

Evaluation of a New, Rapid, and Quantitative D-Dimer Test in Patients with Suspected Pulmonary Embolism

EMMANUEL OGER, CHRISTOPHE LEROYER, LUC BRESSOLLETTE, MICHEL NONENT, EMMANUELLE LE MOIGNE, YVES BIZAIS, JEAN AMIRAL, MARC GRIMAUX, JEAN CLAVIER, PATRICK ILL, JEAN-FRANÇOIS ABGRALL, and DOMINIQUE MOTTIER

Department of Internal Medicine and Chest Diseases, Department of Radiology, Department of Biophysics, and Department of Haematology, CHRU de la Cavale Blanche, Brest; Serbio Research Laboratory, Gennevilliers; and Rhône-Poulenc-Rorer Laboratories, Montrouge, France

Previous studies have suggested the utility of D-Dimer ELISA assays in eliminating a diagnosis of pulmonary embolism (PE). Our objectives were to evaluate the performance of a new, rapid, quantitative, and automated Liatest D-Dimer Assay in patients with suspected PE. Three hundred eighty-six consecutive patients referred to our institution between March 1992 and December 1996 for clinically suspected PE, with recent clinical signs not exceeding 1 wk, were included in this study. Diagnosis of PE was based on clinical evaluation, radionuclide lung imaging, lower limb examination, and, when required, pulmonary angiography. D-Dimer performances, for both Liatest D-Dimer and standard D-Dimer ELISA (Asserachrom DDI), assays, were assessed at the end of the study. Among the 386 patients tested, 146 (37.8%) were classified as PE-positive. Liatest D-Dimer assay had a 100% sensitivity (95% confidence interval, 97 to 100%) and a negative predictive value of 100% (95% confidence interval, 94 to 100%). A normal result, below the cutoff of 500 ng/ml, occurred in 83 of the 386 (21%) patients. There was a strong agreement between Liatest D-Dimer and Asserachrom DDI analyses. These findings suggest that this rapid, quantitative, and automated D-Dimer assay provides a useful diagnostic tool for the clinician with regard to exclusion of PE. Oger E, Leroyer C, Bressollette L, Nonent M, Le Moigne E, Bizais Y, Amiral J, Grimaux M, Clavier J, Ill P, Abgrall J-F, Mottier D. Evaluation of a new, rapid, and quantitative D-Dimer test in patients with suspected pulmonary embolism.

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Pulmonary embolism (PE) is a frequent and potentially severe disease. Its annual incidence in the United States has been estimated at 0.02 to 0.1% (1-3). Diagnosing PE is troublesome: clinical symptoms and signs are nonspecific and objective testing is necessary (4, 5). The most reliable method remains pulmonary angiography. However, angiography is invasive, with a morbidity rate of 1% and a mortality rate of 0.5%, and its availability is limited (6, 7). Diagnostic algorithms usually involve clinical probability, combined with ventilation and perfusion radionuclide lung imaging. If the perfusion study is normal, the diagnosis of PE can be excluded. A high probability radionuclide lung imaging associated with an intermediate or high clinical probability results in a diagnosis of PE. All other combinations require further investigations, as is the case in about 50% of patients with a clinical suspicion of PE (4, 5). In this instance, compression ultrasonography is a noninvasive and useful tool; a positive result supports the diagnosis of venous thromboembolism and may therefore avoid the need for angiography in as much as 40% of patients (8); however, a

normal lower limb compression ultrasonography does not rule out PE, and a pulmonary angiography is required. Such diagnostic algorithms, although validated, involve procedures that are unavailable in many centers in the evenings and on weekends.

Measurement of D-Dimer, which represents cross-linked fibrin degradation products, is a simple test and has potential advantages (9, 10). Many laboratory tests have been introduced for the D-Dimer assay, and they are primarily based on the use of specific monoclonal antibodies that are reactive with the neoepitope exposed on D-Dimer. In the event of suspected PE, D-Dimer enzyme-linked immunosorbent assay (ELISA) has demonstrated high sensitivity; thus, it has been suggested that the finding of a low concentration, usually less than 500 ng/ml, may rule out the development of PE (11-17). But ELISA assays are poorly suited for testing in an emergency setting since the kits are designed for batch assays and the results take several hours. Semiquantitative Latex agglutination assays are rapid, but their sensitivity is too low for them to be used as an exclusion test. New rapid D-Dimer assays have recently been developed, and pilot studies have proved promising; however, because of the limited number of patients tested, large confidence intervals of their diagnostic performances have been reported (18, 19).

Therefore, the aim of this prospective study was to evaluate the diagnostic performance of a new rapid, quantitative, and automated D-Dimer assay in a large group of consecutive patients with clinically suspected PE.

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Correspondence and requests for reprints should be addressed to Dr. Christophe Leroyer, Department of Internal Medicine and Chest Diseases, CHRU de la Cavale Blanche, F-29609, Brest Cedex, France.

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METHODS

Study Population

Since March 1992, data have been collected on a register of all consecutive patients with suspected PE admitted to our Medical Department of Internal Medicine and Chest Diseases. Recent clinical symptoms of PE had to be present, thus excluding subjects with symptoms that had been reported more than 7 d previously. In our institution, greater than 90% of patients with suspected PE are referred to this department. The clinical suspicion of PE took place prior to hospitalization, thus patients were referred for diagnosis, or during the first clinical examination on admission by the physician on duty at the emergency ward. Written informed consent was asked for in order to obtain blood samples for research purposes, including D-Dimer analysis.

Diagnosis Process

In the event of suspected PE, the diagnostic process was conducted by one of us (E.O., C.L., L.B., E.L.M., J.C., D.M.) as illustrated by the flowchart shown in Figure 1.

The medical history of each patient and the findings of the physical examination were recorded. Chest radiography and electrocardiography were performed. On the basis of these findings, we assessed a clinical probability of PE as low, intermediate, or high (20).

Ventilation-perfusion radionuclide lung imaging was performed within 24 hours of admission in all patients. Ventilation studies were performed with technetium-99m (^{99m}Tc) pyrophosphate radioaerosol, and six views were obtained. For the perfusion studies, 2 to 3 mCi of ^{99m}Tc macroaggregated albumin were injected intravenously; images consisted of anterior, posterior, and right and left anterior-oblique views. Abnormalities in perfusion and ventilation were graded, in accordance with PLOPED criteria (21), by a nuclear medicine reader unaware of our pretest clinical probability classification. If the radionuclide lung imaging was normal, PE was excluded. A high probability radionuclide lung imaging diagnosed PE. In all other combinations, lower limb investigations were conducted.

From March 1992 to December 1994, a contrast venography was performed. Then, after a 6-mo evaluation period, compression ultrasonography became the routine diagnostic procedure, and venography was performed only in the case of insufficient visualization of the veins by compression ultrasonography.

The ascending roentgenographic bilateral venography technique was used, using a bolus injection of low osmolar nonionic contrast medium (Omnipaque; Nycomed Imaging, Ås, Norway), via scalp needles inserted in a dorsal vein; tourniquets were placed around the lower third of the calf and around the lower third of the thigh. Six conventional films 30 × 120 cm were taken while the tourniquets were being sequentially removed. If the iliac veins and/or the vena cava

were not clearly visualized, digitalized venograms were taken after a unilateral or bilateral distal contrast medium injection. If the vena cava remained nonvisualized, digitalized proximal cavography was performed after a unilateral femoral injection. The diagnosis of a recent thrombus was based on the appearance of a constant intraluminal filling defect within an opacified vein. Thrombosis was considered as distal if only the calf veins (anterior tibial veins, posterior tibial veins, peroneal veins) below the trifurcation of the popliteal vein were involved. Thrombosis was considered as proximal if the deep veins in the pelvis, the thigh, and popliteal region proximal to the trifurcation, with or without calf-vein thrombosis, were involved. If patients had bilateral vein thrombosis, they were classified according to the more proximal extension of the thrombus.

Compression ultrasonography (Prisma Dasonics, Les Ulis, France) examined the superficial and the deep veins of the lower limbs, longitudinally and transversally, from the calf to the inferior vena cava, using 3.5- and 7.5-MHz transducers. The diagnosis of a recent thrombus was based on the finding of a direct intraluminal image, the absence of complete venous compressibility, and abnormalities of the doppler signal. If there was no intraluminal defect, a full venous compressibility, and a normal flow, the test results were considered as negative. In other cases, compression ultrasonography was considered as inconclusive, and a venography was performed.

Those patients with either a positive venography or a positive compression ultrasound were considered as having PE. In the event of a negative lower limb examination (venography or compression ultrasonography), we used both the findings of the radionuclide lung imaging and the pretest clinical probability: those patients with a very low or low radionuclide lung imaging probability combined with a low clinical probability were considered as free from PE. Otherwise, a pulmonary angiography was conducted, using a 5 French pigtail catheter directed into the main trunk of the pulmonary artery, and selective injections of both right and left pulmonary arteries were obtained. Forty milliliters of nonionic contrast medium were used at a flow rate of 20 ml/s in the main trunk and 25 ml at 15 ml/s in the right and left pulmonary arteries. Three views were taken (anteroposterior, both anterior oblique). Subtraction-digitalized images were obtained during injections with a minimal rate of six images per second. A PE was diagnosed if a persistent intraluminal defect was seen in more than one view.

Finally, according to these findings, patients were classified as PE-positive when one of the following occurred: (1) positive pulmonary angiography (diagnostic Level 1), (2) high probability radionuclide lung imaging (Level 2), (3) inconclusive radionuclide lung imaging and positive lower limb examination (Level 3) or PE-negative when one of the following occurred: (1) normal perfusion radionuclide lung imaging, (2) low clinical probability and very low or low radionuclide lung imaging probability in the absence of deep vein thrombosis on lower limb examination, (3) normal pulmonary angiography.

D-Dimer Analysis

Blood samples were collected within 24 h of presentation in plastic tubes containing 0.109 M sodium citrate at a ratio of nine parts blood to one part sodium citrate, and centrifuged for 10 min at $2,500 \times g$. Plasma was aliquoted and stored at -70°C . All samples were sent to the Serbio Research Laboratory at the end of the study, and both the standard ELISA assay (Asserachrom DDI; Stago, Asnières, France) and the new Liatest D-Dimer test (Stago) were performed. Each method was interpreted independently by separate biologists, blinded to all clinical results.

The standard ELISA method has been described elsewhere (22). This enzyme-linked immunosorbent assay is of the sandwich type and makes use of microtitration plates. D-Dimers are bound to murine antihuman D-Dimer monoclonal antibodies fixed on the surface of the wells of test plates. After incubation and washing using phosphate or TRIS-buffer, an excess of polyclonal rabbit anti-D-Dimer coupled with peroxidase was added to the test wells and bound to the fixed D-Dimer-anti-D-Dimer complex. The latter antibodies are specific for the degradation products of cross-linked fibrin. After washing the excess enzyme conjugated antibody, the amount of D-Dimer fixed to the wells was quantified by adding a substrate that converts to a colored substance using peroxidase.

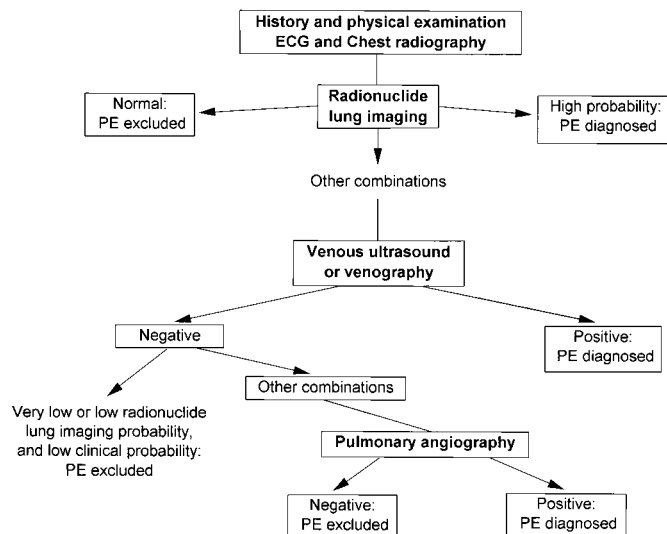


Figure 1. Diagnosis process.

TABLE 1

CHARACTERISTICS OF THE 386 CONSECUTIVE PATIENTS WITH CLINICALLY SUSPECTED PULMONARY EMBOLISM (PE)

Characteristics	PE Positive (n = 146)	PE Negative (n = 240)
Sex		
Female, n (%)	81 (55.5)	137 (57.1)
Male, n (%)	65 (44.5)	103 (42.9)
Age, yr, mean (SD)	67 (14.7)	60 (18.0)
Venous thrombosis present, n (%)	122 (83.5)	
Location		
Distal, n (%)	29 (19.9)	
Proximal, n (%)	93 (63.7)	
Diagnostic level*		
Level 1, n (%)	45 (30.8)	88 (36.7)
Level 2, n (%)	87 (59.6)	108 (45)
Level 3, n (%)	14 (9.6)	44 (18.3)

* For PE positive: Level 1 = positive pulmonary angiography; Level 2 = high probability radionuclide lung imaging; Level 3 = inconclusive radionuclide lung imaging and positive lower limb examination (venography or compression ultrasound). For PE negative: Level 1 = normal pulmonary angiography; Level 2 = normal perfusion radionuclide lung imaging; Level 3 = low clinical probability and very low or low radionuclide lung imaging probability in the absence of deep vein thrombosis on lower-limb examination.

The Liatest D-Dimer assay is a new quantitative and automated immunoassay that uses an immunoturbidimetric technology. A micro-latex suspension (chloro-methyl-polystyrene-latex particles of $0.1 \pm 0.02 \mu\text{m}$) was coated covalently with two complementary monoclonal antibodies specific for fibrin degradation products, then stabilized and stored at $0.075 \pm 0.025\%$ concentration. The assay was performed by mixing $50 \mu\text{l}$ of undiluted plasma with $100 \mu\text{l}$ of reaction buffer for 4 min at 37°C and the test was initiated with $150 \mu\text{l}$ of latex suspension. The test was fully automated: the change in absorbance, measured at 540 nm on a biochemical analyzer (STA; Stago), was automatically recorded for 140 s and represented a direct relationship of D-Dimer concentration in the specimen. The assay is precalibrated and allows a one-time testing on a walk-away instrument. Controls are run weekly since the calibration curve on the instrument is stable for at least 1 wk.

The results collected from both methods were expressed in nanograms per milliliter of fibrinogen equivalent units (FEU). The cutoff value was 500 ng/ml. This value is the standard cutoff for ELISA Asserachrom DDi and this is the 99th percentile of the D-Dimer distribution assayed by Liatest D-Dimer in a normal population (data provided by the Serbio laboratory).

Statistical Analysis

Firstly, to evaluate the diagnostic performances of the Liatest D-Dimer assay and the Asserachrom DDi (ELISA) assay, sensitivity, specificity, and negative and positive predictive values and their 95% confidence intervals (95% CI) were calculated according to standard methods for proportions (23).

Secondly, to evaluate the accuracy of D-Dimer measurement by this new Liatest assay, the agreement between the Asserachrom DDi (ELISA) assay and the Liatest D-Dimer assay was assessed by plotting the difference between the two methods against their mean and estimating the 95% confidence limits of agreement, according to the method described by Bland and Altman (24, 25).

RESULTS

From March 1992 to December 1996, 388 consecutive patients were registered with suspicion of a recent symptomatic PE. Of these, two patients (PE-negative) were excluded for insufficient plasma sampling. Three hundred eighty-six patients were kept for analysis. Mean age was 63 yr (range, 16 to 93 yr); 218 were women and 168 were men. Of the 386 patients, 146 (37.8%) were classified as PE-positive (Table 1). The diagnosis of PE was based on a high probability radionuclide lung

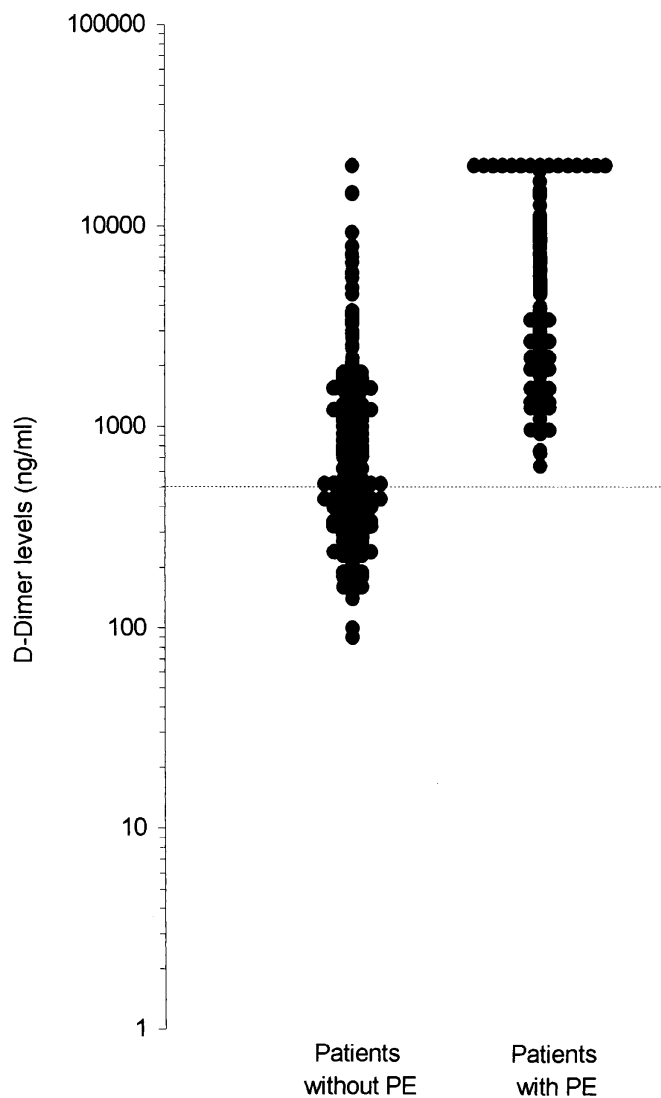


Figure 2. Distribution of D-Dimer concentrations, measured with Liatest D-Dimer, in patients with pulmonary embolism (PE) (n = 146) and without PE (n = 240). The horizontal dashed line indicates the cutoff at 500 ng/ml.

imaging in 87 patients, on a positive pulmonary angiography in 45 patients, and on the association of an inconclusive radionuclide lung imaging and a positive lower limb examination in 14 patients. Among the 146 PE-positive patients, 122 (83%) had a deep venous thrombosis (DVT), of whom 93 were proximal and 29 were distal. Two hundred and forty patients were classified as PE-negative.

The distribution of individual D-Dimer concentrations assessed with the Liatest D-Dimer assay, sorted according to the presence of PE, is shown in Figure 2. D-Dimer ELISA assays were available in 364 of 386 patients (in the remaining 22, insufficient blood sampling was obtained). The distribution of individual D-Dimer ELISA concentrations is shown in Figure 3. The diagnostic performance of this Liatest D-Dimer assay, using the cut-off value of 500 ng/ml, is shown in Table 2. Liatest D-Dimer test was positive in all PE-positive patients and in 157 PE-negative patients. Eighty-three patients with a clinical suspicion of PE (21%) had a D-Dimer level below 500 ng/ml. The diagnosis of PE was excluded by a normal pulmonary angiography in two patients, a normal radionuclide perfusion

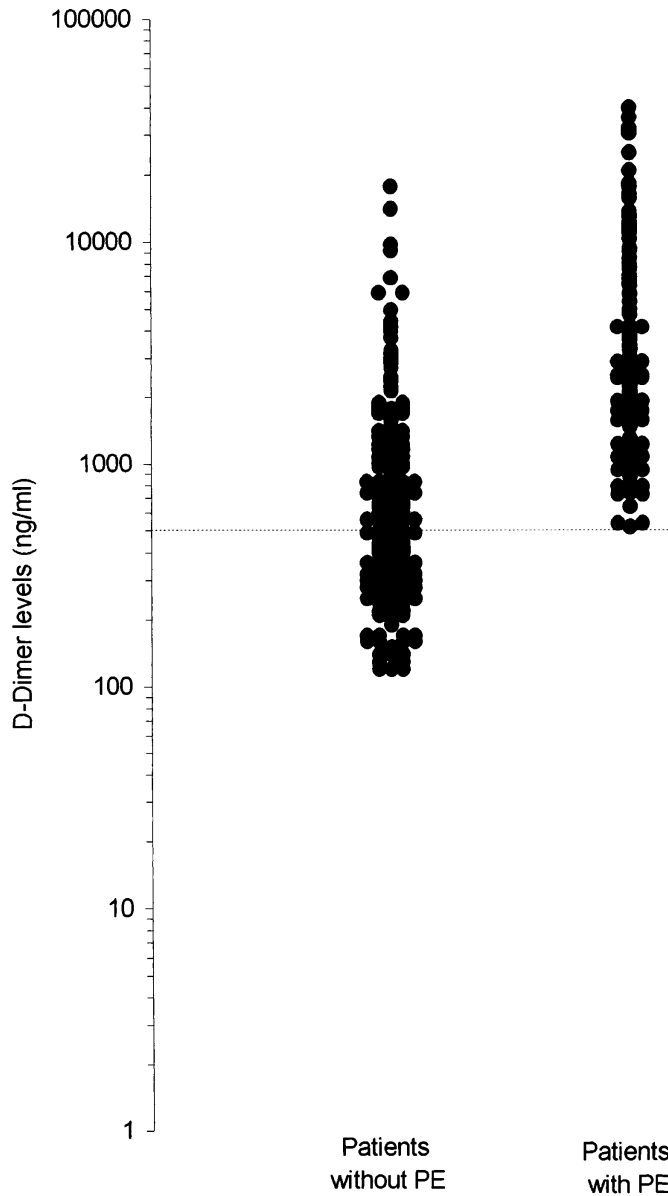


Figure 3. Distribution of D-Dimer concentrations, measured with Asserachrom DDi ELISA test, in patients with pulmonary embolism (PE) (n = 128) and without EP (n = 236). The horizontal dashed line indicates the cutoff at 500 ng/ml.

lung imaging in 66 patients, and the association of a normal venography or compression ultrasonography with a very low or low probability radionuclide lung imaging and a low clinical probability in the remaining 15 patients. Sensitivity reached 100% (95% CI, 97 to 100) and specificity was 35% (95% CI, 29 to 41); the negative predictive value reached 100% (95% CI, 94 to 100), and the positive predictive value was 48% (95% CI, 42 to 54). Asserachrom DDi (ELISA) test, using a cutoff of 500 ng/ml, showed the same performances (data not shown).

The agreement between the two methods (Liatest D-Dimer assay and Asserachrom DDi assay), by plotting the difference between the two measurements against their mean, is shown in Figure 4. This difference exceeded the 95% confidence limits of agreement in 11 of the 364 patients (3%). However, such

TABLE 2
DIAGNOSTIC PERFORMANCE OF LIATEST D-DIMER ASSAY IN THE 386 PATIENTS WITH CLINICALLY SUSPECTED PULMONARY EMBOLISM (PE)

Diagnosis	Liatest D-Dimer	
	< 500 ng/ml	≥ 500 ng/ml
PE-positive	0	146
PE-negative	83	157
Diagnostic Performances	Percentages (95% Confidence Intervals)	
Sensitivity	100 (97-100)	
Specificity	35 (29-41)	
Positive predictive value	48 (42-54)	
Negative predictive value	100 (94-100)	

differences were seen only for high D-Dimer levels, far above the cutoff point.

DISCUSSION

In this study of 386 patients referred to our institution for clinically suspected PE with recent clinical signs not exceeding a week, the rapid, quantitative and automated Liatest D-Dimer assay demonstrates its ability to exclude PE in the case of a result below the cutoff of 500 ng/ml. Eighty-three of these 386 patients (21%) might therefore have avoided a subsequent examination without failing to diagnose an acute PE.

To the best of our knowledge, two studies have previously evaluated a rapid D-Dimer assay that provides an exclusion diagnosis of PE in an emergency setting. The first study by Ginsberg and coworkers (18) used a whole blood assay, performed at the bedside within a few minutes. Sixteen of 86 pa-

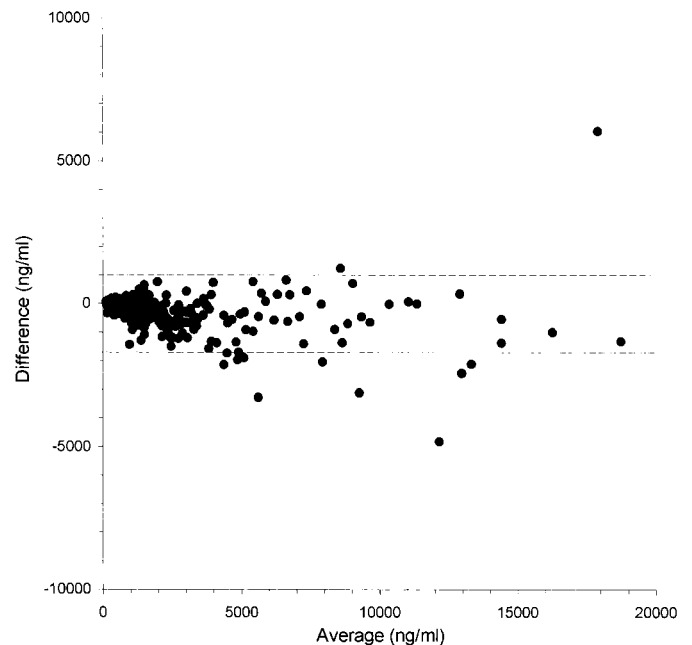


Figure 4. Difference against average of D-Dimer measured by Liatest and Asserachrom DDi, with 95% limits of agreement (dashed lines).

tients with clinically suspected PE had the diagnosis confirmed by objective tests, and the 95% CI for the sensitivity of the assay was 70 to 99. One possible drawback of this semi-quantitative method may lie in interobserver variability or in the lack of proper information available to the health care personnel in the emergency department. More recently, de Moerloose and coworkers (19) studied a quantitative and automated ELISA assay. This immunofiltration technique showed promising results in 195 patients suspected of PE: the 95% confidence interval was 92 to 100, and, during a 6-mo follow-up of 172/195 patients, no new suspicion of PE was found among those subjects with an initial D-Dimer level below the cutoff of 500 ng/ml. The applications of these two methods still require confirmation in large clinical trials.

In the present study, we have evaluated a new assay that may offer potential advantages, as a rapid and easy to perform test, appropriate for individual testing in an emergency setting. This assay on undiluted plasma is fully automated on the coagulation walk-away with STA instrument, with results appearing in less than 10 min. The Liatest D-Dimer test is a quantitative photometric test; the principle of measurement is based on the change in the absorbance of latex agglutination produced by D-Dimer; this change in absorbance is directly related to the D-Dimer concentration in the specimen. More importantly, there is a strong agreement with the standard ELISA method. For these reasons, major technical pitfalls caused by the lack of reproducibility or variation in the interpretation of D-Dimer results in day-to-day use should be avoided.

Other possible biases should be addressed. The comparison was blind and independent, and it was performed using objective tests and a validated strategy as the reference standard. However, the diagnostic standard for classifying patients as free from PE may be questioned. First, pulmonary angiography was performed in only 88 of the 240 patients (36.7%) labeled as PE negative. Second, PE was excluded by means of a normal perfusion radionuclide lung imaging in 108 patients (45%). Both approaches have been tested and confirmed in prospective studies (26). The third diagnostic level incorporated clinical impressions with low probability scans in patients free from deep vein thrombosis, and it ruled out PE in the remaining 44 patients (18.3%). False negative results may appear stronger in this latter subgroup; such bias, however, may appear unlikely because sensitivity of both D-Dimer techniques does not differ according to the diagnostic procedure. We included a large group of consecutive patients referred for a clinical suspicion of PE to a University Hospital; this group of patients represented an extensive spectrum of the disease. The prevalence of the disease was 37.8%. A lower prevalence in an outpatient setting might result in an increase in the negative predictive value of the test, which is already very high. Our results could be applied to a hospital emergency setting, but not to an inpatient population. On the one hand, inpatients with comorbid conditions would have higher levels of D-Dimer and, therefore, the sensitivity would not be affected; on the other hand, fewer inpatients would have D-Dimer levels below the cutoff of 500 ng/ml, thus lowering the clinical utility of such a front method. Finally, a selection bias may consist in excluding from this study those patients with symptoms exceeding 7 d; however, the time lag between the thrombosis event and diagnostic procedures may result in false negative D-Dimer results; thus, when faced with a clinically suspected PE showing old symptoms, these biologic tests may not be suitable.

A rapid, routinely available D-Dimer test with such performance characteristics challenges the diagnostic strategy of PE.

Should we use this D-Dimer assay alone as a front method, or should it be associated with other noninvasive tests for PE such as radionuclide lung imaging or compression ultrasonography (27–29)? Our study meets the previously established methodologic standards for research on testing (9), and the finding of such high sensitivity and negative predictive value may favor the first alternative. Three potential benefits might be expected for those patients with a negative D-Dimer test: reduction in hospitalization rate; avoidance of subsequent tests; and avoidance of unnecessary anticoagulation performed during routine diagnostic procedure. Multicenter patient management trials as well as cost-effectiveness studies should be undertaken in order to further confirm these hypotheses.

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References

- Anderson, F. A., H. B. Wheeler, R. J. Goldberg, D. W. Hosmer, N. A. Patwardhan, B. Jovanovic, A. Forcier, and J. E. Dalen. 1991. A population-based perspective of the hospital incidence and case-facility rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. *Arch. Intern. Med.* 151:933–938.
- Coon, W. W., P. W. Willis, and J. B. Keller. 1973. Venous thromboembolism and other venous diseases in the Tecumseh Community Health Study. *Circulation* 48:839–846.
- Gillum, R. F. 1987. Pulmonary embolism in the United States, 1970–1985. *Am. Heart J.* 113:1262–1264.
- Hirsh, J., and J. Hoak. 1996. Management of deep vein thrombosis and pulmonary embolism: a statement for healthcare professionals. *Circulation* 93:2212–2245.
- Ginsberg, J. S. 1996. Management of venous thromboembolism. *N. Engl. J. Med.* 335:1816–1828.
- Stein, P. D., C. Athanasoulis, and A. Alavi. 1992. Complications and validity of pulmonary angiography in acute pulmonary embolism. *Circulation* 85:462–468.
- Hudson, E. R., T. P. Smith, V. G. McDermott, G. E. Newman, P. V. Suhocki, C. S. Payne, and D. J. Stakhouse. 1996. Pulmonary angiography performed with iopamidol: complications in 1,434 patients. *Radiology* 198:61–65.
- Oudkerk, M., E. J. R. van Beek, W. L. J. van Putten, and H. R. Büller. 1993. Cost-effectiveness analysis of various strategies in the diagnostic management of pulmonary embolism. *Arch. Intern. Med.* 153:947–954.
- Becker, D. M., J. T. Philbrick, T. L. Bachhuber, and J. E. Humphries. 1996. D-Dimer testing and acute venous thromboembolism. *Arch. Intern. Med.* 156:939–946.
- Bounameaux, H., P. de Moerloose, A. Perrier, and G. Reber. 1994. Plasma measurement of D-Dimer as a diagnostic aid in suspected venous thromboembolism: an overview. *Thromb. Haemost.* 71:4–6.
- Goldhaber, S. Z., D. E. Vaughan, S. S. Tumei, and J. Loscalzo. 1988. Utility of cross-linked fibrin degradation products in the diagnosis of pulmonary embolism. *Am. Heart J.* 116:505–508.
- Bounameaux, H., P. A. Schneider, D. Slosman, P. de Moerloose, and G. Reber. 1990. Plasma D-dimer in suspected pulmonary embolism: a comparison with pulmonary angiography and ventilation-perfusion scintigraphy. *Blood Coagul. Fibrinolysis* 1:577–579.
- Demers, C., J. S. Ginsberg, M. Johnston, P. A. Brill-Edwards, and A. Panju. 1992. D-dimer and thrombin-antithrombin III complexes in patients with clinically suspected pulmonary embolism. *Thromb. Haemost.* 67:408–412.
- Ginsberg, J. S., P. A. Brill-Edwards, C. Demers, D. Donovan, and A. Panju. 1993. D-Dimer in patients with clinically suspected pulmonary embolism. *Chest* 104:1679–1684.
- Goldhaber, S. Z., G. R. Simons, C. G. Elliott, W. D. Haire, R. Toltzis, S. C. Blacklow, M. H. Doolittle, and D. S. Weinberg. 1993. Quantitative plasma D-Dimer levels among patients undergoing pulmonary angiography for suspected pulmonary embolism. *J.A.M.A.* 270:2819–2822.
- van Beek, E. J. R., B. van den Ende, R. J. Berckmans, Y. van der Heide, D. P. M. Brandjes, A. Sturk, and J. W. ten Cate. 1993. A comparative analysis of D-dimer assays in patients with clinically suspected pulmonary embolism. *Thromb. Haemost.* 70:408–413.
- Flores, J., C. Lancha, E. P. Rodrigues, A. G. Avello, E. Bollo, and L. J. G.

- Frade. 1995. Efficacy of D-dimer and total fibrin degradation products evaluation in suspected pulmonary embolism. *Respiration* 62:258-262.
18. Ginsberg, J. S., P. S. Wells, P. A. Brill-Edwards, D. Donovan, A. Panju, E. J. R. Beek, and A. Patel. 1995. Application of a novel and rapid whole blood assay for D-dimer in patients with clinically suspected pulmonary embolism. *Thromb. Haemost.* 73:35-38.
19. de Moerloose, P., S. Desmarais, H. Bounameaux, G. Reber, A. Perrier, G. Dupuy, and J. L. Pittet. 1996. Contribution of a new, rapid, individual and quantitative automated D-dimer ELISA to exclude pulmonary embolism. *Thromb. Haemost.* 75:11-13.
20. Stein, P. D., J. W. Henry, and A. Gottschalk. 1993. The addition of clinical assessment to stratification according to prior cardiopulmonary disease further optimizes the interpretation of ventilation/perfusion lung scans in pulmonary embolism. *Chest* 104:1472-1476.
21. The PIOPED Investigators. 1990. Value of the ventilation/perfusion scan in acute pulmonary embolism. *J.A.M.A.* 263:2753-2759.
22. Leroyer, C., M. Escoffre, E. Le Moigne, M. Grimaux, O. Cagnioncle, E. Oger, L. Bressollette, J. F. Abgrall, J. Amiral, and D. Mottier. 1997. Diagnostic value of a new sensitive membrane based technique for instantaneous D-dimer evaluation in patients with clinically suspected deep venous thrombosis. *Thromb. Haemost.* 77:637-640.
23. Fleiss, J. L. 1981. Inferences about a single proportion. In J. L. Fleiss, editor. *Statistical Methods for Rates and Proportions*. John Wiley and Sons, New York. 13-15.
24. Bland, J. M., and D. G. Altman. 1986. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 8476: 307-310.
25. Bland, J. M., and D. G. Altman. 1995. Comparing methods of measurement: why plotting difference against standard method is misleading. *Lancet* 346:307-310.
26. Grant, B. J. B. 1994. Noninvasive tests for acute venous thromboembolism. *Am. J. Respir. Crit. Care Med.* 149:1044-1047.
27. Perrier, A., H. Bounameaux, A. Morabia, P. de Moerloose, D. Slosman, P. F. Unger, and A. Junod. 1994. Contribution of D-dimer plasma measurement and lower-limb venous ultrasound to the diagnosis of pulmonary embolism: a decision analysis model. *Am. Heart J.* 124: 624-635.
28. Perrier, A., H. Bounameaux, A. Morabia, P. de Moerloose, D. Slosman, D. Didier, P. F. Unger, and A. Junod. 1996. Diagnosis of pulmonary embolism by a decision analysis-based strategy including clinical probability, D-dimer levels, and ultrasonography: a management study. *Arch. Intern. Med.* 156:531-536.
29. van Beek, E. J. R., B. E. Schenk, B. C. Michel, B. van den Ende, D. P. M. Brandjes, Y. T. van der Heide, P. M. M. Bossuyt, and H. R. Büller. 1996. The role of plasma D-dimer concentration in the exclusion of pulmonary embolism. *Br. J. Haematol.* 92:725-732.