Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Stroke Association
A Division of American Heart Association

Hemostatic Function and Progressing Ischemic Stroke : D-dimer Predicts Early Clinical Progression

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

Stroke 2004, 35:1421-1425: originally published online April 8, 2004
doi: 10.1161/01.STR.0000126890.63512.41
Stroke is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0039-2499. Online ISSN: 1524-4628

Hemostatic Function and Progressing Ischemic Stroke
D-dimer Predicts Early Clinical Progression

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

Background and Purpose—Early clinical progression of ischemic stroke is common and is associated with increased risk of death and dependency. We hypothesized that activation of the coagulation system is an important contributor in some cases of deterioration. We aimed to characterize alterations in circulating hemostatic markers in patients with progressing stroke.

Methods—Consecutive acute ischemic stroke admissions were recruited. Progressing stroke was defined by deterioration in components of the Scandinavian Stroke Scale. Hemostatic markers (coagulation factors VIIc, VIIIc, and IXc, prothrombin fragments 1+2 [F1+2], thrombin–antithrombin complexes [TAT], D-dimer, fibrinogen, von Willebrand factor [vWF] and tissue plasminogen activator) were measured within 24 hours of symptom recognition.

Results—Fifty-four (25%) of the 219 patients met criteria for progressing stroke. F1+2 (median 1.28 versus 1.06 nmol/L, $P=0.01$), TAT (5.28 versus 4.07 μg/L, $P<0.01$), D-dimer (443 versus 194 ng/mL, $P<0.001$) and vWF (216 versus 198 IU/dL, $P<0.05$) levels were higher in these patients than in stable/improving patients. In logistic regression analysis, with all important clinical and laboratory variables included, only natural log D-dimer (odds ratio [OR]: 1.87; 95% confidence interval [CI]: 1.38 to 2.54; $P=0.0001$) and mean arterial blood pressure (OR: 1.26 per 10 mm Hg change; 95% CI: 1.05 to 1.51; $P=0.01$) remained independent predictors of progressing stroke.

Conclusions—There is evidence of excess thrombin generation and fibrin turnover in patients with progressing ischemic stroke. Measurement of D-dimer levels can identify patients at high risk for stroke progression. Further research is required to determine whether such patients benefit from acute interventions aimed at modifying hemostatic function. **(*Stroke*. 2004;35:1421-1425.)**

Key Words: cerebral infarction ■ hemostasis ■ fibrin ■ blood pressure

Early clinical progression of ischemic stroke is common and is associated with poor prognosis.[1–3] Hemostatic activation may be an important cause, or contributor, to progressing ischemic stroke. There is evidence of increased thrombin generation and fibrin turnover, altered fibrinolytic activity, and disturbed endothelial function in acute stroke.[4–8] There is little evidence to date regarding alterations in hemostatic measures and stroke progression. A small Japanese study found elevated thrombin–antithrombin complex (TAT) and fibrin D-dimer levels in patients with progressing stroke when samples were withdrawn within 7 days of symptom onset.[9] As part of a heparin intervention study, de Boer et al found a trend toward elevated admission serum fragment E levels in patients who later had motor progression.[10] Analysis of baseline variables in the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Trial demonstrated that fibrin degradation product levels were independently associated with late, but not early, clinical deterioration.[11]

Trials of interventions (such as heparin) that potentially alter hemostatic function in ischemic stroke have so far proved negative in terms of preventing neurological deterioration in the first days after stroke;[12,13] perhaps partly because reduced thrombus formation is balanced by an increased risk of intracranial and extracranial hemorrhage. These studies, however, did not target patients likely to be at a high risk for progressing stroke. We hypothesized that circulating hemostatic markers would predict progressing ischemic stroke. This study aimed to characterize alterations in these markers in ischemic stroke patients with progressing neurological signs, compared with patients without such progression. If measuring blood markers of hemostatic function could identify patients at high risk for progressing ischemic stroke, this might allow more effective targeting of early antithrombotic therapy to prevent progressing stroke and improve clinical outcome.

Subjects and Methods

Patients were recruited from consecutive ischemic stroke admissions to a large urban teaching hospital between April 2002 and October

Received December 29, 2003; final revision received February 18, 2004; accepted February 24, 2004.
From University Section of Clinical Gerontology and Vascular Medicine, Royal Infirmary, Glasgow, UK.
Correspondence to Dr Mark Barber, Academic Section of Geriatric Medicine, 3rd Floor, Centre Block, Royal Infirmary, 84 Castle Street, Glasgow, G4 OSF, UK. E-mail M.Barber@clinmed.gla.ac.uk

Stroke **is available at http://www.strokeaha.org** **DOI: 10.1161/01.STR.0000126890.63512.41**

TABLE 1. Demographic and Clinical Differences Between Patients With Progressing Stroke and Those With Stable or Improving Stroke

Variable	Progressing Stroke n=54	No Progression n=165	*P*
Age (y)	74 (65–83)	71 (62–78)	0.02
Female	36 (67%)	84 (51%)	0.04
Prestroke Rankin 3–5	11 (20%)	28 (17%)	0.57
Previous hypertension	31 (57%)	80 (48%)	0.26
Known diabetes	9 (17%)	24 (15%)	0.70
Previous stroke	9 (17%)	39 (24%)	0.28
Antiplatelet therapy	26 (48%)	76 (46%)	0.69
Current smoker	22 (41%)	56 (34%)	0.41
Clinical Differences			
Admission delay (h)	5 (2–13)	6 (2–12)	0.76
Left hemisphere lesion	29 (54%)	89 (54%)	0.98
OCSP classification			
TACI	25 (46%)	39 (24%)	<0.01
PACI	22 (41%)	71 (43%)	
LACI	5 (9%)	42 (25%)	
POCI	2 (4%)	13 (8%)	
Admission SSS score (minus gait) (points)	30.5 (20–40)	39 (26–42)	<0.01
Admission MABP (mm Hg)	111 (20)	106 (20)	0.10
Atrial fibrillation on ECG	12 (22%)	17 (10%)	0.03
Pyrexia >37.5°C in first 72 h	24 (44%)	46 (28%)	0.02
Aspirin prescribed between admission and venipuncture	0 (0%)	2 (1%)	1.00

For continuous variables, results are expressed as median (interquartile range) except for blood pressure, for which results are expressed as mean (standard deviation).

OCSP indicates Oxfordshire Community Stroke Project; TACI, total anterior circulation infarct; PACI, partial anterior circulation infarct; LACI, lacunar infarct; POCI, posterior circulation infarct; SSS, Scandinavian Stroke Scale; MABP, mean arterial blood pressure.

2003. Patients were excluded if any of the following criteria were met: a delay of >24 hours from symptom recognition to admission, age younger than 18 years, coma (only responding to pain on admission),[14] or epileptic seizure activity. Patients who were anticoagulated before admission were also excluded. No recruited patients were prescribed thrombolysis or heparin in the first 72 hours after stroke onset. All patients were treated on a standardized protocol for the management of dehydration (2.5 L of 0.9% sodium chloride solution intravenously, over the first 24 hours, unless contraindicated), hyperglycemia, hypoxia, and pyrexia.

A single experienced examiner saw all patients. Assessment included clinical classification (Oxfordshire Community Stroke Project [OCSP] classification[15]) and measurement of stroke severity using the Scandinavian Stroke Scale (SSS).[16] Blood pressure was measured noninvasively using the Passport II multiparameter monitoring system (Datascope Corporation). Follow-up was at 30 days using the Rankin scale and Barthel Index.[17,18]

Progressing stroke was defined using a modification of the European Progressing Stroke Study (EPSS) criteria.[14] The EPSS definition of progressing stroke requires a reduction of ≥2 SSS points in conscious level or eye movements or leg or arm motor power between baseline and day 3, a reduction of ≥3 SSS points in speech score, or both. Progression cannot be said to have occurred if the conscious level improves significantly between the 2 assessments, even if there has been a worsening of other domains. For the purpose of this analysis, eye movement changes were excluded, because there is concern about reliability of this domain of the SSS.[19,20] Removing the gaze palsy component of the EPSS definition does little to change its validity.[14]

Blood samples were separated and plasma aliquots stored at −80°C before analysis. Plasma viscosity was measured at 37°C using a semiautomated capillary viscometer (Coulter Electronics). Fibrinogen was measured by the Clauss method using a MDA180 coagulometer (Biomerieux) with reagents from the manufacturer. The calibrant used was the 8th British Standard (NIBSC). Plasma levels of fibrin D-dimer and tissue plasminogen activator (t-PA) antigen were measured with commercially available enzyme-linked immunosorbent assays from Biopool AB. Plasma von Willebrand factor (vWF) antigen levels were measured using an enzyme-linked immunosorbent assays using rabbit antihuman polyclonal antibodies obtained from DAKO (High Wycombe). Highly sensitive C-reactive protein (CRP) was measured immunologically using the BN ProSpec nephelometer (Dade Behring) using calibrants and reagents provided by the manufacturer. Prothrombin fragment 1+2 (F1+2) and TAT were measured using commercially available enzyme-linked immunosorbent assays from Dade Behring (Milton Keynes). Activated partial thromboplastin time and coagulation factors VIIc, VIIIc, and IXc were measured by standard clotting assays on an automated coagulometer (MDA 180; Biomerieux) using calibrants and reagents provided by the manufacturer. Activated protein C ratio was measured on the MDA 180 using the Chromogenix Coatest kit from Quadratec. The local research ethics committee approved this study.

Statistical Analysis

Power calculations were based on the findings of Uchiyama et al[9] and assumed a 25% rate of progressing stroke. For 90% power ($P<0.05$), to determine similar abnormalities in TAT and D-dimer

TABLE 2. Circulating Hemostatic and Hemorheological Variables in Patients With Progressing Stroke and Those With Stable or Improving Stroke

Variable	Progressing Stroke n=54	No Progression n=165	*P*
Time from admission to venipuncture (h)	11 (4–15)	8 (3–16)	0.541
Factor VIIc (IU/dL)	139 (111–171)	148 (127–165)	0.126
Factor VIIIc (IU/dL)	204 (166–240)	195 (162–235)	0.150
Factor IXc (IU/dL)	170 (148–188)	157 (142–184)	0.085
Prothrombin F1+2 (nmol/L)	1.28 (0.92–1.74)	1.06 (0.76–1.48)	0.011
Thrombin-antithrombin complexes (μg/L)	5.28 (3.90–8.46)	4.07 (3.28–6.25)	0.009
Fibrin D-dimer (ng/mL)	443 (164–1091)	194 (92–481)	<0.001
APC ratio (n=164)	2.73 (2.44–3.07)	2.81 (2.53–3.12)	0.430
Tissue plasminogen activator antigen (ng/mL)	12.7 (8.9–18.0)	11.0 (8.2–15.2)	0.102
von Willebrand Factor antigen (IU/dL)	216 (178–273)	198 (157–244)	0.045
Plasma viscosity (mPa.s)	1.32 (1.21–1.38)	1.26 (1.20–1.34)	0.066
Hematocrit	0.40 (0.37–0.43)	0.40 (0.36–0.43)	0.467
Fibrinogen (g/L)	3.97 (3.50–5.02)	3.90 (3.16–4.54)	0.079
C-reactive protein (mg/L)	8.66 (3.69–30.45)	5.26 (1.64–18.4)	0.049
Leukocyte count ($\times 10^9$/L)	10.25 (8.05–12.78)	9.30 (7.4–11.5)	0.017

Results are expressed as median (interquartile range).
APC indicates activated protein C.

levels, it was estimated that a total group size of 189 patients would be required.

Results are expressed as medians throughout the text unless otherwise stated. For univariate comparison of categorical variables, the Pearson χ^2 was used. For nonnormally distributed hemostatic variables, transformations to normality were made where possible. Univariate analysis of normally distributed and transformed variables was by the unpaired *t* test. For other nonnormally distributed continuous variables, the Mann–Whitney *U* test was used. Multivariate analysis was by step-wise binary logistic regression. Variables were included in this analysis when significance levels in univariate analysis fell below $P<0.10$. OCSP classification was included in the model as a categorical variable. All analyses were performed using SPSS for Windows version 9.0.

Results

Of 474 admissions assessed, 280 patients were initially considered as potentially suitable for recruitment to the study. Sixty-one of these were subsequently excluded, because they did not meet our inclusion criteria (these exclusions were made blind to results of the blood analyses). This left a database of 219 patients for further analysis, of whom 54 (25%) met the criteria for progressing stroke.

Important demographic differences between the progressing stroke patients and the stable/ improving patients are shown in Table 1. Significant differences included older age (74 versus 71 years, $P=0.02$) and a higher prevalence of female gender (67% versus 51%, $P=0.04$) in the progressing group. Clinical differences between the progressing stroke patients and the stable/improving patients are also illustrated in Table 1. Admission neurological deficit, as measured by the SSS, was more severe (30.5 versus 39 points, $P<0.01$) and there was a higher prevalence of OCSP classification total anterior circulation infarctions in the progressing group (46% versus 24%, $P<0.01$). There was a trend toward higher mean arterial blood pressure (mean 111 versus 106 mm Hg, $P=0.099$), and there was a higher prevalence of atrial fibrillation on admission electrocardiogram (22% verus 10%, $P=0.03$) in the progressing stroke group.

Patients with progressing stroke had significantly elevated levels of prothrombin fragments 1+2 (1.28 versus 1.06 nmol/L, $P=0.01$), TAT complexes (5.28 versus 4.07 μg/L, $P=0.009$), fibrin D-dimer (443 versus 194 ng/mL, $P<0.001$) and vWF (216 versus 198 IU/dL, $P<0.05$) compared with patients with no progression (see Table 2). These patients also had higher leukocyte counts (10.25 versus 9.30×10^9/L, $P=0.02$) and CRP levels (8.66 versus 5.26 mg/L, $P<0.05$) on univariate analysis. The results of a logistic regression model of predictors of progressing stroke are shown in Table 3. Of all demographic, clinical, and hemostatic variables, only mean arterial blood pressure (odds ratio: 1.26 for each 10 mm Hg increase) and D-dimer (odds ratio: 1.87 for each natural log unit increase) were independently associated with progressing stroke. The area under the receiver-operating characteristic curve for D-dimer as a predictor of progressing stroke was 0.678 (95% confidence interval: 0.600 to 0.756).

Outcome was poorer in the progressing stroke group. Death was more common at 30 days (33% versus 5%, $P<0.001$) and there were also important differences with respect to outcomes in survivors as measured using the Rankin scale and Barthel Index (results not presented).

TABLE 3. Step-Wise Logistic Regression Model of Predictors of Progressing Ischemic Stroke

	B (SE)	R	Odds Ratio	*P*
Constant	−7.297 (1.531)			
MABP (per 10 mm Hg)	0.233 (0.093)	0.140	1.26	0.01
Natural log D-dimer	0.628 (0.156)	0.254	1.87	0.0001

All variables with $P<0.10$ in univariate analysis were included in this model.
MABP indicates mean arterial blood pressure.

Hospital stay was significantly longer in surviving patients with progressing stroke (67 versus 13 days, $P<0.001$).

Discussion

We have confirmed that progressing ischemic stroke is a common problem that is associated with high morbidity and mortality. Our important new findings, in this large prospective study, are that a number of hemostatic variables are higher in those patients admitted with ischemic stroke who later deteriorate. In particular, once other potentially important factors are taken into consideration, fibrin D-dimer levels independently predict progressing stroke.

F1+2 and TAT are markers of thrombin generation, whereas D-dimer (a fibrin degradation product) is a marker not only of thrombin generation but also of cross-linked fibrin turnover. D-dimer is the most stable of these 3 measures.[21] Previous studies demonstrated evidence of early activation of the coagulation system in patients with acute stroke, when compared with nonstroke controls. Measured markers included raised F1+2, TAT, and D-dimer levels.[4–8] Admission D-dimer may also play a role in differentiating between stroke subtypes.[4] In our study, these 3 markers of coagulation activation were each significantly raised in patients with progressing stroke. Only D-dimer levels, however, remained statistically significant after multivariate analysis.

There are plausible mechanisms through which D-dimer levels could be closely related to progressing stroke. Increased D-dimer levels may reflect ongoing thrombus formation within cerebral vessels or may be a marker of systemic hypercoagulability. A small study of selected stroke patients suggested that duration of arterial occlusion, as demonstrated on serial transcranial Doppler, was significantly associated with neurological progression.[22] Transcranial Doppler evidence of middle cerebral artery asymmetry or "no-flow" within 6 hours of stroke has predictive value for stroke progression/improvement.[23]

Some markers of hemostatic function are acute-phase reactants; D-dimer is one of these. Hence, it is possible that elevated D-dimer levels in patients with progressing stroke are simply a marker of a more severe stroke (there was an excess of total anterior circulation infarctions in this group), as part of a reactant inflammatory process. Bacterial infection (mainly chest and urinary tract) and venous thrombosis are other possible contributors, although these usually occur after the first week.[24] We have minimized these possibilities by withdrawing samples soon after admission. We have also included other recognized acute-phase reactants (CRP, fibrinogen, and leukocyte count), together with recorded episodes of pyrexia in the first 72 hours, in our analysis. Adjustment of the association of D-dimer with progressing stroke for these inflammatory indices did not account for the association. There is, in fact, some evidence that fibrin degradation products, including D-dimer, may act to stimulate the inflammatory process,[25–28] and this might provide a further pathological mechanism through which D-dimer is linked to progressing stroke.[29,30]

The finding that admission mean arterial blood pressure independently predicts progressing stroke is interesting. This mirrors findings of our previous retrospective case control study[3] and those of other groups.[22,23,31] An exception to these findings was the study of Jørgensen et al, which showed an inverse relationship between systolic blood pressure and the incidence of deterioration.[32] The relevance of these findings is uncertain, because there is not enough evidence to support interventions for deliberately altering blood pressure in acute stroke.[33]

This study has a number of strengths. Patients were recruited from consecutive admissions to a general hospital, few exclusion criteria were used, and a single observer made all assessments. Samples were obtained relatively early after admission and a validated definition of progressing stroke was used.[14] Our study also has potential weaknesses. Blood samples were not taken at the time of admission but instead were withdrawn as soon as was practical (and always within 24 hours of symptom recognition). A number of different commercial D-dimer assays are available, and so our results may not necessarily be generalized to all assays.

Our analysis cannot exclude the possibility that elevated coagulation markers predated the acute event. These patients may have had widespread vascular disease before stroke onset and are, therefore, likely to have increased pre-event levels when compared with population controls. The measured levels in the present study, however, far exceed those recorded even in a population of patients with clinical atherosclerosis who later have stroke.[34] Acute and convalescent samples suggest that D-dimer levels may decrease over the months after acute stroke.[35] The difference in levels between those patients with progressing stroke and stable patients also suggest that D-dimer elevations are connected, in some way, to an acute process rather than to chronic inflammation and atherosclerosis.

We cannot be certain of all the mechanisms responsible for the excessive elevation of D-dimer in the acute phase of progressing stroke. The extent of local arterial thrombosis and tissue death is likely to be important (as reflected by the excess of total anterior circulation infarctions in the progressing stroke group), although other systemic factors may be important in some patients. We have, however, shown in our analysis that measurement of D-dimer, a cheap and widely available assay, independently predicts progressing stroke. This provides useful prognostic information, but may also be helpful in selecting patients who could benefit from interventions aimed at preventing early neurological deterioration after ischemic stroke; in particular, those specifically targeted at manipulating the coagulation system.

Acknowledgments

M.B. is a NHS Education for Scotland/Chief Scientist Office Clinical Research Fellow. The study was supported by a grant from the Chief Scientist Office of the Scottish Executive Health Department. E. Poorhang and K. Craig assisted with laboratory analysis of samples.

References

1. Tei H, Uchiyama S, Ohara K, Kobayashi M, Uchiyama Y, Fukuzawa M. Deteriorating ischemic stroke in 4 clinical categories classified by the Oxfordshire Community Stroke Project. *Stroke.* 2000;31:2049–2054.
2. Rödén-Jüllig Å. Progressing stroke: epidemiology. *Cerebrovasc Dis.* 1997;7:2–5.

3. Barber M, Wright F, Stott DJ, Langhorne P. Predictors of early neurological deterioration after ischaemic stroke: a case control study. *Gerontology.* 2004;50:102–109.
4. Ageno W, Finazzi S, Steidl L, Biotti MG, Mera V, Melzi DG, Venco A. Plasma measurement of D-dimer levels for the early diagnosis of ischemic stroke subtypes. *Arch Intern Med.* 2002;162:2589–2593.
5. Altès A, Abellán MT, Mateo J, Avila A, Martí-Vilalta JL, Fontcuberta J. Hemostatic disturbances in acute ischemic stroke: a study of 86 patients. *Acta Haematol.* 1995;94:10–15.
6. Lip G, Blann A, Farooqi I, Zarifis J, Sagar G, Beevers D. Abnormal haemorheology, endothelial function and thrombogenesis in relation to hypertension in acute (ictus <12 h) stroke patients: the West Birmingham Stroke Project. *Blood Coagul Fibrinolysis.* 2001;12:307–315.
7. McConnell JP, Cheryk LA, Durocher A, Bruno A, Bang NU, Fleck JD, Williams L, Biller J, Meschia JF. Urinary 11-dehydro-thromboxane B(2) and coagulation activation markers measured within 24 h of human acute ischemic stroke. *Neurosci Lett.* 2001;313:88–92.
8. Tohgi H, Konno S, Takahashi S, Koizumi D, Kondo R, Takahashi H. Activated coagulation/fibrinolysis system and platelet function in acute thrombotic stroke patients with increased C-reactive protein levels. *Thromb Res.* 2000;100:373–379.
9. Uchiyama S, Yamazaki M, Hara Y, Makato I. Alterations of platelet, coagulation, and fibrinolysis markers in patients with acute ischemic stroke. *Semin Thromb Hemost.* 1997;23:535–541.
10. de Boer AC, Turpie AG, Butt RW, Duke RJ, Bloch RF, Genton E. Plasma betathromboglobulin and serum fragment E in acute partial stroke. *Br J Haematol.* 1982;50:327–334.
11. Grotta JC, Welch KMA, Fagan SC, Lu M, Frankel MR, Brott T, Levine SR, Lyden PD. Clinical deterioration following improvement in the NINDS rt-PA Stroke Trial. *Stroke.* 2001;32:661–668.
12. 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.
13. Bath P, Lindenstrøm E, Boysen G, De Deyn P, Friis P, Leys D, Marttila R, Olsson J-E, O'Neill D, Orgogozo JM, Ringelstein EB, van der Sande J-J, Turpie AG. Tinzaparin in acute ischaemic stroke (TAIST): a randomised aspirin-controlled trial. *Lancet.* 2001;358:702–710.
14. Birschel P, Ellul J, Barer D, on behalf of the European Progressing Stroke Study (EPSS) Group. "Progressing stroke": towards an internationally agreed definition. *Cerebrovasc Dis.* 2004;17:242–252.
15. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet.* 1991;337:1521–1526.
16. Scandinavian Stroke Study Group. Multicenter trial of hemodilution in ischaemic stroke—background and study protocol. *Stroke.* 1985;16:885–890.
17. Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke.* 1988;19:604–607.
18. Wade D. *Measurement in neurological rehabilitation.* 1st ed. Oxford/New York/Tokyo: Oxford University Press; 1992.
19. Edwards DF, Chen Y-W, Diringer MN. Unified neurological stroke scale is valid in ischemic and hemorrhagic Stroke. *Stroke.* 1995;26:1852–1858.
20. Barber M, Fail M, Shields M, Stott DJ, Langhorne P. Validity and reliability of estimating the Scandinavian Stroke Scale score from medical records. *Cerebrovasc Dis.* 2004;17:224–227.
21. Lowe GDO, Rumley A, Whincup P, Danesh J. Hemostatic and rheological variables and risk of cardiovascular disease. *Semin Vasc Med.* 2002;2:429–439.
22. Arenillas JF, Rovira A, Molina CA, Grive E, Montaner J, Alvarez-Sabin J, Lovblad KO. Prediction of early neurological deterioration using diffusion- and perfusion-weighted imaging in hyperacute middle cerebral artery ischemic stroke. *Stroke.* 2002;33:2197–2205.
23. Toni D, Fiorelli M, Zanette E, Sacchetti M, Salerno A, Argentino C, Solaro M, Fieschi C. Early spontaneous improvement and deterioration of ischaemic stroke patients: a serial study with transcranial Doppler ultrasonography. *Stroke.* 1998;29:1144–1148.
24. Langhorne P, Stott D, Robertson L, MacDonald J, Jones L, McAlpine C, Dick F, Taylor G, Murray G. Medical complications after stroke. *Stroke.* 2000;31:1223–1229.
25. Robson SC, Shephard EG, Kirsch RE. Fibrin degradation product D-dimer induces the synthesis and release of biologically active IL-1 beta, IL-6 and plasminogen activator inhibitors from monocytes in vitro. *Br J Haematol.* 1994;86:322–326.
26. Csala M, Léránt I, Bánhegyi G, Kardon T, Puskás F, Mucha I, Machovich R, Falus A, Mandl J. Prostaglandin-independent stimulation of interleukin-6 production by fibrinogen degradation product D in perfused murine liver. *Scand J Immunol.* 1998;48:269–271.
27. Mandl J, Csala M, Lerant I, Banhegyi G, Biro J, Machovich R, Falus A. Enhancement of interleukin-6 production by fibrinogen degradation product D in human peripheral monocytes and perfused murine liver. *Scand J Immunol.* 1995;42:175–178.
28. Lee ME, Rhee KJ, Nham SU. Fragment E derived from both fibrin and fibrinogen stimulates interleukin-6 production in rat peritoneal macrophages. *Mol Cells.* 1999;9:7–13.
29. Castellanos M, Castillo J, García MM, Leira R, Serena J, Chamorro Á, Dávalos A. Inflammation-mediated damage in progressing lacunar infarctions: a potential therapeutic target. *Stroke.* 2002;33:982–987.
30. Vila N, Castillo J, Dávalos A, Chamorro Á. Proinflammatory Cytokines and early neurological worsening in ischaemic stroke. *Stroke.* 2000;31:2325–2329.
31. Dávalos A, Cendra E, Tereul J, Martinez M, Genís D. Deteriorating ischemic stroke: risk factors and prognosis. *Neurology.* 1990;40:1865–1869.
32. Jørgensen HS, Nakayama H, Raaschou HO, Olsen TS. Effect of blood pressure and diabetes on stroke in progression. *Lancet.* 1994;344:156–159.
33. Blood pressure in Acute Stroke Collaboration (BASC). Interventions for deliberately altering blood pressure in acute stroke (Cochrane Review). In: *The Cochrane Library,* Issue 4, 2003. Oxford: Update Software.
34. Smith FB, Rumley A, Lee AJ, Leng GC, Fowkes FG, Lowe GDO. Haemostatic factors and prediction of ischaemic heart disease and stroke in claudicants. *Br J Haematol.* 1998;100:758–763.
35. 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.