European Review for Medical and Pharmacological Sciences 2015; 19: 2608-2613

Recurrent ischemic events and risk factors in patients with symptomatic intracranial artery stenosis

P.-Q. WANG, J.-J. LIU, A.-P. WANG, G.-B. ZHANG, Z.-H. CAO, P. WANG, P.-Y. ZHOU

Department of Neurology, Xiangyang Hospital Affiliated to Hubei University of Medicine, Xiangyang, Hubei, China

Pu-Qing Wang and *Juan-Juan Liu* contributed equally to this work

Abstract. – OBJECTIVE: To evaluate the recurrent ischemic events and risk factors in patients with symptomatic intracranial artery stenosis.

PATIENTS AND METHODS: Patients with acute cerebral infarction or transient ischemia attach (TIA) and intracranial arterial stenosis confirmed through CTA examination, were enrolled from the Department of Neurology. All cases were followed-up regularly and divided into recurrent group and non-recurrent group according to occurrence of cerebrovascular events. Major observation index: (1) the occurrence of endpoint; (2) new stroke in responsible artery; (3) drug therapy compliance was used.

RESULTS: A total of 142 cases fulfilled the inclusion criteria, among them 121 cases (85.2%) completed the follow-up, and in 16 cases (13.2%) ischemic cerebrovascular stroke events occurred within one year, while among these vascular lesions recurred on the ipsilateral side in 12 cases (75%). Single factor analysis showed that difference between recurrent group and non-recurrent group on irregular use of statins (p = 0.017), diabetes mellitus (p = 0.017) and severe arterial stenosis (p = 0.030) were statistically significant. Logistic regression analysis showed that irregular use of statins (OR=3.719, p = 0.005), diabetes (OR=1.842. p = 029) and severe arterial stenosis (OR=1.503. p = 0.045) were correlated with the recurrence of symptomatic intracranial artery stenosis.

CONCLUSIONS: Patients with symptomatic intracranial artery stenosis had a higher recurrence rate of stroke; whereas patients with irregular use of statins, diabetes and severe arterial stenosis had a higher recurrence risk of stroke.

Key Words:
IAS; Stroke; Recurrence; Non-recurrence.

Introduction

Intracranial arterial stenosis (IAS) was one of the most important mechanisms of ischemic stroke. It was reported that the Asians are more vulnerable to IAS[1-2]. Although a great many therapeutic measures have been taken, IAS patients still have a high of stroke[3-7]. This study followed and observed the prognosis of symptomatic IAS patients in the region, and made an analysis on relevant risk factors.

Patients and Methods

Case Selection

A total of 172 patients were selected with cerebral infarction or TIA who were hospitalized in the Neurology Department of Xiang Yang Affiliated Hospital of Hubei Medical University from June, 2009 to January, 2011.

Inclusion criteria: Within 7 days from the onset of the disease until the visit to a doctor, and excluding silent stroke (determined by neuroimaging), and cerebral hemorrhage through head CT scanning and clinically asymptomatic; intracranial artery stenosis was revealed through a computed tomographic angiography (CTA) and stroke occurred in the blood supplying area of the narrow artery. Intracranial artery included intracranial internal carotid artery I-ICA, middle cerebral artery (MCA), anterior cerebral anterior (ACA), posterior cerebral artery (PCA), intracranial vertebral artery (I-VA), and basilar artery (BA); aged 40-80 years; patients who could not accept stent implantation (catheter unable to reach the affected region because of blood vessel stenosis or distortion, consecutive multi-segment stenosis or overlong stenosis segment, artery occluded) or patients were unwilling to accept stent implantation. Authorization of the Hospital's Ethics Committees and the informed consent of the patients as well as their authorizers were obtained prior to study.

Corresponding Author: Gui-bin Zhang, MD; e-mail: zgb1969@126.com

Exclusion Criteria

Patients who had potential cardiogenic brain embolism (including auricular fibrillation, rheumatic mitral stenosis, artificial valve, intracardiac thrombus or tumor, myocardiopathy, myocardial infarction within three months, left ventricular aneurysm after myocardial infarction or incongruous ventricular wall motion, endocarditis, patent foramen ovale and pulmonary embolism or interatrial septum and paradoxical embolism aneurysms etc.); patients who had been administered with thrombolysis, intravascular interventional treatment or carotid endarterectomy treatment in acute stage; ipsilateral extracranial carotid stenosis ≥50% through cervical vascular ultrasonic inspection; patients with severe heart, liver and renal insufficiency; patients with stroke caused by non-atherosclerotic vascular stenosis; patients in critical condition and could not join the research

Follow-up Observation

All patients included in research was adjusted (100 mg d-1 aspirin or 75 mg d-1 clopidogrel, 20 mg d-1 atorvastatin calcium or simvastatin). The level of blood sugar of the diabetics was controlled and the blood pressure of hypertensive patients was adjusted (nifedipine sustain-released tablet or benazepril). A regular follow-up was conducted on the symptomatic stenosis patients, home visit follow-up, or outpatient follow-up. The duration of follow-up was recorded since registration. Telephone follow-up was regularly made once a month to all the cerebrovascular disease patients.

Endpoint: including primary endpoint (cerebral infarction and TIA), secondary end point (acute angina and myocardial infarction), and death due to various reasons, once any endpoint appeared, follow-up was ended.

Laboratory and Imaging Assessment

All of the patients went through MRI, CTA, complete blood count, blood biochemistry, blood coagulation function, and electrocardiographic examinations. Baseline data included age, gender, and major stroke risk factors (including hypertension, diabetes, coronary heart disease, high cholesterol, smoking, drinking and family history of stroke) and a physical examination.

Observation index: the occurrence of endpoint; the relationship between new stroke and responsible artery; drug therapy compliance: a regular use of 100 mg.d-1 aspirin or 75 mg.d-1 clopidogrel, missing rate < 20%; a regular use of statin drugs, missing rate < 20%; a regular use of hypotensive drugs, missing rate < 20%.

Assessment of Cerebral Infarction and Intracranial Artery Stenosis

MRI assessment: SIEMENS 1.5T NOVUS MRI scanner was employed for scanning phased array body coil. Scanning parameters were 5mm thickness, 1 mm interval, 256×256 matrix; diffusion imaging (DWI) SE-EPI axial view TR 3400 ms, TE98 ms, single-shot echo planar imaging was applied, diffusion sensitizing gradient pulse along X, Y or Z direction was developed, diffusion sensitive coefficient (b value) were 0 and 1000 s/mm^2. High signal on DWI image was confirmed as acute cerebral infarct.

CTA: 64-slice CT, CTA of intracranial and cervical arteries (superior border of arcus aortae reaching calvarium), post-processing techniques, including volume rendering (VR), three dimensional multiplanar reconstruction (3D-MPR), curve planar reconstruction (CPR) and three dimensional maximum intensity projection (3D-MIP), combined with original axial images were employed to observe the stenosis extent, occlusion and other characteristics of artery lumen, and also make quantitative measurement on luminal stenosis.

MRI and CTA imaging were measured and evaluated respectively by two vice directors of imaging department and the results were confirmed by both doctors. Consulting literature for MRI-DWI infarction positioning[8]; North American Symptomatic Carotid Endomembrane test (NASCET)[9] was implemented to calculate the rate of arterial stenosis: stenosis = (original lumen diameter-residual lumen diameter on stenosis area)/original lumen diameter × 100%. The degree of stenosis was divided into mild stenosis (1%-39%), moderate stenosis (40%-69%), severe stenosis (70%-99%) and occlusion.

Statistical Analysis

All of the data were analyzed using SPSS software. χ^2 test was applied to test enumeration data and *t*-test was applied to test measurement data. χ^2 test was also applied on single factor analysis of recurrence relative factors and Logistic regression analysis was applied on multi factor analysis, $p < 0.05$ was considered statistically significant.

Results

General Clinical Information

Through clinical and MRI diagnosis, 172 cases were diagnosed as cerebral infarction and TIA and 142 patients satisfied the inclusion criteria for intracranial artery stenosis. These patients included 102 males and 40 females, aged 40-80 years (average age 63.5±11.5 years); 85 cases of cerebral infarction, 57 cases of TIA; 27 cases of combined diabetes, 119 cases of hypertension, 45 cases of dyslipidemia, 16 cases of coronary heart disease; 31 cases with a history of cerebral infarction, 71 cases with a history of smoking and 52 cases with a history of drinking.

There were 23 cases (16.2%) of single vascular stenosis, 119 cases (83.8%) of multiple vascular stenosis, 87 cases of pure intracranial artery stenosis, and 55 cases were intracranial-extracranial stenosis. The location of intracranial artery lesion was in order, MCA, I-VA, PCA, ACA, I-ICA, BA. From 142 patients, a total of 384 pieces of lesion vessels were detected, among which 124 pieces were of mild stenosis, 126 pieces of moderate stenosis, 96 pieces of severe stenosis, and 38 pieces of occlusion.

Follow-up Observation

Among 142 patients, 21 cases (14.8%) were lost during follow up, two patients died (1.4% 1 case of nonvascular death), and 121 cases (85.2%) completed the follow up, with an average follow-up period of 15.2 ± 2.3 months. Sixteen cases of ischemic stroke appeared within one year (13.2%), among them there were 2 cases of cerebral infarction, 2 cases of TIA, 1 case of myocardial infarction. Recurrence occurred on the ipsilateral vascular lesions in 12 cases (75%).

After dividing the participants into ischemic events recurrent group and non-recurrent group in accordance with the follow-up results and comparing the demographics, clinical features, and intervention compliance of the two groups, we found that the differences for irregular use of statin drugs, diabetes, and severe stenosis arteries between recurrent group and non-recurrent group were statistically significant. While other risk factors of stroke, including hypertension, hyperlipidemia, smoking, irregular use of hypotensor, irregular use of antiplatelet drugs, multiple arteriostenosis, and multiple infarction were not statistically significant between the two groups (Table 1).

Table I. The demographic, clinical characteristics and intervention compliance of the two groups.

Relevant factor	Recurrent group (n=16)	Non-recurrent group (n=105)	χ^2/t	*p*-value
Age (years old, x±s)	63.9±12.6	62.2±10.1	1.024	0.256
Male (n, %)	10 (62.5)	76 (72.4)	0.659	0.417
Smoking (n, %)	7 (43.8)	58 (55.2)	0.737	0.391
Drinking (n, %)	8 (50.0)	40 (38.1)	0.822	0.365
TIA history (n, %)	2 (12.5)	7 (6.7)	0.686	0.407
Diabetes mellitus (n, %)	7 (43.8)	17 (16.2)	6.632	0.017
Hypertension (n, %)	14 (87.5)	89 (84.8)	0.082	0.774
Hyperlipemia (n, %)	7 (43.8)	32 (30.5)	3.137	0.077
Coronary heart disease (n, %)	2 (12.5)	11 (10.5)	0.059	0.808
Stroke history (n, %)	4 (25.0)	24 (22.9)	0.374	0.541
Degree of stenosis (n, %)				
light and moderate degree	6 (37.5)	69 (65.7)	4.690	0.030
severe degree	10 (62.5)	36 (34.3)	4.690	0.030
Arterial stenosis (n, %)				
I-ICA	2 (12.5)	13 (12.4)	0.000	0.989
MCA	6 (37.5)	37 (35.2)	0.031	0.860
ACA	1 (6.25)	12 (11.4)	0.388	0.533
PCA	2 (12.5)	18 (17.1)	0.217	0.641
I-VA	3 (18.8)	18 (17.1)	0.025	0.874
BA	2 (12.5)	7 (6.7)	0.686	0.407
Multiple arteriostenosis (n, %) 13 (81.3)	89 (84.8)	0.129	0.719	
Multiple infarction (n, %)	10 (62.5)	39 (37.1)	3.705	0.062
Drug therapy compliance (n, %)				
Irregular use of hypotensor (n, %)	2 (12.5)	10 (9.5)	0.138	0.711
Irregular use of antiplatelet drugs (n, %)	3 (18.8)	9 (8.6)	1.610	0.204
Irregular use of statin (n, %)	10 (62.5)	28 (26.7)	5.724	0.017

Table II. Independent risk factors of recurrent ischemic events in patients with symptomatic intracranial artery stenosis.

Relevant factor	OR (95% CI)	*p*-value
Irregular use of statin drugs	3.525 (2.141-6.954)	0.005
Diabetes	1.842 (1.396-4.859)	0.029
Severe stenosis arteries	1.503 (1.116-4.240)	0.045
Multiple infarction	0.976 (0.683-1.910)	0.147
Hyperlipemia	0.953 (0.675-1.974)	0.329

Independent Risk Factors of Recurrent Ischemic Events in Patients with Symptomatic Intracranial Artery Stenosis

To take variable, such as irregular use of statin, diabetes, severe stenosis arteries, multiple infarction, hyperlipemia as independent variable, and recurrent ischemic events as dependent variable. Taking multivariable Logistic regression analysis, the result showed that irregular use of statin, diabetes, and severe stenosis arteries was significantly related with the recurrence of stroke in patients with symptomatic intracranial artery stenosis (Table II).

Discussion

This study, through implementing non-invasive vascular imaging technology CTA to detect artery stenosis[10-13], screening patients with ischemic cerebrovascular diseases and intracranial atherosclerotic stenosis tracking and observing their prognosis, and evaluating the factors that affected the stroke recurrence, found out that the incidence of cerebrovascular events within one year had reached 13.2%, which is in coincidence with the results of Famakin et al[14]. Recurrence (75%) had occurred on the same side of lesion vessels, indicating that arterial stenosis was closely related with cerebral infarction recurrence, and also that even with active antiplatelet therapy, the recurrence rate of cerebrovascular events was still very high and worthy of our attention.

This study, further, analyzed the relevant factors that influence the prognosis of patients with symptomatic intracranial artery stenosis, and observed that the irregular use of statin drugs, diabetes, and severe stenosis in recurrent group were significantly higher than that in the non-recurrent group, which was different from other reports. Kasnert and others[15], after making follow-ups on 569 patients discovered that 106 patients (19.0%) had cerebral infarction, with severe arterial stenosis, ≥70% had the highest risk of stroke, and that an increasing risk in women. Location of stenosis and the pretreatment of antithrombotic drugs had no effect. It was analyzed that the differences might be related with the patients' severity of illness, degree of vasculopathy and other relevant factors.

No significant differences were found between recurrent and non-recurrent groups in terms of demography and clinical characteristics: age, gender, history of hypertension, hyperlipidemia, coronary heart disease and stroke. Logistic regression analysis showed that diabetes was significantly related with the recurrence of stroke, indicating that the diabetics with cerebral arterial stenosis were more vulnerable to stroke recurrence and that they were high-risk population that deserved clinician's attention.

In terms of intervention treatments, no significant difference was observed for regular or irregular use of hypotensive drugs and antiplatelet drugs between the two groups, which indicated that people in this region had a good compliance for blood pressure controlling treatment and antiplatelet therapy[16-17]. Whereas, statistical results showed that the number of patients with irregular use of statins in recurrent group was significantly higher than the non-recurrent group and logistic regression analysis also showed that irregular use of statins was closely related with stroke recurrence and it was one of the important factors that influenced the prognosis of the group of patients. This result was not quite consistent with related studies[18-21]. It might be because there were differences in the degree of stenosis and the patients' compliance for different kinds of interventions. Statins are kind of reductase inhibitors, which could improve endothelial cell function, reduce blood flow stress, and stabilize atherosclerotic plaque[22-24]. Researchers have shown that long-term treatment with statins could reduce stroke progress and recurrence, postpone the progress of atherosclerosis, and even reduce the stenosis degree of atherosis that had already occurred[25]. All of these findings had been confirmed in coronary artery[26]. Tan and others[27] had observed 54 narrow vessels from consecutive 40 cases. The observation subjects were administered orally with 40 mg/d atorvastatin (for at least 6 month) until the second MRI test was complet-

ed. By the end of the research, the degree of arterial stenosis in 58% of the patients had been improved, unchanged in 38% of the patients; while in 4% of the patients the condition had worsened. Studies by Chimowitz and others[28] had shown that a decrease in low density lipoprotein, cholesterin could reduce the risk of recurrent stroke. These results indicated that if ischemic symptoms were resulted from arterial-arterial embolism caused by unstable plaque, drug therapy that could stabilize plaque and reduce the falling off of plaque in recovery period should be further intensified.

WASID test found from pooling analysis that 73% of ischemic stroke occurred on the narrow position of the blood vessels, and multivariate analysis showed that the degree of stenosis was the most important predictor of risk and predictability was in linear relationship with the degree of stenosis. Single factor analysis showed that the number of patients with severe stenosis in recurrent group was significantly higher than the non-recurrent group. Logistic regression analysis showed that it was closely related with recurrent stroke. In the meanwhile, statistical results also showed that 75% of recurrence occurred on the ipsilateral vascular lesions, indicating that the patients with severe stenosis had a higher recurrence risk of stroke.

Conclusions

The study results showed that, with the increasing improvement of the clinicians' and patients' awareness, most of the patients could actively cooperate in blood pressure controlling treatment and antiplatelet therapy. But the proportion of the patients who take statin drugs regularly was still quite low and the incidence of recurrent stroke was still very high, which is the general characteristics of our subjects and also one of the major controllable factors that we should pay attention to. Follow-up research on symptomatic intracranial artery stenosis cerebral infarction or TIA prognosis as well as its influencing factors would provide a feasible basis for secondary prevention of stroke patients. The results of this study are still in need of further confirmation in a larger sample.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Pei YZ, Xu GL, Zhu WS, Liu XF. An analysis of angiography result of 300 patients with ischemic stroke. Chinese Journal of Arteriosclerosis 2008; 16: 643-646.
2) Tan TY, Tseng MC, Chang KC. Risk factors for first-ever ischemic stroke: a hospital-based case-control study in Kaohsiung, Taiwan. Chang Gung Med J 2004; 27: 801-807.
3) Karapinar H, Acar G, Kirma C, Kaya Z, Karavelioglu Y, Kucukdurmaz Z, Esen O, Alizade E, Dasli T, Sirma D, Esen AM. Delayed right atrial lateral electromechanical coupling relative to the septal one can be associated with paroxysmal atrial fibrillation. Eur Rev Med Pharmacol Sci 2013; 17: 2172-2178.
4) Wong KS, Li H. Long-term mortality and recurrent stroke risk among Chinese stroke patients with predominant intracranial atherosclerosis. Stroke 2003; 34: 2361-2366.
5) Zaidat OO, Fitzsimmons BF, Woodward BK, Wang Z, Killer-Oberpfalzer M, Wakhloo A, Gupta R, Kirshner H, Megerian JT, Lesko J, Pitzer P, Ramos J, Castonguay AC, Barnwell S, Smith WS, Gress DR; VISSIT Trial Investigators. Effect of a balloon-expandable intracranial stent vs medical therapy on risk of stroke in patients with symptomatic intracranial stenosis: the VISSIT randomized clinical trial. JAMA 2015; 313: 1240-1248.
6) Chimowitz MI, Derdeyn CP. Endovascular therapy for atherosclerotic intracranial arterial stenosis: back to the drawing board. JAMA 2015; 313: 1219-1220.
7) Uchiyama S, Sakai N, Toi S, Ezura M, Okada Y, Takagi M, Nagai Y, Matsubara Y, Minematsu K, Suzuki N, Tanahashi N, Taki W, Nagata I, Matsumoto M; CATHARSIS Study Group. Final Results of Cilostazol-Aspirin Therapy against Recurrent Stroke with Intracranial Artery Stenosis (CATHARSIS), Cerebrovasc Dis Extra 2015; 5: 1-13.
8) Taty L, Moulin T, Bogousslavsky J, Duvernoy H. Arterial territories of the human brain cerebral hemispheres. Neurology 1998; 50: 1699-1708.
9) Beneficial effect of carotid endarterectomy in symptomatic patients with high grade stenosis. North American Symptomatic Carotid Endarterectomy Trail Collaborators. N Engl J Med 1991; 325: 445-453.
10) Vonk Noordegraaf A, Haddad F, Bogaard HJ, Hassoun PM. Noninvasive imaging in the assessment of the cardiopulmonary vascular unit. Circulation 2015; 131: 899-913.
11) Liu H, Chen Y, Yan F, Han X, Wu J, Liu X, Zheng H. Ultrasound molecular imaging of vascular endothelial growth factor receptor 2 expression for endometrial receptivity evaluation. Theranostics 2015; 5: 206-217.
12) Emami H, Tawakol A. Noninvasive imaging of arterial inflammation using FDG-PET/CT. Curr Opin Lipidol 2014; 25: 431-437.

13) Wang PQ, Wang Y, Wang AP. Study of 64-slice CT on carotid atherosclerosis in ischemic cerebrovascular patients. Chinese Journal of Arteriosclerosis 2012; 20: 819-823.

14) Famakin BM, Chimowitz MI, Lynn MJ, Stern BJ, George MG; WASID Trial Investigators. Causes and severity of ischemic stroke in patients with symptomatic intracranial arterial stenosis, Stroke, 2009; 40: 1999-2003.

15) Kasner SE, Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, Levine SR, Chaturvedi S, Benesch CG, Sila CA, Jovin TG, Romano JG, Cloft HJ; Warfarin Aspirin Symptomatic Intracranial Disease Trial Investigators. Predictors of ischemic stroke in the territory of a symptomatic intracranial arterial stenosis. Circulation 2006; 113: 555-563.

16) Chen H, Wu B, Zhu G, Wintermark M, Wu X, Su Z, Xu X, Tian C, Ma L, Zhang W, Lou X. Permeability imaging as a biomarker of leptomeningeal collateral flow in patients with intracranial arterial stenosis. Cell Biochem Biophys 2014 Dec. 12. [Epub ahead of print].

17) Wang A, Li Z, Luo Y, Liu X, Guo X, Wu S, Zhao X, Jonas JB. Asymptomatic intracranial arterial stenosis and metabolic syndrome: the APAC study. PLoS One 2014; 9: e113205.

18) Tan L, Margaret B, Zhang JH, Hu R, Yin Y, Cao L, Feng H, Zhang Y. Efficacy and safety of cilostazol therapy in ischemic stroke: a meta-analysis. J Stroke Cerebrovasc Dis 2015; 24: 930-938.

19) Erdur H, Scheitz JF, Ebinger M, Rocco A, Grittner U, Meisel A, Rothwell PM, Endres M, Nolte CH. In-hospital stroke recurrence and stroke after transient ischemic attack: frequency and risk factors. Stroke 2015; 46: 1031-1037.

20) Ryu WS, Park SS, Kim YS, Lee SH, Kang K, Kim C, Sohn CH, Lee SH, Yoon BW. Long-term natural history of intracranial arterial stenosis: an MRA follow-up study. Cerebrovasc Dis 2014; 38: 290-296.

21) Oh HG, Chung PW, Rhee EJ. Increased risk for intracranial arterial stenosis in subjects with coronary artery calcification. Stroke 2015; 46: 151-156.

22) Hashimoto S, Urushihara H, Hinotsu S, Kosugi S, Kawakami K. Effect of HMG-CoA reductase inhibitors on blood pressure in hypertensive patients treated with blood pressure-lowering agents: retrospective study using an anti-hypertensive drug database. Eur Rev Med Pharmacol Sci 2012; 16: 235-241.

23) Vural K, Tuglu MI. Neurotoxic effect of statins on mouse neuroblastoma NB2a cell line. Eur Rev Med Pharmacol Sci 2011; 15: 985-991.

24) Cheng HH, Tang TT, He Q, Huang LJ, Lin XL, Chen M, Yang C, Geng DF, Jiang SP. Beneficial effects of statins on outcomes in pneumonia: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci 2014; 18: 2294-305.

25) Crouse JR, Raichlen JS, Riley WA, Evans GW, Palmer MK, O'Leary DH, Grobbee DE, Bots ML; METEOR Study Group. Effect of rosuvastantin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trail. JAMA 2007; 297: 1344-1353.

26) Rodriguez-Cranillo GA, Agostoni P, Garcia-Garcia HM, Biondi-Zoccai GG, McFadden E, Amoroso G, de Jaegere P, Bruining N, de Feyter P, Serruys PW. Meta-analysis of the studies assessing temporal changes in coronary plaque volume using intravascular ultrasound. Am J Cardiol 2007; 99: 5-10.

27) Tan TY, Kuo YL, Lin WC, Chen TY. Effect of lipid-lowering therapy on the progression of intracranial arterial stenosis. J Neurol 2009; 256: 187-193.

28) Chimowitz MI,Lynn MJ, Derdeyn CP, Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, Janis LS, Lutsep HL, Barnwell SL, Waters MF, Hoh BL, Hourihane JM, Levy EI, Alexandrov AV, Harrigan MR, Chiu D, Klucznik RP, Clark JM, McDougall CG, Johnson MD, Pride GL Jr, Torbey MT, Zaidat OO, Rumboldt Z, Cloft HJ; SAMMPRIS Trial Investigators. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med 2011; 365: 993-1003.