Survey on D-dimer utilization in the diagnosis of venous thromboembolism (VTE)

Dear Colleague,

Thank you very much for returning the questionnaire **on D-dimer utilization in the diagnosis of venous thromboembolism (VTE)** which you received in summer/autumn 2012.

Attached below is a national feedback report that presents the distribution of the results from all participants in your country compared to the results from all participants in the study (7 European countries altogether). The report includes an update on guidelines/recommendations on the use of D-dimer test in patients with suspected pulmonary embolism (PE) and deep venous thrombosis (DVT).

Best regards,
On behalf of the organisers,

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Project leader   Chair of the EFLM-EQALM Working group on
                                                     Postanalytical phase and national coordinator

Personal and Practice particulars:

In Hungary, all members of the National Society of Emergency Medicine with a registered email address (n=203 physicians) received an invitation to participate in the web based questionnaire, of which 69 responded (response rate 34%). The 2 physicians stating that they did not work with patients with suspected venous thromboembolism (VTE) and 3 who did not fill in the questionnaire were excluded. Of the 64 included physicians, the majority worked within emergency medicine (n= 26, 40.6%), internal medicine (n=20, 31.3%) or intensive care (n=12, 18.8%), but a few physicians did not state speciality or worked within other specialities (n=6, 10.2% altogether). Within the group of emergency medicine, intensive care and internal medicine physicians, 71.9% were specialists (n=46), 18.8% were non-specialists (n=12) and the rest did not give this information. Specialists handled patients with suspected VTE somewhat more often than the non-specialists, and clinical decision rules to estimate the probability of PE or DVT by clinical signs and symptoms (pre-test probability estimation) were also used more often among specialists (81.2%) than among non-specialists (50%). The only used clinical decision rules among the responders were the Wells scores for DVT and PE and the Geneva score for PE.

Case history A:

Slightly overweight 48-year-old female smoker with acute dyspnoea, tachycardia (heart rate 102/min) and chest pain has been admitted to the Emergency Unit. The patient has no known comorbidity, takes no medication regularly and has no previous surgery or immobilisation. At physical examination her blood pressure is slightly elevated 145/85 and her heart rate is 102/min. Her left lower extremity is slightly swollen and slightly tender on palpation. Arterial blood gas analysis showed PaO2 10.1 kPa (reference 11-13 kPa), otherwise the blood gas analyses are normal. Chest X-ray was normal and acute myocardial infarction was excluded by ECG and cardiac biomarkers.

Question 1. Do you think she has pulmonary embolism based on the information in the case history?
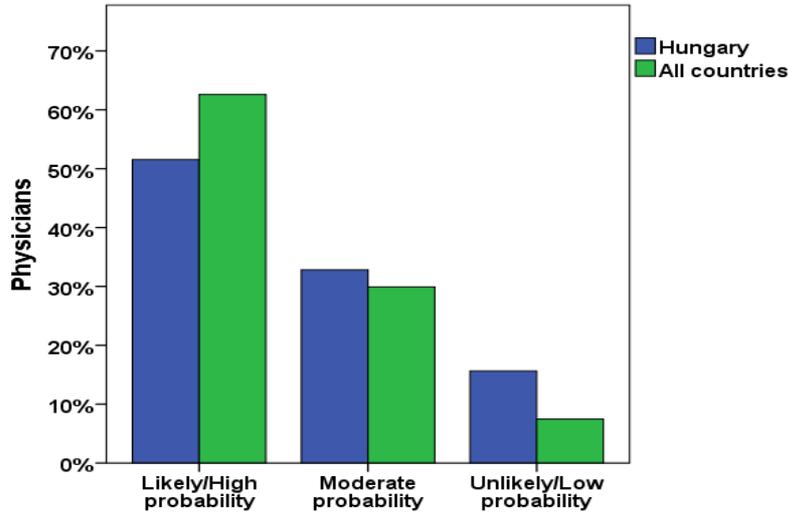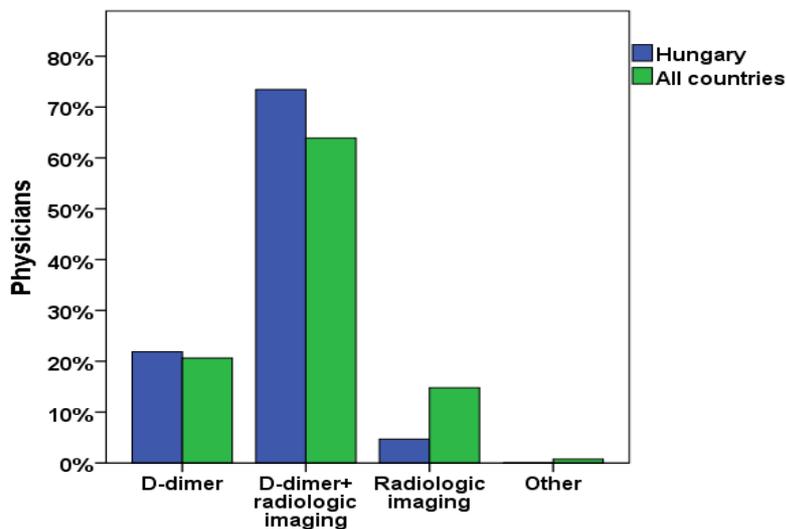

Question 2. What do you suggest her probability of pulmonary embolism is in percent?
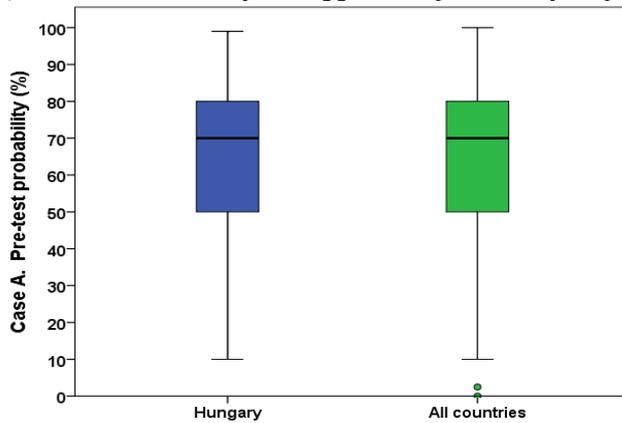
Explanation to box-plots: The horizontal lines in the boxes represent the medians. The lower and upper edges of the boxes are the 25th and 75th percentiles, respectively, and therefore 50% of the responses are included in the box. The vertical lines going out of the box represents the range of responses, except outliers and extremes which are outlined by the blue circles and asterisks.

Question 3. What would you do in this situation?

Question 4. Your colleague had already requested a D-dimer, and you receive the results before you have ordered any diagnostic tests: D-dimer concentration 0.45 mg/L (cutoff 0.5 mg/L).
After this result, what do you suggest her probability of pulmonary embolism is?
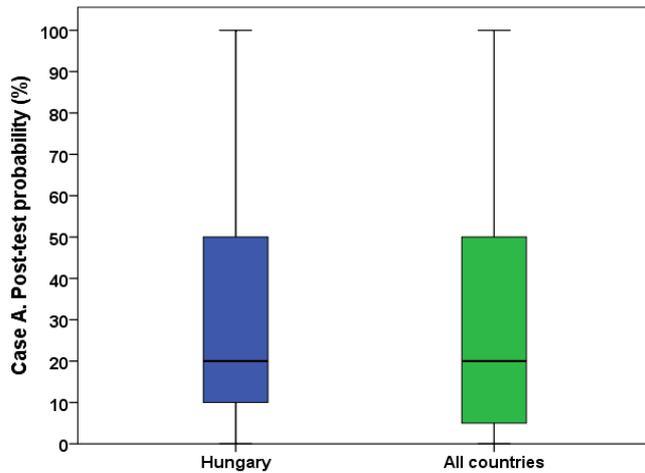
Question 5. What would you do after receiving the normal D-dimer result?
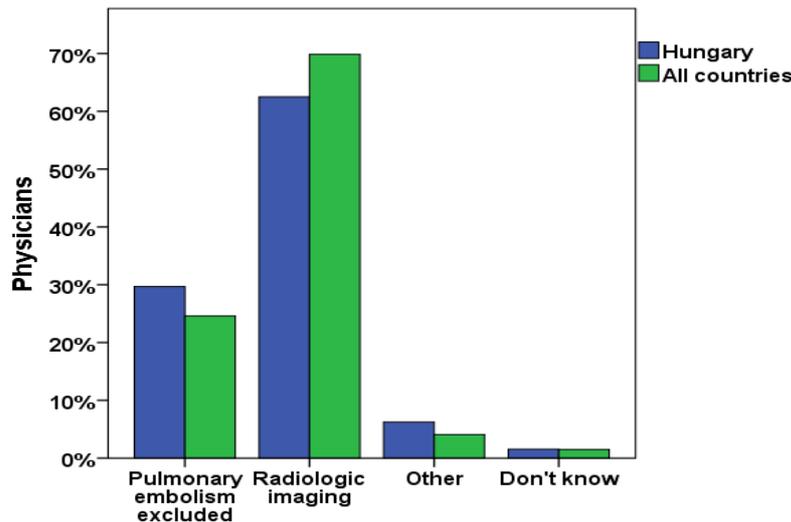
Comments to patient A.

Diagnostic work-up in a patient with suspected pulmonary embolism (PE)
When evaluating a patient with suspected PE, without shock or hypotension (non-high risk), it is recommended first to estimate the probability of PE by clinical signs and symptoms (pre-test probability estimation of PE) (1-4). This can be performed either by clinical experience or by using standardised clinical decision rules for PE, e.g. the Wells score or the Geneva rule, by which patients are classified into low, moderate and high probability of PE – or alternatively "unlikely" and "likely" PE (2). The use of two-level clinical decision rules (likely versus unlikely PE) is supported since further diagnostic work-up based on three level clinical decision rules requires knowledge of the D-dimer test that is seldom known by clinicians (3). The different clinical decision rules for PE show similar clinical performance (5, 6).
The rationale behind estimating the pre-test probability is to separate the patients with 1) low or moderate probability of PE or unlikely PE from those with 2) high probability or likely PE, to be able to select a safe and efficient diagnostic work-up. A negative D-dimer result in patients belonging to the first group (low/moderate or unlikely) can rule out PE without further diagnostic work-up. In those belonging to the second group (high or likely) or in those with a positive D-dimer in the first group,

further diagnostic work-up (e.g. computer tomography pulmonary angiography) should be performed to diagnose or exclude PE (1-4). D-dimer should not be requested in patients with high/likely probability of PE. In this group, the probability of PE after a negative D-dimer (the post-test probability) is still too high (about 10% (7)) to exclude PE (6, 8, 9). D-dimer should therefore never be analysed before the probability of PE is estimated by using clinical signs and symptoms (7-9). D-dimer testing in this group is also a waste of resources.

By using the recommended strategy, PE can be ruled out without diagnostic imaging in about 40% of the patients where PE is suspected (2, 5), while only about 1% of the patients are diagnosed with PE during 3 months follow-up (6).

Question 1 and 2: Patient A has a high pre-test probability for PE (likely PE) when estimating the probability by clinical decision rules. In patients with a high pre-test probability or likely PE, the probability of PE has been shown to be about 65%, while it is about 30% in moderate probability patients and 10% in low probability (unlikely PE) patients (2).

Question 3, 4 and 5: Since patient A has a high probability of PE (likely PE), she should be referred for radiologic imaging independently of the D-dimer result, and D-dimer testing is not indicated (1, 2). A clinical pre-test probability assessment should always be done prior to D-dimer testing to decide upon further diagnostic work-up. A negative D-dimer result, without prior pre-test probability estimation of PE, might put the patient which actually has PE (as in patient A, question 4), at a significant risk if PE is excluded without further imaging (7).

Case history B:

A 19-year-old woman is admitted to the emergency unit and complains about pain in her left leg. The pain started when she was out running the morning before. The pain is worse today. She mentions that her 75 year old grandmother has had a deep venous thrombosis recently, and she is afraid she also has a deep venous thrombosis (DVT). She has not heard of any other family members suffering from venous thromboembolism. She is a non-smoker, and she does not use oral contraceptives. On clinical examination you find a slight tenderness when pressing deeply right below the popliteal area, otherwise your clinical examination is normal.
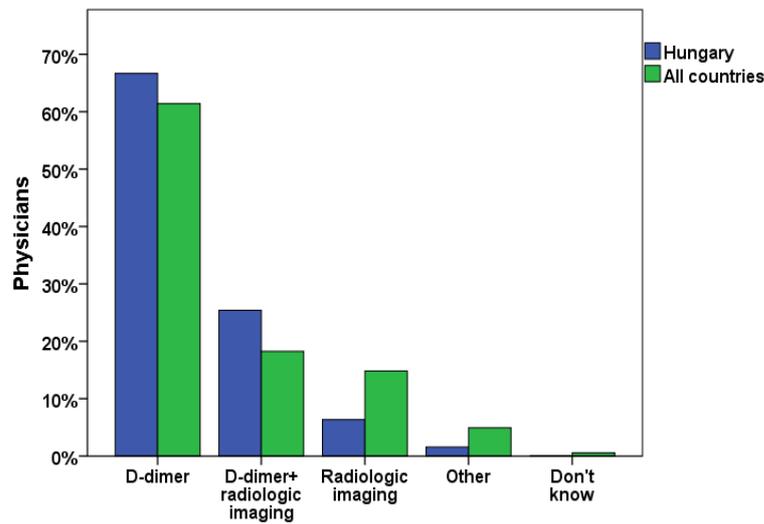
Question 6. Do you think she has a deep venous thrombosis (DVT) based on the information in the case history?
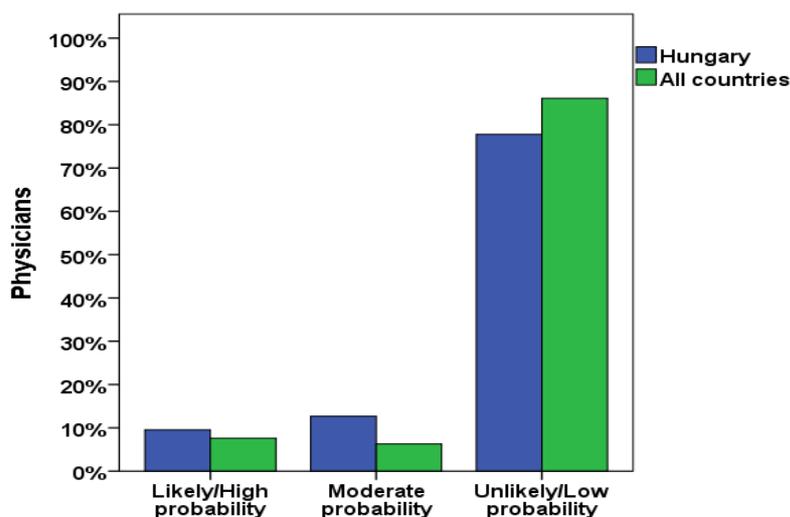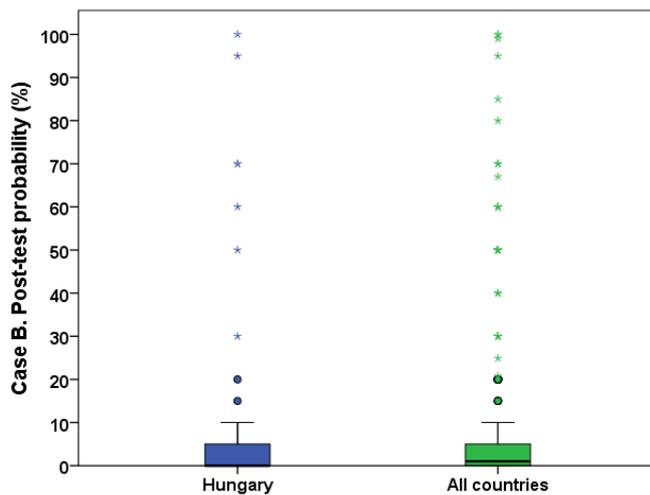
Question 7. What do you suggest her probability of DVT is in percent?
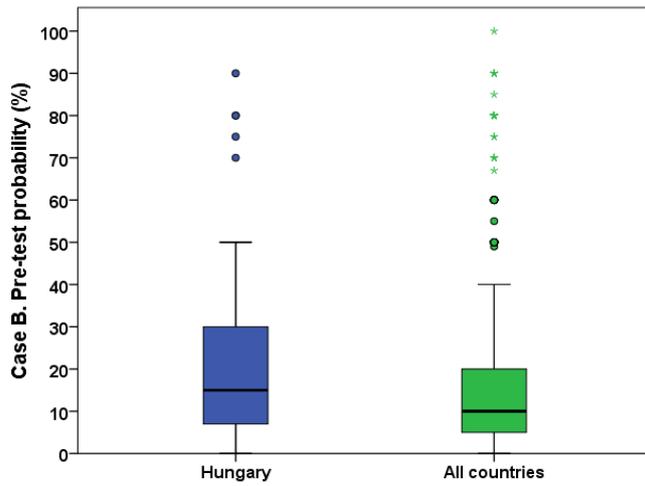
Question 8. What would you do to confirm or exclude DVT in this situation?

Question 9. D-dimer was already requested by your colleague, and the D-dimer concentration was 0.31 mg/L (cut-off 0.5 mg/L). What do you suggest the probability of DVT is now (in percent)?

Question 10. What would you do after receiving the normal D-dimer result?
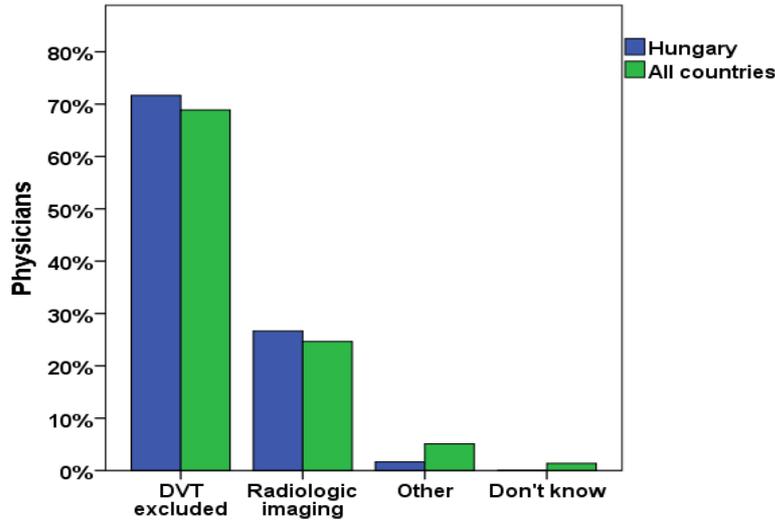
Question 11. If you excluded DVT in the question above, how high should the D-dimer concentration be for you to request radiologic imaging? (cut-off 0.5 mg/L)
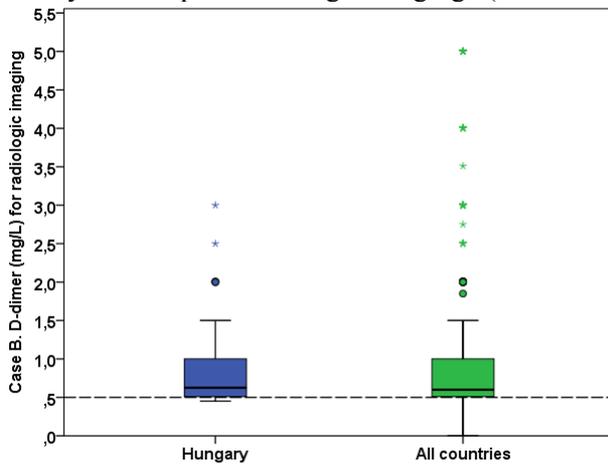
The stipulated line represents the D-dimer cut-off value of 0.5 mg/L. The most extreme D-dimer values for all countries are excluded (one of 20 mg/L, one of 15 mg/L and four of 10 mg/l) to make figure more readable.

Question 12. In a similar patient, the D-dimer concentration was 1.85 mg/L (cutoff 0.5 mg/L). What do you think the probability of DVT is in this patient (in percent)?
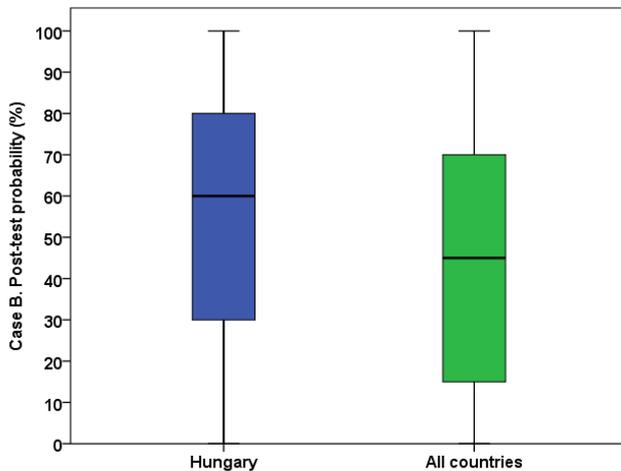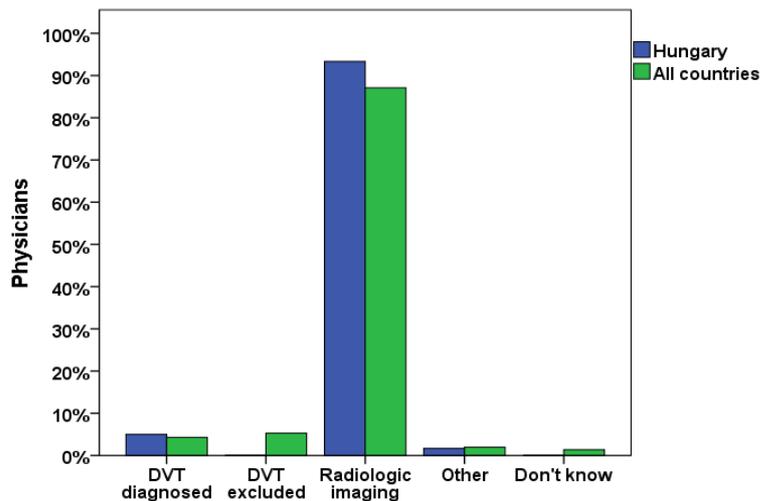
Question 13. What would you do after receiving the pathological D-dimer result?

Comments to patient B.

Diagnostic work-up in a patient with suspected deep venous thrombosis (DVT)

When evaluating a patient with suspected DVT, it is recommended to estimate the probability of DVT by clinical signs and symptoms (pre-test probability estimation of DVT), as described above for PE, to guide the further diagnostic process (1, 3, 10, 11). This can be performed either by clinical experience or by using standardised clinical decision rules for DVT, e.g. the Wells score, by which patients are classified into low, moderate and high probability of DVT – or alternatively unlikely and likely DVT (10). The use of two-level clinical decision rules (likely versus unlikely VTE) should be supported because of the same reason described in diagnostic work-up of PE (3).
The rationale behind estimating the pre-test probability is also the same, to separate the patients with 1) low or moderate probability of DVT or unlikely DVT from those with 2) high probability or likely DVT, to be able to select a safe and efficient diagnostic work-up. A negative D-dimer result in patients belonging to the first group (low/moderate or unlikely) can rule out DVT without further diagnostic work-up resulting in exclusion of DVT in about 40% of the patients without using radiologic imaging (12). In those belonging to the second group (high or likely) or in those with a positive D-dimer in the first group, further diagnostic work-up (e.g. compression ultrasound) should be performed to diagnose or exclude DVT (1, 3, 10, 12). D-dimer should not be requested in patients with high/likely probability of DVT. In this group, the probability of DVT after a negative D-dimer (the post-test probability) might be too high to exclude DVT (8). D-dimer should therefore never be analysed before the probability of PE is estimated using clinical signs and symptoms (8, 9). D-dimer testing in patients with high/likely probability of DVT is a waste of resources.

Question 9 and 10: Patient B has a low pre-test probability of DVT (unlikely DVT) when estimating the probability by clinical decision rules. In patients with a low pre-test probability or unlikely DVT, the probability of DVT has been shown to be 5 - 6% (95%CI 4 – 8%), whereas it is about 17% (13 – 23%) in moderate probability and 53% (44 – 61%) in high probability (likely) patients (12).

Question 11, 12 and 13: In patient B, with a low pre-test probability for DVT (unlikely DVT), and no comorbidity[1], D-dimer testing should be performed before other diagnostic work-ups (10). No further diagnostic work-ups for DVT are needed in such a patient after a negative D-dimer (1, 10), i.e. DVT can be excluded. The post-test probability of DVT in a patient with low pre-test probability (unlikely DVT) and a negative D-dimer is about 1% (rate of false negatives in D-dimer testing), which is very

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[1] In patients with comorbidities which increase the D-dimer value without a DVT (e.g. infections, trauma or post-surgery) or in pregnancy, D-dimer testing is generally not recommended as a part of the diagnostic work-up (1).

similar to the rate of false negatives seen after alternative diagnostic tools; i.e. compression ultrasonography (1, 10-12).

Question 11: The cut-off for the D-dimer method in use in the case history was 0.5 mg/L, and if patient B (unlikely DVT) has a D-dimer result above 0.5 mg/L, she should be referred for radiologic imaging to confirm or exclude DVT (3, 10). A strategy where the D-dimer cut-off is increased with decreasing pre-test probability has been proposed to increase the diagnostic efficacy (13, 14), but this strategy has not been fully evaluated.

Question 12 and 13: A positive D-dimer cannot be used to predict the probability of DVT or to diagnose DVT. Further diagnostic work-up with radiologic imaging to exclude or confirm DVT is therefore recommended (3, 10).

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