Thrombosis Research (2007) xx, xxx–xxx

THROMBOSIS RESEARCH

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REGULAR ARTICLE

A rapid and quantitative D-Dimer assay in whole blood and plasma on the point-of-care PATHFAST analyzer

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Received 11 July 2006; received in revised form 7 December 2006; accepted 28 December 2006

KEYWORDS
D-Dimer;
Deep-vein thrombosis;
Point-of-care testing;
Chemiluminescent immunoassay

Abstract The objective of this study was to evaluate the accuracy indices of the new rapid and quantitative PATHFAST D-Dimer assay in patients with clinically suspected deep-vein thrombosis (DVT). Eighty two consecutive patients (34% DVT, 66% non-DVT) with suspected DVT of a lower limb were tested with the D-Dimer assay with a PATHFAST analyzer. The diagnostic value of the PATHFAST D-Dimer assay (which is based on the principle of a chemiluminescent enzyme immunoassay) for DVT was evaluated with pre-test clinical probability, compression ultrasonography (CUS). Furthermore, each patient underwent contrast venography and computed tomography, if necessary. The sensitivity and specificity of the D-Dimer assay using 0.570 μg/mL FEU as a clinical cut-off value was found to be 100% and 63.2%, respectively, for the diagnosis of DVT, with a positive predictive value (PPV) and negative predictive value (NPV) of 66.7% and 100%, respectively. The correlation between the results of PATHFAST D-Dimer and VIDAS D-Dimer was acceptable ($y=1.134\times+0.003$, $r=0.902$). The test reproducibility was good (CV%: from 4.0% to 5.0% for plasma and from 7.1% to 7.5% for whole blood) and the total imprecision was very good (CV%: 3.6–5.7%). Whole blood as well as plasma can be used as samples in this assay ($y=1.013\times-0.010$, $r=0.971$ for heparinized specimens; $y=1.068\times+0.003$, $r=0.989$ for citrated specimens). Because of its high sensitivity and NPV PATHFAST D-Dimer assay can be useful for the rapid rule out of DVT in patients admitted with suspected thrombosis.

Abbreviations: DVT, deep-vein thrombosis; CUS, compression ultrasonography; PPV, positive predictive value; NPV, negative predictive value; ELISA, enzyme-linked immunosorbent assay; POCT, point-of-care testing; ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; FEU, fibrinogen equivalent unit.

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doi:10.1016/j.thromres.2006.12.021

Please cite this article as: Fukuda T et al. A rapid and quantitative D-Dimer assay in whole blood and plasma on the point-of-care PATHFAST analyzer. *Thromb Res* (2007), doi:10.1016/j.thromres.2006.12.021

Introduction

Suspected deep-vein thrombosis (DVT) is a common condition, with a lifetime cumulative incidence of 2 to 5% [1]. Compression ultrasonography (CUS) and contrast venography are the most reliable methods for diagnosis of DVT [2]. Contract venography is the gold standard for diagnosis of DVT [3] but it is not ideal because of its invasive nature and the risks associated with contrast media. CUS requires skilled investigators and its sensitivity and specificity can vary considerably depending on which part on the lower extremity the examination is performed.

D-Dimer is a mixture of cross-linked fibrin degradation products which is a marker of endogenous fibrinolysis and thus it can be detected in patients with DVT. Retrospective studies have shown a high negative predictive value of a D-Dimer concentration for the exclusion of DVT when taking into account a defined cut-off value for the used assay [4]. Moreover, various studies have proven the safety of withholding anticoagulation in those patients with a negative D-Dimer test result and a normal ultrasonography [5,6].

Several D-Dimer assays including enzyme immunoassays, latex assays and immunoturbidimetric assays are currently available but their clinical efficiency can differ markedly. Among them, enzyme immunoassays show a high sensitivity and negative predictive value (NPV) in the presence of DVT in comparison to latex assays [7–13]. Some of these assays can be used as point-of-care tests (POCT) for an emergency need and among them the VIDAS D-Dimer assay is one of the well-established methods for diagnosis or exclusion of DVT. The newly developed PATHFAST D-Dimer assay is a sensitive and quantitative method based on the principle of enzyme immunoassay using a chemiluminescent substrate. Whole blood as well as plasma can be used as samples and the reaction time takes only 5 min. In this study, our aim has been the evaluation of the diagnostic value of the PATHFAST D-Dimer assay when used as a screening test to exclude DVT.

Materials and Methods

Clinical samples

This study included 82 consecutive outpatients (40 women and 42 men; age range: 23–85 years; women, 56.1±18.0 years; men, 46.8±17.7 years) referred to our hospital for diagnostic work-up for suspected DVT of a lower limb. Twenty eight patients were diagnosed as having a DVT. Patients with any of the following criteria were excluded: previous episode of DVT, stable symptoms at presentation or prophylactic anticoagulants already applied at presentation. Heparinized or citrated blood samples (n=124; 52 women and 72 men; age range 24–52 years) were obtained from apparently healthy subjects who had given informed consent among the staff of the company Mitsubishi Kagaku Iatron, Inc., Chiba, Japan. Blood samples were collected into 10 mL vacuum tubes containing 0.129 M trisodium citrate or 9 IU lithium heparin. All whole blood samples were tested within 6 h. In order to obtain plasma samples, blood samples containing anticoagulants were centrifuged at 2000 ×g for 15 min to obtain platelet poor plasma. The plasma samples were tested either within 6 h or stored frozen at −40 °C or −80 °C prior to use. A stability check indicated that plasma samples stored at −40 °C or −80 °C were stable over a period of at least 3 months and longer.

Diagnosis of deep venous thrombosis

The DVT diagnostic work-up used in our institution is based on pre-test clinical probability, according to the score proposed by Wells et al. [14] and compression ultrasonography (CUS), according to standard criteria [15]. Furthermore, each patient underwent contrast venography, and computed tomography.

D-Dimer testing

The PATHFAST™ D-Dimer assay (Mitsubishi Kagaku Iatron, Inc., Tokyo, Japan) is a fully automated, rapid and quantitative chemiluminescence enzyme immunoassay for measurement of degradation products of cross-linked fibrin (D-Dimer) in human whole blood and plasma samples. Both heparin and citrate can be used as anticoagulants to obtain plasma. The PATHFAST analyzer can automatically distinguish whole blood and plasma samples by means of a sample recognition sensor. Results obtained with whole blood samples are corrected optionally by input of the individual hematocrit value in percent (%) in the PATHFAST analyzer. A default hematocrit value (40%) is used by the PATHFAST analyzer, when no value adjustment is performed. When whole blood is tested, the manufacturer recommends to start the PATHFAST D-Dimer assay within 5 min after whole blood sample has been dispensed into a sample well of a PATHFAST cartridge. The PATHFAST D-Dimer assay is a one-step sandwich immunoassay method

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automated on PATHFAST analyzer which permits single tests with ready-to-use reagents including magnetic particles covalently conjugated with a D-Dimer monoclonal antibody and alkaline phosphatase-conjugated D-Dimer monoclonal antibody. The D-Dimer antibodies used by Mitsubishi Kagaku Iatron, Inc. were raised against degradation products of cross-linked fibrin as an immunogen. The antibodies recognize neo-antigens of degradation products of cross-linked fibrin prepared after digestion by plasmin. After the immuno-reaction of D-Dimer antigen contained in the blood sample and the reagents for 5 min during which an immune complex is formed, bound/free separation is performed by Magtration® procedure. Chemiluminescent signal is measured after the addition of a chemiluminescent substrate (CDP-Star®) to the immune complex.

The measuring range of the assay is from 0.005 to 5.00 μg/mL FEU (fibrinogen equivalent unit) and the final result can be read after 17 min from application of the blood sample using the PATHFAST analyzer. Six samples can be assayed in one PATHFAST running.

The intra-assay reproducibility of the PATHFAST D-Dimer assay was tested using two fresh samples of heparinized whole blood and plasma with normal and abnormal D-Dimer concentrations, respectively. Experiments for measuring the intra-assay reproducibility ($n=20$) were performed on the same working day. The total imprecision was evaluated using three heparinized plasma samples with normal and abnormal D-Dimer concentrations in twenty different working days.

Statistical analysis

A receiver operating characteristic (ROC) curve was constructed by plotting the values for the sensitivity versus those for 1-specificity and the area under the curve (AUC) was then calculated. The results from the ROC curve were used to determine the optimal D-Dimer cut-off value. The sensitivity, specificity and the positive and negative predictive values for the PATHFAST D-Dimer assay were calculated according to standard methods for proportions. The 95% confidence intervals (CI) were calculated according to the binomial distribution. The correlation was calculated according to Spearman and a regression analysis was performed using the method of Passing and Bablok [16].

Comparison method

The Biomerieux VIDAS® D-Dimer assay [17] was used as the comparison method in this study. This assay was performed according to the manufacturer's instructions. The VIDAS D-Dimer assay is an enzyme immunoassay with a detection limit of 45 ng/mL FEU (0.045 μg/mL FEU) and an upper assay range of 10,000 ng/mL FEU (10 μg/mL FEU). A cut-off value of 500 ng/mL FEU (0.500 μg/mL FEU) is used for that assay.

Results

Assay performance of PATHFAST D-Dimer

The intra-assay reproducibility and the total imprecision of the PATHFAST D-Dimer assay are listed in Table 1. The intra-assay reproducibility of the PATHFAST D-Dimer assay for two samples with different concentrations of D-Dimer was good (CV %: normal concentration sample = 5.0% for plasma and 7.5% for whole blood, abnormal concentration sample = 4.0% for plasma and 7.1% for whole blood). The total imprecision of the PATHFAST D-Dimer assay was acceptable (CV%: normal concentration sample = 4.1%, abnormal concentration samples = 3.6–5.7%).

Reference values

Reference interval of the PATHFAST D-Dimer assay was found in citrated plasma samples taken from apparently healthy volunteers ($n=124$). The median D-Dimer concentration was 0.225 μg/mL FEU, with the highest measured concentration of 0.710 μg/mL FEU. The upper reference limit based on the 95th

Table 1 Intra-assay reproducibility and total imprecision for measurements with PATHFAST D-Dimer

	Intra-assay reproducibility ($n=20$)			Total imprecision ($n=20$)		
	Mean ± SD	Range	CV%	Mean ± SD	Range	CV%
Plasma normal level	0.192 ± 0.010	0.210–0.170	5.0	0.150 ± 0.006	0.137–0.163	4.1
Plasma abnormal level-1	2.40 ± 0.10	2.26–2.62	4.0	2.52 ± 0.14	2.28–2.75	5.7
plasma abnormal level-2		–		4.15 ± 0.15	3.85–4.47	3.6
WB normal level	0.123 ± 0.009	0.120–0.150	7.5		_	
WB abnormal level	1.84 ± 0.13	1.62–2.10	7.1		_	

CV%, coefficient of variation.

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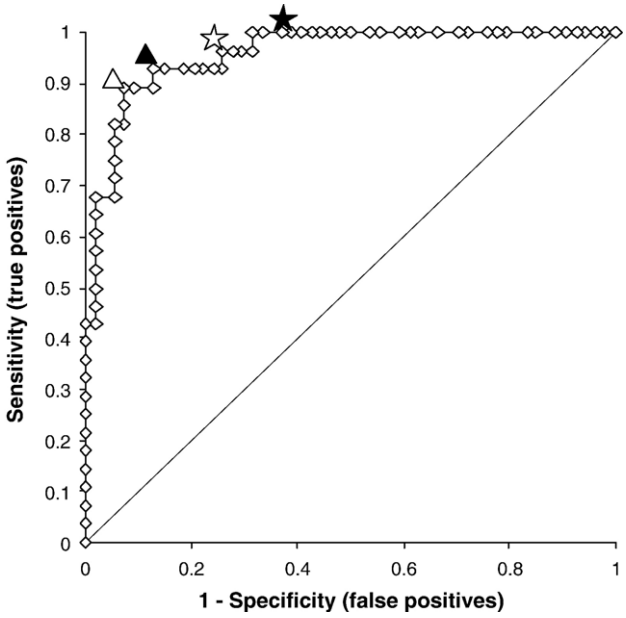

Figure 1 Receiver operating characteristic (ROC) curve analysis of accuracy indices of the PATHFAST D-Dimer assay for the presence of deep venous thrombosis. (★) indicates cut-off values of 0.570 μg/mL FEU, (☆) 0.800 μg/mL FEU, (▲) 1.28 μg/mL FEU and (△) 1.50 μg/mL FEU.

percentile was 0.528 μg/mL FEU. The result supported that the provisional clinical cut-off value (0.570 μg/mL FEU) for the PATHFAST D-Dimer assay is available in this study.

Results with patients' samples

Eighty two patients (40 women and 42 men: age range 23–85 years; 34% DVT) were included in the analysis. As shown in Fig. 1, an ROC curve was obtained displaying the sensitivity and specificity values for the PATHFAST D-Dimer assay at different cut-off values having an AUC of 0.957 (95% CI: 0.918–0.996). The clinical cut-off value for the PATHFAST D-Dimer assay of 0.570 μg/mL FEU was established taking into consideration the results deriving from the ROC curves as well as from the reference interval. The total imprecision of the PATHFAST D-Dimer assay around the decision level of 0.570 μg/mL FEU was with 5% very good. The distribution of the sensitivity, specificity, and positive and negative predictive values of the PATHFAST D-Dimer assay is reported in Table 2. As it can be expected, the use of higher cut-off values (1.50 μg/mL FEU) was associated with a lower sensitivity (92.9%) and negative predictive value (94.3%) and a higher specificity (86.8%).

Correlation between whole blood and plasma

The compatibility of D-Dimer results obtained using whole blood and plasma in the PATHFAST D-Dimer assay is shown in Fig. 2. Blood samples having normal as well as abnormal concentrations of D-Dimer antigen were used with sodium citrate or lithium heparin as an anticoagulant. The linear regression analysis yielded slopes of 1.013 (95% CI: 0.931–1.063; *x*-axis plasma, *y*-axis whole blood; $n=40$) for heparin and 1.068 (95% CI: 1.030–1.112; *x*-axis plasma, *y*-axis whole blood; $n=56$) for citrate, and *y*-intercepts of −0.010 μg/mL FEU (95% CI: −0.055 to 0.089) for heparin and 0.003 μg/mL FEU (95% CI: −0.005 to 0.011) for citrate. The correlation coefficients for heparin and citrate were found to be 0.971 and 0.989, respectively.

Correlation between heparinized whole blood and citrated whole blood

Using 58 plasma samples from apparently healthy subjects, a comparison between D-Dimer results in heparinized whole blood and citrated whole blood was performed in the PATHFAST D-Dimer assay. The linear regression analysis yielded a slope of 0.952 (95% CI: 0.926–0.981; *x*-axis, heparin; *y*-axis, citrate) and a *y*-intercept of 0.001 μg/mL FEU (95% CI: −0.005 to 0.006). The correlation coefficient was found to be 0.995.

Table 2 Clinical performance of PATHFAST D-Dimer for exclusion of DVT

Decision threshold (μg/mL FEU)	Sensitivity (%) (95% CI)		Specificity (%) (95% CI)		NPV (%)[a]	PPV (%)[b]	Efficiency (%)[c]
0.570	100	(87.7–100)	63.2	(46.0–78.2)	100	66.7	78.8
0.800	96.4	(81.7–99.9)	71.1	(54.1–84.6)	96.4	71.1	81.8
1.280	92.9	(76.5–99.1)	84.2	(68.7–94.0)	94.1	81.3	87.9
1.500	92.9	(76.5–99.1)	86.8	(71.9–95.6)	94.3	83.9	89.4

[a] NPV, negative predictive value.
[b] PPV, positive predictive value.
[c] Calculated as the sum of true positives and true negatives divided by the number of all results.

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Method comparison

The results obtained with PATHFAST D-Dimer assay were compared with those obtained with Biomerieux VIDAS D-Dimer assay using citrated plasma samples collected from hospitalized patients and apparently healthy subjects. Highly significant correlation was found between results with the PATHFAST D-Dimer assay and the VIDAS assay ($n=66$) as shown in Fig. 3. The correlation coefficient between results with PATHFAST D-Dimer assay and those with the VIDAS assay was found to be 0.902 and the regression line showed a y-intercept of 0.0025 μg/mL FEU (95% CI: −0.125 to 0.087) and a slope of 1.134 (95% CI: 1.030–1.329). The clinical cut-off value of the VIDAS D-Dimer assay is 500 ng/mL FEU (0.500 μg/mL FEU) [17].

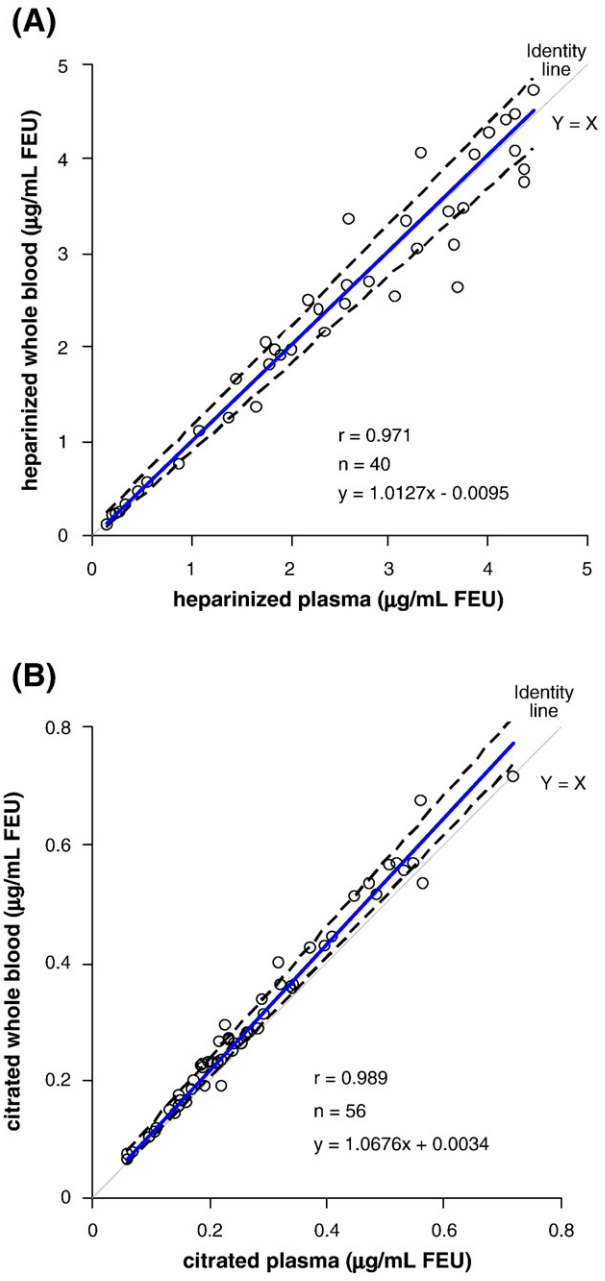

Figure 2 Correlation between results obtained using plasma and whole blood on PATHFAST. (A) Lithium heparin blood samples having elevated D-Dimer concentrations. (B) Sodium citrate blood samples having normal D-Dimer concentrations.

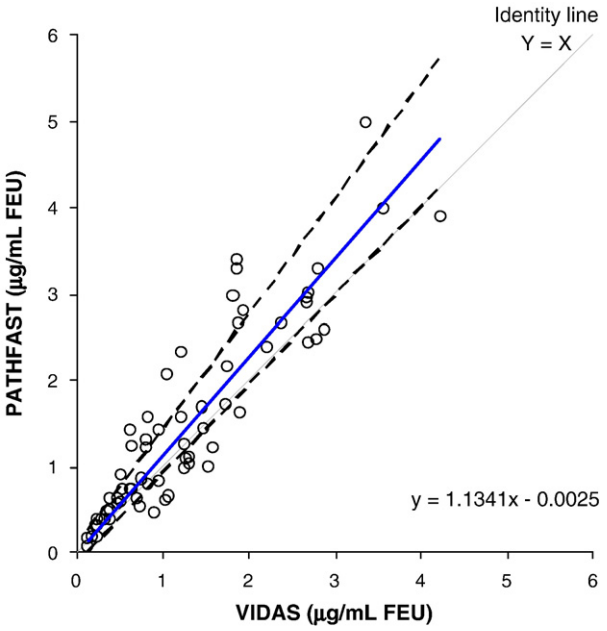

Figure 3 Correlation between results with PATHFAST D-Dimer and VIDAS D-Dimer.

Discussion

The purpose of this study was to evaluate the technical characteristics and diagnostic performance of the PATHFAST D-Dimer assay. The clinical D-Dimer cut-off value using ROC curve analysis was established and the sensitivity, specificity, NPV and PPV of the assay were investigated.

Tests for D-Dimer to help in the exclusion of DVT have been available since the 1980s [18]. The intra-assay reproducibility as well as the total imprecision at the upper limit of D-Dimer values in healthy subjects plays an important role since high imprecision at that level can cause false-negative results. Using the PATHFAST D-Dimer assay, a very good intra-assay reproducibility (CV=5.0% for plasma, 7.5% for whole blood) and total imprecision (CV=4.1% for plasma) were observed at low D-Dimer concentration as well as at elevated D-Dimer concentration (intra-assay CV=4.0% for plasma, 7.1% for whole blood; total imprecision CV=3.6–5.7% for plasma). These characteristics make PATHFAST D-Dimer assay an accurate quantitative

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method although it is tested with a point-of-care bench-top analyzer.

In order to rule out DVT not only accuracy but also high sensitivity and NPV are important for a D-Dimer assay. Sensitive assays for D-Dimer are sometimes criticized as being too unspecific and to generate a large number of positive results that require further studies to establish a final diagnosis. However, it should be considered that the cut-off value of sensitive methods can be freely selected. This fact, especially when used in combination with clinical probability assessment, allows to select a higher cut-off value in order to enhance the specificity of the assay and thus to exclude DVT in a significantly large number of patients [19].

The sensitivity and NPV observed for the PATHFAST D-Dimer assay in our study and the analysis of the ROC curves indicate that this assay can be used as a valuable tool for ruling out DVT. In general, lowering the cut-off values of an assay may improve the sensitivity, although rendering it less valuable in clinical practice due to a lower number of negative results. The specificity and PPV of the PATHFAST D-Dimer assay were found to be 63.2% and 66.7%, respectively when the cut-off value was set at 0.570 μg/mL FEU. The results were comparable to those of the VIDAS D-Dimer assay as described previously [20,21]. Based on the results of this study a concentration of 0.570 μg/mL FEU can be established as the clinical cut-off value for the PATHFAST D-Dimer assay since at that value the sensitivity was 100% to rule out DVT also taking into account that the upper reference limit of apparently healthy subjects was 0.528 μg/mL FEU.

The comparability of results obtained using whole blood and plasma samples in the PATHFAST D-Dimer assay was acceptable even without correction for the hematocrit value. The correlation between whole blood and plasma was somewhat improved when each whole blood result was corrected by the respective hematocrit value in percent (data not shown). In the comparison study between whole blood and plasma, a good correlation was observed without hematocrit value correction for the whole blood samples around the clinical cut-off value (0.570 μg/mL FEU on the PATHFAST D-Dimer assay) although the hematocrit value of the used citrated whole blood samples ranged from 29.3 to 49.9% (mean ± SD = 40.8 ± 3.8). The PATHFAST analyzer can also correct each whole blood result to the plasma D-Dimer concentration by entering the respective hematocrit value into the system for samples with an abnormal hematocrit value such as in the case of patients with polycythemia and severe anemia.

As shown in Fig. 3, the method comparison between the PATHFAST D-Dimer assay and the VIDAS D-Dimer assay indicated a very good correlation between the two D-Dimer assays was observed. Watanabe et al. reported on the clinical cut-off value of the VIDAS D-Dimer assay for ruling out DVT in Japanese patients which was established at 0.6 μg/mL FEU [22]. This result is comparable to that found for the PATHFAST D-Dimer assay.

In conclusion, the new quantitative 5-min D-Dimer assay PATHFAST D-Dimer, in combination with preclinical scores provides a valuable tool for the clinician to rule out DVT. Because of the high sensitivity and NPV obtained in this study, the PATHFAST D-Dimer assay could potentially be employed as a stand-alone test. However, further studies using a larger number of patients are required to better establish the clinical cut-off value of this assay for ruling out DVT and to confirm the potential use in patients on anticoagulant therapy with a D-Dimer concentration below the cut-off value.

Acknowledgment

The PATHFAST D-Dimer reagents were kindly provided by Mitsubishi Kagaku Iatron, Inc., Tokyo, Japan.

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