The 2-Year Outcomes Comparison between Ischemic Stroke Patients with Intracranial Arterial Stenosis without Significant Extracranial Carotid Stenosis and Patients with Extracranial Carotid Stenosis

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Objective: *The risk of recurrent ischemic stroke and acute coronary syndrome increased in the large artery atherosclerotic subtype. The purpose of this study was to compare 2-year outcomes between the ischemic stroke patients with intracranial arterial stenosis without significant extracranial carotid stenosis and the patients with extracranial carotid stenosis.*
Material and Method: *This study prospectively compared 123 ischemic stroke patients: 71 patients with intracranial arterial stenosis without significant extracranial carotid stenosis and 52 patients with extracranial carotid stenosis. Neurologic and radiologic investigations were performed at the beginning of the study. All of them were treated as regular outpatients of the neurology unit with a mean follow-up of 24 months. Recurrent stroke, myocardial infarction, and death were recorded.*
Results: *Fifteen patients of the extracranial carotid stenosis group and eighteen patients of the intracranial arterial stenosis without significant extracranial carotid stenosis group developed recurrent stroke during follow-up (p = 0.40). Acute coronary syndrome occurred in eight patients of the extracranial carotid stenosis group and only one of the intracranial arterial stenosis without significant extracranial carotid stenosis group (p = 0.004). Causes of death were end stage cancers, stroke and related conditions, and acute coronary syndrome. The multivariate analysis showed that symptomatic extracranial carotid stenosis is an important risk factor of the acute coronary syndrome (p = 0.03, OR = 10.81, 95% CI 1.23-94.77).*
Conclusion: *There was no significant difference of recurrent ischemic stroke and recurrent stroke between patients with intracranial arterial stenosis without extracranial carotid stenosis and patients with extracranial carotid stenosis. On the other hand, patients with extracranial carotid stenosis had more incidences of acute coronary syndrome significantly than patients with intracranial arterial stenosis.*

Keywords: *Ischemic stroke, Intracranial arterial stenosis, Extracranial carotid stenosis, Stroke outcomes*

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In general, the risk of recurrent stroke has gradually increased with a longer follow-up period[1,2]. However, ischemic stroke patients with large artery atherosclerotic subtype had a higher risk of recurrent stroke than cardiac embolism and the small vessel disease subtype[3]. Previous studies reported the high prevalence of coexisting coronary artery disease of this stroke subtype as well[4-10], which finally becomes the major cause of death in ischemic stroke patients. The prevalence of extracranial internal carotid stenosis was commonly found in Europeans[11], whereas the intracranial arterial stenosis was significantly found in Africans, Americans and Asians[12-16]. To achieve a successful treatment and prevention of morbidity and mortality for the large artery ischemic stroke subtype, knowledge of the course of the disease is needed. The aim of this study was to compare the 2-year outcomes between Thai ischemic stroke patients with and without extracranial carotid stenosis.

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Material and Method

The population of this study was continued from the previous study project "Comparison of Atherosclerotic Risk Factors between Patients with

Intracranial Arterial Stenosis without Significant Extracranial Carotid Stenosis and Patients with Extracranial Carotid Stenosis". Thai patients diagnosed with ischemic stroke, transient ischemic attack (TIA), or ocular stroke of King Chulalongkorn Memorial Hospital were included from January to December 2004. All of them were evaluated for their vascular status by Transcranial doppler ultrasonography (TCD) and carotid duplex ultrasonography (CDUS). They were divided into three subgroups: small vessels, intracranial arterial stenosis without significant extracranial carotid stenosis, and extracranial carotid stenosis. The definition of the intracranial arterial stenosis without significant extracranial carotid stenosis was that the TCD revealed the more than 50% stenosis of the middle cerebral artery, anterior cerebral artery, posterior cerebral artery, vertebral artery, or basilar artery, without significant stenosis of the extracranial carotid artery. For the extracranial carotid stenosis, patients presented the more than 50% stenosis of the extracranial carotid artery detected by CDUS. Patients with evidence of large artery atherosclerosis were entered into this study with inclusion criteria: 1) they had ischemic stroke, TIA or ocular strokes, 2) age $\geq$45 years old, 3) the vascular study revealed the large artery atherosclerotic subtype, 4) they accepted to be candidates and signed consent forms. The exclusion criteria were 1) non-atherosclerotic ischemic stroke such as arterial dissection, arterio-venous malformation or arteritis, 2) coexisting atrial fibrillation with cardiogenic embolism, 3) ischemic stroke caused by hematologic abnormalities such as hyperviscosity syndrome, polycythemia vera or acute myeloid leukemia, and 4) venous sinus thrombosis.

The follow-up period was between January 2004 and December 2006. An initial assessment of each patient consisted of date of the first onset, general status (age, gender, bodyweight, body mass index (BMI)), neurovascular history, history of other medical illnesses, and physical examinations. Hematologic and biochemical laboratory parameters were investigated. Neuroradiologic studies included CT scan of the brain, MRI of the brain, MRA of the brain and neck, transcranial doppler ultrasonography, and carotid duplex ultrasonography. A 12-lead EKG and chest x-ray were done at the beginning of the study. Treatments of the first episode of ischemic attack (antiplatelets, anticoagulant, lipid lowering agents) were recorded. All patients were followed-up as regular outpatients of the neurology clinic. Recurrent stroke was recorded in details as the ischemic or hemorrhagic type, the onset, the history and neurological deficits, images of CT scan or MRI of the brain, and death. Acute coronary syndrome was recorded when it occurred either in the history, at a physical examination or at death. Hypertension, diabetes mellitus (DM), dyslipidemia, and lifestyle modifications (smoking, alcohol drinking, and exercises) were recorded. For patients who migrated to other provinces or were preferably followed up at local hospitals, data were collected by a principle investigator using telephone interviewing or questionnaire letter. The research was approved for ethical consideration by the ethical committee of Faculty of Medicine, Chulalongkorn University.

Statistical analysis

Summarization of general data, the incidence of recurrent stroke and major vascular events were presented as a percentage. The odds ratio (OR) at 95% confidence interval was used to compare outcomes between two groups at p-value <0.05. Chi-square test or Fisher's exact test was used to estimate differences of qualitative data by two by two tables. The numerical data were estimated by t-test. Logistic regression analysis was for identification of significant risk factors including confounding factors, associated to outcomes. Cumulative mortality, recurrent stroke and acute coronary syndrome were determined using Kaplan-Meier survival analysis and log-rank statistic. The computerized program used was SPSS for Windows, version 11.5.0 (Copyright SPSS Inc., 1989-2002).

Results

This prospective study was ongoing from 153 ischemic stroke patients of the large artery atherosclerotic subtype. After exclusion, 84 patients with intracranial arterial stenosis without significant extracranial carotid stenosis and 58 patients with extracranial carotid stenosis were enrolled. Thirteen patients with the intracranial arterial stenosis without significant extracranial carotid stenosis and six patients with the extracranial carotid stenosis were excluded from the study due to loss of contact. Finally, 71 patients with the intracranial arterial stenosis without significant extracranial carotid stenosis and 52 patients with the extracranial carotid stenosis were included. The baseline characteristics of two groups are presented in Table 1. DM was significantly found in the intracranial arterial stenosis without significant extracranial carotid stenosis group.

There were 18 patients of the intracranial arterial stenosis group experienced recurrent stroke: 16 persons (22.5%) developed recurrent cerebral infarction

Table 1. Baseline characteristics

Factors	Extracranial carotid stenosis (n = 52)	Intracranial arterial stenosis (n = 71)	*p*-value
Male (%)	36 (69.2)	48 (67.6)	0.50**
Age (year)	70.75±10.27	67.63±10.54	0.52***
Weight (kg)	61.30±11.98	62.30±12.19	0.70***
Height (cm)	159.90±9.93	160.80±8.11	0.14***
BMI (kg/m^2)	23.90±3.89	24.20±4.41	0.96***
Hypertension (%)	34 (65.4)	53 (74.6)	0.18***
DM (%)	12 (23.1)	34 (47.9)	0.004*,***
Dyslipidemia (%)	31 (59.6)	34 (47.9)	0.13***
Smoking (%) (within 5 years)	21 (40.4)	20 (28.2)	0.11***
Alcohol (%) (within 6 months)	14 (26.9)	10 (14.1)	0.06***

* significant; ** Chi-square; *** t-test

and 2 persons (3.8%) developed intracranial hemorrhage. Fifteen patients of the extracranial carotid stenosis group developed recurrent stroke: 13 persons (25.0%) were ischemia and 2 persons (3.8%) were hemorrhage. The Chi-square test showed no significant difference of recurrent ischemic stroke ($p = 0.45$) and recurrent stroke ($p = 0.40$). Mortality rates of recurrent stroke within 2-years follow-up were 2.8% in the intracranial arterial stenosis group and 7.7% in the extracranial carotid stenosis group.

There was only one patient of the intracranial arterial stenosis without significant extracranial carotid stenosis group developed acute myocardial infarction, whereas eight patients of the extracranial carotid stenosis group developed acute myocardial infarction. The mortality rates of acute coronary syndrome were 1.8% and 7.7%, respectively. The Fisher's exact test revealed the significant incidence of acute coronary syndrome in the extracranial carotid stenosis group ($p = 0.004$). There was no significant difference in mortality rates of recurrent stroke and acute coronary syndrome of these two groups.

Kaplan-Meier survival analysis showed that over all cumulative survival and cumulative stroke-free rate were approximately constant across the time (Fig. 1, 2).

Comparison of the two curves by log-rank test yielded non-significant differences of survival and recurrent stroke-free mean times between two groups ($p = 0.12$ and $p = 0.52$). On the contrary, the survival curve for acute coronary syndrome of the intracranial arterial stenosis group was steady whereas the curve of the extracranial carotid stenosis group revealed the

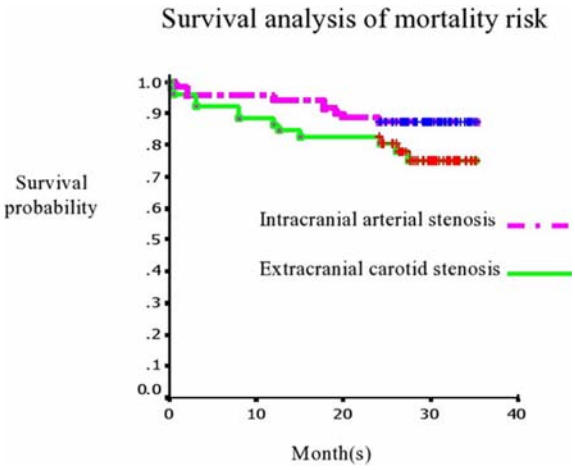

Fig. 1 Survival analysis of overall mortality risk between intracranial arterial stenosis with and without extracranial carotid stenosis.

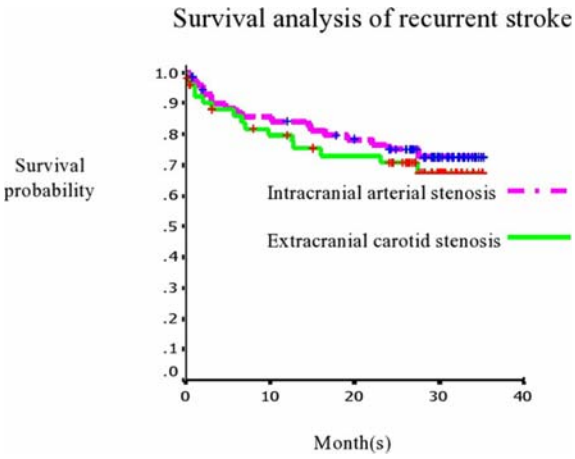

Fig. 2 Survival analysis of recurrent stroke.

decrement of myocardial infarction-free rate from the initiation of the course (Fig. 3). Comparison of the two curves by log-rank test yielded a significant difference of mean time of being myocardial infarction-free between the two groups ($p = 0.0023$). This information confirmed the statistically significant incidence of acute coronary syndrome in patients with extracranial carotid stenosis.

In the extracranial carotid stenosis group, the patients were divided into two subgroups: the isolated extracranial carotid stenosis subgroup and the combined intracranial arterial stenosis and extracranial carotid stenosis subgroup. The statistical analysis showed no significant differences of recurrent ischemic stroke, recurrent stroke, and acute coronary syndrome between these two subgroups.

Statistical analysis of risk factors for acute coronary syndrome: extracranial carotid stenosis, age groups, gender, BMI >25 kg/m^2, hypertension, DM, hyperlipidemia, smoking and alcohol consumption was showed in Table 2. The final result, the significant risk factor related to developing acute coronary syndrome were extracranial carotid stenosis ($p = 0.03$, OR = 10.81, 95% CI 1.23-94.77).

Regarding cases of death, 12 patients with extracranial internal carotid stenosis died due to fatal stroke, acute coronary syndrome and other causes at 4, 4, and 4 persons, respectively. For intracranial arterial stenosis without significant extracranial carotid stenosis group, nine patients died due to fatal stroke, myocardial infarction and other causes at 2, 1, and 6 persons, respectively. Fisher's exact test revealed no statistical significance of mortality rates between these two groups. Other causes of death are gastrointestinal, genitourinary, and pulmonary cancers, septicemia, and foreign body aspiration. We divided all dead cases into four groups according to causes of death for the logistic regression analysis; fatal vascular events, fatal stroke, coronary artery death and overall death. The recurrent stroke either ischemia or hemorrhage was a significant risk factor for fatal vascular events ($p = 0.021$, OR = 106.12, 95% CI 2.043-5512-39). However, there was no significant risk factor for the fatal stroke as well as the coronary artery death. For overall death of this study, acute myocardial infarction and hyperlipidemia yielded significant effects ($p = 0.001$, OR = 25.51, 95% CI 3.78-172.04 and $p = 0.023$, OR = 0.21, 95% CI 0.05-0.81).

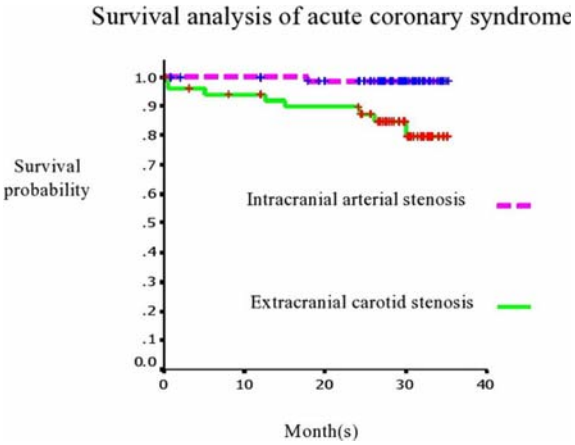

Fig. 3 Survival analysis of acute coronary syndrome.

Table 2. Risk factors for acute coronary syndrome

Risk factors	OR of 95% CI	*p*-value
Extracranial internal carotid stenosis	12.72 (1.53-105.27)	0.01*
Age groups		
<65 years	1.00	
65-74 years	5.13 (0.57-45.99)	0.14
75 or more years	3.16 (0.31-31.77)	0.32
Gender (male)	4.00 (0.48-33.15)	0.19
BMI >25 kg/m^2	0.80 (0.18-3.38)	0.76
Hypertension	0.81 (0.19-3.45)	0.78
DM	0.45 (0.09-2.28)	0.33
Dyslipidemia	8.00 (0.96-66.05)	0.05
Smoking	1.66 (0.42-6.56)	0.46
Alcohol	1.19 (0.23-6.15)	0.83

* significant

Discussion

The aim of this study is to compare 2-years of outcome of two different ischemic stroke groups. There is no significant difference in baseline characteristics except DM was found to be higher in the intracranial arterial stenosis group. However, it had no effect on the incidence of either recurrent stroke or acute coronary syndrome.

Some studies reported that ischemic stroke patients had a high risk to develop recurrent stroke within 2 weeks after the first onset of TIA or stroke[17-19] after which this risk gradually increased through the time-course of the disease[20]. However, the mortality of stroke was less than the mortality of coronary events in long follow-up period[21]. The recurrent rate and the mortality rate of stroke in patients with the intracranial arterial stenosis without significant

extracranial carotid stenosis were similar to previous reports[22-24]. Two of those reports were from western countries and one was from China. When comparing the recurrent stroke rate of the extracranial carotid artery group to results of NASCET, the subgroup analysis of patients with extracranial carotid stenosis that delayed carotid endarterectomy, the 3-year recurrent stroke rate was equal to our research[25]. Although, a statistical analysis of recurrent stroke and recurrent ischemic stroke outcomes between these two groups of the patients in this study was not significant, a long-term study might be able to show clearer differences than the intermediate-term study.

Patients with extracranial carotid artery stenosis significantly developed acute coronary syndrome greater than patients with intracranial arterial stenosis without significant extracranial carotid stenosis. This outcome supported the strong relationship of the coronary artery disease and the carotid stenosis. Previous studies reported asymptomatic coronary artery disease detected by the exercise stress test or the perfusion imaging of myocardium in the patients with carotid artery stenosis[4,26-28]. Interestingly, the highest percentage of abnormal exercise electrocardiography was found in ischemic stroke patients with combined extracranial carotid and intracranial arterial stenosis, which was carefully followed by the percentage of patients with isolated carotid stenosis and patients with intracranial arterial stenosis[29]. With refererence to the results of our study, the outcomes of subgroup analysis between patients with the isolated extracranial carotid stenosis and patients with combined intracranial arterial stenosis and extracranial carotid stenosis, and the multivariate analysis of risk factors related to acute coronary syndrome simultaneously, indicated that the most important factor to develop acute myocardial infarction in stroke patient was a preexisting carotid stenosis. However, the results of this subgroup analysis need to be carefully interpreted due to the small sample size for each subgroup.

In Asians, intracranial arterial stenosis is common in both Chinese and South Asians[30,31]. This prevalence is similar to our study. Although, patients with intracranial arterial stenosis seemed to have vascular complications less than patients with internal carotid artery stenosis, one prospective study revealed high incidence of the central nervous system complications in intracranial arterial stenosis patients underwent CABG surgery[32]. Additionally, combined significant extracranial carotid artery stenosis and intracranial arterial stenosis can be frequently found in DM patients[33]. This aspect sparks an idea for the more consideration and major vascular events prevention in the clinical practice for all patients developed cerebrovascular disease.

It is for this reason proposed that the carefully clinical practice, of taking extra care of ischemic stroke patients, should be considered. The ischemic stroke subtype should be identified as well as the surveillance of acute coronary syndrome in high-risk stroke patients. Good cooperation among neurologists, neuroradiologists, neurosurgeons and cardiologists might be included in the clinical practice guidelines for stroke in Thailand, so to ensure effective treatment for the long-term.

There are some limitations of our study. Firstly, it has the small sample size of cases. Secondly, personal bias could occur due to only one investigator worked for data collection. Thirdly, a 2-year follow-up is usually not long term for stroke patients. Thus, more clinical studies including data from different races/ nationalities, a larger sample size, and long-term (more than 5-years) outcomes should be conducted.

Conclusion

There was no significant difference of recurrent ischemic stroke and recurrent stroke between the patients with intracranial arterial stenosis without extracranial carotid stenosis and the patients with extracranial carotid stenosis. On the other hand, the patients with extracranial carotid stenosis had significantly more incidences of acute coronary syndrome than the patients with intracranial arterial stenosis without extracranial carotid stenosis.

Abbreviations

TIA = transient ischemic attack, TCD = transcranial doppler ultrasonography, CDUS = carotid duplex ultrasonography, BMI = body mass index, CT = computed tomography, MRI = magnetic resonance imaging, MRA = magnetic resonance angiography, EKG = electrocardiography, DM = diabetes mellitus, NASCET = the North American Symptomatic Carotid Endarterectomy Trial, CABG = coronary artery bypass graph.

What is already known on this topic ?

The recurrent ischemic stroke is common in the clinical practice. Major vascular complications, especially the acute coronary syndrome, can occur in stroke patients.

What this study adds ?

The incidence of significant extracranial carotid stenosis is still less than the incidence of intracranial arterial stenosis in Thai stroke patients. Once, the angiographic studies reveal evidence of the significant extracranial carotid stenosis, physicians should pay attention for the acute coronary syndrome as well.

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Potential conflicts of interest

None.

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การเปรียบเทียบผลของโรคภายในระยะเวลา 2 ปี ของผู้ที่มีภาวะสมองขาดเลือด โดยเปรียบเทียบระหว่างผู้ที่มีหลอดเลือดแดงภายในโพรงกระโหลกศีรษะตีบโดยไม่มีการตีบของหลอดเลือดแดงอินเทอร์นอลคาโรติดส่วนนอกโพรงกระโหลกศีรษะอย่างมีนัยสำคัญกับผู้ที่มีการตีบของหลอดเลือดแดงอินเทอร์นอลคาโรติดส่วนนอกโพรงกระโหลกศีรษะ

กุลธิดา เมธาวศิน, นิจศรี สุวรรณเวลา, กัมมันต์ พันธุมจินดา

วัตถุประสงค์: *ความเสี่ยงในการเกิดสมองขาดเลือดซ้ำและภาวะกล้ามเนื้อหัวใจขาดเลือดจากหลอดเลือดโคโรนารีอุดตันเพิ่มขึ้น ในผู้ป่วยสมองขาดเลือดที่มีสาเหตุจากภาวะหลอดเลือดแดงแข็งของหลอดเลือดแดงขนาดใหญ่ เป้าหมายของการศึกษานี้เพื่อเปรียบเทียบผลของโรคภายในระยะเวลา 2 ปี ของผู้ที่มีภาวะสมองขาดเลือดระหว่างผู้ที่มีหลอดเลือดแดงภายในโพรงกะโหลกศีรษะตีบโดยไม่มีการตีบของหลอดเลือดแดงอินเทอร์นอลคาโรติดส่วนนอกโพรงกะโหลกศีรษะอย่างมีนัยสำคัญกับผู้ที่มีการตีบของหลอดเลือดแดงอินเทอร์นอลคาโรติดส่วนนอกโพรงกะโหลกศีรษะ*

วัสดุและวิธีการ: *ผู้วิจัยทำการวิจัยแบบไปข้างหน้าของผู้ป่วยสมองขาดเลือดจำนวน 123 คน ซึ่ง 71 คน มาจากกลุ่มหลอดเลือดแดงในโพรงกะโหลกศีรษะตีบและ 52 คน มีหลอดเลือดแดงอินเทอร์นอลคาโรติดนอกโพรงกะโหลกศีรษะตีบ โดยตรวจร่างกายทางประสาทวิทยาและตรวจทางรังสีวิทยาของสมองตั้งแต่เริ่มการวิจัย ผู้ป่วยทั้งหมดได้รับการรักษาแบบผู้ป่วยนอกของหน่วยประสาทวิทยาในระยะเวลาติดตามอาการ 24 เดือน โรคหลอดเลือดสมองซ้ำ, กล้ามเนื้อหัวใจขาดเลือด และเสียชีวิตจะถูกบันทึกไว้*

ผลการศึกษา: *ผู้ป่วย 15 คนจากกลุ่มหลอดเลือดแดงอินเทอร์นอลคาโรติดนอกโพรงกะโหลกศีรษะตีบและ 18 คน จากกลุ่มหลอดเลือดแดงในโพรงกะโหลกศีรษะตีบ โดยไม่มีการตีบของหลอดเลือดแดงอินเทอร์นอลคาโรติดส่วนนอกโพรงกะโหลกศีรษะอย่างมีนัยสำคัญ เกิดโรคหลอดเลือดสมองซ้ำระหว่างติดตามอาการ ($p = 0.40$) ภาวะกล้ามเนื้อหัวใจขาดเลือดจากหลอดเลือดโคโรนารีอุดตัน เกิดขึ้น 8 คน ในกลุ่มหลอดเลือดแดงอินเทอร์นอลคาโรติดนอกโพรงกะโหลกศีรษะตีบ และมีเพียง 1 คน ในกลุ่มหลอดเลือดแดงในโพรงกะโหลกศีรษะตีบ ($p = 0.004$) สาเหตุการเสียชีวิตคือมะเร็งระยะสุดท้าย โรคหลอดเลือดสมองและภาวะที่เกี่ยวข้อง และกล้ามเนื้อหัวใจขาดเลือดจากหลอดเลือดโคโรนารีอุดตัน โดยปัจจัยเสี่ยงสำคัญต่อการเกิดกล้ามเนื้อหัวใจขาดเลือดจากหลอดเลือดโคโรนารีอุดตันคือ หลอดเลือดแดงอินเทอร์นอลคาโรติดนอกโพรงกะโหลกศีรษะตีบแบบมีอาการ ($p = 0.03$, $OR = 10.81$, 95% CI $1.23\text{-}94.77$)*

สรุป: *การเกิดสมองขาดเลือดซ้ำและโรคหลอดเลือดสมองซ้ำระหว่างผู้ป่วยที่มีหลอดเลือดแดงในโพรงกะโหลกศีรษะตีบ โดยไม่มีการตีบของหลอดเลือดแดงอินเทอร์นอลคาโรติดนอกโพรงกะโหลกศีรษะอย่างมีนัยสำคัญไม่มีความแตกต่างทางสถิติ ในทางกลับกันผู้ป่วยที่มีหลอดเลือดแดงอินเทอร์นอลคาโรติดนอกโพรงกะโหลกศีรษะตีบมีอุบัติการณ์ของกล้ามเนื้อหัวใจขาดเลือดจากหลอดเลือดโคโรนารีอุดตันมากกว่า*