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Diagnostic strategies in venous thromboembolism

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Abstract

Background and Objective. **Diagnosis of acute deep vein thrombosis (DVT) and of pulmonary embolism (PE) is often difficult: symptomatic patients are usually investigated employing several diagnostic tests, which should be appropriately selected and sequenced, taking into account their sensitivity, specificity, safety and cost. The objective of this paper is to evaluate the performance of the new diagnostic tests and their combination in rational diagnostic strategies.**

Design and Methods. **A literature review was made using a Medline® database search for the period 1988-1998 on the following key words in various combinations: diagnosis, diagnostic strategy, venous thrombosis, pulmonary embolism, venous thromboembolism. Results of a new study by our group on diagnosis of DVT in hospitalized patients are also discussed.**

Results. **In patients with symptoms or signs suggestive of DVT, compression ultrasound (CUS) appears to be the diagnostic test of first choice, since it is a non-invasive test with high specificity and sensitivity for proximal DVT (about 97%). When CUS gives a negative result it is usually recommended that the test is repeated after one week, since its sensitivity for calf DVT is poor. The positive and negative predictive values (PPV and NPV) of CUS in symptomatic outpatients can be improved if adequate consideration is given to clinical diagnosis, using a standardized model (ref. #9), which allows symptomatic outpatients to be categorized as having a high, moderate or low probability of DVT. In case of agreement between clinical diagnosis and CUS results, no further testing is needed: patients with high or intermediate clinical probability and positive CUS results are treated, while in patients with low clinical probability and negative CUS results the diagnosis of DVT is excluded. In the case of discrepancy between clinical diagnosis and CUS results, D-dimer test and/or venography are requested. However in patients who develop signs or symptoms of DVT in the hospital the clinical model does not work, and diagnosis should be based on an appropriate mix of CUS, D-dimer (DD) test and venography. In patients presenting with signs or symptoms of pulmonary embolism, the ventilation/perfusion (V/P) lung scan remains a pivotal diagnostic test, and pulmonary angiography the reference standard, but both methods have limitations and in recent years other diagnostic tests such as echocardiography, helical (or spiral) computerized tomography, and magnetic resonance imaging have been introduced into clinical practice. Moreover, all the four diagnostic tools mentioned for DVT diagnosis can be considered. Several diagnostic strategies have been proposed and evaluated in comparative studies but there is still debate over the most efficient test combination or sequence.**

Interpretation and Conclusions. **Diagnostic strategies which include adequate consideration of clinical diagnosis using standardized models have the potential of being more efficient for outpatients (but not for inpatients) with symptoms or signs suggesting DVT of lower limbs. For patients with suspected PE, several diagnostic strategies have been assessed: V/P lung scan remains a pivotal diagnostic test, but its limitations have been increasingly recognized and newer non-invasive techniques are gaining credit. A consensus is still to be reached over the most appropriate combination of diagnostic tests.**

Key words: diagnostic strategy, venous thrombosis, pulmonary embolism, venous thromboembolism

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A number of studies have assessed the pros and cons of the different tests employed in the diagnosis of acute deep vein thrombosis (DVT) and pulmonary embolism (PE). No single test is endowed with ideal properties (100% sensitivity and specificity, low cost, no risk) and often several tests are ordered, either sequentially or in combination. Clinical research in this area is currently involved in the evaluation of the different diagnostic strategies, and recent studies suggest that, in patients with symptoms and/or signs suggesting DVT of lower limbs, a correct diagnosis can be most efficiently accomplished by the appropriate selection and sequence of two or more among the followings: clinical assessment, compression or Duplex ultrasound (US), D-dimer test (DD), venography.

Patients with clinically suspected deep vein thombosis of lower limbs

Compression US is considered the best non-invasive diagnostic method in symptomatic patients: it has been evaluated against venography in several studies, showing an average sensitivity of 97% for proximal DVT (95% CI, 83-100%), and a mean speci-

ficity of 97% (95% CI, 86-100%).[1,2] The test is, however, insensitive for calf vein thrombosis, which usually does not cause clinically significant PE unless it extends to the proximal veins. For this reason it was recommended that, in case of negative ultrasound result, the examination should be repeated at least twice in the following week (serial US).

This diagnostic strategy was compared to serial impedance plethysmography (IPG) by Heijboer *et al.*, who randomized 985 symptomatic outpatients to serial US or to serial IPG, both tests being performed on the 1st, 2nd and 8th day.[3] Serial US proved to be more accurate (more sensitive and more specific) than serial IPG. This and other studies[4] documented the superior diagnostic efficiency of compression US over IPG. A further advantage of US resides in its capacity to diagnose other diseases that may simulate a DVT of lower limbs, such as Baker's cysts, muscular strains, abscesses, hematomas or arterial aneurysms. Compression US has therefore become the diagnostic method of first choice in patients with symptoms or signs of DVT. The problem now is how to optimize its use.

Two recent management studies evaluated the strategy of repeating negative ultrasonographic examinations just once, after about 7 days, and anticoagulating only those patients with abnormal US results. Birdwell *et al.* followed a cohort of 342 adults who had a normal US result at the first examination: 7 (2%) had abnormal results on repeat US 5-7 days after, 304 had normal results on both tests, and 31 did not have a repeat US. Of these 335 patients, only 2 developed symptoms of possible thromboembolism during 3 months of follow-up. None died of pulmonary embolism.[5] Cogo *et al.* evaluated 1702 patients with clinically suspected DVT: 400 (23.5%) tested positive for DVT on the first ultrasound, while 1302 (76.5%) were negative. Another 12 (<1%) tested positive on the second US, performed after one week. Of the 1,290 patients who had two negative tests and who therefore did not receive any anticoagulant treatment, 9 (0.7%) had a thromboembolic event during three months of follow-up; one was fatal.[6] An accompanying editorial agrees with the two-test strategy.[7]

The serial US approach has, however, a number of limitations, the most relevant being that all patients with negative US (about 75% of outpatients who come to the hospital to check for suspected DVT) must come back after one week – with the attendant inconveniences and costs – to pick up a tiny fraction of late positivities (1-2%). This fraction of late positivities is just a little greater than the number of clinically relevant false negative results.

The positive and negative predictive value (PPV and NPV) of US can be increased simply considering clinical diagnosis. This has been shown by Wells *et al.* who, using a standardized clinical model, identified 3 categories of patients with high, intermediate and low probability of DVT. Items included in this clinical model were derived and assembled from information they obtained by a literature review and from a consensus of participating investigators. Objective tests found a prevalence of DVT of 85%, 33% and 5% respectively in the 3 categories, and the sensitivity of US was significantly higher in the first category than the other two.[8] The PPV was 100% in the high probability category, 96% in the intermediate risk category, but only 63% in the low risk one. Similarly the NPV was 99% in the low risk group, 95% in the intermediate risk group, and 76% in the high risk one. The clinical model has been simplified in a second study by Wells *et al*.[9] who used a score list of 8 clinical features, reported in Table 1.

This new version is very similar to the predictive factors for DVT identified by Landefeld *et al*.[10] Thus, by means of clinical assessment, one can confidently exclude DVT in the patient with a low clinical probability and negative US result, without scheduling a repeat examination. This strategy generates great savings for the NHS, since this category covers the largest fraction of outpatients presenting at the Emergency Room or at the Angiology Laboratory with clinically suspected DVT, and should be formally assessed in a management study.

Another potentially useful diagnostic tool is D-dimer assay. Some of the newer tests which have been evaluated in this setting are listed in Table 2. Clinical usefulness seems to be confined to the ELISA and VIDAS assays, which have shown high negative predictive values. Less satisfactory are the results obtained using NycoCard, SimpliRed, and other assays methods.[11-20]

Table 1. A simple clinical model for predicting pre-test probability of proximal deep vein thrombosis (Wells *et al.*, 1997).

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
Alternative diagnosis as likely or more likely than DVT	*-2*

In patients with symptoms in both legs the more symptomatic leg is used

Score 0 = Low Clinical Probability; Score 1 or 2 = Moderate Clinical Probability; Score 3 or more = High Clinical Probability.

Table 2. Accuracy of some D-Dimer assay methods in symptomatic DVT.

Assay	*Cut-off (µg/mL)*	*Diagnosis*	*# pat*	*Sens. (%)*	*Spec. (%)*	*PPV (%)*	*NPV (%)*
NycoCard (14)	0.5	VG	92	95	25	52	87
SimpliRED (15)	–	VG	214	89	77	56	95
SimpliRED (16)		Non-invasive	86	94	61	77	88
LPIA D-Dimer (17)	2.3	Non-invasive	103	100	79	56	100
VIDAS D-D (18)	1.0	Non-invasive	99	100	75	49	100
VIDAS D-D (19)	1.0	Non-invasive	171	97	26	51	93
Instant D-D (19)	0.3	Non-invasive	163	93	19	49	77
NycoCard (19)	0.5	Non-invasive	163	80	38	50	71
Instant D-D (20)	0.3	VG	70	95	76		93
VIDAS D-D (21)	0.5	US + VG	132	100	19	72	100
Tinaquant (21)	0.5	US + VG	132	99	33	76	93
SimpliRED (21)		US + VG	132	61	90	93	52
Minutex (21)		US + VG	132	77	64	82	56
Ortho (21)		US + VG	132	51	47	94	47
VIDAS D-D (22)	0.5	Non-invasive	76	94	52	59	92
SimpliRED (23)		Non-invasive	50	58			73

Sens. = sensitivity; Spec. = specificity; PPV = positive predictive value; NPV = negative predictive value; VG = venography.

Two studies evaluated the accuracy of the explicit clinical model associated with DD determination. In the study by Borg *et al.*,[19] the positive and negative predictive values of the concordant test results were < 95%, which is considered by many as the minimal probability needed to take therapeutic decisions confidently.[21] In a study by Wells *et al.*, however, the NPV of a negative SimpliRed D-dimer assay associated with a low clinical probability was > 99.5%,[12] thus potentially useful for clinical decision making.

Another appealing diagnostic strategy associates D-dimer testing with CUS. This approach was evaluated by Bernardi *et al.* in a recent management study which enrolled 946 subjects referred to hospital because of clinically suspected DVT of lower limbs.[22] CUS results were positive in 260 patients (27.5%), who were thus anticoagulated, and negative in 686 subjects, who underwent D-dimer testing with the Simply Red assay. In 598 of these subjects the D-dimer test was negative, and they were not anticoagulated. Just one clinically apparent venous thromboembolic event was observed in this cohort within a 3 month follow-up. In 88 patients the D-dimer test was positive, and in these cases a repeat CUS examination was scheduled at day 7. After one week CUS results turned positive in 5 patients, who were thus anticoagulated, while it remained negative in 83 patients, who were not anticoagulated. Two of these patients developed clinically apparent pulmonary embolism within 3 months.

We are evaluating a diagnostic strategy which includes Wells' clinical model, US, D-dimer, and venography, following the algorithm shown in Figure 1.

Wells' clinical model, however, loses its discriminating power in hospitalized patients, as shown in a recent study by our group,[23] which enrolled 70 elderly patients with clinically suspected DVT. They were examined by means of the clinical model, CUS examination, ELISA D-dimer (cut-off = 250 ng/mL), and venography. Forty-two patients (60%) had DVT at venography, and the frequency of DVT was about the same in the 3 clinical categories: 60.6% in the *High Clinical Probability* patients, 64.3% in the *Intermediate Probability* group, and 54.5% in the *Low Probability* group (p = NS).

The sensitivity of the D-dimer assay was 90.5%; its specificity 64.2%; NPV 81%. The sensitivity of CUS

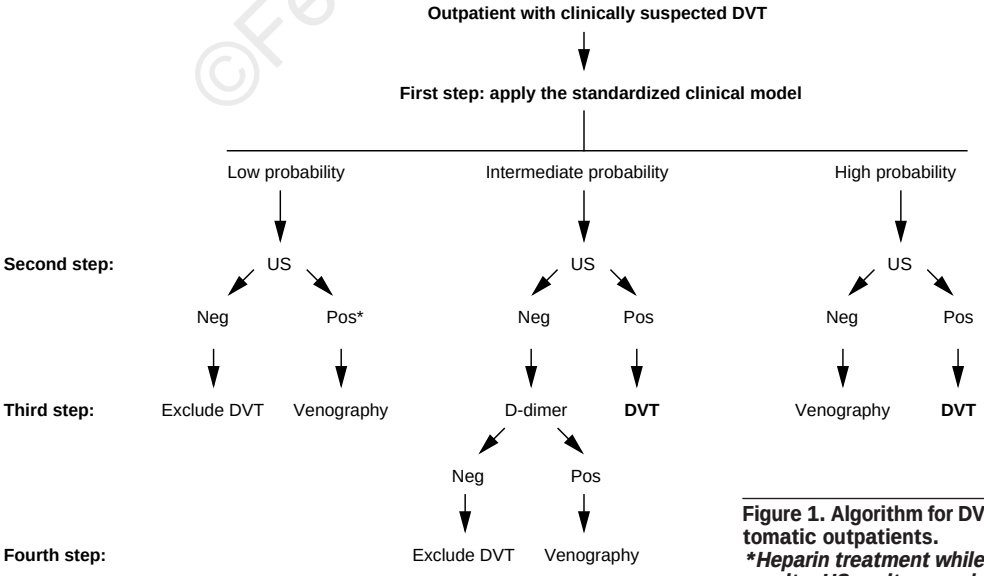

Figure 1. Algorithm for DVT diagnosis in symptomatic outpatients.
Heparin treatment while waiting venography results; US = ultrasound.

was 92.8%; specificity 96.4%; PPV 97.5%; NPV 90%. Of the 3 false negative US results, 1 was a proximal DVT, thus the NPV for proximal DVT was 96.4%. In the patient with isolated iliac vein thrombosis which was not detected at US, the D-dimer test was positive.

According to the results of this study, Wells' clinical model appears to be useless in elderly inpatients, while Duplex US confirms its accuracy. D-dimer assay discriminates better than the clinical model but it should not be used as a single screening test in these patients.

Patients with clinically suspected pulmonary embolism

In patients with signs or symptoms of pulmonary embolism (PE), the ventilation/perfusion (V/P) lung scan remains a pivotal diagnostic test, and pulmonary angiography the reference standard, but both methods have limitations and in recent years other diagnostic tests such as echocardiography, helical (or spiral) computerized tomography (CT), and magnetic resonance (MR) imaging have been introduced into clinical practice. Moreover, all the four diagnostic tools mentioned for DVT diagnosis can be considered.

The importance of clinical diagnosis was clarified by the *Prospective Investigation of Pulmonary Embolism Diagnosis* (PIOPED), a landmark study which documented that patients with so called *low probability* V/P scans still have a 14% chance of pulmonary embolism at angiography, that the risk decreased to 4% if their pretest clinical probability was low, and increased to 40% if they were in the high clinical risk group.[24]

The danger of the low-probability term was appreciated,[25,26] as well as the need of formulating the clinical assessment before looking at the lung scans results, in order not to be influenced by these. Lung scan results are more conservatively categorized into 3 classes: high probability, normal (or near normal), or non-diagnostic (which includes both previous readings: intermediate and low probability). A normal lung scan rules out pulmonary embolism, while a high-probability lung scan is considered diagnostic of PE.[27]

To reduce the number of necessary angiograms in patients with a non-diagnostic lung scan, non-invasive tests such as D-dimer measurement and lower-limb compression US have been introduced. Perrier *et al.* performed a cost-effectiveness analysis comparing six diagnostic strategies versus the reference standard: lung scan followed, when non-diagnostic, by angiography. In all strategies, PE was ruled out by a normal or near-normal lung scan, a negative ELISA D-dimer (plasma level below 500 µg/L), or a negative angiogram. Pulmonary emobolism was diagnosed and anticoagulant treatment was undertaken in the presence of a high-probability lung scan, a positive compression US result, or a positive angiogram. In patients with average clinical probability (prevalence of PE, 35%), strategies combining DD and US with lung scans, angiography being done only in the case of an inconclusive non-invasive work-up (DD level > 500 µg/L, normal US, and non-diagnostic lung scan) were most cost-effective. This approach yielded a 9% incremental cost reduction and a 37% to 47% decrease in the number of necessary angiograms compared with the reference strategy.[28] Anticoagulation can be safely withheld from patients with a low clinical probability of PE, a low-probability lung scan, and a normal US.

The appropriateness of a strategy which allows a diagnosis of PE to be made and anticoagulant treatment to be given solely on the basis of a positive US result has been questioned by Turkstra *et al.*, who calculated that in patients suspected of having pulmonary embolism, compression US theoretically has a false positive rate for DVT of 13 to 26%.[29] Further studies are necessary to clarify this point.

Among the newer diagnostic methods, spiral CT is particularly promising and its accuracy favorably compares to ventilation/perfusion scans. Spiral CT involves the continuous movement of the patient through a scanner with the use of a constantly rotating gantry and detector system and requires a bolus of contrast material for vascular imaging. The limitations of spiral CT include poor visualization of horizontally oriented vessels in the right middle lobe and lingula because of volume averaging. The peripheral areas of the upper and lower lobes may be inadequately scanned, and the presence of intersegmental lymph nodes may result in false positive readings. Spiral CT may reveal emboli in the main, lobar, or segmental pulmonary arteries, with a sensitivity of 73-97 percent and a specificity of 86 to 98 percent.[30]

A recent study by van Erkel *et al.* investigated the cost-effectiveness of diagnostic strategies involving spiral CT or conventional pulmonary angiography in the diagnosis of PE. Diagnostic algorithms consisting of a combination of perfusion and ventilation scintigraphy, ultrasound, D-dimer assay, conventional angiography and spiral CT angiography were compared. Preference for strategies was determined on the basis of the mortality and cost per life saved. For all realistic values of the pretest probability of pulmonary embolism and coexisting deep vein thrombosis and of the specificity of spiral CT angiography, all the best strategies included spiral CT angiography. With an assumed sensitivity of spiral CT angiography of less than 85%, a conventional angiographic strategy yielded a lower mortality but was not more cost-effective.[31] Goodman and Lipchik have strongly endorsed the use of CT when pulmonary embolism is suspected.[32]

Recently, gadolinium-enhanced magnetic resonance angiography (MR angiography) has been added to the diagnostic armamentarium of PE, and it has been compared with standard pulmonary angiography in 30 patients with suspected pulmonary embolism.[33] The 30 patients were enrolled consecutively, and the studies were interpreted independently in a blind man-

ner by 3 radiologists. In the 8 patients with emboli demonstrated by pulmonary angiography, all 5 lobar and 16 of 17 segmental emboli were identified by the MR technique. The sensitivities of the 3 readings were 100, 87 and 75 percent, with specificities of 95, 100, and 95 percent, respectively.

A major advantage of MR angiography is that it provides excellent resolution of the inferior vena cava and pelvic veins. Preliminary experience suggests that MR angiography is at least as accurate as contrast venography in detecting proximal vein thrombosis in the leg and is perhaps even more sensitive for pelvic vein thromboses.[34] There are however a number of draw-backs with MR angiography: it is unsuitable for patients with shortness of breath, it is expensive, and it is not readily available on an emergency basis.

Among older techniques, echocardiography is usually carried out in cases of suspected pulmonary embolism. A number of echocardiographic features are suggestive of acute pulmonary embolism (right ventricle enlargement or hypokinesis, flattening or paradoxical movement of the interventricular septum, tricuspid reflux, pulmonary artery dilatation) but only the visualization of emboli in the heart or in the pulmonary artery is a specific finding. Nonetheless the test often gives useful information about the severity of the disease and may be used to establish the clinical probability of PE.

In conclusion, several new diagnostic tests are now available for the diagnostic work-up of pulmonary embolism, among which plasma D-dimer, lower limb ultrasonography and spiral CT may be of special interest.[35] However, the most appropriate combination and/or sequence of non-invasive tests is still to be defined.

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MP did most of the computer search and literature analysis, and wrote the final version of the paper. LM and AG performed the study on hospitalized patients and contributed in the given order to the literature analysis and to the writing.

Disclosures

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