Plasma Measurement of D-Dimer Levels for the Early Diagnosis of Ischemic Stroke Subtypes

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Background: Different coagulation abnormalities according to stroke subtypes have been reported. We have assessed the clinical utility of D-dimer, a product of fibrin degradation, in the early diagnosis of stroke subtypes.

Methods: Patients hospitalized after an acute ischemic cerebrovascular event underwent D-dimer assay (STA Liatest D-Dimer) (reference level, <0.50 µg/mL) on days 1, 6 ± 1, and 12 ± 1 and were studied to identify stroke subtypes.

Results: We included 126 patients (mean age, 75.5 years) and 63 age-matched control subjects. Stroke subtypes were cardioembolic in 34 patients (27%), atherothrombotic in 34 (27%), lacunar in 31 (25%), and unknown in 27 (21%). At all 3 measurements, D-dimer levels were significantly higher in the cardioembolic group (mean ± SEM, 2.96 ± 0.51, 2.58 ± 0.40, and 3.79 ± 0.30 µg/mL, respectively) than in the atherothrombotic (1.34 ± 0.21,

1.53 ± 0.26, and 2.91 ± 0.23 µg/mL, respectively) (*P*<.05) and lacunar (0.67 ± 0.08, 0.72 ± 0.15, and 0.64 ± 0.06 µg/mL, respectively) groups (*P*<.01). The difference was also significant between the latter 2 groups (*P*<.01). We found no difference between the lacunar group and controls (0.53 ± 0.14 µg/mL). According to day 1 measurements, the optimal cutoff point for predicting cardioembolic stroke was 2.00 µg/mL, resulting in a specificity of 93.2% and in a sensitivity of 59.3%. For predicting lacunar stroke, the cutoff point was 0.54 µg/mL, with a specificity of 96.2% and a sensitivity of 61.3%.

Conclusion: The increasing use of the D-dimer assay in clinical practice could be extended to patients presenting with acute cerebrovascular ischemic events to help predict stroke subtype.

Arch Intern Med. 2002;162:2589-2593

O NE OF the first objectives in the management of patients presenting with acute ischemic stroke is the diagnosis of the subtype. Advances in the diagnostic evaluations of stroke have helped to identify the most common mechanisms, such as atherosclerosis, cardiac embolism, and lacunae. However, as many as 40% of all ischemic events can remain classified as cryptogenic, because no potential mechanisms are detected or because more than 1 mechanism has been recognized.[1,2] In the early 1990s, a number of clinical studies[3-6] have shown an abnormal hemostatic function in patients with cerebral ischemia. Markers of fibrin formation were found to be significantly increased after acute ischemic stroke[3,4] and transient ischemic attack (TIA)[5]; most of all, their levels significantly differed according to stroke subtype.[6] When Takano and colleagues[6] hypothesized that assessment of hematologic variables could provide a useful marker for the early classification of stroke subtypes, none of the coagulation and fibrinolytic variables that were evaluated were available in routine clinical practice. In the past decade, one of these variables, D-dimer, a specific product of degradation of cross-linked fibrin, has gained a wide popularity after the results of a number of studies proved its potential role in the diagnostic approach of venous thromboembolic disorders.[7] Reference concentrations of plasma D-dimer (usually <0.50 µg/mL) are a useful negative predictor to rule out venous thromboembolism in patients with clinical suggestions,[8] and several D-dimer assays are now available in many clinical settings for rapid emergency testing. Our study aimed to confirm the results of previous reports and to suggest the potential clinical utility of measurement of plasma D-dimer levels in the early diagnosis of ischemic stroke or TIA subtypes when used as an emergency test in addition to the routine clinical and instrumental assessments.

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METHODS

From September 1, 1998, through December 31, 1999, we enrolled into the study patients

Table 1. Demographic Data*

	Sex, No. M/F	Mean Age, y
Healthy controls (n = 63)	31/32	75.4
TIA (n = 40)	18/22	75.6
Ischemic stroke (n = 86)	44/42	75.7

*TIA indicates transient ischemic attack.

admitted to the University Hospital of Varese, Italy, with a clinical diagnosis of acute ischemic stroke or TIA according to the definition of the World Health Organization.[9] Immediately after their arrival at the emergency department, or, at latest, the morning after, all patients underwent a computed tomographic scan of the brain to rule out hemorrhagic stroke or other intracerebral processes. During hospital admission, the possible mechanism of the ischemic event was assessed by means of electrocardiography, echocardiography (SONOS 5500; Agilent Technologies, Milan, Italy; probe S4 MHz), and duplex ultrasonography of the cervical arteries (Agilent Sonos 5500; probe 3-11L MHz). Stroke subtype was then classified according to the criteria of the Baltimore-Washington Cooperative Young Study and the Oxfordshire Community Stroke Project.[10,11] Evaluation of stroke severity was performed using the Unified Neurological Stroke Scale.[12] Patients were excluded if they had conditions known to independently affect D-dimer levels, such as the concomitant use of anticoagulants, sepsis, malignancy, acute venous thromboembolism, collagenopathy, recent surgery or trauma, or acute myocardial infarction that occurred in the preceding 10 days. We first measured D-dimer levels in the morning after hospital admission (day 1) and then after 6 ± 1 and 12 ± 1 days to evaluate possible changes in the subacute phase according to the different subtype groups. For comparison, D-dimer levels were also measured in a control group of age-matched healthy subjects.

BLOOD SAMPLING AND BIOCHEMICAL ASSAY

Blood samples were mixed with one-tenth volume of 3.8% sodium citrate anticoagulant and immediately centrifuged at 3000 rpm for 10 minutes. The plasma was divided into aliquots and frozen at –80°C until assayed. Plasma samples was stored with clinical investigators masked to plasma D-dimer levels until a clinical and instrumental definition of stroke subtype was obtained. Levels of D-dimer were measured by means of the STA Liatest D-Dimer assay (Roche Diagnostics SpA, Milan). This D-dimer assay is a new quantitative and automated immunoassay that uses an immunoturbidimetric technology. A microlatex suspension (chloromethyl-polystyrene latex particles) was coated covalently with 2 complementary monoclonal antibodies (8D2 and 2.1.16) specific for fibrin degradation products. The assay was performed by mixing 50 µL of undiluted plasma with 100 µL of reaction buffer for 4 minutes at 37°C, and the test was initiated with 150 µL of latex suspension. The test was fully automated; the change in absorbance, measured at 540 nm on a biochemical analyzer (STA Compact; Roche Diagnostics SpA), was automatically recorded for 140 seconds and represented a direct relationship of D-dimer concentration in the specimen. The assay was precalibrated and allowed 1-time testing on a walkaway instrument. Controls were run weekly, since the calibration curve on the instrument is stable for at least 1 week. The results collected were expressed in micrograms per milliliter of fibrinogen equivalent units. The term *fibrinogen equivalent* refers to the amount of fibrinogen used in the production of the standards. The intra-assay coefficient of variation was below 5%, and the interassay coefficient of variation

was below 6%. The detection threshold is 0.20 µg/mL. The dynamic range was from 0.20 to 20 µg/mL. The upper reference limit was 0.50 µg/mL. All procedures were conducted in accordance with the Declaration of Helsinki.

STATISTICAL ANALYSIS

Data are expressed as mean ± SEM. We evaluated differences between 2 or more groups using the Mann-Whitney rank sum test and the Kruskal-Wallis 1-way analysis of variance. We used the Bonferroni method to correct for multiple comparisons, and linear regression analysis to compare D-dimer levels and the scores for stroke severity. $P<.05$ was considered statistically significant. Statistical analyses were performed with SPSS 8.0 software (SPSS Inc, Chicago, Ill).

To determine the clinical performance of the D-dimer assay for stroke subtypes, we constructed diagnostic sensitivity, specificity, positive and negative predictive values, positive likelihood ratio (sensitivity/[1 – specificity]), negative likelihood ratio ([1 – sensitivity]/specificity), and receiver operating characteristic (ROC) curves from individual admission data. The ROC curves and the areas under the ROC curves were calculated with MedCalc software 4.3 for Windows programs (MedCalc Software, Mariakerke, Belgium).

RESULTS

We initially enrolled 178 patients who presented with suspected acute ischemic stroke or TIA and 63 healthy controls in the study. All these patients had at least 1 blood sample drawn for the assessment of plasma D-dimer levels. In 8 of the 178 patients, the initial diagnosis subsequently failed to be confirmed. In 1 patient, the second computed tomographic scan of the brain showed small metastases that were not visible in the previous one performed at the emergency department, and in 7 patients the initial diagnosis of a suspected TIA was subsequently denied (2 patients had convulsions, 2 had vertigo, and 3 had an isolated syncope). Plasma D-dimer levels were within the reference range (<0.50 µg/mL) in 7 patients and slightly abnormal in the patient with malignancy. Exclusion criteria were subsequently identified in 44 patients. An acute infection developed in 29. Ten had malignancy; 7, a recent trauma; 2, a recent acute myocardial infarction; 1, deep vein thrombosis in the hospital; 1, a recent surgical procedure; and 1, a chronic rheumatologic disorder (rheumatoid arthritis). Although the primary end point of the study was the correlation between stroke subtype and D-dimer level measured on admission, patients were also excluded if the criterion was identified during hospitalization to not interfere with the subsequent assays. Of the 126 remaining patients, 40 had a TIA (mean age, 75.6 years; 18 men) and 86 had an acute ischemic stroke (mean age, 75.7 years; 44 men) (**Table 1**). Among the 63 healthy controls, the mean age was 75.4 years and 31 were men. We initially compared the 3 measures of D-dimer levels among the patients with acute ischemic stroke, those with TIA, and controls (with a single measure). Patients with stroke and TIA had significantly higher D-dimer levels than controls at all 3 measurements, whereas no statistical difference was found in any of the measurements between the patients with stroke and TIA (**Table 2**). No correlation was found between D-dimer levels and stroke severity as assessed using the Unified Neurological Stroke Scale ($r=0.2284$). We subse-

quently compared D-dimer levels according to stroke subtypes. Among the 126 patients undergoing evaluation, 34 (27%; mean age, 79.9 years) had a cardioembolic event; 34 (27%; mean age, 74.1 years), an atherothrombotic event; 31 (25%; mean age, 74.7 years), a lacunar event; and 27 (21%; mean age, 74.1 years), an unknown mechanism of acute cerebrovascular ischemia (**Table 3**). Mechanisms for the cardioembolic event were atrial fibrillation in 21 patients receiving aspirin or not receiving any antithrombotic prophylaxis, congestive heart failure in 8, severe mitral valve disease in 3, ischemic heart disease in 1, and heart valve replacement with a mechanical valve in 1 who spontaneously stopped warfarin sodium treatment 1 week before the event. On day 1, D-dimer levels were significantly higher in the groups of patients with a cardioembolic stroke or a TIA (2.96±0.51 µg/mL) than in the groups with an atherothrombotic (1.34±0.21 µg/mL; $P<.05$) or a lacunar (0.67±0.08 µg/mL; $P<.01$) event (Table 3). There was also a statistically significant difference between these latter 2 groups ($P<.01$), whereas no difference was shown between patients with lacunar events and controls. According to these results, the optimal D-dimer level cutoff point for discriminating the presence or absence of a cardioembolic source was determined to be 2.00 µg/mL, with a specificity of 93.2%, a sensitivity of 59.3%, a positive predictive value of 72.7%, and a negative predictive value of 88.2% (**Table 4** and **Figure 1**). On the other hand, the optimal cutoff point for discriminating a lacunar event was determined to be 0.54 µg/mL, with a specificity of 96.2%, a sensitivity of 61.3%, a positive predictive value of 86.4, and a negative predictive value of 86.2% (Table 4 and **Figure 2**). After 6±1 days, D-dimer levels were substantially stable in all 3 groups, whereas after 12±1 days, we found a clear increase in the cardioembolic and atherothrombotic groups, but no change in the lacunar group (Table 3).

Table 2. D-Dimer Levels*

Groups	D-Dimer Level, Mean ± SEM, µg/mL		
	Day 1	Day 6 ± 1	Day 12 ± 1
Control subjects	0.53 ± 0.14	. . .	. . .
Patients			
TIA	1.17 ± 0.35†	1.37 ± 0.26†	2.15 ± 0.43†
Acute ischemic stroke	1.74 ± 0.13‡§	1.66 ± 0.18‡||	2.73 ± 0.34‡¶

*TIA indicates transient ischemic attack.
†$P<.05$, patients with TIA vs controls.
‡$P<.05$, patients with acute ischemic stroke vs controls.
§$P = .10$ compared with patients with TIA.
||$P = .09$ compared with patients with TIA.
¶$P = .08$ compared with patients with TIA.

Table 3. D-Dimer Levels According to Stroke Subtypes*

Stroke Subtype	D-Dimer Level, Mean ± SEM, µg/mL		
	Day 1†	Day 6 ± 1‡	Day 12 ± 1§
CE (n = 34)	2.96 ± 0.51	2.58 ± 0.40	3.79 ± 0.53
AT (n = 34)	1.34 ± 0.21	1.53 ± 0.26	2.91 ± 0.59
LAC (n = 31)	0.67 ± 0.08	0.72 ± 0.06	0.64 ± 0.10
CRY (n = 27)	1.08 ± 0.15	1.19 ± 0.17	1.72 ± 0.30

*CE indicates cardioembolic; AT, atherothrombotic; LAC, lacunar; and CRY, cryptogenic.
†AT vs LAC, $P = .01$; AT vs CE, $P = .02$; CE vs LAC, $P = .009$; AT vs CRY, $P = .77$; CE vs CRY, $P = .003$; and LAC vs CRY, $P = .04$.
‡AT vs LAC, $P = .002$; AT vs CE, $P = .02$; CE vs LAC, $P = .009$; AT vs CRY, $P = .72$; CE vs CRY, $P = .01$; and LAC vs CRY; $P = .01$.
§AT vs LAC, $P = .03$; AT vs CE, $P = .02$; AT vs LAC, $P = .009$; AT vs CRY, $P = .06$; CE vs CRY, $P = .01$; and LAC vs CRY, $P = .05$.

COMMENT

The results of our study demonstrate that D-dimer levels significantly differ among stroke subtypes after an acute ischemic event and that measurement of D-dimer levels can be reliable in the early diagnosis of the mechanism underlying the acute cerebrovascular disorder. Our results support previous pathophysiological findings and suggest some important clinical implications. As described by Fisher and Francis[4] and by Takano and colleagues,[6] significant differences exist in the levels of plasma D-dimer among stroke subtypes. This finding seems to apply also to patients presenting with a TIA. Despite the rapid reversibility of the clinical signs, D-dimer levels remain increased for at least 2 weeks. These data support those of Fon and colleagues,[5] who showed a persisting increase in D-dimer levels 1 and 3 months after the acute event in patients with TIA and are in contrast with those of Fisher and Francis,[4] who failed to show a correlation between D-dimer levels and TIA.

Hemostatic abnormalities after cerebral ischemia apparently are not related to the extent of the neurological damage, in terms of clinical severity or duration of the symptoms, but to the mechanism responsible for the cerebrovascular ischemia. Patients with cardioembolic events have significantly higher levels than patients with different etiologic factors, and patients with lacunar events have D-dimer levels within the reference range, thus suggesting the possibility of a nonthrombotic mechanism underlying the occlusion of small vessels. Thrombus formation in the cardiac chambers is in most cases caused by blood stasis, leading to a fibrin-rich clot very similar to venous thrombi. Thrombi originating in the large arteries are mostly platelet rich, and fibrin formation is secondary to platelet activation. Finally, little is known about the mechanism responsible for small penetrating artery occlusion. Fisher and Francis[4] hypothesized that in subjects with lacunar disease, thrombi are too small to produce detectable elevations of plasma D-dimer levels. Another possibility is a nonthrombotic, lipohyalinotic, degenerative process of the vessel walls related to arterial hypertension or diabetes.

The results of our study support the clinical utility of D-dimer testing in the emergency setting. Previous reports were based on assays performed with the reference standard method, the enzyme-linked immunosorbent assay. In clinical practice, these conventional enzyme-linked immunosorbent D-dimer assays are of little use, because they are very labor intensive and time-consuming and because they are designed for batch analysis, not a routine emergency test.[13] The STA Liatest D-Dimer assay used in this study is a fully automated quantitative latex assay and offers several advantages because it is simple and rapid to perform. It has been compared with excellent results

Table 4. Predictive Value of D-Dimer Assay

Stroke Subtype	Cutoff D-Dimer Value, µg/mL	Sensitivity, % (95% CI)	Specificity, % (95% CI)	NPV, %	PPV, %	LR+	LR−
Cardioembolic	>2.00	59.3 (38.8-77.6)	93.2 (85.7-97.4)	88.2	72.7	8.69	0.44
Lacunar	<0.54	61.3 (42.2-78.1)	96.2 (89.2-99.2)	86.4	86.2	15.94	0.40

*CI indicates confidence interval; NPV, negative predictive value; PPV, positive predictive value; LR+, positive likelihood ratio; and LR−, negative likelihood ratio.
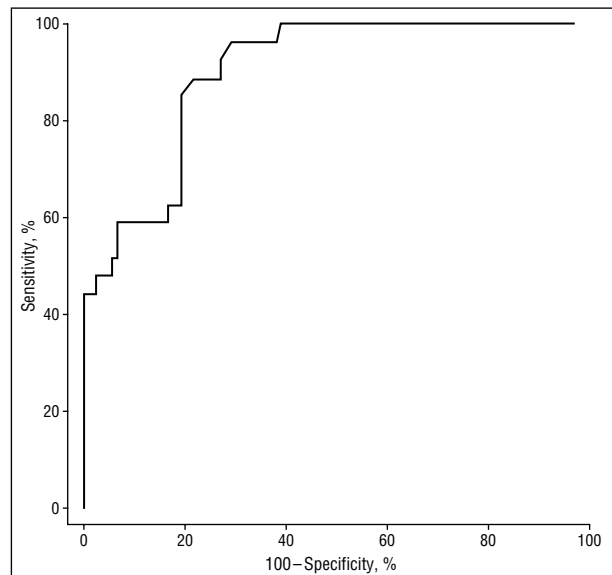
Figure 1. Receiver operating characteristic curve for cardioembolic subtypes with a D-dimer level of greater than 2.00 µg/mL. Sensitivity was 59.3%; specificity, 93.2%.
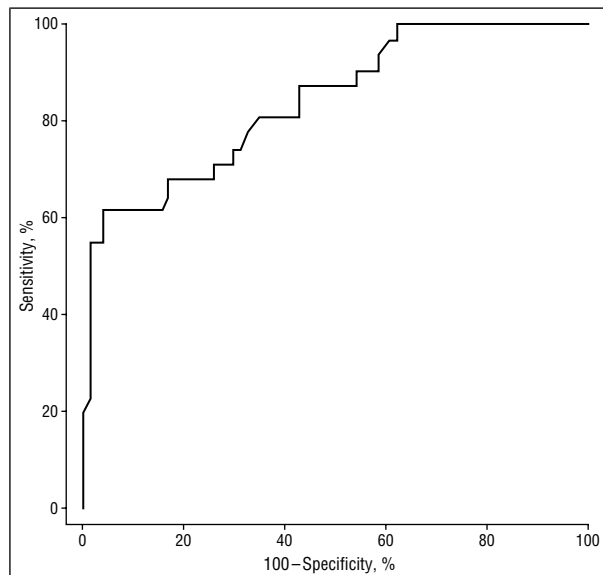
Figure 2. Receiver operating characteristic curve for lacunar subtypes with a D-dimer level of less than 0.54 µg/mL. Sensitivity was 61.3%; specificity, 96.2%.

with reference standard methods in the field of venous thromboembolism.[14-16] We suggest that levels above the cutoff point of 2.00 µg/mL should offer a reliable suspect for a cardioembolic source and that levels below 0.54 µg/mL can be diagnostic for a lacunar event in the absence of clear alternative hypotheses. In addition to the standard procedures, measurement of D-dimer levels in patients presenting with an acute ischemic cerebrovascular event can be a specific marker to rapidly address the diagnosis in the emergency department, to direct more aggressive diagnostic procedures, or to address secondary prevention when a diagnosis has not been reached, despite results of instrumental tests.

Our study presents some practical limitations. First, our results are based on etiologic classifications proposed by other groups. When such guidelines were applied, the clinical accuracy of the initial stroke subtype diagnosis was shown to be subsequently confirmed in only 62% of the cases.[2] Second, no extra tests were systematically performed to search for less common causes of stroke, and some cases of patent foramen ovale or aortic arch atheroma, to name a few, may have been missed. Most of our patients with a cardioembolic stroke or TIA had atrial fibrillation, which is the most frequent cause. The presence of increased plasma levels of D-dimer in patients with atrial fibrillation was already shown.[17-19] The results observed in the cardioembolic group might have been partly influenced by the hemostatic abnormalities

of atrial fibrillation. Third, in the diagnostic approach of venous thromboembolism, the D-dimer assay is approved as a negative predictor to rule out deep vein thrombosis or pulmonary embolism. It has a low specificity because several conditions such as sepsis, malignancy, recent trauma or surgery, and recent thrombosis can increase D-dimer levels. In the diagnostic approach of a cardioembolic stroke, it is of paramount importance to rule out all of these concomitant conditions.

A future direction for the use of the D-dimer assay can be in the choice of the best treatment for secondary prevention. Lip and colleagues[19] have previously shown that warfarin but not aspirin reduces plasma D-dimer levels in patients with atrial fibrillation. The benefit of oral anticoagulants in patients with atherothrombotic strokes or TIAs has been suggested but not yet proved. It is likely that some but not all patients receive more benefit from warfarin than from antiplatelet agents. As already suggested by Lowe and Rumley,[20] high levels of D-dimer may suggest a role for anticoagulants, even in noncardioembolic strokes.

CONCLUSIONS

The plasma D-dimer assay is a simple method now easily available as an emergency test that can reliably identify stroke subtypes in association with the common routine instrumental tests. Further clinical studies with dif-

ferent assays are warranted to support these findings and to test the possibility of incorporating the D-dimer assay in diagnostic decision trees.

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