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Guidelines

The Saudi clinical practice guideline for the diagnosis of the first deep venous thrombosis of the lower extremity

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Abstract:

The diagnosis of deep venous thrombosis (DVT) may be challenging due to the inaccuracy of clinical assessment and diversity of diagnostic tests. On one hand, missed diagnosis may result in life-threatening conditions. On the other hand, unnecessary treatment may lead to serious complications. As a result of an initiative of the Ministry of Health of the Kingdom of Saudi Arabia (KSA), an expert panel led by the Saudi Association for Venous Thrombo-Embolism (SAVTE; a subsidiary of the Saudi Thoracic Society) with the methodological support of the McMaster University Working Group, produced this clinical practice guideline to assist healthcare providers in evidence-based clinical decision-making for the diagnosis of a suspected first DVT of the lower extremity. Twenty-four questions were identified and corresponding recommendations were made following the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. These recommendations included assessing the clinical probability of DVT using Wells criteria before requesting any test and undergoing a sequential diagnostic evaluation, mainly using highly sensitive D-dimer by enzyme-linked immunosorbent assay (ELISA) and compression ultrasound. Although venography is the reference standard test for the diagnosis of DVT, its use was not recommended.

Key words:

Clinical practice guideline, deep venous thrombosis, diagnosis, Saudi Arabia, venous thromboembolism

Venous thromboembolism (VTE), comprised of deep venous thrombosis (DVT) and pulmonary embolism (PE), is a common condition, affecting approximately 100 per 100,000 people per year.[1-3] Its 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.[4,5] The major risk factors other than age include surgery, hospitalization, immobility, trauma, pregnancy and puerperium, hormone use, cancer, obesity, and inherited and acquired hypercoagulable states.[6] VTE incidence varies among the different ethnic groups. Compared to whites, blacks have higher incidence (age-adjusted hazard ratio, 1.6; 95% confidence interval (CI), 1.2-2.2);[7] while Asians, Pacific Islanders, and Hispanics have lower incidence, at least in the United States.[8] The true incidence of VTE in the Kingdom of Saudi Arabia (KSA) is unknown. Assuming similar rate to those present in other parts of the world, approximately 25,000 people are affected in the KSA annually. For DVT, patients may present with swelling, redness, and pain of the leg; but are frequently asymptomatic. Clinical assessment is frequently inaccurate,[9] leading to important concerns about misdiagnosis. Complications of lower extremity

DVT include PE in 15-32%,[10,11] recurrence at 12 months in 10%,[12] and post-thrombotic syndrome in up to 56%.[13] Death within 1 month of a DVT episode occurs in about 6%, compared with 10% in those with PE.[14] While not treating DVT may result in serious complications, overtreatment is associated with higher bleeding rates, including intracranial and gastrointestinal hemorrhages.[15-18]

As physical examination frequently fails to diagnose DVT, several strategies have been developed to improve diagnostic accuracy and minimize health consequences of misdiagnosis and overtreatment. The diagnostic strategies for DVT usually consist of clinical pretest probability assessment, using structured scoring systems, followed by sequential testing using the D-dimer assay and imaging studies. The Wells score [Table 1][19,20] is the most studied structured scoring systems and 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%).[20] Compression ultrasound (CUS) of the proximal veins is the commonly used imaging test. Other tests, such as contrast venography, which is still considered the reference standard for DVT

Table 1: Wells model for assessment of deep venous 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 deep venous thrombosis	1
Alternative diagnosis at least as likely as deep venous thrombosis	-2

*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

diagnosis, computed tomography, and magnetic resonance imaging may be occasionally used.[1,4]

The Ministry of Health in the KSA had begun an initiative to promote evidence-based practice across the country and provide guidance for the diagnosis and management of several common diseases, which included DVT. In this document, we report the recommendations of the Saudi Expert Panel for the diagnosis of the first DVT of the lower extremity. The full guideline is available at: http://www.moh.gov.sa/depts/Proofs/Pages/Guidelines.aspx.

Methods

This clinical practice guideline was a part of the larger initiative of the KSA Ministry of Health to provide guidance for clinicians to ensure high quality of care and reduce variability in clinical practice across the Kingdom. For this purpose, the KSA Ministry of Health, through the Saudi Center for Evidence Based Healthcare, partnered with the McMaster University Working Group to provide methodological support and contacted the Saudi Association for Venous Thrombo-Embolism (SAVTE) to nominate a group of clinicians from various specialties to serve as an expert panel for guideline development on DVT diagnosis. We present the detailed methodology in a separate publication.[21]

First, the invited KSA guideline panel selected all clinical questions addressed herein using a formal prioritization process. For all selected questions, the McMaster University working group updated the existing systematic reviews that were used for the "Diagnosis of DVT" chapter of the 2012 Antithrombotic Therapy and Prevention of Thrombosis Guidelines, 9th edition (AT9).[1] To develop a complete guideline for the KSA, the group also conducted systematic searches for information that were specific to the Saudi context including searches for information about patient values and preferences, cost and resource use. Thereafter, summaries of available evidence related to the selected questions were prepared following the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[22] The quality of evidence was assessed according to the GRADE system[23] and was classified as "high", "moderate", "low", or "very low" based on the methodological characteristics of the available evidence. The definition of each category is as follows:

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

The guideline panel met in Riyadh on December 2 and 3, 2013. On the 1st day, the panel was educated on the GRADE approach. On the 2nd day, the McMaster Working Group provided the panel with pertinent literature summary in the form of GRADE evidence profiles. The assumed rates of fatal and nonfatal PE were 0.3 and 1.4% for treated patients and 1.9 and 9.3% for untreated patients, respectively.[1,4] The assumed risk for fatal bleeding, nonfatal intracranial bleeding, and nonfatal non-intracranial bleeding were 0.3, 0.1, and 2.1%, respectively, for patients given antithrombotic therapy.[1,4] The values and preferences of patients considering antithrombotic therapy were identified using a recent systematic review.[24] Utility values for outcomes considered critical for decision making are summarized in Table 2. The results of diagnostic accuracy studies were summarized as sensitivity, specificity, and post-test probabilities of having DVT during the follow-up period. Figure 1 demonstrates how to calculate these and other diagnostic properties of tests and provides an example. In order to estimate the impact on patient-important outcomes, crude rates of events were provided for the panel members to support the clinical judgment using simulation (Table 3 for events due to lack of treatment and Table 4 for events due to unnecessary treatment). All of the above allowed the guideline panel to follow a structured consensus process and formulate all recommendations according to the GRADE approach, facilitated by the use of evidence-to-decision tables, with each recommendation being either strong or conditional (weak) as described in Table 5. Due to the lack of evidence coming from the Middle East, the panel members assumed that the values placed on outcomes by the patients in the KSA were probably similar to those of other populations. Based on the presented evidence, the panel concluded that there might be some degree of variability in values and preferences of patients, that the importance of major bleeding

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
Non-intracranial nonfatal major bleeding event	0.44-0.84

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

	Condition present	Condition absent	
Test positive	A (true positive)	B (false positive)	Positive predictive value: A/A+B
Test negative	C (false negative)	D (true negative)	Negative predictive value: D/C+D
	Sensitivity: A/(A+C)	Specificity: D/B+D	

Figure 1: Diagnostic properties of a given test. For example, if 1,000 people with low pretest probability for DVT (DVT present in 5% or 50 out of 1,000 people) underwent highly sensitive D-dimer assay (assumed sensitivity = 90% and specificity = 50%), A (true positives) will be 45, B (false positives) = 450, C (false negatives) = 5, D (true negatives) = 450, positive predictive value = 45/495 × 100 = 9.1%, and negative predictive value = 450/455 × 100 = 98.9%

was equivalent to PE, that intracranial bleeding is two to three times worse than major non-intracranial bleeding or PE, and that DVT treatment was generally well accepted by affected patients. All decisions made during the meeting were transparently documented. Potential conflicts of interests of all panel members were managed according to the World Health Organization rules.[25]

Results

The panel provided recommendations on four major issues: I: The need for clinical assessment of the pretest probability of first lower extremity DVT (Question 1), II: The diagnostic strategy in patients with low pretest probability of first lower extremity DVT (Questions 2-8), III: The diagnostic strategy in patients with moderate pretest probability of first lower extremity DVT (Questions 9-16) and IV: The diagnostic strategy in patients with high pretest probability of first lower extremity DVT (Questions 17-24). The recommendations were made taking into account the available evidence, resource use, and the Saudi context. The full document related to this guideline development and recommendations is available online at http://www.moh.gov.sa

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

One important question is related to the 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 be guided by the clinical assessment of pretest probability instead of 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. A randomized controlled trial (RCT) which compared the clinical assessment of the pretest probability of having DVT followed by a diagnostic strategy with a uniform diagnostic strategy without clinical assessment was identified in our update of literature.[26] It randomized 1,723 patients (89% outpatients) and found no differences in VTE risk (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%) during the 3 months of follow-up.[26] (Moderate quality of evidence)

Resource use
The 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).[26] Although there was no formal economic assessment, the strategy was considered cost-saving as 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 to 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 Saudi Expert 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 2-8 are related to the diagnostic strategy of DVT in patients with low clinical pretest probability of first lower extremity DVT. Figure 2 summarizes the diagnostic recommendations.

Question 2: In patients with low pretest probability of first lower extremity DVT, should we use highly sensitive D-dimer by enzyme-linked immunosorbent assay (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.[4] We identified seven additional studies that could not be pooled with the systematic review.[27-33] The ELISA D-dimer assays are highly sensitive with pooled sensitivity and specificity for DVT of 94% (95% CI, 93-95%) and 45% (95% CI,

Table 3: Number of thromboembolic events due to lack of treatment in patients with deep venous thrombosis according to the adopted ruling out strategy

Ruling out strategy for DVT	Post-test probability of DVT (%)	Events per 1,000 tested patients				Quality of evidence
		Patients ruled out	False negatives	Fatal PE	Nonfatal PE	
Low clinical pretest probability of DVT (prevalence: 5%)						
No test and treatment	—	—	—	0.8	3.6	—
D-dimer negative	0.7	431	5	0.08	0.36	Moderate
Proximal CUS negative	0.5	934	3	0.05	0.22	Low
D-dimer negative + proximal CUS negative	<0.1	418	0	0	0	Low
(1) D-dimer negative or (2) D-dimer positive and proximal CUS negative	(1) 0.7 (2) 0.88	947	10	0.16	0.72	Low
Moderate clinical pretest probability of DVT (prevalence: 17%)						
No test and treatment	—	—	—	2.72	12.24	—
D-dimer negative	2.7	384	10	0.16	0.72	Moderate
Proximal CUS negative	2	828	16	0.26	1.15	Low
D-dimer negative + proximal CUS negative	0.3	366	1	0.02	0.07	Low
(1) D-dimer negative or (2) D-dimer positive and proximal CUS negative	(1) 2.7 (2) 3.4	846	26	0.42	1.87	Low
Serial proximal CUS negative[2]	0.6-1.1	—	1-2	0.02-0.04	0.07-0.14	Moderate
High clinical pretest probability of DVT (prevalence: 53%)						
No test and treatment	—	—	—	8.64	38.88	—
D-dimer negative	13.1	242	32	0.51	2.3	Moderate
Proximal CUS negative	10.1	511	51	0.82	3.67	Moderate
D-dimer negative + proximal CUS negative	1.5	210	3	0.05	0.22	Moderate
(1) D-dimer negative or (2) D-dimer positive and proximal CUS negative	(1) 13.1 (2) 16.5%	543	80	1.28	5.76	Moderate
Serial proximal CUS negative	0.9	—	3	0.05	0.22	Moderate
Proximal CUS negative → D-dimer positive → proximal CUS negative	2.8	—	17	0.27	1.22	Low

DVT = Deep venous thrombosis, CUS = compression ultrasound, PE = pulmonary embolism, [2]data from two different studies

Table 4: Number of adverse events due to overtreatment in patients without deep venous thrombosis according to the diagnostic strategy adopted

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

DVT = Deep venous thrombosis, CUS = Compression ultrasound, [1]Bleeding events among patients without DVT (false positives)

44-46%), respectively (Moderate quality of evidence). These data were used for the assessment of all questions related to D-dimer testing as a standalone test or combined with a single proximal CUS. Based on these findings, only 3 patients per 1,000 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 nonfatal PE per 1,000 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 Saudi Expert Panel recommends the use of highly sensitivity D-dimer (ELISA) as an initial test for the diagnosis

Table 5: 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

PTP – Pretest probability; CUS – Compression ultrasound; DVT: Deep vein thrombosis
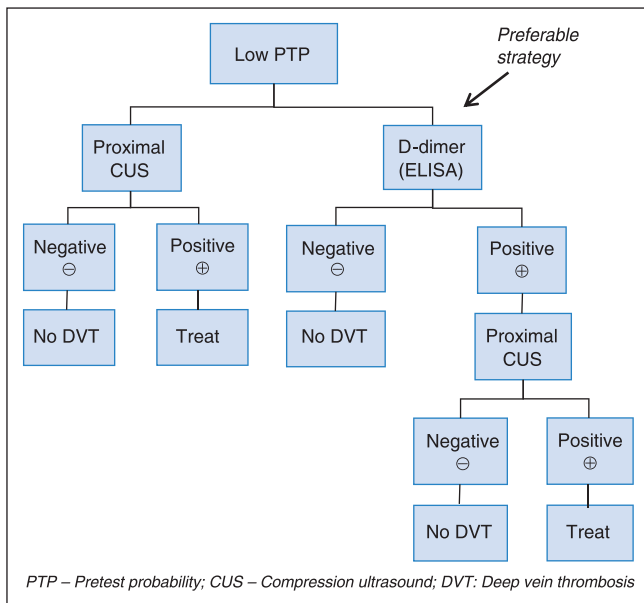
Figure 2: Recommendations for evaluation of suspected first lower extremity DVT in patients with low pretest probability

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 the systematic review cited for Question 2.[4] The meta-analysis pooled 22 studies specifically evaluating proximal CUS.[4] We identified four additional studies, which could not be pooled with the systematic review. [34-37] The pooled sensitivity and specificity of CUS for DVT diagnosis was 90.3% (95% CI, 88.4-92%) and 97.8% (95% CI, 97-98.4%) respectively (Low quality of evidence). Quality of evidence was downgraded due to inconsistency specifically for patients with low and moderate pretest probability because the test sensitivity tended to be higher in patients with higher pretest probability. These data were used for the assessment of all questions related to proximal CUS as a standalone test or combined with D-dimer testing. Based on the above, only

5 per 1,000 tested patients would be incorrectly classified as not having DVT (false negatives). On the other hand, 21 per 1,000 tested 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 nonfatal PE, and 0.35 major bleeding episodes (0.02 intracranial) per 1,000 patients. With no testing or treatment, we would have respectively, 0.8 and 3.6 additional cases of fatal and nonfatal PE per 1,000 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 Saudi Expert 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 D-dimer (ELISA) instead of proximal CUS as initial test for the diagnosis of DVT?

Summary of findings
No evidence directly combining D-dimer test and proximal CUS was identified. To make judgments, we indirectly combined data available from questions 2 and 3.

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 Saudi Expert Panel suggests the use of D-dimer (ELISA) instead of 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 D-dimer test (ELISA), should we perform proximal CUS instead of discharge with no additional evaluation?

Summary of findings

As reported in question 2, using D-dimer as the initial test, 3 patients per 1,000 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 additional testing, we would have 0.05 and 0.22 additional cases of fatal and nonfatal PE among the false negatives per 1,000 patients tested (Moderate quality of evidence).[4] In patients with sequential D-dimer and proximal CUS that are negative, the post-test probability of DVT would be negligible (0.07%). However, performing the two tests sequentially would lead to an increase of 9 patients with false positive tests per 1,000 tested. Thus, we would expect an increase of 0.03 deaths and 0.2 nonfatal major bleeding events per 1,000 tested patients (Low quality of evidence).[4]

Resource use

Performing proximal CUS in these patients would increase costs: 428 additional ultrasounds would be needed per 1,000 tested patients.

Recommendation 5

The Saudi Expert Panel recommends no additional investigation over additional investigation with proximal CUS in patients with low pretest probability of first lower extremity DVT and negative 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 additional 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. After a negative test, the probability of having recurrent VTE during the following 3 months was 1.2% (95% CI, 0.2-4.4%) (Moderate quality of evidence).[38]

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 considerable 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 DVT risk. Additionally, venography is associated with 1-4% incidence of adverse reactions to contrast media, including dizziness and nausea, severe allergic reaction in 0-0.4%, and post-venography DVT in 0-2% of patients.[1]

Implementation considerations

The required technology for performing contrast venography is not widely available in the KSA.

Recommendation 6

The Saudi Expert Panel recommends no additional investigation over additional investigation with 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 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-up is 1.2% (95% CI, 0.2-4.4%) (Moderate quality of evidence).[38] 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 after a positive CUS is 78.69%. Per 1,000 patients initially tested, 11 patients without DVT would be treated and 5 patients with DVT and D-dimer positive would be discharged as false negatives. Due to misdiagnosis, we would have additionally 0.11 deaths, 0.36 cases of nonfatal PE, and 0.23 major bleeding episodes (0.01 intracranial) per 1,000 patients (Low quality of evidence).

Resource use and other considerations

Please refer to those described for question 6.

Recommendation 7

The Saudi Expert Panel recommends performing proximal CUS instead of venography in patients with low pretest probability of first lower extremity DVT and positive 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 additional 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, 0.2-4.4%) (Moderate quality of evidence).[38] As reported in question 3, 21 patients per 1,000 tested with proximal CUS would be incorrectly classified as not having DVT. Treating unnecessarily these patients would result in 0.06 deaths and 0.46 major bleeding episodes (0.02 intracranial) (Moderate quality of evidence).

Resource use and other considerations

Please refer to those described for question 6.

Recommendation 8

The Saudi Expert Panel recommends no additional investigation, instead of 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 9-16 are related to the diagnostic strategy of DVT in patients with moderate clinical pretest probability of first lower extremity DVT. Figure 3 summarizes the diagnostic recommendations.

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

Summary of findings
With D-dimer testing, only 10 patients per 1,000 tested would be incorrectly classified as not having DVT (false negatives).[4] 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 nonfatal PE per 1,000 patients.

Resource use
The cost of ELISA D-dimer assay was considered low.

Recommendation 9
The Saudi Expert 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).
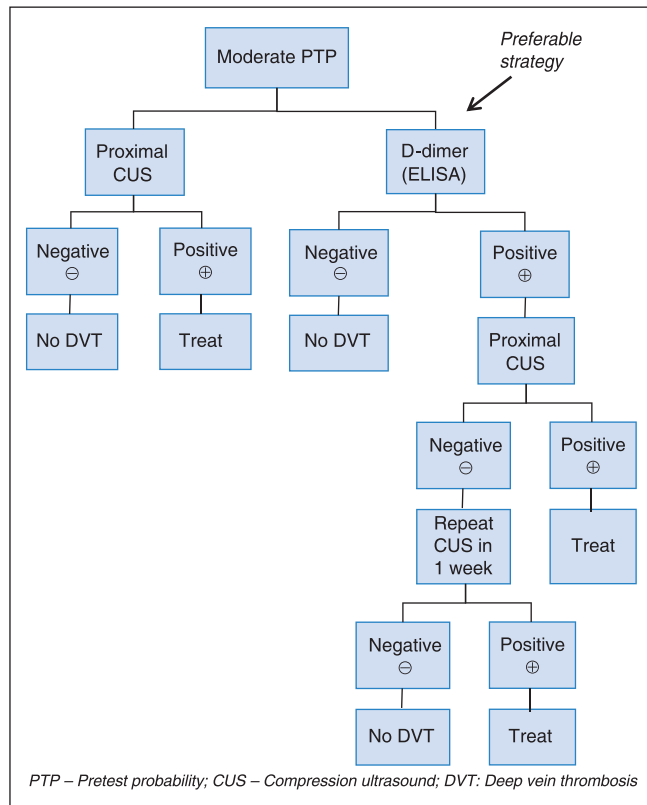

PTP – Pretest probability; CUS – Compression ultrasound; DVT: Deep vein thrombosis

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

Question 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?

Summary of findings
With proximal CUS, 16 patients per 1,000 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 nonfatal PE, and 0.04 major bleeding episodes (0.002 intracranial) per 1,000 patients. With no testing or treatment, we would have respectively, 2.7 and 12.2 additional cases of fatal and nonfatal PE per 1,000 patients.

Resource use
The cost of proximal CUS was considered low.

Recommendation 10
The Saudi Expert 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 pretest probability of first lower extremity DVT, should we use D-dimer (ELISA) instead of proximal CUS as the initial test for the diagnosis of DVT?

Summary of findings
Ruling out patients with negative D-dimer, only 10 patients per 1,000 tested would be incorrectly classified as not having DVT. However, 374 patients would be discharged with no need of a further test.[4] With proximal CUS, 16 patients per 1,000 tested would be incorrectly classified as not having DVT.[4] On the other hand, 18 patients would be incorrectly classified as having DVT.[4]

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 Saudi Expert Panel suggests the use of D-dimer (ELISA) instead of 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 D-dimer test (ELISA), should we perform proximal CUS instead of discharge with no additional evaluation?

Summary of findings
Ruling out DVT with a negative D-dimer, 10 per 1,000 tested patients would be incorrectly classified as not having DVT. 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 nonfatal PE, respectively, among the false negatives per

1,000 tested patients (Moderate quality of evidence). Ruling out patients with sequential D-dimer and proximal CUS, only 1 per 1,000 tested patients would be the false negative (post-test probability = 0.27%). However, the number of false positives would increase to 8 per 1,000 tested patients. This would lead to an increase of 0.02 deaths and 0.2 nonfatal major bleeding events per 1,000 tested patients (Low quality of evidence).

Resource use
Performing proximal CUS in these patients would increase costs such that 374 additional ultrasounds would be needed per 1,000 patients initially tested.

Recommendation 12
The Saudi Expert Panel recommends no additional investigation over additional investigation with proximal CUS in patients with moderate pretest probability of first lower extremity DVT and negative 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 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, 0.2-4.4%) (Moderate quality of evidence).[38] In patients with moderate pretest clinical probability and positive D-dimer test, the probability of having DVT after a negative CUS is 3.36% and after a positive CUS is 93.49%. Per 1,000 patients initially tested, 10 patients without DVT would be treated and 15 patients with DVT would be discharged. Misdiagnosing would lead to additional 0.23 deaths, 1.08 cases of nonfatal PE and fewer 0.11 major bleeding episodes per 1,000 patients (low level of evidence).

Resource use and other considerations
Please refer to those described for question 6.

Recommendation 13
The Saudi Expert Panel recommends performing proximal CUS instead of venography in patients with moderate pretest probability of first lower extremity DVT and positive 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 negative D-dimer test (ELISA), should we repeat proximal CUS in 1 week instead of rule out without additional investigation?

Summary of findings
For single proximal CUS testing, as described in question 10, 16 per 1,000 tested patients 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 nonfatal PE per 1,000 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, 0.4-2.5%) and 0.6% (95% CI, 0.4-0.9%) (Moderate quality of evidence).[39-41] It would represent 1-2 false negatives per 1,000 patients, resulting in additional 0.02-0.04 and 0.07-0.14 fatal and nonfatal PE, 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 1,000 tested patients.

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 Saudi Expert Panel suggests no additional investigation instead of repeat proximal CUS in patients with a moderate pretest probability of first lower extremity DVT and negative initial proximal CUS and negative D-dimer test (ELISA). (Weak recommendation, Low quality of evidence).

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

Summary of findings
In patients with moderate pretest clinical probability and positive D-dimer test, the probability of having DVT after a negative CUS is 3.36%. Hence, 16 will be discharged per 1,000 tested patients. Due to misdiagnosing, we would have additionally 0.25 deaths due to PE and 1.15 cases of nonfatal PE per 1,000 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 positive D-dimer and serial CUS negative was 0% (95% CI, 0 to 3.1%) (Moderate quality of evidence).[39]

Resource use
Performing proximal CUS in patients with moderate clinical pretest probability and negative D-dimer would increase costs such that 616 additional CUS would be needed per 1000 tested patients.

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 Saudi Expert Panel suggests repeating proximal CUS in one week over no additional investigation in patients with moderate pretest probability of first lower extremity DVT and initial negative proximal CUS and positive 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 additional 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, 0.2-4.4%) (Moderate quality of evidence).[38] Among patients with initial positive proximal CUS, 16 per 1,000 patients would be incorrectly classified as not having DVT. Treating them unnecessarily would result in 0.05 deaths and 0.34 major bleeding episodes (0.02 intracranial) per 1000 tested individuals (Low quality of evidence).

Resource use and other considerations
Please refer to those described for question 6.

Recommendation 16
The Saudi Expert Panel recommends no additional investigation, instead of 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 17-24 are related to the diagnostic strategy of DVT in patients with high clinical pretest probability of first lower extremity DVT. Figure 4 summarizes the diagnostic recommendations.

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

Summary of findings
Using D-dimer (ELISA) test, 32 per 1,000 tested patients 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 nonfatal PE, respectively, per 1,000 tested patients (Moderate quality of evidence).

Resource use
The cost of ELISA D-dimer assay was considered low.

Recommendation 17
The Saudi Expert 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?
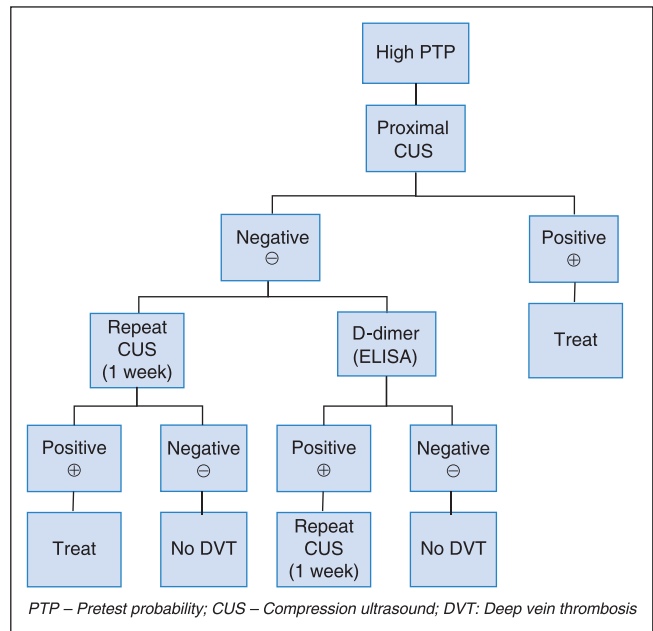

Figure 4: Recommendations for evaluation of suspected first lower extremity DVT in patients with high pretest probability

Summary of findings
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). The sensitivity tends to be higher in individual with higher pretest probability of DVT. Fifty one per 1000 patients 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 nonfatal PE, respectively, per 1,000 patients tested (Moderate quality of evidence).

Resource use
The cost of proximal CUS was considered low.

Recommendation 18
The Saudi Expert 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 and positive proximal CUS, should we perform proximal venography instead of treatment without additional investigation?

Summary of findings
Among individuals with high pretest probability, 10 per 1,000 tested patients with proximal CUS would be incorrectly classified as having DVT.[38] Treating these patients unnecessarily would result in 0.03 deaths and 0.22 major bleeding episodes (0.01 intracranial) per 1,000 tested individuals (Moderate quality of evidence).

Resource use and other considerations
Please refer to those described for question 6.

Recommendation 19

The Saudi Expert Panel recommends no additional investigation, instead of 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 negative initial proximal CUS, should we repeat proximal CUS instead of rule out without additional investigation?

Summary of findings

In single proximal CUS testing, 51 per 1,000 tested patients 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 nonfatal PE per 1,000 patients tested. For serial CUS in patients with high clinical pretest probability, four studies were identified and found a pooled DVT prevalence of 36.4% with probability of DVT post-negative serial CUS of 0.9% (95% CI, 0.2-2.8%).[41-44] This would represent 3 patients per 1,000 tested. Not treating these individuals would result in additional 0.05 fatal and 0.22 nonfatal PE episodes (Moderate quality of evidence).

Resource use

Repeating proximal CUS in patients with high clinical pretest probability and initial CUS negative would increase costs such that 511 additional ultrasounds would be needed per 1,000 tested patients.

Recommendation 20

The Saudi Expert Panel recommends repeating proximal CUS in 1 week instead of no additional investigation 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 use D-dimer test (ELISA) instead of rule out without additional investigation?

Summary of findings

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 nonfatal PE, respectively, per 1,000 patients tested (Moderate quality of evidence). Among those individuals with negative initial proximal CUS and negative D-dimer (ELISA), only 3 per 1,000 tested patients 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 nonfatal PE, respectively, per 1,000 tested patients. However, 301 patients would present a positive D-dimer test, requiring additional evaluation (Low quality of evidence).

Resource use

With this strategy, 511 D-dimer tests would be required per 1,000 patients. The costs of D-dimer and proximal CUS were considered low.

Recommendation 21

The Saudi Expert Panel recommends additional investigation with D-dimer (ELISA) instead of no additional investigation 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 D-dimer test (ELISA) and negative CUS, should we repeat proximal CUS instead of venography?

Summary of findings

After a negative contrast venography, the probability of having recurrent VTE during 3 months of follow-up is 1.2% (Moderate quality of evidence).[38] 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, 0.1-12.5%) (Low quality of evidence).[45] It would represent 17 patients per 1,000 tested; not treating these individuals would result in additional 0.27 fatal and 1.22 and nonfatal PE episodes (Low quality of evidence).

Resource use and other considerations

Please refer to those described for question 6.

Recommendation 22

The Saudi Expert Panel recommends repeating proximal CUS in 1 week over performing venography in patients with a high pretest probability of first lower extremity DVT, negative initial proximal CUS, and positive 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 additional investigation?

Summary of findings

After a negative contrast venography, the probability of having recurrent VTE during 3 months of follow-up is 1.2% (95% CI, 0.2-4.4%) (Moderate quality of evidence).[38] After negative serial CUS in patients with high clinical pretest probability, the estimate probability of DVT is 0.9% (95% CI, 0.2-2.8%) (Moderate quality of evidence).[41-44]

Resource use and other considerations

Please refer to those described for question 6.

Recommendation 23

The Saudi Expert Panel recommends no additional investigation instead of 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 D-dimer test (ELISA) and negative proximal CUS, should we perform venography instead of rule out without additional investigation?

Summary of findings

As described in question 6, after a negative contrast venography, the probability of having recurrent VTE during 3 months follow-up is 1.2% (95% CI, 0.2-4.4%) (Moderate quality of evidence).[38] As reported in question 21, among those individuals with negative initial proximal CUS and negative D-dimer (ELISA), only 3 per 1,000 tested patients 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 nonfatal PE, respectively, per 1,000 tested patients (Low quality of evidence).

Resource use and other considerations

Please refer to those described for question 6.

Recommendation 24

The Saudi Expert Panel recommends no additional investigation instead of 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).

Discussion

A standardized diagnostic strategy for suspected DVT is crucial to prevent the complications of no treatment and to avoid the risks of unnecessary anticoagulation. This clinical practice guideline is the result of an initiative of the Saudi Ministry of Health to promote the practice of evidence-based medicine across the KSA, applies mainly to the ambulatory setting (i.e., outpatient or emergency department) and targets primary care physicians, specialists in Internal Medicine and Emergency Medicine. It is expected to reduce health inequities in Saudi Arabia. It should be noted that no guideline or recommendation can take into account all of the often-compelling unique features of individual clinical circumstances. Hence, clinicians, patients, third-party payers, institutional review committees, other stakeholders, or courts should never view these recommendations as dictates. Additionally, the values and preferences of individual patients should be taken into consideration in the diagnostic process of DVT.

When developing this guideline, the Saudi expert panel considered the availability of DVT diagnostic tools in the different regions of KSA. It was considered that CUS and highly sensitive D-dimer by ELISA are widely available in KSA, but the panel recommends that the Ministry of Health should ensure the availability of these resources. The Saudi Expert 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, adherence to the course of action proposed by strong recommendations could be used as quality or performance indicators. 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 Saudi expert panel also 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.

Finally, the Saudi expert panel suggests local research on the values and preferences of the Saudi population regarding the relative value of preventing DVT with anticoagulants versus bleeds, and on the burden of treatment with antithrombotic agents and performance of economic evaluations of the different strategies for DVT diagnosis.

Acknowledgments

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