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Diagnosis of Deep Vein Thrombosis : How Many Tests Do we Need ?

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Key words. Deep vein thrombosis ; D-dimer assay ; ultrasonography ; clinical score.

Abstract. The requirement for a safe diagnostic strategy should be based on an overall post-test incidence of venous thromboembolism (VTE) of less than 1% during 3 month follow-up. Compression ultrasonography (CUS) has a negative predictive value (NPV) of 97 to 98% indicating a post-CUS incidence of deep vein thrombosis (DVT) of 2 to 3%. A post-CUS DVT incidence of 3% implicates that 90 to 120 DVTs per 1 million inhabitants will be overlooked each year indicating the need to improve the diagnostic work-up of DVT as much as possible. The qualitative D-dimer test (SimpliRed) has a sensitivity of 82 to 89% and a negative predictive value of 94 to 95% indicating a 5 to 6% post-test incidence of DVT, which is not sensitive enough for venous thrombosis exclusion. The post-test DVT incidence could be reduced from 3.2% to 0.6% in one study and from 11% to 2% in another study by the combination of a normal CUS and low clinical score and from 4,5% to 1.6% by the combination of low clinical score and a negative SimpliRed test in one study. The combination of a negative CUS and a negative SimpliRed test reduced the post-test incidence of DVT from 2.6% to < 1% or even < 1‰ in two management studies without the need of a repeated CUS on the basis of which anticoagulant therapy can safely be withheld. The rapid quantitative turbidimetric D-dimer assay (Tinaquant) has a sensitivity and a negative predictive value (NPV) of 97.7% with a 2.3% post-test incidence of DVT. The combination of a normal Tinaquant D-Dimer test result plus a low to moderate clinical score reduces the post-test incidence of DVT from 2.3 to 0,6% without the need of CUS testing in 29% of patients with suspected DVT. The rapid ELISA VIDAS D-dimer assay has a sensitivity and NPV of 98,6 and 99.5% in two management studies for the exclusion of DVT irrespective of clinical score. The combination of a normal ELISA VIDAS D-Dimer test with clinical score assessment will reduce the post-test DVT incidence of less than 0.5% and the need for CUS testing by 40 to 50%. It is concluded that the sequential use of a rapid quantitative D-dimer test, clinical score and CUS appears to be safe and the most cost-effective diagnostic work-up of DVT.

Introduction

The annual incidence of a first episode of deep venous thrombosis (DVT) has been estimated at 2 to 4 per 1000 inhabitants per year (1, 2). This suggests that about 3.000 to 4.000 patients per 1 million inhabitants are to be investigated each year for suspected DVT. Accurate probability estimates by the use of a clinical model and objective testing for exclusion or detection of DVT are of huge importance, because proximal DVT is life threatening and can be treated effectively. The requirements for a safe diagnostic strategy should be based on an overall post-test incidence of VTE of less than 1% during 3 month follow-up (1, 2). A post-test incidence of DVT of 1% = 10‰ implicates that 10 × 3 to 4 = 30 to 40 DVTs per 1 million inhabitants are still be overlooked each year. This article reviews the non-invasive strategies to exclude and diagnose DVT.

Diagnosis and exclusion of DVT by phlebography

Phlebography is the reference gold standard for research studies to exclude and diagnose proximal DVT and calf vein thrombosis. Phlebography has two main disadvantages : it is invasive and the phlebogram will be inconclusive in 4 to 12% of cases. A normal venogram of the leg veins in patients with suspected DVT excludes both proximal and distal deep vein thrombosis irrespective of clinical score on the basis of which anticoagulant treatment can safely be withheld. In a prospective study of 160 patients with suspected DVT and a normal venogram, three patients (1.9%) developed non-fatal venous thromboembolic complications with a few days to weeks (3). This indicates that a normal venogram has a negative predictive value of 98.1% (Table 1). These data are very close to our working hypothesis for the requirement of a consensus strategy, which should be

Tabel I

Results for the exclusion of deep vein thrombosis in management studies of outpatients with suspected deep vein thrombosis

Management study	Number of patients with negative test	Negative predictive value : NPV	Specificity
Venography negative (3)	160	98.1%	100%
First CUS negative (5, 6)	1304 311	98.3% 97.1%	98-100% 98-100%
Serial CUS negative (5, 6)	1615	99.4%	98-100%
Negative SimpliRed : against CUS (17) against venogram (18)	1075 214	82,6% 89%	70% 77%
Low clinical score / negative SimpliRed (17)	313	98.4%	29%
CUS negative plus low clinical score (10, 14)	609 250	99.7% 98%	56% 51%
CUS negative plus negative SimpliRed (13, 14)	1348 231	99.3% 100%	61% 64%
CUS negative plus VIDAS < 1000 ng/ml	675	99.3%	68.1%
A normal ELISA VIDAS (21, 22)	129 197	98.6% 99.5%	35% 37%
Turbidimetric DD Tinaquant (23) : 1) Irrespective of clinical score 2) Clinical score low/moderate	 213 175	 97.7% 99.4	 44% 36%

The requirement for a safe diagnostic strategy should be based on an overall negative predictive valus of > 99% indicating a post-test incidence of VTE of less than 1% during 3 months follow-up (1, 2).

based on an overall post-test VTE incidence of less than 1% (1, 2). Due to its invasive nature and associated side effects, contrast phlebography has not become a routine test in daily practice for venous thrombosis and has been replaced by compression ultrasonography.

Diagnosis and exclusion of DVT by compression ultrasonography

Compression ultrasonography (CUS) has many adavantages over phlebography (1, 2). It is non-invasive, easy to repeat, free of complications and relatively inexpensive. In addition, abnormalities such as Baker's cyst or aneurysma, hematoma etc, which could mimic DVT are easily recognized by CUS but not by phlebography. Clinicians should be aware of the two main disadvantages of CUS. First, isolated thrombi in the iliac and superficial femoral veins within the adductor canal are rare but difficult to detect and therefore easily overlooked in clearcut symptomatic patients with suspected DVT. Second, calf vein thrombosis (CVT) will be overlooked by CUS, because it is safe to limit CUS estimation to the popliteal and femoral veins for the diagnosis of symptomatic proximal DVT[6]. The most accurate and single criterion for the presence of proximal DVT is noncompressibility of the popliteal and femoral vein under gently probe pressure (compression ultrasonography : CUS).

In 1072 outpatients with a first suspicion of DVT from 5 large management studies, the incidence of DVT on a phlebogram ranged from 26 to 46% for proximal DVT and from 4 to 10% for CVT (1, 2). Only about a fourth of CVT extends into the proximal veins within a few days to 1 week. Therefore, it can be calculated that after a first negative CUS, a second CUS will become positive in only 2 to 3% within one week because of extension of CVT into proximal deep veins. Two large management studies indeed showed that the post-test incidence of venous thromboembolism (VTE) after a negative 1st CUS in outpatients with suspected DVT was very low, 1.7 and 2.9% respectively (Table 2) (5, 6). A post-CUS DVT incidence of 3% = 30‰ implicates that 30 × 3 to 4 = 90 to 120 DVTs per 1 million inhabitants will be overlooked each year. A 2nd CUS on day 7 was positive in 1.1 and 2.3% respectively and 0.6% slipped through the two CUS examinations in both studies to present VTE within 3 months (table 2)5,6. Thus, the real contribution of serial CUS testing in outpatients with a 1st negative CUS is a slight reduction of the posttest incidence of VTE from 2-3% to less than 1% (Tables I and II). Serial CUS testing

Table II

Results of serial CUS testing in two prospective management studies of symptomatic outpatients with a first suspicion of deep venous thrombosis

Management study, reference Number of patients :	COGO 1998 (5)	BIRDWELL 1998 (6)
CUS day 1	1703 (100%)	405 (110%)
CUS pos day 1	400 (23%)	63 (16%)
CUS neg day 1	1304 (77%)	342 (84%)
Repeated CUS day 7	1271 (75%)	311 (77%)
Repeated CUS pos day 7	12 = 1%	7 = 1.4%
PE within 1 week	1 PE 1 PE[+]	–
Serial CUS neg and no anticoagulation	1259 (74%)	304 (75%)
VTE during 3 months follow-up :	7 DVT 1 PE	1 DVT 1 PE
Post-test VTE incidence	0.7%	0.6%
CUS positive and anticoagulation	no data	70
Recurrence VTE	no data	4 VTE

is safe but you have to repeat 100 CUSs to find 1 or 2 CUS positive for DVT, which is not cost-effective.

As the negative predictive value of a normal first CUS is 97 to 98% (Table 1), the central question is whether a second CUS can be restricted to those with persistent symptoms or should be routinely be performed in all of them. In a large retrospective study of 1111 patients with a negative first CUS followed by a second CUS restricted to a small group of 132 patients with persistent symptoms for 48 and 72 hours, the overall post-test VTE incidence during 3 to 6 months follow-up was 0.9% indicating a negative predictive value of 99.1% (7). Therefore, it has become daily practice by experienced clinicians that a significant number of outpatients with a normal initial CUS and minor or atypical symptoms suspicious of DVT do not undergo repeated CUS within a week, except when signs and symptoms persist or increase (1, 2).

The rehabilitation of clinical score assessment in the diagnosis and exclusion of DVT

Landefeld identified five clinical findings, which could be independently related to positive venograms for proximal DVT by linear discriminant analysis : swelling of the leg below or above the knee, measurement of calf circumference difference of both lower legs, immobility and cancer (8). In the group of patients with none, one and two or more of these clinical findings, phlebographically proven DVT was present in 5%, 15% and 42% respectively (8). Landefeld introduced the concept that a reasonable clinician might defer further testing for proximal DVT when the probability of proximal DVT is 1% or less and institute long-term anticoagulant therapy when the probability of proximal DVT is higher than 90% (8). WELLS *et al.* extended the concept of Landefeld and developed a simple clinical model to stratify pretest clinical probability for DVT into low, moderate and high risk groups of having proximal DVT (9, 10). Based on a checklist of 8 clinical features (Table III), pretest clinical probability (clinical score) for proximal DVT could be estimated as low, moderate and high (5, 6, 7). Fifty-six percent, 30% and 18% of 1122 patients with suspected DVT belonged to the low, moderate and high clinical score group respectively (Table IV). The incidence of proximal DVT in the low, moderate and high clinical score groups was 3.8, 18 and 76% respectively (9, 10). As the incidence of DVT in the low clinical score group is 3.8% testing by a first CUS for the exclusion or diagnosis is still warranted. The combination of a negative CUS and low clinical score (asymptomatic) excluded DVT with a post-CUS prevalence of VTE of 0.3%, thus obviating the need for serial CUS testing (Tables 1 and 4). This comprises about 50 to 60% of the patients with suspected DVT. Patients with a negative CUS and moderate to high clinical score have a post-CUS incidence of VTE of 3.6% and 31% respectively and therefore candidates for repeated CUS testing (Table 4). The strategy in figure 1 of the combined use of CUS and clinical score reduced the number of repeated CUS testing by 63% in the study of Wells (Table 4) (9, 10).

Pitfalls of clinical score assessment in the diagnostic work-up of DVT

Estimates of clinical score as low, moderate and high for the probability of proximal DVT should be used as the first step followed by choosing proper diagnostic tests to

Table III

Clinical score list for predicting pre-test probability for proximal DVT (9, 10)

Clinical feature	score
Active cancer treatment ongoing or within previous 6 months or palliative	1
Paralysis, paresis or recent plaster immobilization of the lower legs	1
Recent immobilization for more than 3 days or major surgery within last 4 weeks	1
Localized tenderness/pain along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by more than 2 cm when compared with the asymptomatic leg (measured 10 cm below tibial tuberosity)	1
Pitting edema greater in the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Total score :	……
Alternative diagnosis as likely or greater than DVT	-2*
Wells Clinical score : 0 = low, 1 or 2 = moderate, and 3 or more = high	

* A significant number of alternative diagnoses like Bakers cyst, hematoma etc can only be made by CUS and a large number of alternative diagnoses simulating the clinical picture of DVT can best be confirmed by exclusion of DVT by CUS. Therefore, elimination of score minus 2 for an alternative diagnosis as likely or greater than DVT surely will improve the reproducibility of the clinical score assessment (11).

Table IV

Contribution of the Wells clinical score assessment in the diagnostic work-up of deep vein thrombosis (DVT) in outpatients with suspected DVT

WELLS *et al.*[9,10]	1122 outpatients with suspected DVT			
Clinical score DVT	low	moderate	high	Total
Number of patients (N)	630 56%	336 30%	156 14%	1122 100%
Prevalence of proximal DVT on CUS : N	21 3.8%	61 18%	118 76%	200 18%
No DVT at first CUS	609	275	38	922
Post-CUS prevalence of VTE	0.3%	3.6%	31%	
Need for repeated CUS testing	no	yes	yes	

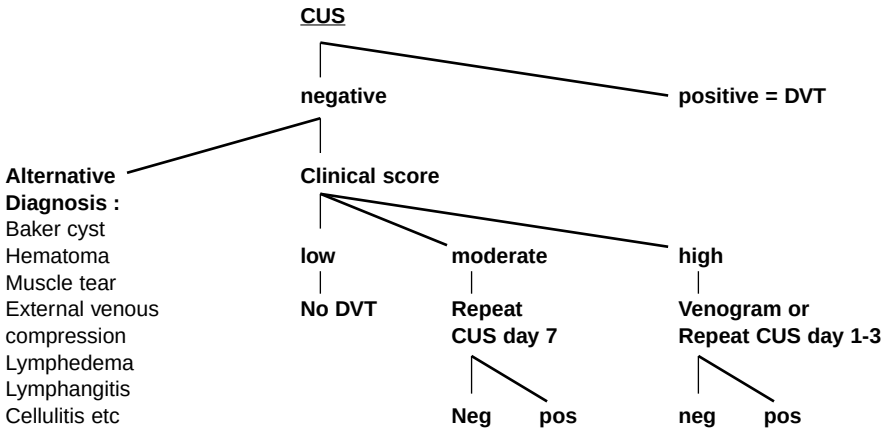

Fig. 1

Exclusion of DVT by the combined use of Compression Ultrasonography (CUS) and Clinical Score in outpatients with Suspected DVT (1, 2, 9, 10, 11).

Table V

Distribution of the Wells clinical score estimates of DVT and the prevalence of DVT in seven studies of outpatients with suspected DVT

Study	1	2	3	4	5	6	7
Suspicion DVT, N	1122	270	1756	811	278	273	1075
Alternative diagnosis	–	–	–	361	169	–	–
				45%	61%		
Prevalence DVT, N	200	57	440	330	82	66	200
	18%	21%	25%	40%	29%	24%	18.6%
Assigned to clinical score :							
Low	3.8%	3.2%	8%	11%	14%	9%	4.5%
Moderate	18%	19%	27%	56%	36%	19%	18.5%
High	76%	74%	66%	–	32%	51%	47.1%
Proportion of patients assigned to clinical score :							
Low	56%	47%	51%	35%	39%	23%	41.5%
Moderate	30%	36%	29%	65%*	44%	49%	39.8%
High	14%	17%	20%	–	17%	24%	18.7%

* = moderate/high

Study 1 = Wells *et al.* (9, 10), 2 = Miron *et al.* (12), 3 = Kraayenhagen *et al.* (13), 4 = Tick *et al.* (14) 5 = Cornus *et al.* (15), 6 = Constans *et al.* (16), and 7 = Anderson *et al.* (17).

exclude or diagnose DVT and to evaluate the results in prospective management studies (8, 9, 10, 11). Inclusion of a subjective estimation of the presence of an alternative diagnosis as likely or greater than DVT as score minus 2 is very surely not reproducible by inexperienced observers such as physicians in training and by a multidisciplinary group of clinicians in multicenter clinical studies (1, 2, 10, 11). The distribution of the Wells clinical score estimates of DVT and the prediction of DVT in the different clinical score groups from 7 studies of outpatients with suspected DVT is shown in table V (9, 19, 12-17). The proportion of patients with an alternative diagnosis was as high as 45% to 61% in two studies (14, 15), and was not evaluated in 5 studies (Table V). The overall prevalence of DVT in the seven studies ranged from 18% to 44% (Table V). The proportion of patients belonging to the low clinical score group was the highest (about 50%) when the overall prevalence is the lowest (< 20%) and vice versa. The prevalence of DVT in the low clinical score is the lowest (< 5%) when the overall prevalence of DVT is also low (< 21%). The prevalence of DVT ranged from 3.2% to 14% in the low clinical score group and from 18% to 56% in the moderate clinical score group (Table V). This wide variation is very probably due to the "score of minus 2" for subjective evaluation of an alternative diagnosis as or more likely than DVT. Elimination of "minus 2 score" for alternative diagnosis surely will improve the reproducibility of the Wells clinical score assessment (Table III) (11). Clinicians should be aware that a significant number of alternative diagnoses like Bakers cyst, hematoma etc can only be made by CUS and that a large number of alternative diagnoses simulating the clinical picture of DVT can best be confirmed by exclusion of DVT by CUS (11).

Exclusion of DVT by a negative CUS and a negative SimpliRed D-Dimer test

As compared to clinical score plus CUS in the EDITED study, the qualitative latex D-dimer test, SimpliRed (Agen Biomedical Ltd, Brisbane, Australia) has a sensitivity of 82.6%, a specificity of 70% and a negative predictive value of 94.5% (Tables I and VI) (17). As compared to the gold standard, venography, SimpliRed has sensitivity of 89% and specificity of 77% for the exclusion of DVT (18). These data clearly indicate that the SimpliRed is not sensitive enough for the exclusion of DVT irrespective of clinical score. Results of clinical outcome in the EDITED study of 1075 outpatients with suspected DVT show that a negative SimpliRed test reduces the prevalence of DVT from 4.5% to 1.6% in the low clinical score group (Table 6) (17). This is very near to but does not completely meet the requirement for a safe diagnostic strategy of less than 1% during 3 months follow-up (1, 2). Another and a more promising possibility is to use the SimpliRed test after a negative CUS (13, 14). Kraayenhagen *et al.* demonstrated that the combination of a 1st negative CUS and a negative SimpliRed test reduced the post-test incidence of DVT

Table VI

Results of clinical outcome after a negative SimpliRed test in the EDITED study of 1075 outpatients with suspected Deep Vein Thrombosis (DVT) (17)

	Number of patients (N)	Prevalence DVT	Negative SimpliRed N	Prevalence DVT	NPV
Overall	1075	18.6%	636	5.4%	94.5%
Clinical score					
Low	448	4.5%	313	1.6%*	98.4%
Moderate	426	18.5%	258	5.8%	94.2%
High	201	47.1%	65	23%	67%

* Out of 313 with a low clinical score 3 had DVT and 2 calf vein thrombosis for anticoagulation was given because of a positive CUS result.

Table VII

Contribution of the Wells clinical score assessment and SimpliRed in the diagnostic tract of deep vein thrombosis (DVT) in outpatients with suspected DVT

Tick *et al.* (14) Clinical score	811 outpatients with suspected DVT			
	Low	Moderate/high		Total
Number of patients	280 35%	531 65%		811 100%
Prevalence DVT on CUS	30 11%	300 56%		330 40%
Study design :				
First CUS negative	250	231 SimpliRed		481
		neg	pos	
		148	83	
Second CUS	no	no	yes	
Post-test prevalence DVT	5 2%	0 0%	9 11%	14 3%
Negative predictive value	98%	100%	–	97%

The study of Tick *et al.* (14) demonstrates that the negative predictive value (NPV) of normal CUS alone is 97%, the NPV of the combination normal CUS/low clinical score is 98% and the NPV of the combination of a normal CUS, moderate to high clinical score and negative SimpliRed is 99.3 to 100% indicating that only the combination of normal CUS and a negative SimpiRed is safe and cost-effective without the need of a CUS repeat. This conclusion is confirmed by Kraaijenhagen *et al.* in a large prospective management study (Fig. 2) (13).

from 2.6% to < 1% without the need of a repeated CUS on the basis of which anticoagulant therapy can safely be withheld, whereas patients with a negative CUS and a positive SimpliRed test are candidates for serial CUS testing (Fig. 2) (13). This strategy reduced the number of repeated CUS testing from 77% to 30%.

The study of Tick *et al.* very nicely evaluated the contribution of the Wells clinical score assessment and the SimliRed D-dimer in the diagnostic work-up of deep vein thrombosis in outpatients with suspected DVT (14). This study demonstrates 1) that the negative predictive value (NPV) of normal CUS alone is 97%, 2) that the NPV of the combination normal CUS plus low clinical score is 98% and 3) that the NPV of the combination of a normal CUS, moderate to high clinical score and negative SimpliRed is 100% (Table 7). These data confirm that the combination of normal CUS and a negative SimpiRed in figure 2 indeed is safe and cost-effective irrespective of clinical score without the need of a CUS repeat.

Exclusion of DVT by the use of a rapid quantitative D-dimer, clinical score, and CUS

As compared to the gold standard, the quantitative ELISA or ELISA-based rapid D-Dimer assays at a proper cut-off level had a sensitivity and negative predictive value of 100% for the exclusion of proximal DVT and distal calf vein thrombosis (19, 20). This implicates that a negative rapid sensitive test will safely exclude DVT without the need of CUS, and also excludes pulmonary embolism (PE). In contrast, a negative CUS only excludes proximal DVT, overlooks CVT, and does not exclude PE (1, 2).

The sensitivity of the ELISA VIDAS D-dimer (BioMérieux, Marcy l'Etoile, France) in two large prospective management studies for the exclusion of DVT was 98.4% and 99.5% respectively at a specificity of 36% (Table 1, figure 3 and 4) (21, 22). As compared to venography a normal ELISA VIDAS test result (< 500 ng/ml) is equal or even better for the exclusion of DVT irrespective of the clinical score and without the need of CUS in about one third of the patients with suspected DVT (Table 1, Fig. 3 and 4). Clinicians should be aware that no laboratory test is 100% sensitive and specific. Therefore every patients with a negative ELISA VIDAS D-Dimer test but with persistent or recurrent symptoms suspicious of DVT is a candidate for CUS to exclude a detect DVT or an alternative diagnosis (Fig. 1). MICHIELS *et al.* demonstrated that the combination of a negative CUS and an ELISA VIDAS D-dimer test of < 1000 ng/ml has a negative predictive value of 99.5% at a specificity of 68% (22). This implicates no need to repeat CUS in two third of the patients with a negative CUS and an ELISA VIDAS of < 1000 ng/ml (Fig. 3 and 4) (22). The combination of the ELISA VIDAS D-dimer, clinical score and CUS in figure 3 will reduce the number of CUS by 40 to 50%.

In recent large prospective management study, the sensitivity of the turbidimetric D-dimer assay Tinaquant (Roche Diagnostics, Marburg Germany) for the exclusion of DVT was 97.7% at a specificity of 44% (22). A normal Tinaquant test result (< 500 ng/ml) alone is not sensitive enough for the exclusion of DVT irrespective of clinical score. However, the combination with a low to moderate clinical score and a normal Tinaquant test result (< 500 ng/ml) had a sensitivity and negative predictive value of > 99% without the need of CUS testing and thus reduced the number of CUS testing by 29% (Table 1, figure 3) (22). As clinical score assessment is not perfect, every patient with a negative Tinaquant and persistent or recurrent symptoms suspected for DVT is a candidate for CUS testing to exclude or diagnose DVT or an alternative diagnosis (Fig. 3).

In conclusion, the presented critical appraisal of the literature demonstrates that the sequential use of a rapid, sensitive quantitative D-dimer test, clinical score and CUS appears to be safe and the most cost-effective diagnostic work-up of DVT.

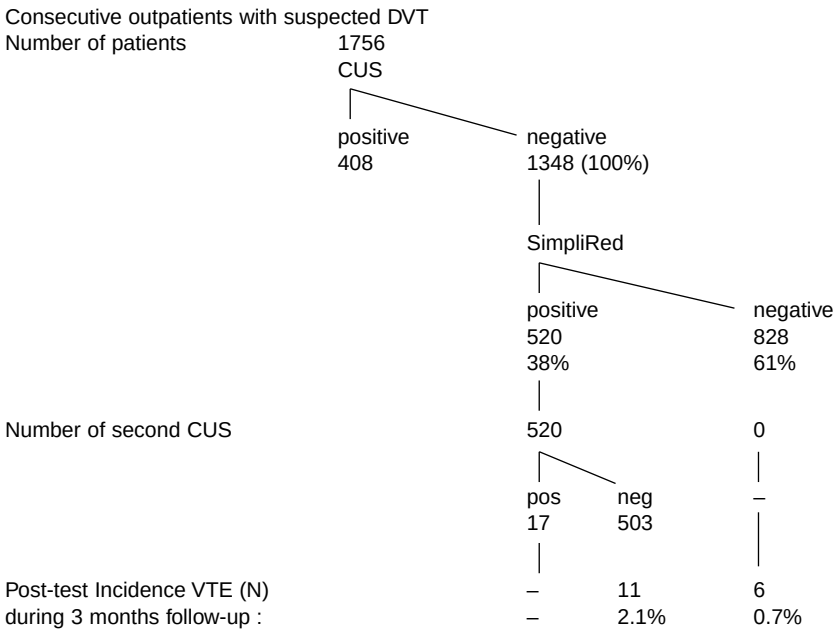

Fig. 2
Exclusion of DVT by the combined use of the SimpliRed latex D-Dimer test in outpatients in the study of KRAAIJENHAGEN (13)

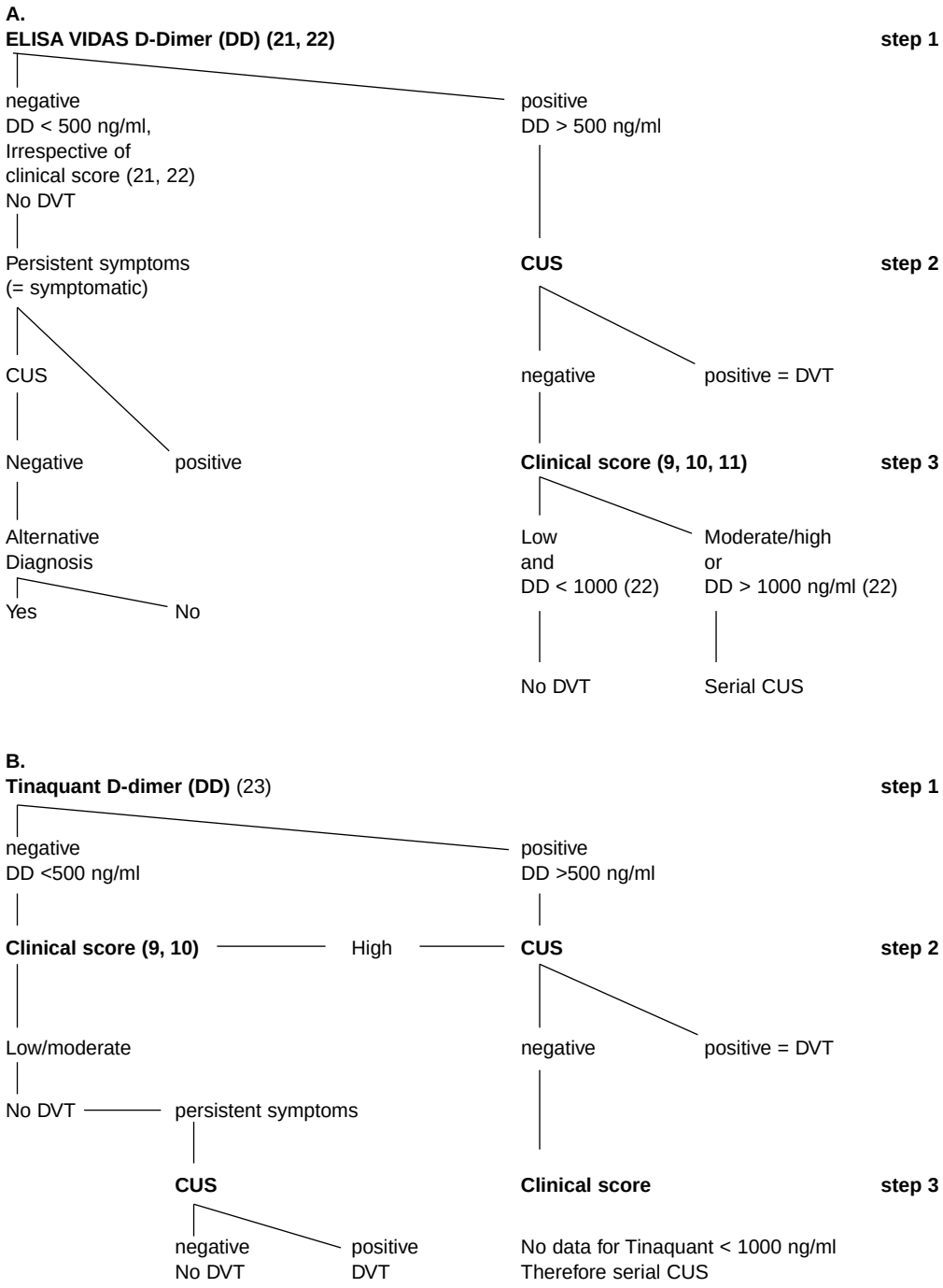

Fig. 3
Non-invasive diagnosis of deep vein trombosis by the sequential use of a sensitive rapid quantitative D-Dimer, clinical score and CUS

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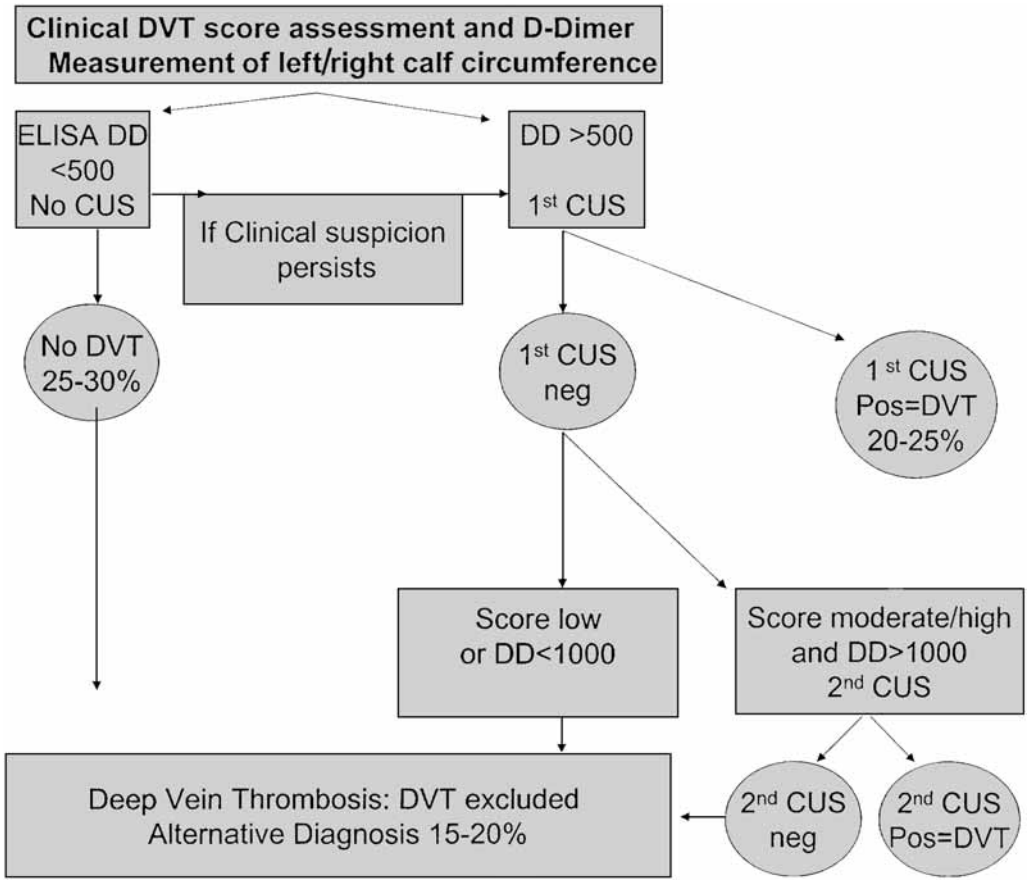

Fig. 4
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