95%CI: 93% to 95%)
Pooled specificity	45% (95%CI: 44% to 46%)

Outcome	Study design	Factors that may decrease quality of evidence					Quality of Evidence	Effect per 1000 patients, according to different clinical pre-test probabilities			Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		5% (low)	17% (moderate)	53% (high)	
True positives (patients with DVT)	Systematic reviews of management cohorts and of accuracy studies	Not Serious	Not Serious[1]	Serious[2]	None	Undetected	⊕⊕⊕⊖ moderate	47 (47 to 48)	160 (158 to 162)	498 (493 to 504)	CRITICAL
False negatives (patients incorrectly classified as not having DVT)								3 (3 to 4)	10 (9 to 12)	32 (27 to 37)	CRITICAL
True negatives (patients without DVT)	Systematic reviews of management cohorts and of accuracy studies	Not Serious	Not Serious[1]	Serious[2]	None	Undetected	⊕⊕⊕⊖ moderate	428 (418 to 437	374 (365 to 382)	212 (207 to 216)	CRITICAL
False positives (patients incorrectly classified as not having DVT)								523 513 to 532)	457 (448 to 465)	259 (254 to 263)	CRITICAL

Footnotes:

[1] Estimates consistent with estimates from similar ELISA methods. Similar estimates for different clinical pretest probability.

[2] Accuracy studies included in the meta-analysis, which may increase the specificity estimate

References:

1. Di Nisio M, Squizzato A, Rutjes AW, Büller HR, Zwinderman AH, Bossuyt PM. Diagnostic accuracy of D-dimer test for exclusion of venous thromboembolism: a systematic review. J Thromb Haemost. 2007 Feb;5(2):296-304.
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.
3. Schouten HJ. Geersing GJ. Koek HL. Zuithoff NP. Janssen KJ. Douma RA. van Delden JJ. Moons KG. Reitsma JB. Diagnostic accuracy of conventional or age adjusted D-dimer cut-off values in older patients with suspected venous thromboembolism: systematic review and meta-analysis. BMJ. 346:f2492, 2013.
4. Der Sahakian G. Claessens YE. Allo JC. Kansao J. Kierzek G. Pourriat JL. Accuracy of D-Dimers to Rule Out Venous Thromboembolism Events across Age Categories. emerg. med. int.. 2010:185453, 2010
5. Elías-Hernández T, Otero-Candelera R, Fernández-Jiménez D, Jara-Palomares L, Jiménez-Castro V, Barrot-Cortés E. [Clinical usefulness of three quantitative D-dimers tests in outpatients with suspected deep vein thrombosis]. Rev Clin Esp. 2012 May;212(5):235-41.
6. Douma RA. Tan M. Schutgens RE. Bates SM. Perrier A. Legnani C. Biesma DH. Ginsberg JS. Bounameaux H. Palareti G. Carrier M. Mol GC. Le Gal G. Kamphuisen PW. Righini M. Using an age-dependent D-dimer cut-off value increases the number of older patients in whom deep vein thrombosis can be safely excluded. Haematologica. 97(10):1507-13, 2012 Oct.
7. Boeer K. Siegmund R. Schmidt D. Deufel T. Kiehntopf M. Comparison of six D-dimer assays for the detection of clinically suspected deep venous thrombosis of the lower extremities. Blood Coagulation & Fibrinolysis. 20(2):141-5, 2009 Mar.
8. Luxembourg B. Schwonberg J. Hecking C. Schindewolf M. Zgouras D. Lehmeyer S. Lindhoff-Last E. Performance of five D-dimer assays for the exclusion of symptomatic distal leg vein thrombosis. Thromb Haemost. 107(2):369-78, 2012 Feb.

Evidence to recommendation framework 13

Question 13: In patients with a moderate pretest probability of first lower extremity DVT and DD positive, should we perform proximal CUS instead of venography?

Population: Patients with suspected first lower extremity DVT, with moderate clinical pretest probability and D-Dimer positive
Diagnostic test: proximal CUS
Comparison: Venography
Setting: Outpatients
Perspective: Public health

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐	**Estimate pre-test probability of prevalence of proximal DVT in patients with D-dimer (ELISA) positive:** - 25.93% **Risk estimates for undesirable outcomes**	The panel considered adequate the use of Wells criteria in the Saudi population. The panel agreed that the estimates of risk presented also could apply for the Saudi population.

Outcome	Incidence (treated)	Incidence (untreated)
Fatal pulmonary embolism	0.3%	1.9%
Nonfatal pulmonary embolism	1.4%	9.3%
Fatal bleeding	0.3%	-
Nonfatal intracranial bleeding	2.1%	-
Nonfatal non-intracranial bleeding	0.1%	-
Venographic mortality	0.03%	-
Propagation to proximal veins (distal DVT)	-	21.4%

Estimate incidence for 3 months

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ | *Low* ☒ | *Moderate* ☐ | *High* ☐	No evidence specific for the Middle East setting identified. Importance and estimate utility values for outcomes	Since there are no evidence specific for the KSA, panel members assumed that the values on outcomes should be probably similar than in other populations. The panel highlighted that there are a need for studies of values and preferences in the KSA setting. There are no studies evaluating Venography in patients with low risk for DVT. Venography is considered reference standard for DVT, however it is subject to a considerably variation. Although often considered as 100%, post-test probability of a positive test cannot be estimated with confidence. There are no studies evaluating Venography in patients with low risk for DVT. Additionally, venography is associated with 1 to 4% of incidence of adverse reactions to contrast media, including dizziness and nausea, severe allergic reaction in 0 to 0.4% and post-venography DVT in 0 to 2% of patients. As described in the question 6, post a negative venography, the probability of having recurrent venous thromboembolism during 3 months follow of up is 1.2% (95%CI 0.2% to 4.4%). (ref) (Moderate-quality evidence). In patients with moderate pretest clinical probability and D-Dimer test positive (ELISA), the probability of having DVT after a negative CUS is 3.36% and the
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☐ | *Probably no important uncertainty or variability* ☒ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐		
Are the desirable anticipated effects large?	*No* ☐ | *Probably No* ☒ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		
Are the undesirable anticipated effects small?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | ***Varies*** ☐		
Are the desirable effects large relative to undesirable effects?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | ***Varies*** ☐		

Outcome	Utility (range)	Importance
Death	0	Critical
Nonfatal Intracranial Bleed (severe)	0.1 – 0.51	Critical
Nonfatal Intracranial Bleed (moderate)	0.29 – 0.77	Critical
Nonfatal Intracranial Bleed (mild)	0.47 – 0.94	Critical
Nonfatal Pulmonary Embolism	0.63	Critical
Major bleed	0.44 – 0.84	Critical

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
				probability after a positive CUS is 93.49%. Per 1000 patients initially tested, 10 patients without DVT will be treated and 15 patients with DVT and D-dimer positive will be discharged. Due to misdiagnosing, we would have additionally 0.27 deaths, 1.08 cases of non-fatal pulmonary embolism and fewer 0.11 major bleeding episodes per 1000 patients.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
RESOURCE USE	Is the incremental cost small relative to the net benefits?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	Contrast venography is a costly intervention compared to proximal CUS
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☒ / Varies ☐	No evidence found	
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☒ / Yes ☐ / Varies ☐	No evidence found	Technology is not widely available for contrast venography

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	☒

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☐	☒

Recommendation (text)	The Ministry of Health of Saudi Arabia guideline panel recommends performing proximal CUS rather than venography in patients with moderate pretest probability of first lower extremity DVT and positive highly sensitive D-dimer (ELISA) (Strong recommendation, Low-quality evidence)
Justification	-The panel considered contrast venography an expansive, potentially harmful and difficult to implement alternative for a situations when there are no clear benefit established.
Subgroup considerations	-
Implementation considerations	-
Monitoring and evaluation	-
Research priorities	-

Evidence Profile Table for Studies Assessing Venography in Patients with Suspected First Lower Extremity Deep Vein Thrombosis (DVT):

Should Venography Be Used to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT and negative result for contrast venography
Outcome: Recurrent venous thromboembolism during 3 months follow-up

Diagnostic test accuracy

Pooled sensitivity	Not Available
Pooled specificity	Not Available
Accuracy[1]	98.8% (95% CI: 95.6% to 99.8%)

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease quality of evidence					Quality of Evidence [2]	Post-test probability of negative test	Importance
			Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias			
Venous thromboembolism (3 months)	1 Study (160 patients)	Single-arm prospective cohort study	Serious [3]	None [4]	Not Serious	Not Serious	Undetected [4]	⊕⊕⊕⊖ moderate	1.2% (0.2 to 4.4%)	CRITICAL

Footnotes:

[1] Individuals with normal venography and without venous thromboembolism during 3 months follow-up.

[2] Judgement according to the original systematic review; no additional study had been identified.

[3] Prevalence of DVT in original population not specified

[4] Only one study identified, not allowing adequate assessment of inconsistency and publication bias.

References:

1. Hull R, Hirsh J, Sackett DL, Taylor DW, Carter C, Turpie AG, Powers P, Gent M. Clinical validity of a negative venogram in patients with clinically suspected venous thrombosis. Circulation. 1981 Sep;64(3):622-5.
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.

Evidence Profile Table for Studies Assessing Compression Ultrasound in Patients with Suspected First Lower Extremity DVT and D-dimer (ELISA) positive: Should Compression Ultrasound Be Used to Diagnose or to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT and D-dimer (ELISA) positive
Intervention: Proximal Compression Ultrasound
Comparison: Recurrent VTE during 3 months follow up
Outcome: DVT

Diagnostic test accuracy of proximal CUS [1]

Pooled sensitivity	90.3% (95%CI: 88.4% to 92%)
Pooled specificity	97.8% (95%CI: 97% to 98.4%)

Outcome	Study design	Factors that may decrease quality of evidence					Quality of Evidence	Effect per 616 patients (equivalent to patients with D-dimer positive per 1000) Proportion of patients with low pretest probability and D-dimer positive: 25.93%	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias			
True positives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	144 (141 to 147)	CRITICAL
False negatives (patients incorrectly classified as not having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	16 (13 to 19)	CRITICAL
True negatives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	446 (441 to 449)	CRITICAL
False positives (patients incorrectly classified as having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	10 (7 to 14)	CRITICAL

Footnotes:

[1] Data obtained from a meta-analysis with 22 studies evaluating compression ultrasonography alone (Goodacre 2006)

[2] Higher sensitivity observed in studies with higher prevalence.

[3] Accuracy studies included in the meta-analysis, which may increase the specificity estimate. Median prevalence of DVT: 48%, results tend to be more applicable for high risk individuals

[4] Estimates consistent with estimates from similar studies

References:

1. Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, Locker T, Ryan A. Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis. Health Technol Assess. 2006 May;10(15):1-168, iii-iv
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.
3. Pomero F. Dentali F. Borretta V. Bonzini M. Melchio R. Douketis JD. Fenoglio LM. Accuracy of emergency physician–performed ultrasonography in the diagnosis of deep-vein thrombosis. Thromb Haemost. 109(1):137-45, 2013 Jan.
4. Kory PD. Pellecchia CM. Shiloh AL. Mayo PH. DiBello C. Koenig S. Accuracy of ultrasonography performed by critical care physicians for the diagnosis of DVT. Chest. 139(3):538-42, 2011 Mar.
5. Crisp JG. Lovato LM. Jang TB. Compression ultrasonography of the lower extremity with portable vascular ultrasonography can accurately detect deep venous thrombosis in the emergency department. Ann Emerg Med. 56(6):601-10, 2010 Dec.
6. Gibson NS. Schellong SM. Kheir DY. Beyer-Westendorf J. Gallus AS. McRae S. Schutgens RE. Piovella F. Gerdes VE. Buller HR. Safety and sensitivity of two ultrasound strategies in patients with clinically suspected deep venous thrombosis: a prospective management study. J Thromb Haemost. 7(12):2035-41, 2009 Dec.

Evidence to recommendation framework 14

Question 14: In patients with moderate pretest probability of first lower extremity DVT and initial proximal CUS negative, should we repeat proximal CUS instead of rule out without further investigation?

Population: Patients with suspected first lower extremity DVT, with moderate clinical pretest probability and initial CUS negative
Diagnostic test: repeat CUS in 1 week
Comparison: No testing
Setting: Outpatients
Perspective: Public health

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐	**Estimate pre-test probability of prevalence of proximal DVT:** - 17% (13 – 23%) **Risk estimates for undesirable outcomes**	The panel considered adequate the use of Wells criteria in the Saudi population. The panel agreed that the estimates of risk presented also could apply for the Saudi population.

Outcome	Incidence (treated)	Incidence (untreated)
Fatal pulmonary embolism	0.3%	1.9%
Nonfatal pulmonary embolism	1.4%	9.3%
Fatal bleeding	0.3%	-
Nonfatal intracranial bleeding	2.1%	-
Nonfatal non-intracranial bleeding	0.1%	-
Venographic mortality	0.03%	-
Propagation to proximal veins (distal DVT)	-	21.4%

Estimate incidence for 3 months

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ | *Low* ☒ | *Moderate* ☐ | *High* ☐	No evidence specific for the Middle East setting identified. Importance and estimate utility values for outcomes	Since there are no evidence specific for the KSA, panel members assumed that the values on outcomes should be probably similar than in other populations. The panel highlighted that there are a need for studies of values and preferences in the KSA setting. The probability of having DVT after a negative test is 2%. Discharging those patients with negative test would result on 0.26 deaths, 1.15 cases of non-fatal pulmonary embolism per 1000 patients initially tested. For serial CUS in patients with moderate clinical pretest probability, three observational studies were identified in the systematic review. In these studies, the pooled prevalence of DVT was 15.8% and the probability of DVT post-negative serial CUS were 1.1% (95%CI 0.4% to 2.5%) and 0.6% (95%CI 0.4% to 0.9%). Repeating the proximal CUS would reduce the rate of false negatives, however would increase the number of false positives, resulting in higher bleeding rates.
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☐ | *Probably no important uncertainty or variability* ☒ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐		
Are the desirable anticipated effects large?	*No* ☐ | *Probably No* ☒ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		
Are the undesirable anticipated effects small?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | ***Varies*** ☐		
Are the desirable effects large relative to undesirable effects?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☒ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		

Outcome	Utility (range)	Importance
Death	0	Critical
Nonfatal Intracranial Bleed (severe)	0.1 – 0.51	Critical
Nonfatal Intracranial Bleed (moderate)	0.29 – 0.77	Critical
Nonfatal Intracranial Bleed (mild)	0.47 – 0.94	Critical
Nonfatal Pulmonary Embolism	0.63	Critical
Major bleed	0.44 – 0.84	Critical

Cate-hoek 2009, MacLean 2012

Assumptions (outcomes):

- Major bleeding equivalent to pulmonary embolism
- Intracranial bleed (overall): 2 to 3 times worse than major bleed or pulmonary embolism
- DVT treatment generally well accepted

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☒ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐	No evidence found	
	Is the incremental cost small relative to the net benefits?	No ☐ / Probably No ☒ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐	No evidence found	Performing proximal CUS in patients with moderate clinical pre-test probability and initial CUS negative would increase costs: 831 additional ultrasounds would be needed per 1000 patients initially tested.
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☒ / Varies ☐	No evidence found	
ACCEPTABILITY	Is the option acceptable to key stakeholders ?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☒	☐	☐

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☒	☐	☐

Recommendation (text)	The Ministry of Health of Saudi Arabia guideline panel suggests no further testing rather than repeat proximal CUS in patients with a moderate pretest probability of first lower extremity DVT and initial negative proximal CUS. (Weak recommendation, Low-quality evidence)
Justification	Repeating proximal CUS in patients with moderate clinical pre-test probability and initial proximal CUS negative would increase costs, without impacting on patient important outcomes. False negative rates in this population were considered adequate by the panel members.
Subgroup considerations	-
Implementation considerations	-
Monitoring and evaluation	-
Research priorities	-

Evidence Profile Table for Studies Assessing Serial Compression Ultrasound (CUS) in Patients with Suspected First Lower Extremity Deep Vein Thrombosis (DVT):

Should Serial CUS be Used to Rule Out DVT in patients with moderate pretest probability?

Population: Patients with suspected first lower extremity DVT and moderate clinical pretest probability
Intervention: Serial CUS
Outcome: Recurrent venous thromboembolism during 3 months follow-up

Diagnostic test accuracy

Pooled sensitivity	Not Available
Pooled specificity	Not Available

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease quality of evidence					Quality of Evidence [1]	Pretest probability (prevalence)	Post-test probability of negative test	Importance
			Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias				
Venous thromboembolism (3 months)	1 study (426 patients)	Management Cohort	Not Serious	Not serious	Not Serious	Serious	Undetected	⊕⊕⊕⊖ moderate	18.8%	0% (0 to 3.1%)	CRITICAL

Footnotes:

[1] Judgement according to the original systematic review; no additional study had been identified.

References:

1. 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

Evidence Profile Table for Studies Assessing Compression Ultrasound in Patients with Suspected First Lower Extremity DVT: Should Compression Ultrasound Be Used to Diagnose or to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT
Intervention: Proximal Compression Ultrasound
Comparison: Recurrent VTE during 3 months follow up
Outcome: DVT

Diagnostic test accuracy [1]

Pooled sensitivity	90.3% (95%CI: 88.4% to 92%)
Pooled specificity	97.8% (95%CI: 97% to 98.4%)

Outcome	Study design	Factors that may decrease quality of evidence					Quality of Evidence	Effect per 1000 patients, according to different clinical pre-test probabilities			Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		5% (low)	17% (mod-erate)	53% (high)	
True positives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	45 (44 to 46)	154 (150 to 156)	479 (469 to 488)	CRITICAL
False negatives (patients incorrectly classified as not having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	5 (6 to 4)	16 (20 to 14)	51 (61 to 42)	CRITICAL
True negatives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	929 (922 to 935)	812 (805 to 817)	460 (456 to 462)	CRITICAL
False positives (patients incorrectly classified as having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	21 (28 to 15)	18 (25 to 13)	10 (14 to 8)	CRITICAL

Footnotes:

[1] Data obtained from a meta-analysis with 22 studies evaluating compression ultrasonography alone (Goodacre 2006)

[2] Higher sensitivity observed in studies with higher prevalence.

[3] Accuracy studies included in the meta-analysis, which may increase the specificity estimate. Median prevalence of DVT: 48%, results tend to be more applicable for high risk individuals

[4] Estimates consistent with estimates from similar studies

References:

1. Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, Locker T, Ryan A. Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis. Health Technol Assess. 2006 May;10(15):1-168, iii-iv
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.
3. Pomero F. Dentali F. Borretta V. Bonzini M. Melchio R. Douketis JD. Fenoglio LM. Accuracy of emergency physician–performed ultrasonography in the diagnosis of deep-vein thrombosis. Thromb Haemost. 109(1):137-45, 2013 Jan.
4. Kory PD. Pellecchia CM. Shiloh AL. Mayo PH. DiBello C. Koenig S. Accuracy of ultrasonography performed by critical care physicians for the diagnosis of DVT. Chest. 139(3):538-42, 2011 Mar.
5. Crisp JG. Lovato LM. Jang TB. Compression ultrasonography of the lower extremity with portable vascular ultrasonography can accurately detect deep venous thrombosis in the emergency department. Ann Emerg Med. 56(6):601-10, 2010 Dec.
6. Gibson NS. Schellong SM. Kheir DY. Beyer-Westendorf J. Gallus AS. McRae S. Schutgens RE. Piovella F. Gerdes VE. Buller HR. Safety and sensitivity of two ultrasound strategies in patients with clinically suspected deep venous thrombosis: a prospective management study. J Thromb Haemost. 7(12):2035-41, 2009 Dec.

Evidence to recommendation framework 15

Question 15: In patients with moderate pretest probability of first lower extremity DVT, proximal CUS negative and D-Dimer positive (ELI-SA), should we repeat proximal CUS in 1 week instead of rule out without further investigation?

Population: Patients with suspected first lower extremity DVT, with moderate clinical pretest probability, DD positive and CUS negative
Diagnostic test: repeat CUS in 1 week
Comparison: No testing
Setting: Outpatients
Perspective: Public health

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐	**Estimate pre-test probability of prevalence of proximal DVT:** - 17% (13 – 23%) **Risk estimates for undesirable outcomes**	The panel considered adequate the use of Wells criteria in the Saudi population. The panel agreed that the estimates of risk presented also could apply for the Saudi population.

Outcome	Incidence (treated)	Incidence (untreated)
Fatal pulmonary embolism	0.3%	1.9%
Nonfatal pulmonary embolism	1.4%	9.3%
Fatal bleeding	0.3%	-
Nonfatal intracranial bleeding	2.1%	-
Nonfatal non-intracranial bleeding	0.1%	-
Venographic mortality	0.03%	-
Propagation to proximal veins (distal DVT)	-	21.4%

Estimate incidence for 3 months

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ | *Low* ☒ | *Moderate* ☐ | *High* ☐	No evidence specific for the Middle East setting identified. Importance and estimate utility values for outcomes **Outcome** / **Utility (range)** / **Importance** Death / 0 / Critical Nonfatal Intracranial Bleed (severe) / 0.1 – 0.51 / Critical Nonfatal Intracranial Bleed (moderate) / 0.29 – 0.77 / Critical Nonfatal Intracranial Bleed (mild) / 0.47 – 0.94 / Critical Nonfatal Pulmonary Embolism / 0.63 / Critical Major bleed / 0.44 – 0.84 / Critical *Cate-hoek 2009, MacLean 2012* Assumptions (outcomes): - Major bleeding equivalent to pulmonary embolism - Intracranial bleed (overall): 2 to 3 times worse than major bleed or pulmonary embolism - DVT treatment generally well accepted	Since there are no evidence specific for the KSA, panel members assumed that the values on outcomes should be probably similar than in other populations. The panel highlighted that there are a need for studies of values and preferences in the KSA setting. As reported in question 13, in patients with moderate pretest clinical probability and D-Dimer test positive, the probability of having DVT after a negative CUS is 3.36%. Per 1000 patients initially tested, 16 patients with DVT and D-dimer positive will be discharged. Due to misdiagnosing, we would have additionally 0.25 deaths due to pulmonary embolism and 1.15 cases of non-fatal pulmonary embolism 1000 patients (low quality evidence) For repeated proximal CUS in patients with D-dimer positive and initial proximal CUS negative, one study with 426 patients was in the systematic review. The prevalence of DVT was 18.8% and the probability of DVT after a D-dimer positive and serial CUS negative was 0% (95%CI 0 to 3.1%). (ref) (Moderate-quality evidence) Repeating the proximal CUS would reduce the rate of false negatives, however it may increase the number of false positives, resulting in higher bleeding rates.
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☐ | *Probably no important uncertainty or variability* ☒ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐		
Are the desirable anticipated effects large?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | ***Varies*** ☐		
Are the undesirable anticipated effects small?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | ***Varies*** ☐		
Are the desirable effects large relative to undesirable effects?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | ***Varies*** ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☐ / Uncertain ☒ / Probably Yes ☐ / Yes ☐ / Varies ☐	No evidence found	
RESOURCE USE	Is the incremental cost small relative to the net benefits?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☒ / Yes ☐ / Varies ☐	No evidence found	Performing proximal CUS in patients with moderate clinical pre-test probability and D-Dimer negative would increase costs: 616 additional ultrasounds would be needed per 1000 patients initially tested.
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☒ / Varies ☐	No evidence found	
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐	No evidence found	

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☒	☐

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☒	☐

Recommendation (text)	The Ministry of Health of Saudi Arabia guideline suggests repeat proximal CUS in one week over no further testing in patients with moderate pretest probability of first lower extremity DVT and initial negative proximal CUS and positive D-dimer (Weak recommendation, Low-quality evidence)
Justification	The number of false negatives and the post-test probability of a combined D-dimer with a proximal CUS were considered high and it would justify the extra costs.
Subgroup considerations	
Implementation considerations	
Monitoring and evaluation	
Research priorities	

Evidence Profile Table for Studies Assessing Compression Ultrasound in Patients with Suspected First Lower Extremity DVT and D-dimer (ELISA) positive: Should Compression Ultrasound Be Used to Diagnose or to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT, moderate pretest probability and D-dimer (ELISA) positive
Intervention: Proximal Compression Ultrasound
Comparison: Recurrent VTE during 3 months follow up
Outcome: DVT

Diagnostic test accuracy of proximal CUS [1]

Pooled sensitivity	90.3% (95%CI: 88.4% to 92%)
Pooled specificity	97.8% (95%CI: 97% to 98.4%)

Outcome	Study design	Factors that may decrease quality of evidence					Quality of Evidence	Effect per 616 patients (equivalent to patients with D-dimer positive per 1000) Proportion of patients with moderatei pretest probability and D-dimer positive: 25.93%	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias			
True positives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	144 (141 to 147)	CRITICAL
False negatives (patients incorrectly classified as not having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	16 (13 to 19)	CRITICAL
True negatives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	446 (441 to 449)	CRITICAL
False positives (patients incorrectly classified as having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	10 (7 to 14)	CRITICAL

Footnotes:

[1] Data obtained from a meta-analysis with 22 studies evaluating compression ultrasonography alone (Goodacre 2006)

[2] Higher sensitivity observed in studies with higher prevalence.

[3] Accuracy studies included in the meta-analysis, which may increase the specificity estimate. Median prevalence of DVT: 48%, results tend to be more applicable for high risk individuals

[4] Estimates consistent with estimates from similar studies

References:

1. Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, Locker T, Ryan A. Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis. Health Technol Assess. 2006 May;10(15):1-168, iii-iv
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.
3. Pomero F. Dentali F. Borretta V. Bonzini M. Melchio R. Douketis JD. Fenoglio LM. Accuracy of emergency physician–performed ultrasonography in the diagnosis of deep-vein thrombosis. Thromb Haemost. 109(1):137-45, 2013 Jan.
4. Kory PD. Pellecchia CM. Shiloh AL. Mayo PH. DiBello C. Koenig S. Accuracy of ultrasonography performed by critical care physicians for the diagnosis of DVT. Chest. 139(3):538-42, 2011 Mar.
5. Crisp JG. Lovato LM. Jang TB. Compression ultrasonography of the lower extremity with portable vascular ultrasonography can accurately detect deep venous thrombosis in the emergency department. Ann Emerg Med. 56(6):601-10, 2010 Dec.
6. Gibson NS. Schellong SM. Kheir DY. Beyer-Westendorf J. Gallus AS. McRae S. Schutgens RE. Piovella F. Gerdes VE. Buller HR. Safety and sensitivity of two ultrasound strategies in patients with clinically suspected deep venous thrombosis: a prospective management study. J Thromb Haemost. 7(12):2035-41, 2009 Dec.

Evidence Profile Table for Studies Assessing Serial Compression Ultrasound (CUS) in Patients with Suspected First Lower Extremity Deep Vein Thrombosis (DVT):

Should Serial CUS be Used to Rule Out DVT in patients with moderate pretest probability and D-Dimer (ELISA) positive?

Population: Patients with suspected first lower extremity DVT and moderate clinical pretest probability
Test result: D-dimer positive (ELISA) and Serial CUS negative.
Outcome: Recurrent venous thromboembolism during 3 months follow-up

Diagnostic test accuracy

Pooled sensitivity	Not Available
Pooled specificity	Not Available

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease quality of evidence					Quality of Evidence [1]	Prevalence	Post-test probability of negative test	Importance
			Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias				
Venous thromboembolism (3 months)	3 Studies	Management Cohort	Not Serious	Not serious	Serious[2]	Not Serious	Undetected	⊕⊕⊕⊖ moderate	15.8% [3]	1.1% (0.4 to 2.5%) 0.6% (0.4 – 0.9%)	CRITICAL

Footnotes:

[1] Judgement according to the original systematic review; no additional study had been identified.

[2] Inclusion of accuracy studies

[3] Based on 2 of 3 studies. Information available in the systematic review, not retrieved from the original studies.

References:

1. 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
2. Wells PS , Anderson DR , Bormanis J , et al . Value of assessment of pretest probability of deep-vein thrombosis in clinical management . Lancet . 1997 ; 350 (9094): 1795 - 1798 .
3. 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.

Evidence to recommendation framework 16

Question 16: In patients with moderate pretest probability of first lower extremity DVT and proximal CUS positive, should we perform proximal venography instead of treating, without further investigation?

Population: Patients with suspected first lower extremity DVT, with moderate clinical pretest probability and proximal CUS positive
Diagnostic test: venography
Comparison: no testing (treat)
Setting: Outpatients
Perspective: Public health

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐	**Estimate pre-test probability of prevalence of proximal DVT:** - 17% (13 – 23%) **Risk estimates for undesirable outcomes**	The panel considered adequate the use of Wells criteria in the Saudi population. The panel agreed that the estimates of risk presented also could apply for the Saudi population.

Outcome	Incidence (treated)	Incidence (untreated)
Fatal pulmonary embolism	0.3%	1.9%
Nonfatal pulmonary embolism	1.4%	9.3%
Fatal bleeding	0.3%	-
Nonfatal intracranial bleeding	2.1%	-
Nonfatal non-intracranial bleeding	0.1%	-
Venographic mortality	0.03%	-
Propagation to proximal veins (distal DVT)	-	21.4%

Estimate incidence for 3 months

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ | *Low* ☒ | *Moderate* ☐ | *High* ☐	No evidence specific for the Middle East setting identified. Importance and estimate utility values for outcomes	Since there are no evidence specific for the KSA, panel members assumed that the values on outcomes should be probably similar than in other populations. The panel highlighted that there are a need for studies of values and preferences in the KSA setting.
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☐ | *Probably no important uncertainty or variability* ☐ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐		Venography is considered reference standard for DVT, however it is subject to a consideserver variation. Posttest probability of a positive test cannot be estimated with confidence.
Are the desirable anticipated effects large?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | ***Varies*** ☐	Assumptions (outcomes): - Major bleeding equivalent to pulmonary embolism - Intracranial bleed (overall): 2 to 3 times worse than major bleed or pulmonary embolism - DVT treatment generally well accepted	As described in the question 6, after a contrast venography negative, the probability of having recurrent venous thromboembolism during 3 months follow of up is 1.2% (95%CI 0.2% to 4.4%). (Moderate quality of evidence)
Are the undesirable anticipated effects small?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | ***Varies*** ☐	Diagnostic properties of CUS Pretest probability: moderate (17%). **QoE: Moderate**	Among patients with tested initially with proximal CUS positive, 16 patients per 1000 would be incorrectly classified as not having DVT. Treating unnecessary this patients we would result in 0.05 deaths and 0.34 major bleeding episodes (0.02 intracranial) per 1000 individuals tested. (Low quality of evidence).
Are the desirable effects large relative to undesirable effects?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | ***Varies*** ☐	Diagnostic properties Venography: Pretest probability: **Unknown. QoE: Moderate**	Venography is considered the reference standard for DVT, however it is subject to a considerably variation. Although often considered as 100%, the posttest probability of a positive test cannot be estimated with confidence. There are no studies evaluating contrast venography in patients with low risk for DVT. Additionally,

Outcome	Utility (range)	Importance
Death	0	Critical
Nonfatal Intracranial Bleed (severe)	0.1 – 0.51	Critical
Nonfatal Intracranial Bleed (moderate)	0.29 – 0.77	Critical
Nonfatal Intracranial Bleed (mild)	0.47 – 0.94	Critical
Nonfatal Pulmonary Embolism	0.63	Critical
Major bleed	0.44 – 0.84	Critical

Cate-hoek 2009, MacLean 2012

Specificity	97.8% (97% - 98.4%)
False negatives (not treated)	16 (14 – 20) per 1000
False positives (treated unnecessarily)	18 (13- 25)
Negative tests (ruled out)	812 per 1000
Posttest probability (negative test)	1.99%
Posttest probability (positive test)	89.37%

(evidence profile below)

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			Posttest probability (negative test) 1.2% (0.2 – 4.2%) (evidence profile below)	venography is associated with 1 to 4% of incidence of adverse reactions to contrast media, including dizziness and nausea, severe allergic reaction in 0 to 0.4% and post-venography DVT in 0 to 2% of patients.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
RESOURCE USE	Is the incremental cost small relative to the net benefits?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	Contrast venography is a costly intervention compared to proximal CUS
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☒ / Varies ☐	No evidence found	
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	Technology is not widely available for contrast venography

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	☒

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☐	☒

Recommendation (text)	The Ministry of Health of Saudi Arabia panel recommends no further investigation, rather than confirmatory venography, in patients with moderate pretest probability of first lower extremity DVT and positive proximal CUS. (Strong recommendation, Low-quality evidence).
Justification	The panel considered contrast venography an expansive, potentially harmful and difficult to implement alternative for a situations when there are no clear benefit established.
Subgroup considerations	-
Implementation considerations	-
Monitoring and evaluation	-
Research priorities	-

Evidence Profile Table for Studies Assessing Venography in Patients with Suspected First Lower Extremity Deep Vein Thrombosis (DVT):

Should Venography Be Used to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT and negative result for contrast venography
Outcome: Recurrent venous thromboembolism during 3 months follow-up

Diagnostic test accuracy

Pooled sensitivity	Not Available
Pooled specificity	Not Available
Accuracy[1]	98.8% (95% CI: 95.6% to 99.8%)

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease quality of evidence					Quality of Evidence [2]	Post-test probability of negative test	Importance
			Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias			
Venous thromboembolism (3 months)	1 Study (160 patients)	Single-arm prospective cohort study	Serious [3]	None [4]	Not Serious	Not Serious	Undetected [4]	⊕⊕⊕⊖ moderate	1.2% (0.2 to 4.4%)	CRITICAL

Footnotes:

[1] Individuals with normal venography and without venous thromboembolism during 3 months follow-up.

[2] Judgement according to the original systematic review; no additional study had been identified.

[3] Prevalence of DVT in original population not specified

[4] Only one study identified, not allowing adequate assessment of inconsistency and publication bias.

References:

1. Hull R, Hirsh J, Sackett DL, Taylor DW, Carter C, Turpie AG, Powers P, Gent M. Clinical validity of a negative venogram in patients with clinically suspected venous thrombosis. Circulation. 1981 Sep;64(3):622-5.
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.

Evidence Profile Table for Studies Assessing Compression Ultrasound in Patients with Suspected First Lower Extremity DVT: Should Compression Ultrasound Be Used to Diagnose or to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT
Intervention: Compression Ultrasound
Comparison: Recurrent VTE during 3 months follow up
Outcome: DVT

Diagnostic test accuracy [1]

Pooled sensitivity	90.3% (95%CI: 88.4% to 92%)
Pooled specificity	97.8% (95%CI: 97% to 98.4%)

Outcome	Study design	Factors that may decrease quality of evidence					Quality of Evidence	Effect per 1000 patients, according to different clinical pre-test probabilities			Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		5% (low)	17% (moderate)	53% (high)	
True positives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	45 (44 to 46)	154 (150 to 156)	479 (469 to 488)	CRITICAL
False negatives (patients incorrectly classified as not having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	5 (6 to 4)	16 (20 to 14)	51 (61 to 42)	CRITICAL
True negatives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	929 (922 to 935)	812 (805 to 817)	460 (456 to 462)	CRITICAL
False positives (patients incorrectly classified as having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	21 (28 to 15)	18 (25 to 13)	10 (14 to 8)	CRITICAL

Footnotes:

[1] Data obtained from a meta-analysis with 22 studies evaluating compression ultrasonography alone (Goodacre 2006)

[2] Higher sensitivity observed in studies with higher prevalence.

[3] Accuracy studies included in the meta-analysis, which may increase the specificity estimate. Median prevalence of DVT: 48%, results tend to be more applicable for high risk individuals

[4] Estimates consistent with estimates from similar studies

References:

1. Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, Locker T, Ryan A. Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis. Health Technol Assess. 2006 May;10(15):1-168, iii-iv
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.
3. Pomero F. Dentali F. Borretta V. Bonzini M. Melchio R. Douketis JD. Fenoglio LM. Accuracy of emergency physician–performed ultrasonography in the diagnosis of deep-vein thrombosis. Thromb Haemost. 109(1):137-45, 2013 Jan.
4. Kory PD. Pellecchia CM. Shiloh AL. Mayo PH. DiBello C. Koenig S. Accuracy of ultrasonography performed by critical care physicians for the diagnosis of DVT. Chest. 139(3):538-42, 2011 Mar.
5. Crisp JG. Lovato LM. Jang TB. Compression ultrasonography of the lower extremity with portable vascular ultrasonography can accurately detect deep venous thrombosis in the emergency department. Ann Emerg Med. 56(6):601-10, 2010 Dec.
6. Gibson NS. Schellong SM. Kheir DY. Beyer-Westendorf J. Gallus AS. McRae S. Schutgens RE. Piovella F. Gerdes VE. Buller HR. Safety and sensitivity of two ultrasound strategies in patients with clinically suspected deep venous thrombosis: a prospective management study. J Thromb Haemost. 7(12):2035-41, 2009 Dec.

Evidence to recommendation framework 17

Question 17: In patients with high pretest probability of first lower extremity DVT, should we use D-Dimer (ELISA) as initial test for the diagnosis of DVT?

Population: Patients with suspected first lower extremity DVT, with high clinical pretest probability.
Diagnostic test: D-dimer (ELISA)
Comparison: No testing
Setting: Outpatients
Perspective: Public health

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐	**Estimate pre-test probability of prevalence of proximal DVT:** - 53% (44 –61%) **Risk estimates for undesirable outcomes**	The panel considered adequate the use of Wells criteria in the Saudi population. The panel agreed that the estimates of risk presented also could apply for the Saudi population.

Outcome	Incidence (treated)	Incidence (untreated)
Fatal pulmonary embolism	0.3%	1.9%
Nonfatal pulmonary embolism	1.4%	9.3%
Fatal bleeding	0.3%	-
Nonfatal intracranial bleeding	2.1%	-
Nonfatal non-intracranial bleeding	0.1%	-
Venographic mortality	0.03%	-
Propagation to proximal veins (distal DVT)	-	21.4%

Estimate incidence for 3 months

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Moderate* ☒ | *High* ☐	No evidence specific for the Middle East setting identified. Importance and estimate utility values for outcomes	Since there are no evidence specific for the KSA, panel members assumed that the values on outcomes should be probably similar than in other populations. The panel highlighted that there are a need for studies of values and preferences in the KSA setting. Thirty two patients per 1000 tested would be incorrectly classified as not having DVT (false negatives). The probability of having DVT after a negative test is 13.1% and after a positive test is 65.8%. Not treating these individuals would result in additional 0.51 and 2.3 fatal and non-fatal pulmonary embolism per 1000 patients tested.
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☐ | *Probably no important uncertainty or variability* ☒ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐		
Are the desirable anticipated effects large?	*No* ☒ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		
Are the undesirable anticipated effects small?	*No* ☒ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		
Are the desirable effects large relative to undesirable effects?	*No* ☒ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		

Outcome	Utility (range)	Importance
Death	0	Critical
Nonfatal Intracranial Bleed (severe)	0.1 – 0.51	Critical
Nonfatal Intracranial Bleed (moderate)	0.29 – 0.77	Critical
Nonfatal Intracranial Bleed (mild)	0.47 – 0.94	Critical
Nonfatal Pulmonary Embolism	0.63	Critical
Major bleed	0.44 – 0.84	Critical

Assumptions (outcomes):

- Major bleeding equivalent to pulmonary embolism
- Intracranial bleed (overall): 2 to 3 times worse than major bleed or pulmonary embolism
- DVT treatment generally well accepted

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
	Is the incremental cost small relative to the net benefits?	No ☒ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐	No evidence found	
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☒ / Varies ☐	No evidence found	
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☒	☐	☐	☐	☐

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☒	☐	☐	☐

Recommendation (text)

The Ministry of Health of Saudi Arabia panel recommends agaist the use of highly sensitivity D-Dimer (ELISA) as a stand alone test to rule out DVT in patients with high pretest probability of first lower extremity DVT. (Strong recommendation, Moderate-quality evidence)

Justification

The panel considered the rate of false negatives and the probability posttest negative high to recommend the use of D-dimer as a stand alone test to rule out DVT in patients with high clinical pretest probability of DVT.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

Evidence Profile Table for Studies Assessing Highly Sensitive D-Dimer in Patients with Suspected First Lower Extremity DVT: Should Highly Sensitive D-Dimer Be Used to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT
Intervention: D-Dimer (e ELISA)
Comparison: Recurrent VTE during 3 months follow
Outcome: DVT

Diagnostic test accuracy

Pooled sensitivity	94% (95%CI: 93% to 95%)
Pooled specificity	45% (95%CI: 44% to 46%)

Outcome	Study design	Factors that may decrease quality of evidence					Quality of Evidence	Effect per 1000 patients, according to different clinical pre-test probabilities			Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		5% (low)	17% (moderate)	53% (high)	
True positives (patients with DVT)	Systematic reviews of management cohorts and of accuracy studies	Not Serious	Not Serious[1]	Serious[2]	None	Undetected	⊕⊕⊕⊖ moderate	47 (47 to 48)	160 (158 to 162)	498 (493 to 504)	CRITICAL
False negatives (patients incorrectly classified as not having DVT)								3 (3 to 4)	10 (9 to 12)	32 (27 to 37)	CRITICAL
True negatives (patients without DVT)	Systematic reviews of management cohorts and of accuracy studies	Not Serious	Not Serious[1]	Serious[2]	None	Undetected	⊕⊕⊕⊖ moderate	428 (418 to 437	374 (365 to 382)	212 (207 to 216)	CRITICAL
False positives (patients incorrectly classified as not having DVT)								523 513 to 532)	457 (448 to 465)	259 (254 to 263)	CRITICAL

Footnotes:

[1] Estimates consistent with estimates from similar ELISA methods. Similar estimates for different clinical pretest probability.

[2] Accuracy studies included in the meta-analysis, which may increase the specificity estimate

References:

1. Di Nisio M, Squizzato A, Rutjes AW, Büller HR, Zwinderman AH, Bossuyt PM. Diagnostic accuracy of D-dimer test for exclusion of venous thromboembolism: a systematic review. J Thromb Haemost. 2007 Feb;5(2):296-304.
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.
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4. Der Sahakian G. Claessens YE. Allo JC. Kansao J. Kierzek G. Pourriat JL. Accuracy of D-Dimers to Rule Out Venous Thromboembolism Events across Age Categories. emerg. med. int.. 2010:185453, 2010
5. Elías-Hernández T, Otero-Candelera R, Fernández-Jiménez D, Jara-Palomares L, Jiménez-Castro V, Barrot-Cortés E. [Clinical usefulness of three quantitative D-dimers tests in outpatients with suspected deep vein thrombosis]. Rev Clin Esp. 2012 May;212(5):235-41.
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8. Luxembourg B. Schwonberg J. Hecking C. Schindewolf M. Zgouras D. Lehmeyer S. Lindhoff-Last E. Performance of five D-dimer assays for the exclusion of symptomatic distal leg vein thrombosis. Thromb Haemost. 107(2):369-78, 2012 Feb.

Evidence to recommendation framework 18

Question 18: In patients with high pretest probability of first lower extremity DVT, should we use proximal CUS as initial test for the diagnosis of DVT?

Population: Patients with suspected first lower extremity DVT, with high clinical pretest probability.
Diagnostic test: Proximal CUS
Comparison: No testing
Setting: Outpatients
Perspective: Public health

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐	**Estimate pre-test probability of prevalence of proximal DVT:** - 53% (44 – 61%) **Risk estimates for undesirable outcomes**	The panel considered adequate the use of Wells criteria in the Saudi population. The panel agreed that the estimates of risk presented also could apply for the Saudi population.

Outcome	Incidence (treated)	Incidence (untreated)
Fatal pulmonary embolism	0.3%	1.9%
Nonfatal pulmonary embolism	1.4%	9.3%
Fatal bleeding	0.3%	-
Nonfatal intracranial bleeding	2.1%	-
Nonfatal non-intracranial bleeding	0.1%	-
Venographic mortality	0.03%	-
Propagation to proximal veins (distal DVT)	-	21.4%

Estimate incidence for 3 months

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Moderate* ☒ | *High* ☐	No evidence specific for the Middle East setting identified. Importance and estimate utility values for outcomes **Outcome** / **Utility (range)** / **Importance** Death / 0 / Critical Nonfatal Intracranial Bleed (severe) / 0.1 – 0.51 / Critical Nonfatal Intracranial Bleed (moderate) / 0.29 – 0.77 / Critical Nonfatal Intracranial Bleed (mild) / 0.47 – 0.94 / Critical Nonfatal Pulmonary Embolism / 0.63 / Critical Major bleed / 0.44 – 0.84 / Critical Assumptions (outcomes): - Major bleeding equivalent to pulmonary embolism - Intracranial bleed (overall): 2 to 3 times worse than major bleed or pulmonary embolism - DVT treatment generally well accepted	Since there are no evidence specific for the KSA, panel members assumed that the values on outcomes should be probably similar than in other populations. The panel highlighted that there are a need for studies of values and preferences in the KSA setting.
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☐ | *Probably no important uncertainty or variability* ☒ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐		
Are the desirable anticipated effects large?	*No* ☒ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		
Are the undesirable anticipated effects small?	*No* ☒ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		
Are the desirable effects large relative to undesirable effects?	*No* ☒ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☒ / Yes ☐ / Varies ☐	No evidence found	
	Is the incremental cost small relative to the net benefits?	No ☒ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐	No evidence found	
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☒ / Varies ☐	No evidence found	
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☒	☐	☐	☐	☐

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☒	☐	☐	☐

Recommendation (text)	The Ministry of Health of Saudi Arabia panel recommends agaist the use of proximal CUS as a stand alone test to rule out DVT in patients with high pretest probability of first lower extremity DVT. (Strong recommendation, Moderate-quality evidence)
Justification	The panel considered the rate of false negatives and the probability posttest negative high to recommend the use of proximal CUS as a stand alone test to rule out DVT in patients with high clinical pretest probability of DVT.
Subgroup considerations	-
Implementation considerations	-
Monitoring and evaluation	-
Research priorities	-

Evidence Profile Table for Studies Assessing Compression Ultrasound in Patients with Suspected First Lower Extremity DVT: Should Compression Ultrasound Be Used to Diagnose or to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT
Intervention: Compression Ultrasound
Comparison: Recurrent VTE during 3 months follow up
Outcome: DVT

Diagnostic test accuracy [1]

Pooled sensitivity	90.3% (95%CI: 88.4% to 92%)
Pooled specificity	97.8% (95%CI: 97% to 98.4%)

Outcome	Study design	Factors that may decrease quality of evidence					Quality of Evidence	Effect per 1000 patients, according to different clinical pre-test probabilities			Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		5% (low)	17% (moderate)	53% (high)	
True positives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	45 (44 to 46)	154 (150 to 156)	479 (469 to 488)	CRITICAL
False negatives (patients incorrectly classified as not having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	5 (6 to 4)	16 (20 to 14)	51 (61 to 42)	CRITICAL
True negatives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	929 (922 to 935)	812 (805 to 817)	460 (456 to 462)	CRITICAL
False positives (patients incorrectly classified as having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	21 (28 to 15)	18 (25 to 13)	10 (14 to 8)	CRITICAL

Footnotes:

[1] Data obtained from a meta-analysis with 22 studies evaluating compression ultrasonography alone (Goodacre 2006)

[2] Higher sensitivity observed in studies with higher prevalence.

[3] Accuracy studies included in the meta-analysis, which may increase the specificity estimate. Median prevalence of DVT: 48%, results tend to be more applicable for high risk individuals

[4] Estimates consistent with estimates from similar studies

References:

1. Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, Locker T, Ryan A. Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis. Health Technol Assess. 2006 May;10(15):1-168, iii-iv
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.
3. Pomero F. Dentali F. Borretta V. Bonzini M. Melchio R. Douketis JD. Fenoglio LM. Accuracy of emergency physician–performed ultrasonography in the diagnosis of deep-vein thrombosis. Thromb Haemost. 109(1):137-45, 2013 Jan.
4. Kory PD. Pellecchia CM. Shiloh AL. Mayo PH. DiBello C. Koenig S. Accuracy of ultrasonography performed by critical care physicians for the diagnosis of DVT. Chest. 139(3):538-42, 2011 Mar.
5. Crisp JG. Lovato LM. Jang TB. Compression ultrasonography of the lower extremity with portable vascular ultrasonography can accurately detect deep venous thrombosis in the emergency department. Ann Emerg Med. 56(6):601-10, 2010 Dec.
6. Gibson NS. Schellong SM. Kheir DY. Beyer-Westendorf J. Gallus AS. McRae S. Schutgens RE. Piovella F. Gerdes VE. Buller HR. Safety and sensitivity of two ultrasound strategies in patients with clinically suspected deep venous thrombosis: a prospective management study. J Thromb Haemost. 7(12):2035-41, 2009 Dec.

Evidence to recommendation framework 19

Question 19: In patients with high pretest probability of first lower extremity DVT and proximal CUS positive, should we perform proximal venography instead of treating, without further investigation?

Population: Patients with suspected first lower extremity DVT, with high clinical pretest probability and proximal CUS positive
Diagnostic test: venography
Comparison: no testing (treat)
Setting: Outpatients
Perspective: Public health

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐	**Estimate pre-test probability of prevalence of proximal DVT:** - 53% (44 – 61%) **Risk estimates for undesirable outcomes** *Estimate incidence for 3 months*	The panel considered adequate the use of Wells criteria in the Saudi population. The panel agreed that the estimates of risk presented also could apply for the Saudi population.

Outcome	Incidence (treated)	Incidence (untreated)
Fatal pulmonary embolism	0.3%	1.9%
Nonfatal pulmonary embolism	1.4%	9.3%
Fatal bleeding	0.3%	-
Nonfatal intracranial bleeding	2.1%	-
Nonfatal non-intracranial bleeding	0.1%	-
Venographic mortality	0.03%	-
Propagation to proximal veins (distal DVT)	-	21.4%

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Moderate* ☒ | *High* ☐	No evidence specific for the Middle East setting identified. Importance and estimate utility values for outcomes **Outcome** | **Utility (range)** | **Importance** Death | 0 | Critical Nonfatal Intracranial Bleed (severe) | 0.1 – 0.51 | Critical Nonfatal Intracranial Bleed (moderate) | 0.29 – 0.77 | Critical Nonfatal Intracranial Bleed (mild) | 0.47 – 0.94 | Critical Nonfatal Pulmonary Embolism | 0.63 | Critical Major bleed | 0.44 – 0.84 | Critical *Cate-hoek 2009, MacLean 2012* Assumptions (outcomes): - Major bleeding equivalent to pulmonary embolism - Intracranial bleed (overall): 2 to 3 times worse than major bleed or pulmonary embolism - DVT treatment generally well accepted	Since there are no evidence specific for the KSA, panel members assumed that the values on outcomes should be probably similar than in other populations. The panel highlighted that there are a need for studies of values and preferences in the KSA setting. After a contrast venography negative, the probability of having recurrent venous thromboembolism during 3 months follow of up is 1.2% (95%CI 0.2% to 4.4%). (ref) (Moderate quality of evidence). Venography is considered the reference standard for DVT. Among those with high pretest probability, 10 patients per 1000 tested with proximal CUS would be incorrectly classified as not having DVT (Moderate quality of evidence). Treating unnecessary this patients we would result in 0.03 deaths and 0.21 major bleeding episodes (0.01 intracranial) per 1000 individuals tested. (Moderate quality of evidence) Venography is considered reference standard for DVT, however it is subject to a considerably variation. Although often considered as 100%, posttest probability of a positive test cannot be estimated with confidence. There are no studies evaluating Venography in patients with low risk for DVT. Additionally, venography is associated with 1 to 4% of incidence of adverse reactions to contrast media, including dizziness and nausea, severe allergic reaction in 0 to 0.4% and post-venography DVT in 0 to 2% of patients
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☐ | *Probably no important uncertainty or variability* ☒ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐		
Are the desirable anticipated effects large?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☒ | ***Varies*** ☐		
Are the undesirable anticipated effects small?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☒ | ***Varies*** ☐		
Are the desirable effects large relative to undesirable effects?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☒ | ***Varies*** ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
	Is the incremental cost small relative to the net benefits?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	Contrast venography is a costly intervention compared to proximal CUS
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☒ / Varies ☐	No evidence found	
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	Technology is not widely available for contrast venography

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	☒

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☐	☒

Recommendation (text)	The Ministry of Health of Saudi Arabia panel recommends no further investigation, rather than confirmatory venography, in patients with high pretest probability of first lower extremity DVT and positive proximal CUS. (Strong recommendation, Moderate-quality evidence).
Justification	The panel considered contrast venography an expansive, potentially harmful and difficult to implement alternative for a situations when there are no clear benefit established.
Subgroup considerations	-
Implementation considerations	-
Monitoring and evaluation	-
Research priorities	-

Evidence Profile Table for Studies Assessing Venography in Patients with Suspected First Lower Extremity Deep Vein Thrombosis (DVT):

Should Venography Be Used to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT and negative result for contrast venography
Outcome: Recurrent venous thromboembolism during 3 months follow-up

Diagnostic test accuracy

Pooled sensitivity	Not Available
Pooled specificity	Not Available
Accuracy[1]	98.8% (95% CI: 95.6% to 99.8%)

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease quality of evidence					Quality of Evidence [2]	Post-test probability of negative test	Importance
			Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias			
Venous thromboembolism (3 months)	1 Study (160 patients)	Single-arm prospective cohort study	Serious [3]	None [4]	Not Serious	Not Serious	Undetected [4]	⊕⊕⊕⊖ moderate	1.2% (0.2 to 4.4%)	CRITICAL

Footnotes:

[1] Individuals with normal venography and without venous thromboembolism during 3 months follow-up.

[2] Judgement according to the original systematic review; no additional study had been identified.

[3] Prevalence of DVT in original population not specified

[4] Only one study identified, not allowing adequate assessment of inconsistency and publication bias.

References:

1. Hull R, Hirsh J, Sackett DL, Taylor DW, Carter C, Turpie AG, Powers P, Gent M. Clinical validity of a negative venogram in patients with clinically suspected venous thrombosis. Circulation. 1981 Sep;64(3):622-5.
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.

Evidence Profile Table for Studies Assessing Compression Ultrasound in Patients with Suspected First Lower Extremity DVT: Should Compression Ultrasound Be Used to Diagnose or to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT
Intervention: Compression Ultrasound
Comparison: Recurrent VTE during 3 months follow up
Outcome: DVT

Diagnostic test accuracy [1]

Pooled sensitivity	90.3% (95%CI: 88.4% to 92%)
Pooled specificity	97.8% (95%CI: 97% to 98.4%)

Outcome	Study design	Factors that may decrease quality of evidence					Quality of Evidence	Effect per 1000 patients, according to different clinical pre-test probabilities			Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		5% (low)	17% (moderate)	53% (high)	
True positives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	45 (44 to 46)	154 (150 to 156)	479 (469 to 488)	CRITICAL
False negatives (patients incorrectly classified as not having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	5 (6 to 4)	16 (20 to 14)	51 (61 to 42)	CRITICAL
True negatives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	929 (922 to 935)	812 (805 to 817)	460 (456 to 462)	CRITICAL
False positives (patients incorrectly classified as having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	21 (28 to 15)	18 (25 to 13)	10 (14 to 8)	CRITICAL

Footnotes:

[1] Data obtained from a meta-analysis with 22 studies evaluating compression ultrasonography alone (Goodacre 2006)

[2] Higher sensitivity observed in studies with higher prevalence.

[3] Accuracy studies included in the meta-analysis, which may increase the specificity estimate. Median prevalence of DVT: 48%, results tend to be more applicable for high risk individuals

[4] Estimates consistent with estimates from similar studies

References:

1. Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, Locker T, Ryan A. Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis. Health Technol Assess. 2006 May;10(15):1-168, iii-iv
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.
3. Pomero F. Dentali F. Borretta V. Bonzini M. Melchio R. Douketis JD. Fenoglio LM. Accuracy of emergency physician–performed ultrasonography in the diagnosis of deep-vein thrombosis. Thromb Haemost. 109(1):137-45, 2013 Jan.
4. Kory PD. Pellecchia CM. Shiloh AL. Mayo PH. DiBello C. Koenig S. Accuracy of ultrasonography performed by critical care physicians for the diagnosis of DVT. Chest. 139(3):538-42, 2011 Mar.
5. Crisp JG. Lovato LM. Jang TB. Compression ultrasonography of the lower extremity with portable vascular ultrasonography can accurately detect deep venous thrombosis in the emergency department. Ann Emerg Med. 56(6):601-10, 2010 Dec.

Gibson NS. Schellong SM. Kheir DY. Beyer-Westendorf J. Gallus AS. McRae S. Schutgens RE. Piovella F. Gerdes VE. Buller HR. Safety and sensitivity of two ultrasound strategies in patients with clinically suspected deep venous thrombosis: a prospective management study. J Thromb Haemost. 7(12):2035-41, 2009 Dec.

Evidence to recommendation framework 20

Question 20: In patients with a high pretest probability of first lower extremity DVT and initial CUS negative, should we repeat proximal CUS instead of rule out without further investigation?

Population: Patients with suspected first lower extremity DVT, with high clinical pretest probability and initial CUS negative
Diagnostic test: repeat CUS in 1 week
Comparison: No testing
Setting: Outpatients
Perspective: Public health

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐	**Estimate pre-test probability of prevalence of proximal DVT:** - 53% (44 – 61%) **Risk estimates for undesirable outcomes**	The panel considered adequate the use of Wells criteria in the Saudi population. The panel agreed that the estimates of risk presented also could apply for the Saudi population.

Outcome	Incidence (treated)	Incidence (untreated)
Fatal pulmonary embolism	0.3%	1.9%
Nonfatal pulmonary embolism	1.4%	9.3%
Fatal bleeding	0.3%	-
Nonfatal intracranial bleeding	2.1%	-
Nonfatal non-intracranial bleeding	0.1%	-
Venographic mortality	0.03%	-
Propagation to proximal veins (distal DVT)	-	21.4%

Estimate incidence for 3 months

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Moderate* ☒ | *High* ☐	No evidence specific for the Middle East setting identified. Importance and estimate utility values for outcomes **Outcome** | **Utility (range)** | **Importance** Death | 0 | Critical Nonfatal Intracranial Bleed (severe) | 0.1 – 0.51 | Critical Nonfatal Intracranial Bleed (moderate) | 0.29 – 0.77 | Critical Nonfatal Intracranial Bleed (mild) | 0.47 – 0.94 | Critical Nonfatal Pulmonary Embolism | 0.63 | Critical Major bleed | 0.44 – 0.84 | Critical Assumptions (outcomes): - Major bleeding equivalent to pulmonary embolism - Intracranial bleed (overall): 2 to 3 times worse than major bleed or pulmonary embolism - DVT treatment generally well accepted	Since there are no evidence specific for the KSA, panel members assumed that the values on outcomes should be probably similar than in other populations. The panel highlighted that there are a need for studies of values and preferences in the KSA setting. For single proximal CUS testing, as described in question 18, 51 patients per 1000 tested would be incorrectly classified as not having DVT (false negatives). The probability of having DVT after a negative test is 10.1%. Not treating these individuals would result in additional 0.82 and 3.67 fatal and non-fatal pulmonary embolism per 1000 patients tested. For serial CUS in patients with high clinical pretest probability, four studies were identified in the systematic review. In these studies, the pooled prevalence of DVT was 36.4% and the probability of DVT post-negative serial CUS was 0.9% (95%CI 0.2% to 2.8%) (Moderate quality of evidence)
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☐ | *Probably no important uncertainty or variability* ☐ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐		
Are the desirable anticipated effects large?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☒ | ***Varies*** ☐		
Are the undesirable anticipated effects small?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☒ | ***Varies*** ☐		
Are the desirable effects large relative to undesirable effects?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☒ | ***Varies*** ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
	Is the incremental cost small relative to the net benefits?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	Repeating proximal CUS in patients with high clinical pretest probability and initial CUS negative would increase costs: 511 additional ultrasounds would be needed per 1000 patients initially tested.
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☒ / Varies ☐	No evidence found	
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	☒

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☐	☒

Recommendation (text)	The Ministry of Health of Saudi Arabia guideline panel recommends to repeat proximal CUS in one week rather than no further testing in patients with a high pretest probability of first lower extremity DVT and initial negative proximal CUS. (Strong recommendation, Moderate quality of evidence)
Justification	The panel considered the rate of false negatives and the probability posttest negative high with a single proximal CUS.
Subgroup considerations	-
Implementation considerations	-
Monitoring and evaluation	-
Research priorities	-

Evidence Profile Table for Studies Assessing Serial Compression Ultrasound (CUS) in Patients with Suspected First Lower Extremity Deep Vein Thrombosis (DVT):

Should Serial CUS be Used to Rule Out DVT in patients with high pretest probability?

Population: Patients with suspected first lower extremity DVT and high clinical pretest probability
Intervention: Serial CUS
Outcome: Recurrent venous thromboembolism during 3 months follow-up

Diagnostic test accuracy

Pooled sensitivity	Not Available
Pooled specificity	Not Available

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease quality of evidence					Quality of Evidence [1]	Pretest probability (prevalence)	Post-test probability of negative test	Importance
			Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias				
Venous thromboembolism (3 months)	4 study (291 patients)	Management Cohort	Not Serious	Not serious	Not Serious	Serious	Undetected	⊕⊕⊕⊖ moderate	36.9%	0.9% (0.2 to 2.8%)	CRITICAL

Footnotes:

[1] Judgement according to the original systematic review; no additional study had been identified.

References:

1. 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.
2. Ruiz-Giménez 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 .
3. 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.
4. Dewar C, Selby C, Jamieson K, Rogers S. Emergency department nurse-based outpatient diagnosis of DVT using an evidence-based protocol . Emerg Med J . 2008 ; 25 (7): 411 - 416 .

Evidence Profile Table for Studies Assessing Compression Ultrasound in Patients with Suspected First Lower Extremity DVT: Should Compression Ultrasound Be Used to Diagnose or to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT
Intervention: Proximal Compression Ultrasound
Comparison: Recurrent VTE during 3 months follow up
Outcome: DVT

Diagnostic test accuracy [1]

Pooled sensitivity	90.3% (95%CI: 88.4% to 92%)
Pooled specificity	97.8% (95%CI: 97% to 98.4%)

Outcome	Study design	Factors that may decrease quality of evidence					Quality of Evidence	Effect per 1000 patients, according to different clinical pre-test probabilities			Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		5% (low)	17% (moderate)	53% (high)	
True positives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	45 (44 to 46)	154 (150 to 156)	479 (469 to 488)	CRITICAL
False negatives (patients incorrectly classified as not having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	5 (6 to 4)	16 (20 to 14)	51 (61 to 42)	CRITICAL
True negatives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	929 (922 to 935)	812 (805 to 817)	460 (456 to 462)	CRITICAL
False positives (patients incorrectly classified as having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	21 (28 to 15)	18 (25 to 13)	10 (14 to 8)	CRITICAL

Footnotes:

[1] Data obtained from a meta-analysis with 22 studies evaluating compression ultrasonography alone (Goodacre 2006)

[2] Higher sensitivity observed in studies with higher prevalence.

[3] Accuracy studies included in the meta-analysis, which may increase the specificity estimate. Median prevalence of DVT: 48%, results tend to be more applicable for high risk individuals

[4] Estimates consistent with estimates from similar studies

References:

1. Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, Locker T, Ryan A. Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis. Health Technol Assess. 2006 May;10(15):1-168, iii-iv
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.
3. Pomero F. Dentali F. Borretta V. Bonzini M. Melchio R. Douketis JD. Fenoglio LM. Accuracy of emergency physician–performed ultrasonography in the diagnosis of deep-vein thrombosis. Thromb Haemost. 109(1):137-45, 2013 Jan.
4. Kory PD. Pellecchia CM. Shiloh AL. Mayo PH. DiBello C. Koenig S. Accuracy of ultrasonography performed by critical care physicians for the diagnosis of DVT. Chest. 139(3):538-42, 2011 Mar.
5. Crisp JG. Lovato LM. Jang TB. Compression ultrasonography of the lower extremity with portable vascular ultrasonography can accurately detect deep venous thrombosis in the emergency department. Ann Emerg Med. 56(6):601-10, 2010 Dec.
6. Gibson NS. Schellong SM. Kheir DY. Beyer-Westendorf J. Gallus AS. McRae S. Schutgens RE. Piovella F. Gerdes VE. Buller HR. Safety and sensitivity of two ultrasound strategies in patients with clinically suspected deep venous thrombosis: a prospective management study. J Thromb Haemost. 7(12):2035-41, 2009 Dec.

Evidence to recommendation framework 21

Question 21: In patients with a high pretest probability of first lower extremity DVT and initial CUS negative, should we use D-Dimer instead of rule out without further investigation?

Population: Patients with suspected first lower extremity DVT, with high clinical pretest probability and initial CUS negative
Diagnostic test: d-dimer
Comparison: No testing
Setting: Outpatients
Perspective: Public health

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐	**Estimate pre-test probability of prevalence of proximal DVT:** - 53% (44 – 61%) **Risk estimates for undesirable outcomes**	The panel considered adequate the use of Wells criteria in the Saudi population. The panel agreed that the estimates of risk presented also could apply for the Saudi population.

Outcome	Incidence (treated)	Incidence (untreated)
Fatal pulmonary embolism	0.3%	1.9%
Nonfatal pulmonary embolism	1.4%	9.3%
Fatal bleeding	0.3%	-
Nonfatal intracranial bleeding	2.1%	-
Nonfatal non-intracranial bleeding	0.1%	-
Venographic mortality	0.03%	-
Propagation to proximal veins (distal DVT)	-	21.4%

Estimate incidence for 3 months

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ | *Low* ☒ | *Moderate* ☐ | *High* ☐	No evidence specific for the Middle East setting identified. Importance and estimate utility values for outcomes **Outcome** / **Utility (range)** / **Importance** Death / 0 / Critical Nonfatal Intracranial Bleed (severe) / 0.1 – 0.51 / Critical Nonfatal Intracranial Bleed (moderate) / 0.29 – 0.77 / Critical Nonfatal Intracranial Bleed (mild) / 0.47 – 0.94 / Critical Nonfatal Pulmonary Embolism / 0.63 / Critical Major bleed / 0.44 – 0.84 / Critical Assumptions (outcomes): - Major bleeding equivalent to pulmonary embolism - Intracranial bleed (overall): 2 to 3 times worse than major bleed or pulmonary embolism - DVT treatment generally well accepted	Since there are no evidence specific for the KSA, panel members assumed that the values on outcomes should be probably similar than in other populations. The panel highlighted that there are a need for studies of values and preferences in the KSA setting. For single proximal CUS testing, as described in question 18, 51 patients per 1000 tested would be incorrectly classified as not having DVT (false negatives). The probability of having DVT after a negative test is 10.1%. Not treating these individuals would result in additional 0.82 and 3.67 fatal and non-fatal pulmonary embolism per 1000 patients tested. Among those individuals with initial proximal CUS negative and D-dimer (ELISA) negative, only 3 patients per 1000 tested would be classified as false negatives. The probability of having DVT after proximal CUS and D-dimer negatives is 1.47%. Not treating these individuals would result only in additional 0.05 and 2.16 fatal and non-fatal pulmonary embolism per 1000 patients tested. However, 301 patients would present a positive D-dimer test, requiring further evaluation.
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☐ | *Probably no important uncertainty or variability* ☒ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐		
Are the desirable anticipated effects large?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☒ | ***Varies*** ☐		
Are the undesirable anticipated effects small?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☒ | ***Varies*** ☐		
Are the desirable effects large relative to undesirable effects?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | ***Varies*** ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	No evidence found	
	Is the incremental cost small relative to the net benefits?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	No evidence found	With this strategy, 511 D-dimer tests would be required per 1000 patients.
EQUITY	What would be the impact on health inequities?	Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ☒ Varies ☐	No evidence found	
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	No evidence found	
FEASIBILITY	Is the option feasible to implement?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☐ Varies ☐	No evidence found	

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	☒

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☐	☒

Recommendation (text)	The Ministry of Health of Saudi Arabia panel recommends additional testing with D-dimer rather than no further testing in patients with a high pretest probability of first lower extremity DVT and initial negative proximal CUS. (Strong recommendation, Low quality of evidence)
Justification	The panel considered the rate of false negatives and the probability posttest negative high to recommend the use of proximal CUS as a stand alone test to rule out DVT in patients with high clinical pretest probability of DVT. Additional testing is required
Subgroup considerations	-
Implementation considerations	-
Monitoring and evaluation	-
Research priorities	-

Evidence Profile Table for Studies Assessing Compression Ultrasound in Patients with Suspected First Lower Extremity DVT: Should Compression Ultrasound Be Used to Diagnose or to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT
Intervention: Proximal Compression Ultrasound
Comparison: Recurrent VTE during 3 months follow up
Outcome: DVT

Diagnostic test accuracy [1]

Pooled sensitivity	90.3% (95%CI: 88.4% to 92%)
Pooled specificity	97.8% (95%CI: 97% to 98.4%)

Outcome	Study design	Factors that may decrease quality of evidence					Quality of Evidence	Effect per 1000 patients, according to different clinical pre-test probabilities			Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		5% (low)	17% (mod-erate)	53% (high)	
True positives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	45 (44 to 46)	154 (150 to 156)	479 (469 to 488)	CRITICAL
False negatives (patients incorrectly classified as not having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	5 (6 to 4)	16 (20 to 14)	51 (61 to 42)	CRITICAL
True negatives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	929 (922 to 935)	812 (805 to 817)	460 (456 to 462)	CRITICAL
False positives (patients incorrectly classified as having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	21 (28 to 15)	18 (25 to 13)	10 (14 to 8)	CRITICAL

Footnotes:

[1] Data obtained from a meta-analysis with 22 studies evaluating compression ultrasonography alone (Goodacre 2006)

[2] Higher sensitivity observed in studies with higher prevalence.

[3] Accuracy studies included in the meta-analysis, which may increase the specificity estimate. Median prevalence of DVT: 48%, results tend to be more applicable for high risk individuals

[4] Estimates consistent with estimates from similar studies

References:

1. Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, Locker T, Ryan A. Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis. Health Technol Assess. 2006 May;10(15):1-168, iii-iv
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.
3. Pomero F. Dentali F. Borretta V. Bonzini M. Melchio R. Douketis JD. Fenoglio LM. Accuracy of emergency physician–performed ultrasonography in the diagnosis of deep-vein thrombosis. Thromb Haemost. 109(1):137-45, 2013 Jan.
4. Kory PD. Pellecchia CM. Shiloh AL. Mayo PH. DiBello C. Koenig S. Accuracy of ultrasonography performed by critical care physicians for the diagnosis of DVT. Chest. 139(3):538-42, 2011 Mar.
5. Crisp JG. Lovato LM. Jang TB. Compression ultrasonography of the lower extremity with portable vascular ultrasonography can accurately detect deep venous thrombosis in the emergency department. Ann Emerg Med. 56(6):601-10, 2010 Dec.
6. Gibson NS. Schellong SM. Kheir DY. Beyer-Westendorf J. Gallus AS. McRae S. Schutgens RE. Piovella F. Gerdes VE. Buller HR. Safety and sensitivity of two ultrasound strategies in patients with clinically suspected deep venous thrombosis: a prospective management study. J Thromb Haemost. 7(12):2035-41, 2009 Dec.

Evidence Profile Table for Studies Assessing Highly Sensitive D-Dimer in Patients with Suspected First Lower Extremity DVT: Should Highly Sensitive D-Dimer Be Used to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT, high clinical pretest probability and proximal CUS negative
Intervention: D-Dimer (ELISA)
Comparison: Recurrent VTE during 3 months follow

Diagnostic test accuracy

Pooled sensitivity	94% (95%CI: 93% to 95%)
Pooled specificity	45% (95%CI: 44% to 46%)

Outcome	Study design	Factors that may decrease quality of evidence					Quality of Evidence	Effect per 511 patients (equivalent to patients with CUS negative per 1000)	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		Proportion of patients with high pretest probability and CUS negative: 10.06%	
True positives (patients with DVT)	Systematic reviews of management cohorts and of accuracy studies	Not Serious	Not Serious[1]	Serious[2]	None	Undetected	⊕⊕⊕⊖ moderate	48 (46 to 49)	CRITICAL
False negatives (patients incorrectly classified as not having DVT)								3 (3 to 4)	CRITICAL
True negatives (patients without DVT)	Systematic reviews of management cohorts and of accuracy studies	Not Serious	Not Serious[1]	Serious[2]	None	Undetected	⊕⊕⊕⊖ moderate	207 (202 to 211)	CRITICAL
False positives (patients incorrectly classified as not having DVT)								253 (248 to 257)	CRITICAL

Footnotes:

[1] Estimates consistent with estimates from similar ELISA methods. Similar estimates for different clinical pretest probability.

[2] Accuracy studies included in the meta-analysis, which may increase the specificity estimate

References:

1. Di Nisio M, Squizzato A, Rutjes AW, Büller HR, Zwinderman AH, Bossuyt PM. Diagnostic accuracy of D-dimer test for exclusion of venous thromboembolism: a systematic review. J Thromb Haemost. 2007 Feb;5(2):296-304.
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.
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Evidence to recommendation framework 22

Question 22: In patients with high pretest probability of first lower extremity DVT, D-dimer (ELISA) positive and CUS negative, should we repeat proximal CUS instead of venography?

Population: Patients with suspected first lower extremity DVT, with high clinical pretest probability, CUS negative and D-dimer positive
Diagnostic test: repeat CUS in 1 week
Comparison: venography
Setting: Outpatients
Perspective: Public health

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐	**Estimate pre-test probability of prevalence of proximal DVT:** - 53% (44 – 61%) **Risk estimates for undesirable outcomes**	The panel considered adequate the use of Wells criteria in the Saudi population. The panel agreed that the estimates of risk presented also could apply for the Saudi population.

Outcome	Incidence (treated)	Incidence (untreated)
Fatal pulmonary embolism	0.3%	1.9%
Nonfatal pulmonary embolism	1.4%	9.3%
Fatal bleeding	0.3%	-
Nonfatal intracranial bleeding	2.1%	-
Nonfatal non-intracranial bleeding	0.1%	-
Venographic mortality	0.03%	-
Propagation to proximal veins (distal DVT)	-	21.4%

Estimate incidence for 3 months

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	No included studies ☐ | Very low ☐ | Low ☐ | Moderate ☒ | High ☐	No evidence specific for the Middle East setting identified. Importance and estimate utility values for outcomes **Outcome** | **Utility (range)** | **Importance** Death | 0 | Critical Nonfatal Intracranial Bleed (severe) | 0.1 – 0.51 | Critical Nonfatal Intracranial Bleed (moderate) | 0.29 – 0.77 | Critical Nonfatal Intracranial Bleed (mild) | 0.47 – 0.94 | Critical Nonfatal Pulmonary Embolism | 0.63 | Critical Major bleed | 0.44 – 0.84 | Critical Assumptions (outcomes): - Major bleeding equivalent to pulmonary embolism - Intracranial bleed (overall): 2 to 3 times worse than major bleed or pulmonary embolism - DVT treatment generally well accepted	Since there are no evidence specific for the KSA, panel members assumed that the values on outcomes should be probably similar than in other populations. The panel highlighted that there are a need for studies of values and preferences in the KSA setting. after a contrast venography negative, the probability of having recurrent venous thromboembolism during 3 months follow of up is 1.2% (95%CI 0.2% to 4.4%) (Moderate quality of evidence). For repeating proximal CUS in patients with high clinical pretest probability, initial CUS negative and D-dimer positive, only one study was identified in the systematic review. In this study, the prevalence of DVT was 59.5% and the post-test probability was 2.8% (95%CI 0.1% to 12.5%) (ref) (Low quality of evidence) Venography is considered reference standard for DVT, however it is subject to a considerably variation. Although often considered as 100%, posttest probability of a positive test cannot be estimated with confidence. There are no studies evaluating Venography in patients with low risk for DVT. Additionally, venography is associated with 1 to 4% of incidence of adverse reactions to contrast media, including dizziness and nausea, severe allergic reaction in 0 to 0.4% and post-venography DVT in 0 to 2% of patients
Is there important uncertainty about how much people value the main outcomes?	Important uncertainty or variability ☐ | Possibly important uncertainty or variability ☐ | Probably no important uncertainty or variability ☒ | No important uncertainty or variability ☐ | No known undesirable outcomes ☐		
Are the desirable anticipated effects large?	No ☐ | Probably No ☒ | Uncertain ☐ | Probably Yes ☐ | Yes ☐ | **Varies** ☐		
Are the undesirable anticipated effects small?	No ☐ | Probably No ☒ | Uncertain ☐ | Probably Yes ☐ | Yes ☐ | **Varies** ☐		
Are the desirable effects large relative to undesirable effects?	No ☐ | Probably No ☒ | Uncertain ☐ | Probably Yes ☐ | Yes ☐ | **Varies** ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
	Is the incremental cost small relative to the net benefits?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	Contrast venography is a costly intervention compared to proximal CUS
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☒ / Varies ☐	No evidence found	
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	Technology is not widely available for contrast venography

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	☒

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☐	☒

Recommendation (text)	The Ministry of Health of Saudi Arabia panel recommends to repeat proximal CUS In one week over performing venography in patients with a high pretest probability of first lower extremity DVT and initial proximal CUS negative and D-dimer positive
Justification	The panel considered contrast venography an expansive, potentially harmful and difficult to implement alternative for a situations when there are no clear benefit established. (Strong recommendation, Low quality of evidence)
Subgroup considerations	
Implementation considerations	CT venography is more increasingly being in use and is more familiar to physicians.
Monitoring and evaluation	
Research priorities	

Evidence Profile Table for Studies Assessing Venography in Patients with Suspected First Lower Extremity Deep Vein Thrombosis (DVT):

Should Venography Be Used to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT and negative result for contrast venography
Outcome: Recurrent venous thromboembolism during 3 months follow-up

Diagnostic test accuracy

Pooled sensitivity	Not Available
Pooled specificity	Not Available
Accuracy[1]	98.8% (95% CI: 95.6% to 99.8%)

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease quality of evidence					Quality of Evidence[2]	Post-test probability of negative test	Importance
			Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias			
Venous thrombo-embolism (3 months)	1 Study (160 patients)	Single-arm prospective cohort study	Serious[3]	None[4]	Not Serious	Not Serious	Undetected[4]	⊕⊕⊕⊖ moderate	1.2% (0.2 to 4.4%)	CRITICAL

Footnotes:

[1] Individuals with normal venography and without venous thromboembolism during 3 months follow-up.

[2] Judgement according to the original systematic review; no additional study had been identified.

[3] Prevalence of DVT in original population not specified

[4] Only one study identified, not allowing adequate assessment of inconsistency and publication bias.

References:

1. Hull R, Hirsh J, Sackett DL, Taylor DW, Carter C, Turpie AG, Powers P, Gent M. Clinical validity of a negative venogram in patients with clinically suspected venous thrombosis. Circulation. 1981 Sep;64(3):622-5.
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.

Evidence Profile Table for Studies Assessing Serial Compression Ultrasound (CUS) in Patients with Suspected First Lower Extremity Deep Vein Thrombosis (DVT):

Should Serial CUS be Used to Rule Out DVT in patients with high pretest probability and D-Dimer (ELISA) positive?

Population: Patients with suspected first lower extremity DVT and high clinical pretest probability
Test result: D-dimer positive (ELISA) and Serial CUS negative.
Outcome: Recurrent venous thromboembolism during 3 months follow-up

Diagnostic test accuracy

Pooled sensitivity	Not Available
Pooled specificity	Not Available

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease quality of evidence					Quality of Evidence [1]	Prevalence	Post-test probability of negative test	Importance
			Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias				
Venous thromboembolism (3 months)	1 Studies (279 patints)	Management Cohort	Not Serious	Not serious	Serious[2]	Very Serious	Undetected	⊕⊕⊖⊖ low	59.5%	2.8% (0.1 to 12.5%)	CRITICAL

Footnotes:

[1] Judgement according to the original systematic review; no additional study had been identified.

References:

1. 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

Evidence to recommendation framework 23

Question 23: In patients with a high pretest probability of first lower extremity DVT and serial CUS negative, should we perform venography instead of rule out without further investigation?

Population: Patients with suspected first lower extremity DVT, with high clinical pretest probability and initial CUS negative
Diagnostic test: venography
Comparison: No testing
Setting: Outpatients
Perspective: Public health

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐	**Estimate pre-test probability of prevalence of proximal DVT:** - 53% (44 – 61%) **Risk estimates for undesirable outcomes**	The panel considered adequate the use of Wells criteria in the Saudi population. The panel agreed that the estimates of risk presented also could apply for the Saudi population.

Outcome	Incidence (treated)	Incidence (untreated)
Fatal pulmonary embolism	0.3%	1.9%
Nonfatal pulmonary embolism	1.4%	9.3%
Fatal bleeding	0.3%	-
Nonfatal intracranial bleeding	2.1%	-
Nonfatal non-intracranial bleeding	0.1%	-
Venographic mortality	0.03%	-
Propagation to proximal veins (distal DVT)	-	21.4%

Estimate incidence for 3 months

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Moderate* ☒ | *High* ☐		Since there are no evidence specific for the KSA, panel members assumed that the values on outcomes should be probably similar than in other populations. The panel highlighted that there are a need for studies of values and preferences in the KSA setting.
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☐ | *Probably no important uncertainty or variability* ☒ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐	No evidence specific for the Middle East setting identified. Importance and estimate utility values for outcomes	After a contrast venography negative, the probability of having recurrent venous thromboembolism during 3 months follow of up is 1.2% (95%CI 0.2% to 4.4%) (Moderate quality of evidence).
Are the desirable anticipated effects large?	*No* ☒ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		For serial proximal CUS in patients with high clinical pretest probability, four studies were identified in the systematic review. In these studies, the pooled prevalence of DVT was 36.4% and the probability of DVT post-negative serial CUS was 0.9% (95%CI 0.2% to 2.8%) (Moderate quality of evidence)
Are the undesirable anticipated effects small?	*No* ☒ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		Venography is considered reference standard for DVT, however it is subject to a considerably variation. Although often considered as 100%, posttest probability of a positive test cannot be estimated with confidence. There are no studies evaluating Venography in patients with low risk for DVT. Additionally, venography is associated with 1 to 4% of incidence of adverse reactions to contrast media, including dizziness and nausea, severe allergic reaction in 0 to 0.4% and post-venography DVT in 0 to 2% of patients
Are the desirable effects large relative to undesirable effects?	*No* ☒ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		

Outcome	Utility (range)	Importance
Death	0	Critical
Nonfatal Intracranial Bleed (severe)	0.1 – 0.51	Critical
Nonfatal Intracranial Bleed (moderate)	0.29 – 0.77	Critical
Nonfatal Intracranial Bleed (mild)	0.47 – 0.94	Critical
Nonfatal Pulmonary Embolism	0.63	Critical
Major bleed	0.44 – 0.84	Critical

Cate-hoek 2009, MacLean 2012

Assumptions (outcomes):

- Major bleeding equivalent to pulmonary embolism
- Intracranial bleed (overall): 2 to 3 times worse than major bleed or pulmonary embolism
- DVT treatment generally well accepted

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
	Is the incremental cost small relative to the net benefits?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	Contrast venography is a costly intervention compared to proximal CUS
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☒ / Varies ☐	No evidence found	
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	Technology is not widely available for contrast venography

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	☒

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☐	☒

Recommendation (text)

The Ministry of Health of Saudi Arabia panel recommends no further testing rather than venography in patients with high pretest probability of first lower extremity DVT and negative serial proximal CUS. (Strong recommendation, Moderate level of evidence)

Justification

The panel considered contrast venography an expansive, potentially harmful and difficult to implement alternative for a situations when there are no clear benefit established. Posttest probabilities after the preferred strategy was considered acceptable by the panel members.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

Evidence Profile Table for Studies Assessing Venography in Patients with Suspected First Lower Extremity Deep Vein Thrombosis (DVT):

Should Venography Be Used to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT and negative result for contrast venography
Outcome: Recurrent venous thromboembolism during 3 months follow-up

Diagnostic test accuracy

Pooled sensitivity	Not Available
Pooled specificity	Not Available
Accuracy[1]	98.8% (95% CI: 95.6% to 99.8%)

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease quality of evidence					Quality of Evidence [2]	Post-test probability of negative test	Importance
			Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias			
Venous thromboembolism (3 months)	1 Study (160 patients)	Single-arm prospective cohort study	Serious [3]	None [4]	Not Serious	Not Serious	Undetected [4]	⊕⊕⊕⊖ moderate	1.2% (0.2 to 4.4%)	CRITICAL

Footnotes:

[1] Individuals with normal venography and without venous thromboembolism during 3 months follow-up.

[2] Judgement according to the original systematic review; no additional study had been identified.

[3] Prevalence of DVT in original population not specified

[4] Only one study identified, not allowing adequate assessment of inconsistency and publication bias.

References:

1. Hull R, Hirsh J, Sackett DL, Taylor DW, Carter C, Turpie AG, Powers P, Gent M. Clinical validity of a negative venogram in patients with clinically suspected venous thrombosis. Circulation. 1981 Sep;64(3):622-5.
2. Bates SM, Jaeschke R, Stevens SM, Goodacre S, Wells PS, Stevenson MD, Kearon C, Schunemann HJ, Crowther M, Pauker SG, Makdissi R, Guyatt GH; American College of Chest Physicians. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e351S-418S.

Evidence Profile Table for Studies Assessing Serial Compression Ultrasound (CUS) in Patients with Suspected First Lower Extremity Deep Vein Thrombosis (DVT):

Should Serial CUS be Used to Rule Out DVT in patients with high pretest probability?

Population: Patients with suspected first lower extremity DVT and high clinical pretest probability
Intervention: Serial CUS
Outcome: Recurrent venous thromboembolism during 3 months follow-up

Diagnostic test accuracy

Pooled sensitivity	Not Available
Pooled specificity	Not Available

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease quality of evidence					Quality of Evidence [1]	Pretest probability (prevalence)	Post-test probability of negative test	Importance
			Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias				
Venous thromboembolism (3 months)	4 study (291 patients)	Management Cohort	Not Serious	Not serious	Not Serious	Serious	Undetected	⊕⊕⊕⊖ moderate	36.9%	0.9% (0.2 to 2.8%)	CRITICAL

Footnotes:

[1] Judgement according to the original systematic review; no additional study had been identified.

References:

1. 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.
2. Ruiz-Giménez 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 .
3. 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.
4. Dewar C, Selby C, Jamieson K, Rogers S. Emergency department nurse-based outpatient diagnosis of DVT using an evidence-based protocol . Emerg Med J . 2008 ; 25 (7): 411 - 416 .

Evidence to recommendation framework 24

Question 24: In patients with a high pretest probability of first lower extremity DVT, DD negative and a proximal CUS negative, should we should we perform venography instead of rule out without further investigation?

Population: Patients with suspected first lower extremity DVT, with high clinical pretest probability and initial CUS negative
Diagnostic test: venography
Comparison: No testing
Setting: Outpatients
Perspective: Public health

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐	**Estimate pre-test probability of prevalence of proximal DVT:** - 53% (44 – 61%) **Risk estimates for undesirable outcomes**	The panel considered adequate the use of Wells criteria in the Saudi population. The panel agreed that the estimates of risk presented also could apply for the Saudi population.

Outcome	Incidence (treated)	Incidence (untreated)
Fatal pulmonary embolism	0.3%	1.9%
Nonfatal pulmonary embolism	1.4%	9.3%
Fatal bleeding	0.3%	-
Nonfatal intracranial bleeding	2.1%	-
Nonfatal non-intracranial bleeding	0.1%	-
Venographic mortality	0.03%	-
Propagation to proximal veins (distal DVT)	-	21.4%

Estimate incidence for 3 months

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ | *Low* ☒ | *Moderate* ☐ | *High* ☐	No evidence specific for the Middle East setting identified. Importance and estimate utility values for outcomes **Outcome** / **Utility (range)** / **Importance** Death / 0 / Critical Nonfatal Intracranial Bleed (severe) / 0.1 – 0.51 / Critical Nonfatal Intracranial Bleed (moderate) / 0.29 – 0.77 / Critical Nonfatal Intracranial Bleed (mild) / 0.47 – 0.94 / Critical Nonfatal Pulmonary Embolism / 0.63 / Critical Major bleed / 0.44 – 0.84 / Critical *Cate-hoek 2009, MacLean 2012* Assumptions (outcomes): - Major bleeding equivalent to pulmonary embolism - Intracranial bleed (overall): 2 to 3 times worse than major bleed or pulmonary embolism - DVT treatment generally well accepted	Since there are no evidence specific for the KSA, panel members assumed that the values on outcomes should be probably similar than in other populations. The panel highlighted that there are a need for studies of values and preferences in the KSA setting. As described in the question 6, after a contrast venography negative, the probability of having recurrent venous thromboembolism during 3 months follow of up is 1.2% (95%CI 0.2% to 4.4%). (ref) (Moderate quality of evidence). Venography is considered reference standard for DVT, however it is subject to a considerably variation. Although often considered as 100%, posttest probability of a positive test cannot be estimated with confidence. There are no studies evaluating Venography in patients with low risk for DVT. Additionally, venography is associated with 1 to 4% of incidence of adverse reactions to contrast media, including dizziness and nausea, severe allergic reaction in 0 to 0.4% and post-venography DVT in 0 to 2% of patients. As reported in question 21, among those individuals with initial proximal CUS negative and D-dimer (ELISA) negative, only 3 patients per 1000 initially tested in the population would be classified as false negatives. The probability of having DVT after proximal CUS and D-dimer negatives is 1.47%. Not treating these individuals would result only in additional 0.05 and 2.16 fatal and non-fatal pulmonary
Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☒ | *Probably no important uncertainty or variability* ☐ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐		
Are the desirable anticipated effects large?	*No* ☒ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		
Are the undesirable anticipated effects small?	*No* ☒ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		
Are the desirable effects large relative to undesirable effects?	*No* ☐ | *Probably No* ☒ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
				embolism per 1000 patients tested. (Low quality of evidence)

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
	Is the incremental cost small relative to the net benefits?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	Contrast venography is a costly intervention compared to proximal CUS
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☒ / Varies ☐	No evidence found	
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	No evidence found	Technology is not widely available for contrast venography

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	☒

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☐	☒

Recommendation (text)	The Ministry of Health of Saudi Arabia panel recommends no further testing rather than venography in patients with high pretest probability of first lower extremity DVT, D-dimer (ELISA) negative and proximal CUS negative. (Strong recommendation, Low level of evidence)
Justification	The panel considered contrast venography an expansive, potentially harmful and difficult to implement alternative for a situations when there are no clear benefit established. Posttest probabilities after the preferred strategy was considered acceptable by the panel members.
Subgroup considerations	
Implementation considerations	
Monitoring and evaluation	
Research priorities	

Evidence Profile Table for Studies Assessing Venography in Patients with Suspected First Lower Extremity Deep Vein Thrombosis (DVT):

Should Venography Be Used to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT and negative result for contrast venography
Outcome: Recurrent venous thromboembolism during 3 months follow-up

Diagnostic test accuracy

Pooled sensitivity	Not Available
Pooled specificity	Not Available
Accuracy[1]	98.8% (95% CI: 95.6% to 99.8%)

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease quality of evidence					Quality of Evidence [2]	Post-test probability of negative test	Importance
			Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias			
Venous thrombo-embolism (3 months)	1 Study (160 patients)	Single-arm prospective cohort study	Serious [3]	None [4]	Not Serious	Not Serious	Undetected [4]	⊕⊕⊕⊖ moderate	1.2% (0.2 to 4.4%)	CRITICAL

Footnotes:

[1] Individuals with normal venography and without venous thromboembolism during 3 months follow-up.

[2] Judgement according to the original systematic review; no additional study had been identified.

[3] Prevalence of DVT in original population not specified

[4] Only one study identified, not allowing adequate assessment of inconsistency and publication bias.

References:

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Evidence Profile Table for Studies Assessing Compression Ultrasound in Patients with Suspected First Lower Extremity DVT and D-dimer (ELISA) positive: Should Compression Ultrasound Be Used to Diagnose or to Rule Out DVT?

Population: Patients with suspected first lower extremity DVT, high pretest probability and D-dimer (ELISA) negative
Intervention: Proximal Compression Ultrasound
Comparison: Recurrent VTE during 3 months follow up
Outcome: DVT

Diagnostic test accuracy of proximal CUS [1]

Pooled sensitivity	90.3% (95%CI: 88.4% to 92%)
Pooled specificity	97.8% (95%CI: 97% to 98.4%)

Outcome	Study design	Factors that may decrease quality of evidence					Quality of Evidence	Effect per 243 patients (equivalent to patients with D-dimer negative per 1000) Proportion of patients with high pretest probability and D-dimer negative: 13.1%	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias			
True positives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	29 (28 to 29)	CRITICAL
False negatives (patients incorrectly classified as not having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Serious[2]	Serious[3]	None	Undetected	⊕⊕⊖⊖ low	3 (3 to 4)	CRITICAL
True negatives (patients without DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	207 (205 to 208)	CRITICAL
False positives (patients incorrectly classified as having DVT)	Systematic review of management cohorts and of accuracy studies	Not serious	Not Serious[4]	Serious[3]	None	Undetected	⊕⊕⊕⊖ moderate	5 (3 to 6)	CRITICAL

Footnotes:

[1] Data obtained from a meta-analysis with 22 studies evaluating compression ultrasonography alone (Goodacre 2006)

[2] Higher sensitivity observed in studies with higher prevalence.

[3] Accuracy studies included in the meta-analysis, which may increase the specificity estimate. Median prevalence of DVT: 48%, results tend to be more applicable for high risk individuals

[4] Estimates consistent with estimates from similar studies

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