Barber, M., Langhorne, P., Rumley, A., Lowe, G.D.O. and Stott, D.J. (2006) *D-dimer predicts early clinical progression in ischemic stroke: confirmation using routine clinical assays.* Stroke, 37 (4). pp. 1113-1115. ISSN 0039-2499

http://eprints.gla.ac.uk/23070/

Deposited on: 23 January 2012

Stroke

American Stroke Association.

A Division of American Heart Association

d-Dimer Predicts Early Clinical Progression in Ischemic Stroke : Confirmation Using Routine Clinical Assays

Mark Barber, Peter Langhorne, Ann Rumley, Gordon D.O. Lowe and David J. Stott

The online version of this article, along with updated information and services, is
located on the World Wide Web at:

http://stroke.ahajournals.org/content/37/4/1113

D-Dimer Predicts Early Clinical Progression in Ischemic Stroke

Confirmation Using Routine Clinical Assays

Mark Barber, MD, MRCP; Peter Langhorne, PhD, FRCP; Ann Rumley, PhD;
Gordon D.O. Lowe, MD, FRCP; David J. Stott, MD, FRCP

Background and Purpose—Plasma D-dimer levels, measured using a research laboratory assay, independently predict progressing ischemic stroke. We wished to confirm these findings using commercially available assays and to provide data to allow the design of intervention studies.

Methods—We studied 219 consecutive acute ischemic stroke admissions of whom 54 (25%) met criteria for progressing stroke.

Results—There were strong correlations between D-dimer results as measured by the Biopool AB, MDA and VIDAS assays; correlation coefficients $r=0.91$ to 0.94; all $P<0.001$. In binary logistic regression analyses, D-dimer, as measured by the 3 different assays, was an independent predictor of progressing stroke (odds ratios, 1.87 to 2.45; all $P<0.001$). This confirms the results of our original analysis (Biopool AB) using 2 commercial D-dimer assays, demonstrating the potential usefulness of D-dimer in providing early prognostic information after ischemic stroke in different clinical settings. We also provide information on the performance of the 3 assays in predicting progressing stroke at a variety of cutoff values.

Conclusions—Ischemic stroke patients at high risk of early progression can be identified using commercial D-dimer measurements. This could allow selection of high-risk patients for inclusion in randomized trials of early antithrombotic treatments. (***Stroke***. 2006;37:1113-1115.)

Key Words: anticoagulants ■ cerebral infarction ■ coagulation ■ fibrin ■ fibrinogen
■ fibrinolysis ■ thrombin

Early clinical progression of ischemic stroke is common and is associated with poor prognosis.[1] D-dimer levels are elevated in the acute phase of stroke and subsequently fall.[2–4] We previously demonstrated that plasma D-dimer levels (along with mean arterial blood pressure) independently predict progressing ischemic stroke.[5] This measurement of D-dimer was performed with a commercially available ELISA from Biopool AB used in our research laboratory. We wished to confirm our findings using other commercially available assays commonly used by hospital laboratories, particularly the MDA and VIDAS D-dimer assays.

Materials and Methods

We studied consecutive ischemic stroke admissions.[5] Progressing stroke was defined using a modification of the European Progressing Stroke Study definition.[6] This requires deterioration in conscious level, arm or leg weakness, or speech over 72 hours following admission. Blood was taken within 24 hours of symptom onset, and plasma samples were stored at $-80°C$ before analysis. The MDA D-dimer assay is an automated latex particle-based immunoassay, and the VIDAS D-dimer assay is an automated enzyme-linked fluorescent assay.[7]

Univariate analysis of D-dimer levels used unpaired t tests of natural log-transformed levels. Correlations between the different assays were calculated using the Spearman rank method. Multivariate analysis was performed using a stepwise binary logistic regression procedure including variables when significance was found to be $P<0.10$ in univariate analysis.

Results

Fifty-four (25%) of the 219 patients recruited met the criteria for progressing stroke. Results were unavailable for 7 of the MDA D-dimer assays and 5 of the VIDAS D-dimer assays. There were strong correlations between D-dimer results as measured by the 3 assays: correlation coefficient $r=0.94$ between the Biopool AB and MDA assays; $r=0.92$ between the Biopool AB and VIDAS assays; and $r=0.91$ between the MDA and VIDAS assays (all $P<0.001$). Median D-dimer levels were higher in the progressing stroke group compared

TABLE 1. Logistic Regression Model of Independent Predictors of Progressing Ischemic Stroke, Including D-Dimer, by the MDA assay (a) and the VIDAS assay (b)

	B (SE)	r	Odds Ratio	P Value
a) Constant	−8.989 (1.884)			
MABP (per 10 mm Hg)	0.238 (0.093)	0.146	1.27	0.01
Natural log D-dimer	0.856 (0.217)	0.252	2.35	0.0001
b) Constant	−9.846 (2.028)			
MABP (per 10 mm Hg)	0.219 (0.092)	0.130	1.24	0.02
Natural log D-dimer	0.894 (0.217)	0.263	2.45	<0.0001

MABP indicates mean arterial blood pressure.

with the group with no progression using both the MDA assay (597 versus 348 ng/mL; $P=0.00002$) and the VIDAS assay (863 versus 407 ng/mL; $P=0.00002$). The results of the binary logistic regression analyses for the MDA and VIDAS D-dimer assays are shown in Table 1. These results were very similar to those of the original analysis using the Biopool AB ELISA.[5] Table 2 shows the sensitivity, specificity, and positive predictive values for progressing stroke at percentile cutoffs using the 3 assays.

Discussion

We confirmed the results of our original analysis using 2 alternative and commonly used routine D-dimer assays. This confirms the potential usefulness of D-dimer in providing early prognostic information after ischemic stroke in different clinical settings. As a test, D-dimer has the advantage over other measures of thrombin generation (such as prothrombin fragment 1+2 and thrombin–antithrombin complex levels) in that levels are resistant to ex vivo activation and have a long half-life. The VIDAS assay has already been recently shown to be of potential clinical value in prediction of a high-risk group for proximal deep vein thrombosis among patients with acute stroke.[8]

We also provide information on the performance of the 3 assays at different cutoff values. It appears that the MDA and VIDAS D-dimer assays may perform marginally better than the Biopool assay as predictors of progressing ischemic stroke. This may reflect the fact that the Biopool assay we used has been set up to have greater analytical sensitivity at lower levels (important for epidemiological studies).

Strengths and weaknesses of this study are those of the original project.[5] We studied a large consecutive group of subjects using few exclusion criteria. A single researcher assessed all patients. However, samples were taken within 24 hours of symptom recognition, rather than immediately, and detailed functional imaging was not performed as part of the study protocol.

Previous studies specifically designed to assess prevention of progressing stroke using anticoagulant or antiplatelet therapy have been negative[9–11] (perhaps, in part, because a high-risk subgroup was not identified for recruitment). If, as we suggested previously, D-dimer is used to help target interventions aimed at preventing early neurological deterioration after acute ischemic stroke, then appropriate cutoff levels can be chosen for these different assays depending on the potential risks and benefits of the intervention used.[5] For example, levels above the median (401 ng/mL for MDA; 513 ng/mL for VIDAS) identify 50% of patients in whom the risk of early progression is 33% compared with a risk of 16% in patients with below-median levels. Higher-risk groups for early (ischemic) progression, identified in this way, may merit consideration for randomized trials of early antithrombotic treatments (for example, heparins or new antiplatelet agents). Such trials of selective antithrombotic treatment should record neuroimaging data, stroke etiology, and the causes of progressing stroke. In addition, blood samples should be withdrawn earlier. These studies should ideally include, as end points, not only progressing stroke along with the modified Rankin scale and Barthel Index (the latter 2 at 3 months), but also venous thromboembolism.[8]

TABLE 2. Sensitivity, Specificity, and Positive Predictive Values for Progressing Stroke at Percentile Cutoffs Using the 3 D-Dimer Assays

D-Dimer Assay	Percentile	Value, ng/mL	Sensitivity	Specificity	Positive Predictive Value
Biopool AB	90th	1362	9/54 (17%)	151/164 (92%)	9/22 (41%)
	75th	586	21/54 (39%)	131/164 (80%)	21/54 (39%)
	50th	229	37/54 (69%)	92/164 (56%)	37/109 (34%)
	25th	105	49/54 (91%)	49/164 (30%)	49/164 (30%)
MDA	90th	1294	11/52 (21%)	150/160 (94%)	11/21 (52%)
	75th	672	23/52 (44%)	130/160 (81%)	23/53 (43%)
	50th	401	35/52 (67%)	89/160 (56%)	35/106 (33%)
	25th	211	47/52 (90%)	48/160 (30%)	47/159 (30%)
VIDAS	90th	1749	11/53 (21%)	151/161 (94%)	11/21 (52%)
	75th	964	23/53 (43%)	131/161 (81%)	23/53 (43%)
	50th	513	35/53 (66%)	89/161 (55%)	35/107 (33%)
	25th	277	47/53 (89%)	47/161 (29%)	47/161 (29%)

an NHS Education for Scotland/Chief Scientist Office clinical research fellow. The kits for MDA and VIDAS assays of D-dimer were supplied by bioMérieux.

References

1. Rödén-Jüllig Å. Progressing stroke: epidemiology. *Cerebrovasc Dis.* 1997;7(suppl 5):2–5.
2. Lip GYH, Blann AD, Farooqi IS, Zarifis J, Sagar G, Beevers DG. Sequential alterations in haemorheology, endothelial dysfunction, platelet activation and thrombogenesis in relation to prognosis following acute stroke: the West Birmingham Stroke Project. *Blood Coagul Fibrinolysis.* 2002;13:339–347.
3. Haapaniemi E, Soinne L, Syrjala M, Kaste M, Tatlisumak T. Serial changes in fibrinolysis and coagulation activation markers in acute and convalescent phase of ischemic stroke. *Acta Neurol Scand.* 2004;110:242–247.
4. Reganon E, Vila V, Martinez-Sales V, Vaya A, Lago A, Alonso P, Aznar J. Association between inflammation and hemostatic markers in athero-thrombotic stroke. *Thromb Res.* 2003;112:217–221.
5. Barber M, Langhorne P, Rumley A, Lowe GDO, Stott DJ. Hemostatic function and progressing ischemic stroke: D-dimer predicts early clinical progression. *Stroke.* 2004;35:1421–1425.
6. Barber M, Stott DJ, Langhorne P. An internationally agreed definition of progressing stroke. *Cerebrovasc Dis.* 2004;18:255–256.
7. Houbouyan-Reveillard LL, Mihoubi A, Houdijk WP, Qanadli S, Joseph T, Courret JP, Page B, Goguel AF. Preliminary evaluation of two new rapid immunoturbidimetric D-dimer assays in patients with clinically suspected venous thromboembolism (VTE). *Thromb Haemost.* 2000;84:770–774.
8. Kelly J, Rudd A, Lewis RR, Coshall C, Parmar K, Moody A, Hunt BJ. Screening for proximal deep vein thrombosis after acute ischemic stroke: a prospective study using clinical factors and plasma D-dimers. *J Thromb Haemost.* 2004;2:1321–1326.
9. Rödén-Jüllig Å, Britton M, Malmkvist K, Leijd B. Aspirin in the prevention of progressing stroke: a randomized controlled study. *J Intern Med.* 2003;254:584–590.
10. Duke RJ, Bloch RF, Turpie AG, Trebilcock R, Bayer N. Intravenous heparin for the prevention of stroke progression in acute partial stable stroke. *Ann Intern Med.* 1986;105:825–828.
11. Low molecular weight heparinoid, ORG 10172 (danaparoid), and outcome after acute ischemic stroke: a randomized controlled trial. The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. *J Am Med Assoc.* 1998;279:1265–1272.