ORIGINAL INVESTIGATION

The Clinical Usefulness of D-Dimer Testing in Cancer Patients With Suspected Deep Venous Thrombosis

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Background: Little is known about the diagnostic value of a D-dimer test in cancer patients with clinically suspected deep venous thrombosis (DVT).

Objective: To evaluate the clinical utility of a whole blood rapid D-dimer test (SimpliRED) in cancer patients compared with noncancer patients.

Methods: In consecutive patients with suspected lower limb DVT, a D-dimer test and ultrasonogram were performed. Cancer status was recorded at presentation. If the D-dimer test and ultrasonogram results were normal, DVT was considered absent. If the D-dimer result was abnormal, ultrasonography was performed again 1 week later. Anticoagulant therapy was only instituted in those patients with an abnormal ultrasonography result. All patients were followed up for 3 months to record subsequent thromboembolic events. The accuracy of the D-dimer test was assessed, and the efficiency and safety of withholding additional ultrasonography in cancer patients with normal results on both D-dimer and ultrasonography was compared with noncancer patients.

Results: A total of 1739 consecutive patients were studied, 217 (12%) of whom had cancer. The negative predictive value of the D-dimer test was 97% in both cancer and noncancer patients. In 63 (29%) of all 217 cancer patients, the D-dimer and ultrasonography results were normal at referral; therefore, the diagnosis of DVT was refuted and anticoagulant treatment was withheld. In these 63 patients, one thromboembolic event occurred during follow-up (1.6%; 95% confidence interval, 0.04%-8.53%).

Conclusions: The negative predictive value of a whole blood D-dimer test in cancer patients seems as high as in noncancer patients. In a substantial proportion of cancer patients, the diagnosis can likely be refuted at referral, based on normal D-dimer test and ultrasonogram results. Furthermore, it seems safe to withhold anticoagulant therapy in these patients.

Arch Intern Med. 2002;162:1880-1884

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None of the authors has a financial or proprietary interest in the subject matter or materials discussed in the article.

MAJOR IMPROVEMENTS in the diagnostic management of patients with suspected deep venous thrombosis (DVT) have been achieved in the last decades. At first, the invasive procedure of venography was replaced by noninvasive tests, such as impedance plethysmography and compression ultrasonography. However, additional tests performed during a 2-week period were required to rule out adequately the diagnosis. Subsequently, it was shown for compression ultrasonography that the number of follow-up tests could be safely reduced to a single follow-up test with a 1-week interval.[1,2] Recently, further improvements have been attained by the introduction of the D-dimer test. A D-dimer test represents the level of plasma D-dimers, which are degradation products of cross-linked fibrin. Numerous studies[3,4] have investigated the accuracy of this test for the diagnosis of DVT. Since the sensitivity of the test is approximately 90% to 95% and the specificity is only 55%, the test is best suited for ruling out DVT instead of proving the presence of the disease. However, the test cannot be used as the sole test to exclude DVT, since given a sensitivity of approximately 90% to 95%, still 5% to 10% of DVTs will be missed. Therefore, the test should be used as an adjunct to other diagnostic methods. Management studies have shown that if a rapid D-dimer test is performed with ultrasonography in patients suspected of having DVT, the diagnosis can be ruled out if both test results are normal. Two large studies[5,6] have recently demonstrated that, using this strategy, the follow-up ultrasonogram and thus an extra hospital visit can be safely omitted in more than 45% of patients. A follow-up ul-

trasonogram is necessary to exclude an extending (calf) vein thrombosis only in the remaining patients with an abnormal D-dimer test result at referral.

Although it is well documented that the D-dimer test is useful in the diagnostic workup of patients with suspected DVT, it is thought that the D-dimer test is of less value in patients with underlying cancer. Since D-dimer levels are likely higher in cancer patients,[7,8] more of these patients will have an abnormal test result, making the test less efficient in this population to exclude DVT at referral. Lee and colleagues[9] found that the D-dimer test is of less value in cancer patients because the negative predictive value (NPV) of the test in these patients is lower than in noncancer patients as a consequence of the higher prevalence of DVT among cancer patients. The high prevalence of DVT among cancer patients and the relatively low specificity of the D-dimer test in these patients will result in a decreased NPV. On the other hand, the expected lower NPV could theoretically be counterbalanced by an increased sensitivity. The aim of this article is to examine the clinical utility of a whole blood D-dimer test in cancer patients suspected of having DVT compared with noncancer patients suspected of having DVT. We assessed the sensitivity, specificity, and predictive values of the D-dimer test. In addition, the safety and efficiency of withholding additional ultrasonography in patients with normal results on both the D-dimer test and ultrasonogram were evaluated.

PATIENTS AND METHODS

Consecutive outpatients with clinically suspected DVT of the leg treated from November 1, 1995, to January 31, 1999, were eligible for the study. Patients were referred by their family physician to the thrombosis unit. Patients were excluded if they were pregnant, were younger than 18 years, had experienced a previous episode of DVT in the same leg without documented normalization, had concurrent signs or symptoms suggestive of pulmonary embolism, had received anticoagulant treatment for more than 24 hours, or were unable to return to the study center for follow-up because of geographic inaccessibility. Cancer status was recorded at presentation. Patients were considered to have active cancer if they were receiving (palliative) treatment for cancer or if they had received treatment for cancer in the past 6 months.

STUDY DESIGN

Patients were investigated according to the following diagnostic strategy.[6] All patients underwent compression ultrasonography of the proximal veins and D-dimer testing at the day of referral. Both tests were performed by 2 independent investigators, who were both unaware of the cancer status of each patient. If the D-dimer and ultrasonography results were normal, the patient was considered not to have DVT and no further testing was performed. If the ultrasonography result was normal and the D-dimer test result abnormal, ultrasonography was performed again 1 week later. If this second ultrasonogram result was also normal, DVT was again ruled out. Anticoagulant therapy was only instituted in those patients with an abnormal ultrasonogram result. All patients were followed up for 3 months to record possible subsequent thromboembolic events. All patients were scheduled for a visit after 3 months and were instructed to contact the study center immediately if signs or symptoms of venous thromboembolism occurred before this visit. Objective testing was performed in these patients to confirm or refute the disease. In the case of suspected DVT, ultrasonography and venography were performed; in the case of suspected pulmonary embolism, ventilation perfusion scintigraphy was performed, followed by angiography if a nondiagnostic result was obtained.

For the analysis, patients were divided into 2 groups: patients with cancer and patients without cancer. In both groups, clinical utility was determined by assessing the accuracy indexes, venous thromboembolic complication rates, and the efficiency of D-dimer testing.

Accuracy Indexes

The sensitivity, specificity, NPVs, and positive predictive values were calculated using the 3-month follow-up as the reference standard (ie, DVT was considered absent if no venous thromboembolic event could be detected from referral through 3 months of follow-up, and DVT was considered present when venous thrombosis was shown by objective testing).

Venous Thromboembolic Complication Rate

The safety of withholding additional ultrasonography was determined in both patient groups by calculating the number of subsequent venous thromboembolic complications during the 3-month follow-up period (ie, complication rate).

Efficiency

The efficiency of using the D-dimer test as an adjunct to ultrasonography was defined as the proportion of patients in whom additional ultrasonography could be avoided (which is the proportion of patients in whom the diagnosis could be refuted on the day of referral).

DIAGNOSTIC TESTS

A rapid, whole blood, bedside D-dimer assay (SimpliRED D-dimer assay; Agen Biomedical Ltd, Brisbane, Australia) was used. The test can be performed by using 10 µL of whole blood obtained from a capillary or venipuncture sample. This autologous red blood cell agglutination assay uses as an active agent a chemical conjugate of a monoclonal antibody specific to human D-dimer (DD-3B6/22) linked to a monoclonal antibody that binds to the surface of human red blood cells (RAT-IC3/86).[10] Agglutination occurs at D-dimer concentrations greater than 200 µg/L within 2 minutes. The outcomes of the test were categorized as normal or abnormal.

Compression ultrasonography was performed and interpreted as described previously.[2] Briefly, the common femoral vein and the popliteal vein down to the trifurcation of the calf veins were examined. The compressibility of these veins was assessed in the transverse plane. The outcomes were categorized as normal or abnormal (ie, noncompressible).

STATISTICAL ANALYSIS

Sensitivity, specificity, predictive values, and venous thromboembolic complication rates in both patients groups were calculated. Their exact 95% confidence intervals (CIs) were calculated using Confidence Interval Analysis (Version 1.0).[11]

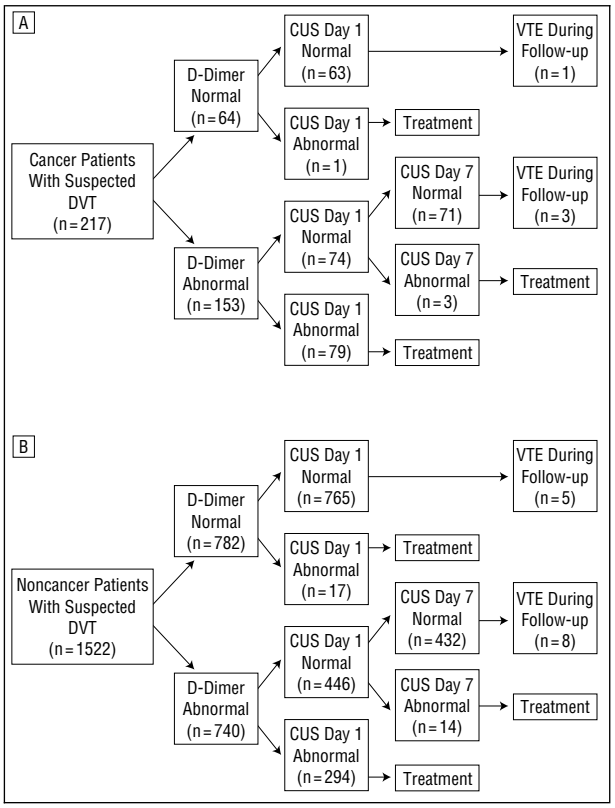
RESULTS

During the study period, 1899 consecutive patients with suspected DVT were screened. Of these, 143 patients (8%)

Table 1. Baseline Characteristics of 1739 Patients Suspected of Having Deep Venous Thrombosis With and Without Cancer

Characteristic	Patients With Cancer	Patients Without Cancer
No. (%) of patients	217 (12)	1522 (88)
Age, mean (range), y	65 (22-94)	60 (18-96)
Female, No. (%)	144 (66)	944 (62)
Median time since onset of symptoms, d	7	7
Underlying disorders, %		
Immobility or surgery in past 4 weeks	21	14
Recent trauma	7	16
Positive family history	4	4
Previous venous thromboembolism*	7	12

*This refers to patients with documented normalized ultrasonogram results of the symptomatic leg.



Overview of the diagnostic strategy arms of the study. CUS indicates compression ultrasonography; VTE, venous thromboembolism; and DVT, deep venous thrombosis.

were excluded for the following reasons: a previous episode of DVT in the same leg without documented ultrasonographic normalization (53%), anticoagulant treatment for more than 24 hours (43%), geographic inaccessibility for follow-up (2%), and refusal of informed consent (2%). In 17 patients, the D-dimer was not performed or performed with knowledge of the ultrasonogram test result, and these patients were excluded from further analysis. Thus, 1739 patients were included in the present analysis. Of these patients, 217 (12%) were known to have cancer at presentation. Twenty-one percent of the cancer patients were bedridden or underwent surgery in the past 4 weeks; 54% of the cancer patients were hospitalized in the past 6 months; and the 3-month mortality rate in the cancer group was 3%. **Table 1** summarizes the characteristics of the patients with and without cancer. Both groups were comparable with respect to age, sex, and median time since onset of symptoms. However, more cancer patients had been immobilized or had undergone surgery. A recent trauma had occurred in a higher percentage of the patients without cancer.

CANCER PATIENTS

Of the 217 cancer patients, 64 (29%) had a normal D-dimer test result and 153 (71%) an abnormal D-dimer test result. The ultrasonogram result was abnormal in 1 patient with a normal D-dimer test result, whereas it was abnormal in 79 patients with an abnormal D-dimer test result. Of those 63 patients (29%; 95% CI, 23%-35%) with both normal D-dimer and normal ultrasonogram results, 1 patient developed a thromboembolic event during follow-up. Those patients with an abnormal D-dimer test result and a normal ultrasonogram result underwent additional ultrasonography, the results of which were abnormal in 3 patients. In 3 of the other patients (with an abnormal D-dimer test result and normal serial ultrasonography result), a thromboembolic complication occurred during follow-up. Thus, overall, in 87 cancer patients venous thromboembolism was present (prevalence, 40%). The **Figure**, A, shows an overview of the diagnostic strategy arms with the corresponding patient numbers.

PATIENTS WITHOUT CANCER

In 782 (51%) of the 1522 noncancer patients, a normal D-dimer test result was obtained. Of these patients, 17 had an abnormal ultrasonogram result. Of the 765 remaining patients with both normal D-dimer test and ultrasound results (50%; 95% CI, 48%-53%), 5 developed a venous thromboembolic event during follow-up. In those patients with an abnormal D-dimer test result, DVT was detected by an abnormal ultrasonogram result in 294 patients. The other 446 patients had a normal ultrasonogram result and underwent follow-up ultrasonography 1 week later, the results of which were abnormal in 14 patients. In the remaining 432 patients (with an abnormal D-dimer test result and normal serial ultrasonography result), a thromboembolic event occurred in 8 patients. Hence, venous thromboembolism was present in 338 noncancer patients (prevalence, 22%; 95% CI, 20%-24%). The Figure, B, outlines the distribution of patients throughout the different strategy arms.

ACCURACY INDEXES

Of the 87 cancer patients with venous thromboembolism, 2 patients had a false-negative D-dimer test result (sensitivity, 98%; 95% CI, 92%-100%; specificity, 48%; 95% CI, 39%-56%). In 22 of the 338 noncancer patients with venous thromboembolism, a false-negative D-dimer

test result was present (sensitivity, 93%; 95% CI, 90%-96%; specificity, 64%; 95% CI, 62%-67%). Of the 64 cancer patients with a negative D-dimer test result, 62 did not have venous thromboembolism, resulting in an NPV of 97% (95% CI, 89%-100%). Of all 782 noncancer patients with a normal D-dimer test result, 760 seemed not to have venous thromboembolism (NPV, 97%; 95% CI, 96%-98%). **Table 2** gives the accuracy indexes for both patient categories.

VENOUS THROMBOEMBOLIC COMPLICATION RATE

In 63 (29%) of the 217 cancer patients, the D-dimer and ultrasonography results were normal at the day of referral; DVT was considered to be excluded, and anticoagulant therapy was withheld. In these 63 patients, only one thromboembolic event occurred during follow-up (complication rate, 1.6%; 95% CI, 0.04%-8.5%). Of those 71 cancer patients who had normal serial ultrasonogram results, 3 thromboembolic events occurred (complication rate, 4.2%; 95% CI, 0.9%-11.9%).

The complication rate of withholding additional ultrasonography in cases of both normal D-dimer and ultrasonogram results in patients without cancer was 0.9% (95% CI, 0.4%-1.9%). In 8 of 432 noncancer patients with normal serial ultrasonography results, thromboembolic complications occurred (complication rate, 1.9%; 95% CI, 0.8%-3.6%).

EFFICIENCY

The need for additional ultrasonography and therefore an extra hospital visit could be avoided in 63 of all 217 cancer patients. The efficiency of using a D-dimer test as an adjunct to ultrasonography is therefore 29% (95% CI, 23%-35%) compared with 50% (95% CI, 48%-53%) in the noncancer patients.

COMMENT

Our results indicate that the use of the D-dimer test, as measured in this study, does seem useful in cancer patients who have suspected DVT. This conclusion is supported in 3 ways. First, we found that the NPV of a whole blood D-dimer test (SimpliRED D-dimer) in cancer patients is as high as in patients who do not have cancer. Second, the low complication rate after withholding anticoagulant therapy indicates that it seems safe to reject the diagnosis in cancer patients with suspected DVT who have normal results on both ultrasonogram and D-dimer test. Third, 29% of cancer patients clinically suspected of having DVT have a normal D-dimer test result in combination with a normal ultrasonogram result (and considering the 95% CI, this proportion is unlikely to be lower than 23%). Therefore, using the D-dimer test, the need for an additional ultrasonogram can potentially be avoided in approximately 25% of the cancer patients with clinically suspected DVT. However, although the D-dimer test could be used as an exclusionary test to rule out DVT when a normal D-dimer test result is obtained, the test is not helpful in cancer patients (which is not different from noncancer patients) to prove DVT in case of a positive or abnormal test result, given the low positive predictive value of 56% (95% CI, 48%-63%). (In noncancer patients, the positive predictive value is 43% [95% CI, 39%-46%].)

Table 2. Accuracy of the SimpliRED D-Dimer Test in Patients Suspected of Having Deep Venous Thrombosis With and Without Cancer*

	Patients With Cancer			Patients Without Cancer		
	VTE+	VTE–	Total	VTE+	VTE–	Total
DD+	85	68	**153**	316	424	**740**
DD–	2	62	**64**	22	760	**782**
Total	**87**	**130**	**217**	**338**	**1184**	**1522**

*VTE indicates venous thromboembolism; DD, D-dimer; +, positive; and –, negative. SimpliRED D-dimer; Agen Biomedical Ltd, Brisbane, Australia.

The predictive values of a test are influenced by the prevalence of the disease in the studied population and the accuracy parameters (ie, the sensitivity and specificity of the test itself).[12] A higher prevalence of the disease and a lower specificity of the test tend to decrease the NPV, whereas a higher sensitivity would tend to increase the NPV. This balancing effect is nicely illustrated by our study results. The prevalence of DVT in cancer patients was almost twice as high as in noncancer patients, and the specificity of the D-dimer test was decreased by 25%, which could have resulted in a lower NPV of the D-dimer test in the cancer group. However, because high D-dimer levels often are present in cancer patients (also in the absence of DVT), it is expected that the D-dimer test will have a higher sensitivity in this subset of patients. Indeed, the sensitivity of the D-dimer test was 98% in cancer patients compared with 93% in noncancer patients. The decreasing effect of the higher prevalence and the lower specificity on the NPV of the test is therefore compensated by the higher sensitivity of the D-dimer test in cancer patients, resulting in an equally high NPV of 97% for both cancer and noncancer patients.

It could be argued that the high sensitivity and NPV found in the cancer patients were partly owing to the relatively high percentage of cancer patients who recently underwent surgery, which can also lead to high D-dimer levels. However, when the same analysis was performed after excluding those cancer patients who recently underwent surgery, a sensitivity of 97% (95% CI, 89%-100%), a prevalence of DVT of 37% (95% CI, 30%-44%), and an NPV of 97% (95% CI, 89%-100%) were observed. Hence, it is unlikely that the relatively high proportion (21%) of patients who were immobilized or underwent surgery has influenced our findings.

Our results are different from the findings of Lee et al,[9] who observed a significantly lower NPV of 79% in cancer patients compared with an NPV of 97% in noncancer patients. Using the same D-dimer assay, they reported a sensitivity of 83% in noncancer patients and a sensitivity of 86% in cancer patients, which are low values compared with the sensitivities in our study but also compared with sensitivities of the SimpliRED D-dimer

assay reported in other studies.[13-17] The prevalence of DVT in their cancer patients (49%) was higher than in our cancer patients (40%; 95% CI, 34%-47%). This high prevalence might be due to the fact that their patients suspected of having DVT were partly referred from a regional cancer center. These patients are possibly more sick compared with cancer patients referred from a general practitioner, as was the case in our study. The low sensitivity of their D-dimer test and the high prevalence of DVT probably resulted in the low NPV.

Apart from assessing the NPV of the D-dimer test, we prospectively demonstrated that it seems safe to reject the diagnosis of DVT in patients suspected of having DVT with concomitant cancer when both normal D-dimer test and ultrasonogram results are obtained. Regarding the complication rate of 4.2% (95% CI, 0.9%-11.9%) for serial ultrasonography (the current diagnostic standard), the observed complication rate of 1.6% (95% CI, 0.04%-8.5%) of withholding anticoagulants after normal D-dimer and ultrasonogram results is acceptable in this particular high-risk group of cancer patients. However, ideally more patients need to be studied to increase the confidence of this observation.

Some issues of our study require comment. Although the results of this study indicate the clinical usefulness of D-dimer testing for the diagnosis of DVT, the CIs are still too wide to draw definite conclusions. Therefore, and also because our study concerns a post hoc analysis, further investigation is necessary before these results can be implemented in daily practice. Moreover, the available D-dimer assays are not interchangeable. Accuracy variables of different D-dimer assays could vary among different populations and should be tested in each patient population before clinical introduction.

In conclusion, our results indicate that D-dimer testing is helpful in cancer patients. When a D-dimer test is used as an adjunct to ultrasonography, a subsequent ultrasonogram can be avoided in about one quarter of all cancer patients referred for clinically suspected DVT.

Accepted for publication January 17, 2002.

We thank Paolo Prandoni, MD, and Franco Piovella, MD, from Padua and Pavia, Italy, and Bert Jan Potter van Loon, MD, Saint Lucas Andreas Hospital, Amsterdam, the Netherlands, for their contributions to this study.

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REFERENCES

1. Birdwell BG, Raskob GE, Whitsett TL, et al. The clinical validity of normal compression ultrasonography in outpatients suspected of having deep venous thrombosis. *Ann Intern Med.* 1998;128:1-7.
2. Cogo A, Lensing AW, Koopman MM, et al. Compression ultrasonography for diagnostic management of patients with clinically suspected deep vein thrombosis: prospective cohort study. *BMJ.* 1998;316:17-20.
3. Becker DM, Philbrick JT, Bachhuber TL, Humphries JE. D-dimer testing and acute venous thromboembolism: a shortcut to accurate diagnosis? *Arch Intern Med.* 1996;156:939-946.
4. Bounameaux H, de Moerloose P, Perrier A, Miron MJ. D-dimer testing in suspected venous thromboembolism: an update. *Q J Med.* 1997;90:437-442.
5. Bernardi E, Prandoni P, Lensing AW, et al, for the Multicentre Italian D-dimer Ultrasound Study Investigators Group. D-dimer testing as an adjunct to ultrasonography in patients with clinically suspected deep vein thrombosis: prospective cohort study. *BMJ.* 1998;317:1037-1040.
6. Kraaijenhagen RA, Piovella F, Bernardi E, et al. Simplification of the diagnostic management of suspected deep vein thrombosis. *Arch Intern Med.* 2002;162:907-911.
7. den Ouden M, Ubachs JM, Stoot JE, van Wersch JW. Thrombin-antithrombin III and D-dimer plasma levels in patients with benign or malignant ovarian tumours. *Scand J Clin Lab Invest.* 1998;58:555-559.
8. Gabazza EC, Taguchi O, Yamakami T, et al. Coagulation-fibrinolysis system and markers of collagen metabolism in lung cancer. *Cancer.* 1992;70:2631-2636.
9. Lee AY, Julian JA, Levine MN, et al. Clinical utility of a rapid whole-blood D-dimer assay in patients with cancer who present with suspected acute deep venous thrombosis. *Ann Intern Med.* 1999;131:417-423.
10. John MA, Elms MJ, O'Reilly EJ, Rylatt DB, Bundesen PG, Hillyard CJ. The SimpliRED D dimer test: a novel assay for the detection of cross-linked fibrin degradation products in whole blood. *Thromb Res.* 1990;58:273-281.
11. Gardner MJ. *Confidence Interval Analysis.* London, England: BMJ Books; 1989.
12. Sacket DL, Haynes RB, Tugwell P. The interpretation of diagnostic data. In: *Clinical Epidemiology: A Basic Science for Clinical Medicine.* Boston, Mass: Little Brown & Co; 1985.
13. Turkstra F, van Beek EJ, ten Cate JW, Buller HR. Reliable rapid blood test for the exclusion of venous thromboembolism in symptomatic outpatients. *Thromb Haemost.* 1996;76:9-11.
14. Ginsberg JS, Wells PS, Brill-Edwards P, et al. Application of a novel and rapid whole blood assay for D-dimer in patients with clinically suspected pulmonary embolism. *Thromb Haemost.* 1995;73:35-38.
15. Wells PS, Brill-Edwards P, Stevens P, et al. A novel and rapid whole-blood assay for D-dimer in patients with clinically suspected deep vein thrombosis. *Circulation.* 1995;91:2184-2187.
16. Wildberger JE, Vorwerk D, Kilbinger M, et al. Bedside testing (SimpliRED) in the diagnosis of deep vein thrombosis: evaluation of 250 patients. *Invest Radiol.* 1998;33:232-235.
17. Mayer W, Hirschwehr R, Hippmann G, Odpadlik H, Bayer P, Partsch H. Whole-blood immunoassay (SimpliRED) versus plasma immunoassay (NycoCard) for the diagnosis of clinically suspected deep vein thrombosis. *Vasa.* 1997;26:97-101.