www.jkns.or.kr http://dx.doi.org/10.3340/jkns.2011.50.2.89
Print ISSN 2005-3711 On-line ISSN 1598-7876
J Korean Neurosurg Soc 50 : 89-94, 2011

Clinical Article

Correlation between Serum D-Dimer Level and Volume in Acute Ischemic Stroke

Young-Woo Park, M.D., Eun-Jeong Koh, M.D., Ph.D., Ha-Young Choi, M.D., Ph.D.

Department of Neurosurgery, Research Institute of Clinical Medicine, Chonbuk National University Medical School/Hospital, Jeonju, Korea

Objective : D-dimer is a breakdown product of fibrin mesh after factor XIII stabilization. Previously, many authors have demonstrated a relationship between D-dimer level and stroke progression or type. This study aimed to investigate the relationship between D-dimer level and stroke volume.

Methods : Between January 2008 and December 2009, we analyzed the D-dimer levels of 59 acute ischemic stroke patients in our neurosurgical department both upon admission and after seven days of initial treatment. Each patient's National Institute of Health Stroke Scale score, modified Rankin Scales score, Glasgow outcome score, and infarction volume were also evaluated.

Results : Mean D-dimer level at admission was 626.6 μg/L (range, 77-4,752 μg/L) and the mean level measured after seven days of treatment was 238.3 μg/L (range, 50-924 μg/L). Mean D-dimer level at admission was 215.3 μg/L in patients with focal infarctions, 385.7 μg/L in patients with multiple embolic infarctions, 566.2 μg/L in those with 1-19 cc infarctions, 668.8 μg/L in 20-49 cc infarctions, 702.5 μg/L in 50-199 cc infarctions, and 844.0 μg/L in >200 cc infarctions (p=0.044). On the 7th day of treatment, the D-dimer levels had fallen to 201.0 μg/L, 293.2 μg/L, 272.0 μg/L, 232.8 μg/L, 336.6 μg/L, and 180.0 μg/L, respectively (p=0.530).

Conclusion : Our study shows that D-dimer level has the positive correlation with infarction volume and can be use to predict infarction-volume.

Key Words : D-dimer · Acute ischemic stroke · Volume.

INTRODUCTION

Acute ischemic stroke (AIS) has recently become a common cause of death and disability in the world[29,36]. Diagnosis of acute ischemic stroke is difficult because computed tomography (CT) results may appear normal in the early stage or in patients with minor symptoms, and magnetic resonance imaging (MRI) is not always possible in golden time of treatment. Thus, many eligible cases experience delays in receiving intravenous thrombolysis treatment. Rapid diagnosis in patients with suspected AIS is critical for the patient's treatment and prognosis[45].

Many studies have shown elevated D-dimer levels during the acute phase of stroke, which eventually fall[14,26,30,34]. However, previous studies have demonstrated only that plasma D-dimer levels predict a progressing ischemic stroke[4,5].

We studied the relationship between D-dimer level and infarction volume and the relationship between D-dimer change and clinical outcome in AIS.

• Received : March 4, 2011 • Revised : June 15, 2011
• Accepted : August 16, 2011
• Address for reprints : Eun-Jeong Koh, M.D., Ph.D.
Department of Neurosurgery, Chonbuk National University Medical School/Hospital, 20 Geonji-ro, Jeonju 561-712, Korea
Tel : +82-63-250-1870, Fax : +82-63-277-3273
E-mail : kohejns@jbnu.ac.kr

MATERIALS AND METHODS

Patient selection and evaluation

Between January 2008 and December 2009, we studied 59 patients out of 125 patients admitted to our department of neurosurgery due to acute ischemic stroke. Patients who were receiving anticoagulation therapy (due to atrial fibrillation, valvular heart disease, deep venous thrombosis, pulmonary embolism, severe hepatic disease, renal disease, malignancy, or drug use) were excluded. We evaluated risk factors : age, sex, hypertension, diabetes mellitus, dyslipidemia, other cardiac diseases (including acute myocardial infarction and angina), and cigarette smoking[37]. There were 32 male and 27 female patients, ranging from 19 to 82 years in age (mean, 65.3 years).

At emergency room we took each patient's history and performed a physical examination, neurologic examination using the National Institutes of Health Stroke Scale (NIHSS), serologic evaluation, and radiological evaluation [brain CT, brain MRI, and magnetic resonance angiography (MRA)]. We classified our patients into two groups according to treatment modality. One group received treatment with recombinant tissue plasminogen activator (rt-PA) and/or intra-arterial thrombolysis (the thrombolysis group), and the others received treatment with intravenous argatroban (the argatroban group). We graded their out-

comes using the modified Rankin Scale (mRS) and modified Glasgow Outcome Scale (GOS), which places the scores in reverse order. To analyze the initial NIHSS results, we divided the patients into three categories according to this baseline NIHSS score : mild (0-6), moderate (7-15), and severe (16 and above)[1,38].

D-dimer analysis

D-dimer levels of patients with AIS were evaluated at admission and after seven days of treatment. The D-dimer test is a latex-enhanced immunoturbidimetric test for quantitative determination of cross-linked fibrin degradation products in human plasma. The D-dimer value is considered abnormal when in excess of 250 μg/L (normal range, 63.8-246.4 μg/L).

Volumetric analysis of infacrted areas

We obtained CT and MRI scans and performed volumetric analyses using DWI. MRI studies used a Siemens Vision 3.0T MR scanner (Magnetom Verio, Siemens, Erlangen, Germany). The imaging protocol comprised DWI, T2-weighted, fluid-attenuated inversion recovery, conventional spin-echo T1- and T2-weighted images, and MRA.

We measured infarction volume using DWI. To calculate the infarction volume, we employed the following formula : A×B×C/2, where A is the largest diameter and B is the perpendicular diameter of the ischemic lesion, as measured, and C is the sum of the thicknesses of the slices where the lesion was visible. One senior experienced neuroradiologist, performed the volumetric analyses.

The criteria used in the analysis of infarction volume have been previously reported[42]. We classified patients into 6 subgroups by infarction volume : focal (volume estimation was difficult), multiple embolic (focal multiple lesions in both hemispheres where volumetric calculation was difficult), 1-19 mL, 20-49 mL, 50-199 mL, and >200 mL.

Treatment

AIS patients received intravenous rt-PA treatment (0.9 mg/kg) if they reached the hospital within 4.5 hours after ictus[43]. For patients with persistent arterial occlusion without signs of early recanalization immediately after IV thrombolysis and for patients visiting the hospital more than 4.5 hours after symptom onset but within 6 hours, we administered combined (IV and IA) thrombolysis therapy, for early recanalization[11,12,17,24,25,46]. The patients who visited the hospital between 6 and 48 hours after symptom onset underwent treatment with IV direct thrombin inhibitor (argatroban) for 7 days. During the first 2 days the argatroban 120 mg (60 mg/day) was administered continuously. And, then during the subsequent 5 days 10 mg of argatroban was injected per 12 hours[20].

Brain CTs were checked immediately after thrombolysis, upon any neurological deterioration associated with an NIHSS increase of 2 points over baseline, and at a conscious level of arm, leg, or eye movement[7].

Statistical analysis

Relationships between plasma D-dimer level, changes in D-dimer, treatment modality, and NIHSS, mRS, and GOS scores were evaluated using the Mann-Whitney test for comparisons between two subgroups. The Mann-Whitney test, Kruskal-Wallis test, and Pearson correlation were used to evaluate correlations between plasma D-dimer level, change of D-dimer level, infarction volume, and NIHSS, mRS, and GOS scores.

RESULTS

Patients

Table 1 presents the patients' profiles. Via the NIHSS, we diagnosed mild stroke in 29 patients (49%), moderate stroke in 23 (40%), and severe stroke in 7 (11%). After 7 days of treatment, NIHSS scores showed 42 (71%) with mild, 15 (26%) with moderate, and 2 (3%) with severe strokes. Modified Rankin scale scores of these patients ranged from 0 to 5 (mean, 1.75±1.38). The thrombolysis group showd a significantly higher mean mRS scale score than the argatroban group had (3.0 vs. 1.5, p=0.005). The mean modified GOS of all patients in this study was 1.68±0.84.

D-dimer and treatment modality

Table 2 shows the plasma D-dimer levels at admission and after seven days of stroke therapy, by treatment modality. Patients treated with rt-PA or intra-arterial thrombolysis showed higher D-dimer levels at admission than patients receiving intravenous argatroban did (922.3 μg/L vs. 573.4 μg/L, p=0.016). The thrombolysis group showed significantly greater changes in D-dimer levels compared to the argatroban group (p=0.019).

D-dimer and volume of infarcted area

Fig. 1 presents the D-dimer and stroke volume data, describ-

Table 1. Patients' profiles

		Number of patients
Age	65.3±11.8 years	
Sex (male : female)	32 : 27	
Risk factors	Previous stroke	7
	Other cardiac condition	7
	Hypertension	28
	Diabetes mellitus	7
	Cigarette smoke	18
	Dyslipidemia	2
Treatment modality	Thrombolysis	9
	IV anticoagulant	50

ing a statistically positive correlation between initial D-dimer value and D-dimer value change (p<0.05). Mean D-dimer level at admission was 215.3 μg/L (77-497 μg/L) in patients with focal infarctions, 385.7 μg/L (161-819 μg/L) in patients with multiple embolic infarctions, 566.2 μg/L (96-2,098 μg/L) in those with 1-19 cc infarctions, 668.8 μg/L (161-4,752 μg/L) in 20-49 cc infarctions, 702.5 μg/L (248-1,991 μg/L) in 50-199 cc infarctions, and 844.0 μg/L in >200 cc infarctions (p=0.044). On the 7th day of treatment, the D-dimer levels had fallen to 201.0 μg/L (50-456 μg/L), 293.2 μg/L (103-528 μg/L), 272.0 μg/L (91-924 μg/L), 232.8 μg/L (97-535 μg/L), 336.6 μg/L (122-421 μg/L), and 180.0 μg/L respectively (p=0.530).

Table 2. Plasma D-dimer levels at admission and after the 7th day of stroke therapy

	Thrombolysis subgroup (n=9)	Argatroban subgroup (n=50)	p-value
At admission (μg/L)	922.3	573.4	0.016
After 7 days (μg/L)	227.0	240.3	0.792
Value change after therapy (%)	57.1	34.1	0.019

D-dimer value did not correlate statistically with stroke volume at the 7th day after stroke (p>0.05). D-dimer levels were higher in the large infarction volume subgroups than in the small volume subgroups, and the D-dimer changes were significantly larger for large infarction volumes than for small infarction volumes (Fig. 2).

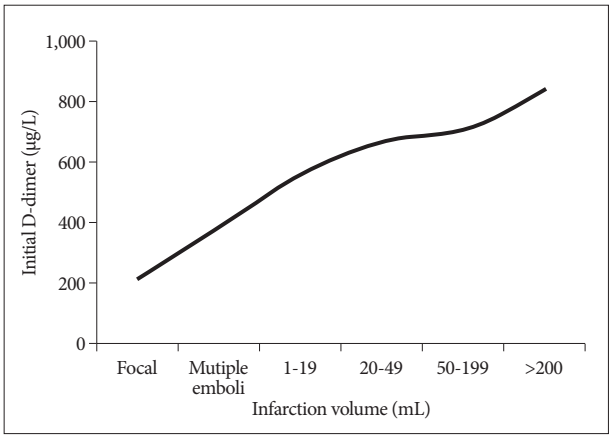

Fig. 1. The positive relationship between intial D-dimer and stroke volume.

D-dimer and neurological outcome

Table 3 shows D-dimer level comparisons between the two groups with regard to the outcome index (mRS, modified GOS, and NIHSS scores). Forty-two patients belonged to the good mRS score (0-2) group and 17 patients to the poor mRS score (3-6) group. The favorable modified GOS (1-2) group had 47 patients, and the unfavorable modified GOS (3-5) group had 12 patients. When we analyzed the final NIHSS scores, 42 patients were in the mild category (71%), 15 in the moderate category (26%), and 2 in the severe (3%). We found no correlation between the D-dimer of the groups and the clinical outcome groups (p>0.05).

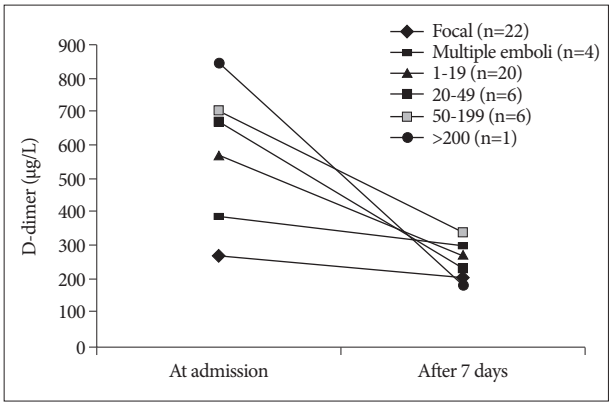

Fig. 2. The changes of D-dimer level each stroke volume group.

DISCUSSION

Although most diagnostic approaches to the evaluation of acute stroke rely on neuroimaging techniques, an alternative strategy could be the evaluation of blood-borne biochemical markers of tissue injury. This approach has precedents in the triage and early management of other urgent medical conditions. For example, biomarkers such as troponin, CK-MB, D-dimer, and B-type natriuretic peptide play important roles in the evaluation of myocardial ischemia, pulmonary embolism, and congestive heart failure[13,32]. In the correct clinical context, such a rapid, noninvasive test would help identify a patient population at risk for cerebral ischemia, who need rapid evaluation and triage. Furthermore, it could provide adjunctive diagnostic information for patients for whom physicians are contemplating acute intervention.

D-dimer can be elevated in any case with deep venous thrombosis, pulmonary thromboembolism, myocardial infarction, disseminated intravascular coagulation, surgery, trauma, or stroke[2,9,16,33,41]. D-dimer, a marker of plasmin-mediated fibrin degradation, is cross-linked to fibrin degradation products (FDP) and indicates vessel occlusion. Plasmin splits the fibrin into FDP and D-dimers when the coagulation and fibrinolytic system is activated. A number of studies have shown that D-dimer, C-reactive protein, and other markers of hemostatic activation associate with a stroke diagnosis[5,18,19,21-23,28,31,35,39] and with progression and death in acute ischemic stroke[5,6,10,30,44]. The report by Laskowitz et al.[22] suggests that a biomarker panel may add valuable and time-sensitive diagnostic information to early stroke evaluation and rapid identification of patients with suspected stroke, which would expand the availability of time-limited treatment strategies. Laskowitz et al.[22] also demonstrated that, for the evaluation of early ischemia, a strategy incorporating the current biomarker test in conjunction with noncontrast CT has significantly greater sensitivity than CT alone possesses.

Table 3. D-dimer (μg/L) levels according to each outcome group

Outcome subgroup	D-dimer (μg/L) at admission	D-dimer (μg/L) at 7days	Change of D-dimer (%)	No. of patients
Modified GOS				
Favorable modified GOS (1-2)	657.8	232.3	37.8	47
Unfavorable modified GOS (3-5)	504.5	261.3	36.7	12
mRS				
Good mRS (0-2)	685.9	239.0	36.9	42
Poor mRS (3-6)	480.2	236.5	39.3	17
Last NIHSS				
Mild (0-6)	444.4	214.8	35.6	42
Moderate (7-15)	812.2	249.5	37.5	15
Severe (beyond 16)	772.0	298.3	45.6	2

mRS : modified Rankin Scale, GOS : Glasgow Outcome Scale, NIHSS : National Institutes of Health Stroke Scale

They have demonstrated the usefulness of some serologic markers, such as D-dimer, brain natriuretic peptide, matrix metalloproteinase-9, and protein S100-beta, for detecting cerebral ischemic stroke.

Skoloudík et al.[40] found that the D-dimer levels increase within 6 hours after stroke onset is greater in patients with large artery occlusion and in patients with cardioembolic stroke than it is in patients with lacunar stroke or in patients without arterial occlusion. Barber et al.[5] showed D-dimer can help physicians target interventions for preventing early neurological deterioration after acute ischemic stroke. However, some studies postulated that D-dimer assessment cannot be used as an AIS index, with the exception of the cardioembolic subtype[15,41]. In this study, D-dimer had a statistical correlation to infarct volume, and D-dimer value changes during stroke therapy appeared greater in patients receiving intravenous rt-PA (with or without intra-arterial thrombolysis) than in those receiving intravenous argatroban therapy.

Lövblad et al.[27] provided evidence that infarction volume may be predictive of clinical severity and outcome. Also, infarction volume has shown significant correlations with NIHSS and brain injury scores[3,8,27]. Our study assessed the relationship between clinical outcome and infarction volume in AIS patients. Compared to previous studies, our results showed similar correlations between infarction volume and mRS, GOS, and NIHSS scores. Infarct volume increase correlated with poor outcomes on the mRS and NIHSS (p<0.05) but showed weaker correlation with the modified GOS (p=0.077).

Baird et al.[3] reported a high correlation between volume change and change in NIHSS score. Our study used DWI to check infarction volume change, comparing the volumes at the acute infarction onset and after 7 days. Only 24 (40%) of 59 patients showed reduced infarction volume on MRI during the follow-up period. Eighteen patients (30%) showed no change, 6 (10%) patients had an increased infarction volume, and 6 (10%) had a decreased volume. Hemorrhagic transformation of the infarcted area occurred in 5 patients (8%). Infarcted volume after seven days of treatment could not predict neurological outcome in our results. However, we found that patients with higher D-dimer levels were more likely to have high NIHSS scores upon admission (p=0.040) and after 7 days (p=0.015).

According to previous studies in the literature, such as the Trial of Org 10172 in Acute Stroke Treatment[1], the stroke subtype categories are atherothrombotic, cardioembolic, small-vessel occlusion or lacunar stroke of undetermined etiology, and stroke of other undetermined etiology. Moreover, Montaner et al.[29] have confirmed the usefulness of a unique biomarker in the etiologic diagnosis of a stroke, especially a cardioembolic stroke. We did not analyze by etiologic stroke diagnosis, as previous studies did, but rather categorized patients into 6 groups by infarction volume. The 6 groups comprised patients with focal, multiple embolic, 1-19 mL, 20-49 mL, 50-199 mL, and >200 mL infarctions, whose D-dimer levels were 215.3 μg/L, 385.7 μg/L, 566.2 μg/L, 668.8 μg/L, 702.5 μg/L, and 844.0 μg/L, respectively (p<0.05), at admission. Average D-dimer levels after 7 days were 201.0 μg/L, 293.2 μg/L, 272.0 μg/L, 232.8 μg/L, 336.6 μg/L, and 180.0 μg/L, respectively (p>0.05). This is the first study assessing the relationship between the D-dimer levels and stroke volume in ischemic stroke patients. Although we did not consider stroke etiology, our results show that knowing the D-dimer level is helpful for predicting infarction volume.

This study has several limitations. First, explaining the measurable variables in volume by our volumetric analysis, particularly in the focal and multiple embolic subgroups, was difficult. Though relationships among the other subgroups in our study correlate positively with D-dimer level and AIS lesion volume, D-dimer level in the focal and multiple embolic subgroups trended toward lower values. Second, we did not take account of potential confounding variables, such as age, gender, and co-morbid medical condition (pneumonia, acute renal failure, GI bleeding). Although many factors can influence an AIS patient's outcome, D-dimer level showed less correlation with patient outcome in our results. However, our data supports a correlation between D-dimer level and infarction volume in acute ischemic strokes. In spite of the confounding factors, D-dimer level revealed a positive correlation with infarction volume in our results. Third, our patient group was relatively small and heterogenous in age and therapeutic modality. Patients with various stroke therapies and various risk factors were included in this one study.

CONCLUSION

This study shows that D-dimer level significantly increases after the onset of an acute ischemic stroke and that the D-dimer level correlates positively with acute ischemic volume. D-dimer can be considered as a valuable marker for predicting infarction

volume in acute ischemic strokes and treatment response.

References

1. Adams HP Jr, Davis PH, Leira EC, Chang KC, Bendixen BH, Clarke WR, et al. : Baseline NIH Stroke Scale score strongly predicts outcome after stroke : a report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). **Neurology 53** : 126-131, 1999
2. Ageno W, Finazzi S, Steidl L, Biotti MG, Mera V, Melzi D'Eril G, et al. : Plasma measurement of D-dimer levels for the early diagnosis of ischemic stroke subtypes. **Arch Intern Med 162** : 2589-2593, 2002
3. Baird AE, Lövblad KO, Dashe JF, Connor A, Burzynski C, Schlaug G, et al. : Clinical correlations of diffusion and perfusion lesion volumes in acute ischemic stroke. **Cerebrovasc Dis 10** : 441-448, 2000
4. Barber M, Langhorne P, Rumley A, Lowe GD, Stott DJ : D-dimer predicts early clinical progression in ischemic stroke : confirmation using routine clinical assays. **Stroke 37** : 1113-1115, 2006
5. Barber M, Langhorne P, Rumley A, Lowe GDO, Stott DJ : Hemostatic function and progressing ischemic stroke : D-dimer predicts early clinical progression. **Stroke 35** : 1421-1425, 2004
6. Berge E, Friis P, Sandset PM : Hemostatic activation in acute ischemic stroke. **Thromb Res 101** : 13-21, 2001
7. Birschel P, Ellul J, Barer D : Progressing stroke : towards an internationally agreed definition. **Cerebrovasc Dis 17** : 242-252, 2004
8. Dastidar P, Heinonen T, Ahonen JP, Jehkonen M, Molnár G : Volumetric measurements of right cerebral hemisphere infarction : use of a semiautomatic MRI segmentation technique. **Comput Biol Med 30** : 41-54, 2000
9. Dunn KL, Wolf JP, Dorfman DM, Fitzpatrick P, Baker JL, Goldhaber SZ : Normal D-dimer levels in emergency department patients suspected of acute pulmonary embolism. **J Am Coll Cardiol 40** : 1475-1478, 2002
10. Feinberg WM, Bruck DC, Ring ME, Corrigan JJ Jr : Hemostatic markers in acute stroke. **Stroke 20** : 592-597, 1989
11. Flaherty ML, Woo D, Kissela B, Jauch E, Pancioli A, Carrozzella J, et al. : Combined IV and intraarterial thrombolysis for acute ischemic stroke. **Neurology 64** : 386-388, 2005
12. Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, et al. : Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study : a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. **JAMA 282** : 2003-2011, 1999
13. Gibler WB, Blomkalns AL, Collins SP : Evaluation of chest pain and heart failure in the emergency department : impact of multimarker strategies and B-type natriuretic peptide. **Rev Cardiovasc Med 4 Suppl 4** : S47-S55, 2003
14. Haapaniemi E, Soinne L, Syrjälä M, Kaste M, Tatlisumak T : Serial changes in fibrinolysis and coagulation activation markers in acute and convalescent phase of ischemic stroke. **Acta Neurol Scand 110** : 242-247, 2004
15. Haapaniemi E, Tatlisumak T : Is D-dimer helpful in evaluating stroke patients? A systematic review. **Acta Neurol Scand 119** : 141-150, 2009
16. Hoffmeister HM, Szabo S, Kastner C, Beyer ME, Helber U, Kazmaier S, et al. : Thrombolytic therapy in acute myocardial infarction : comparison of procoagulant effects of streptokinase and alteplase regimens with focus on the kallikrein system and plasmin. **Circulation 98** : 2527-2533, 1998
17. IMS Study Investigators : Combined intravenous and intra-arterial recanalization for acute ischemic stroke : the Interventional Management of Stroke Study. **Stroke 35** : 904-911, 2004
18. Jauch EC, Lindsell C, Broderick J, Fagan SC, Tilley BC, Levine SR : Association of serial biochemical markers with acute ischemic stroke : the National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study. **Stroke 37** : 2508-2513, 2006
19. Kelly PJ, Morrow JD, Ning M, Koroshetz W, Lo EH, Terry E, et al. : Oxidative stress and matrix metalloproteinase-9 in acute ischemic stroke : the Biomarker Evaluation or Antioxidant Therapies in Stroke (BEAT-Stroke) study. **Stroke 39** : 100-104, 2008
20. Kobayashi S, Tazaki Y : Effect of the thrombin inhibitor argatroban in acute cerebral thrombosis. **Semin Thromb Hemost 23** : 531-534, 1997
21. Koch HJ, Horn M, Bogdahn U, Ickenstein GW : The relationship between plasma D-dimer concentrations and acute ischemic stroke subtypes. **J Stroke Cerebrovasc Dis 14** : 75-79, 2005
22. Laskowitz DT, Blessing R, Floyd J, White WD, Lynch JR : Panel of biomarkers predicts stroke. **Ann N Y Acad Sci 1053** : 30, 2005
23. Laskowitz DT, Kasner SE, Saver J, Remmel KS, Jauch EC : Clinical usefulness of a biomarker-based diagnostic test for acute stroke : the Biomarker Rapid Assessment in Ischemic Injury (BRAIN) study. **Stroke 40** : 77-85, 2009
24. Lee KY, Kim DI, Kim SH, Lee SI, Chung HW, Shim YW, et al. : Sequential combination of intravenous recombinant tissue plasminogen activator and intra-arterial urokinase in acute ischemic stroke. **AJNR Am J Neuroradiol 25** : 1470-1475, 2004
25. Lewandowski CA, Frankel M, Tomsick TA, Broderick J, Frey J, Clark W, et al. : Combined intravenous and intra-arterial r-TPA versus intra-arterial therapy of acute ischemic stroke : Emergency Management of Stroke (EMS) Bridging Trial. **Stroke 30** : 2598-2605, 1999
26. Lip GY, 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 13** : 339-347, 2002
27. Lövblad KO, Baird AE, Schlaug G, Benfield A, Siewert B, Voetsch B, et al. : Ischemic lesion volumes in acute stroke by diffusion-weighted magnetic resonance imaging correlate with clinical outcome. **Ann Neurol 42** : 164-170, 1997
28. Lynch JR, Blessing R, White WD, Grocott HP, Newman MF, Laskowitz DT : Novel diagnostic test for acute stroke. **Stroke 35** : 57-63, 2004
29. Montaner J, Perea-Gainza M, Delgado P, Ribó M, Chacón P, Rosell A, et al. : Etiologic diagnosis of ischemic stroke subtypes with plasma biomarkers. **Stroke 39** : 2280-2287, 2008
30. Muir KW, Weir CJ, Alwan W, Squire IB, Lees KR : C-reactive protein and outcome after ischemic stroke. **Stroke 30** : 981-985, 1999
31. Park SY, Kim MH, Kang SY, Suh JT, Lee WI : Inflammatory marker expression and its implication in Korean ischemic stroke patients. **Korean J Lab Med 27** : 197-204, 2007
32. Penttilä K, Koukkunen H, Halinen M, Rantanen T, Pyörälä K, Punnonen K, et al. : Myoglobin, creatine kinase MB isoforms and creatine kinase MB mass in early diagnosis of myocardial infarction in patients with acute chest pain. **Clin Biochem 35** : 647-653, 2002
33. Perrier A, Desmarais S, Miron MJ, de Moerloose P, Lepage R, Slosman D, et al. : Non-invasive diagnosis of venous thromboembolism in outpatients. **Lancet 353** : 190-195, 1999
34. Reganon E, Vila V, Martínez-Sales V, Vaya A, Lago A, Alonso P, et al. : Association between inflammation and hemostatic markers in atherothrombotic stroke. **Thromb Res 112** : 217-221, 2003
35. Reynolds MA, Kirchick HJ, Dahlen JR, Anderberg JM, McPherson PH, Nakamura KK, et al. : Early biomarkers of stroke. **Clin Chem 49** : 1733-1739, 2003
36. Rosamond W, Flegal K, Friday G : Heart disease and stroke statistics--2007 update : a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. **Circulation 115** : e69-e171, 2007
37. Rundek T, Sacco RL : Risk factor management to prevent first stroke. **Neurol Clin 26** : 1007-1045, ix, 2008
38. Saposnik G, Di Legge S, Webster F, Hachinski V : Predictors of major neurologic improvement after thrombolysis in acute stroke. **Neurology**

65 : 1169-1174, 2005
39. Sibon I, Rouanet F, Meissner W, Orgogozo JM : Use of the Triage Stroke Panel in a neurologic emergency service. **Am J Emerg Med 27** : 558-562, 2009
40. Skoloudík D, Bar M, Sanák D, Bardon P, Roubec M, Langová K, et al. : D-dimers increase in acute ischemic stroke patients with the large artery occlusion, but do not depend on the time of artery recanalization. **J Thromb Thrombolysis 29** : 477-482, 2010
41. Skoloudík D, Bar M, Zapletalová O, Langová K, Herzig R, Kanovský P : D-dimer levels in acute stroke patients. **Cesk Slov Neurol N 103** : 375-379, 2007
42. Takagi S, Shinohara Y : Internal carotid occlusion : volume of cerebral infarction, clinical findings, and prognosis. **Stroke 12** : 835-839, 1981
43. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group : Tissue plasminogen activator for acute ischemic stroke. **N Engl J Med 333** : 1581-1587, 1995
44. Tombul T, Atbas C, Anlar O : Hemostatic markers and platelet aggregation factors as predictive markers for type of stroke and neurological disability following cerebral infarction. **J Clin Neurosci 12** : 429-434, 2005
45. Whiteley W, Tseng MC, Sandercock P : Blood biomarkers in the diagnosis of ischemic stroke : a systematic review. **Stroke 39** : 2902-2909, 2008
46. Zaidat OO, Suarez JI, Santillan C, Sunshine JL, Tarr RW, Paras VH, et al. : Response to intra-arterial and combined intravenous and intra-arterial thrombolytic therapy in patients with distal internal carotid artery occlusion. **Stroke 33** : 1821-1826, 2002