

# Outcomes of dual antiplatelet therapy in ischemic stroke or transient ischemic attack patients with tandem carotid artery stenosis or carotid artery occlusion

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## **Abstract**

**Background and objective:** Carotid artery stenosis is one of the causes of ischemic stroke. However, some ischemic stroke or transient ischemic attack patients with carotid artery stenosis cannot be performed carotid endarterectomy due to the characteristic of carotid artery lesion. Dual antiplatelet therapy was shown to reduce the rate of recurrence of ischemic stroke. The objective of this study was to determine the outcomes of dual antiplatelet therapy in ischemic stroke or transient ischemic attack patients with tandem carotid artery stenosis or occlusion.

**Materials and Methods:** This retrospective cohort study examined the clinical, imaging data and clinical outcomes of ischemic stroke or transient ischemic attack patients with tandem carotid artery stenosis or occlusion. Univariate analysis and multiple logistic regression model of included relevant confounders and potential predictors were performed.

**Results:** Patients who received single antiplatelet therapy had higher risk of recurrent ischemic stroke or transient ischemic attack than patients who received dual antiplatelet therapy at 12-months follow-up (odds ratio (OR), 0.67; confidence interval (95%CI), 0.26–0.98;  $p=0.029$ ) but not significance in number of death (OR, 0.86; 95%CI, 0.32–39.49;  $p=0.556$ ). The rate of extracranial bleeding events was higher in dual antiplatelet group than in single antiplatelet group (10.7% versus 5.3% (OR, 3.33; 95%CI, 1.88–5.80;  $p<0.001$ )).

**Conclusion:** Ischemic stroke or transient ischemic attack patients with tandem carotid artery stenosis or occlusion have potential clinical benefit from dual antiplatelet therapy with increase in the risk of minor extracranial bleeding.

**Keywords:** carotid artery occlusion, dual antiplatelet, stroke, tandem carotid artery stenosis (J Thai Stroke Soc. 2019;18(1):14–24)

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# ผลการรักษาด้วยยาต้านเกล็ดเลือดสองชนิดร่วมกันในผู้ป่วยโรคสมองขาดเลือดหรือสมองขาดเลือดชั่วคราวที่มีหลอดเลือดแดงคาโรติดส่วนภายในและภายนอกโพรงกะโหลกศีรษะตีบหรืออุดตัน

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## บทคัดย่อ

**ความเป็นมาและวัตถุประสงค์:** ภาวะหลอดเลือดแดงคาโรติดตีบ เป็นหนึ่งในสาเหตุของการเกิดโรคหลอดเลือดสมองขาดเลือด ผู้ป่วยบางรายไม่สามารถทำการผ่าตัดหลอดเลือดแดงได้ เนื่องจากลักษณะของหลอดเลือดของหลอดเลือดแดงคาโรติดนั้นมีลักษณะของการตีบต่อเนื่องหรืออุดตันไปแล้ว การรักษาด้วยยาต้านเกล็ดเลือดสองชนิดร่วมกันนั้นในปัจจุบันมีการศึกษาวิจัยที่ผ่านมามีช่วยลดอุบัติการณ์ของการเกิดโรคหลอดเลือดสมองขาดเลือดกลับเป็นซ้ำได้ อย่างไรก็ตามยังไม่มีข้อมูลมากพอในกลุ่มผู้ป่วยโรคหลอดเลือดสมองขาดเลือดที่ตรวจพบหลอดเลือดแดงคาโรติดตีบต่อเนื่องหรืออุดตัน จึงเป็นที่มาของการศึกษาเพื่อติดตามผลการรักษาด้วยยาต้านเกล็ดเลือดสองชนิดร่วมกันในผู้ป่วยกลุ่มนี้

**ระเบียบวิธีวิจัย:** เป็นการศึกษาทบทวนข้อมูลย้อนหลังจากเวชระเบียน โดยเก็บข้อมูลอาการทางคลินิก, รายละเอียดของภาพวินิจฉัยทางสมองและหลอดเลือดสมอง, ผลลัพธ์ของการรักษาในกลุ่มผู้ป่วยโรคหลอดเลือดสมองขาดเลือดที่ตรวจพบหลอดเลือดแดงคาโรติดตีบต่อเนื่องหรือหลอดเลือดคาโรติดอุดตันและวิเคราะห์ข้อมูลทางสถิติ ครอบคลุมข้อมูลปัจจัยพื้นฐานของผู้ป่วย, ปัจจัยเสี่ยงและปัจจัยอื่นๆที่อาจมีผลรบกวนต่อผลลัพธ์ในการรักษา

**ผลการวิจัย:** ผู้ป่วยโรคหลอดเลือดสมองที่รับประทานยาต้านเกล็ดเลือดเพียงชนิดเดียวมีความเสี่ยงต่อการเกิดโรคหลอดเลือดสมองกลับเป็นซ้ำเมื่อติดตามอาการในช่วงระยะเวลาหนึ่งปีมากกว่าผู้ป่วยที่รับประทานยาต้านเกล็ดเลือดสองชนิดร่วมกันอย่างมีนัยสำคัญทางสถิติ (odds ratio (OR), 0.67; confidence interval (95%CI), 0.26–0.98; p=0.029) แต่หากพิจารณาเฉพาะผลลัพธ์ที่เป็นการเสียชีวิตอย่างเดียวยังไม่พบว่ามีนัยสำคัญทางสถิติ (OR, 0.86; 95%CI, 0.32–39.49; p=0.556) การเกิดเลือดออกชนิดนอกสมองพบ 10.7% ในกลุ่มผู้ป่วยที่รับประทานยาต้านเกล็ดเลือดสองชนิดร่วมกันและเกิดเลือดออกชนิดนอกสมอง 5.3% ในกลุ่มผู้ป่วยที่รับประทานยาต้านเกล็ดเลือดเพียงชนิดเดียว (OR, 3.33; 95%CI, 1.88–5.80; p<0.001)

**สรุป:** ผู้ป่วยโรคหลอดเลือดสมองขาดเลือดที่ตรวจพบหลอดเลือดแดงคาโรติดตีบต่อเนื่องหรืออุดตันได้ประโยชน์ในการรับประทานยาต้านเกล็ดเลือดสองชนิดร่วมกัน แต่เพิ่มโอกาสการเกิดเลือดออกชนิดนอกสมองโดยที่ภาวะเลือดออกที่เกิดขึ้นไม่รุนแรง

**คำสำคัญ:** หลอดเลือดแดงคาโรติดอุดตัน, ยาต้านเกล็ดเลือดสองชนิด, โรคหลอดเลือดสมอง, หลอดเลือดแดงคาโรติดตีบต่อเนื่อง (J Thai Stroke Soc. 2019;18(1):14–24)

## **Introduction**

Carotid artery stenosis is one of the causes of ischemic stroke<sup>1</sup>. However, some ischemic stroke or transient ischemic attack patients with carotid artery stenosis cannot be performed carotid endarterectomy due to the characteristic of tandem carotid artery stenosis<sup>2</sup> or carotid artery occlusion<sup>3</sup>. The influence of angiographically identified intracranial vascular lesions on the outcome of carotid endarterectomy remains controversial. Reports of increased perioperative stroke risk<sup>4</sup>, increased symptom recurrence<sup>5</sup>, and shortened long-term, stroke free survival<sup>6</sup>. Dual antiplatelet therapy was shown to reduce the rate of recurrence of ischemic stroke<sup>7,8</sup>. However, there are limited data of outcomes of dual antiplatelet therapy in ischemic stroke or transient ischemic attack patients with tandem carotid artery stenosis or carotid artery occlusion.

## **Materials and methods**

### **Study populations**

This study was retrospective cohort study of ischemic stroke or transient ischemic attack patients with tandem carotid artery stenosis or carotid artery occlusion from June 1, 2013, to May 31, 2017, at Prasat neurological Institute. This study retrospectively examined the clinical, imaging data and clinical outcomes in ischemic stroke or transient ischemic attack patients with tandem carotid artery stenosis or carotid artery occlusion from medical records. Patients were tested for diagnostic imaging of the brain infarction at admission and carotid artery imaging by using carotid doppler ultrasound, computed tomography angiography or magnetic resonance angiography within 3 months after onset of ischemic stroke or transient ischemic attack.

This study excluded any acute ischemic stroke or transient ischemic attack patients who received any type of anticoagulant medications or patients who had indication for carotid endarterectomy. This study collected demographic data, clinical risk factors and clinical outcomes such as age, sex, history of hypertension, history of diabetes mellitus, history of renal disease, history of liver disease, history of heart disease, type of antiplatelet medications, type of lipid-lowering agents, low-density lipoprotein level, severity of neurological deficit by NIH stroke scale, size of infarction, number of patients who deteriorated neurological symptoms, number of recurrent ischemic stroke, number of hemorrhagic stroke, number of intracranial or extracranial bleeding events and number of death.

### **Definitions**

Acute ischemic stroke was defined as acute neurological deficit lasting more than 24 hours with ischemic lesion on brain imaging. Transient ischemic attack was defined as acute neurological deficit with a score of 4 or more on the ABCD2<sup>9</sup> scale lasting less than 24 hours and no any ischemic lesion on brain imaging.

Recurrence ischemic stroke was defined as acute neurological deficit with new ischemic lesion on brain imaging in patient who received either dual antiplatelet therapy or single antiplatelet therapy. Recurrence transient ischemic attack was defined as acute neurological deficit with a score of 4 or more on the ABCD2 lasting less than 24 hours and no new ischemic lesion on brain imaging in patient who received either dual antiplatelet therapy or single antiplatelet therapy.

Tandem carotid artery stenosis was defined as symptomatic proximal internal carotid

artery stenosis more than 70% by criteria established by the North American Symptomatic Carotid Endarterectomy Trial (NASCET)<sup>10</sup> and identifiable stenosis of  $\geq 50\%$  of ipsilateral downstream distal cerebral artery. All of patients were estimated significant symptomatic proximal internal carotid artery stenosis by carotid doppler ultrasound. All of patients were sent to perform either contrast-enhanced magnetic resonance angiography brain included carotid artery or contrasted computed tomography angiography brain included carotid artery for definite diagnosis of tandem carotid artery stenosis.

Carotid artery occlusion was defined as significant symptomatic proximal internal carotid artery lesion (with or without distal internal carotid artery lesion) occluded flow velocity by carotid doppler ultrasound (thud flow pattern) with no detectable flow on contrasted computed tomography angiography brain include carotid artery or contrast-enhanced magnetic resonance angiography brain included carotid artery.

Hypertension was defined as acute ischemic stroke or transient ischemic attack patient who had history of hypertension or need to received antihypertensive drug after ischemic event. Diabetes mellitus was defined as acute ischemic stroke or transient ischemic attack patient who had history of diabetes mellitus or impaired fasting blood glucose more than 126 mg/dl within 3 months after ischemic event. Hypercholesterolemia was defined as acute ischemic stroke or transient ischemic attack patient who had history of hypercholesterolemia before ischemic event. Low-density lipoprotein level was defined by level of low-density lipoprotein within 3 months after ischemic event. Chronic kidney disease was defined as acute ischemic stroke or transient ischemic attack

patient who had creatinine clearance less than 30 ml/min. Liver disease was defined as acute ischemic stroke or transient ischemic attack patient who had Child–Pugh score more than 6 points. Heart disease was defined as acute ischemic stroke or transient ischemic attack patient who had history of coronary artery disease or history of congestive heart failure.

Large infarction was defined as area of hypodensity (for CT brain) or hyperintensity (for MRI brain) more than one-third of middle cerebral artery infarction area.

Major bleeding was defined as life threatening bleeding or bleeding that required blood transfusion or bleeding in vital organs such as eye, intracranial or intra-spinal bleeding. Minor bleeding was defined by bleeding event that does not meet major bleeding definition.

#### **Inclusion criteria**

All of acute ischemic stroke or transient ischemic attack patients with imaging evidence of tandem carotid artery stenosis or carotid artery occlusion within 3 months after onset of focal neurological deficit from June 1, 2013, to May 31, 2017, at Prasat neurological Institute and received clinical follow up more than 1 year.

#### **Exclusion criteria**

1. Patient received any type of anticoagulants for some conditions such as cardio-embolic stroke prevention, deep vein thrombosis treatment.

2. Patient had indication for carotid endarterectomy.

3. Patient had history of malignancy.

#### **Sample size calculation**

Previous study<sup>11,12</sup> showed that patients with carotid artery stenosis or occlusion had annual risk for recurrent ischemic events about 15–20% per year and dual antiplatelet therapy had

decreased risk 44–64% when compared with single antiplatelet therapy. Sample size calculation based on following formula<sup>13</sup>.

$$n_{exposure} = \left[ \frac{z_{1-\frac{\alpha}{2}} \sqrt{\bar{p}\bar{q}\left(1+\frac{1}{r}\right)} + z_{1-\beta} \sqrt{p_1 q_1 + \frac{p_2 q_2}{r}}}{\Delta} \right]^2$$

$$p_1 = P(\text{outcome}|\text{exposure}), q_1 = 1 - p_1$$

$$p_2 = P(\text{outcome}|\text{unexposure}), q_2 = 1 - p_2$$

$$\bar{p} = \frac{p_1 + p_2 r}{1+r}, \bar{q} = 1 - \bar{p}, r = \frac{n_{unexposure}}{n_{exposure}}$$

Estimation of sample size needed more than 172 patients in this study to ensure adequate statistical power to detect primary efficacy outcome.

### Study outcomes

The primary efficacy outcome was a composite event of ischemic stroke, transient ischemic attack and death. Secondary outcomes were bleeding event, recurrence ischemic stroke or transient ischemic attack event and number of death.

### Statistical Analysis

Continuous variables were presented as the mean or median. Categorical variables were described as percentages. The difference in baseline characteristic between dual antiplatelet group and single antiplatelet group were analyzed using Mann–Whitney U test if not normally distributed or the t test if normally distributed; categorical variables were compared between groups with the chi-squared test or, where appropriate, Fisher’s exact test. Multiple logistic regression analyses were used to identify the confounding factors of composite event in this study. Confounding factors were selected if there were statistical differences by univariate analysis. Odd ratios and 95% confidence interval were

used to illustrate the association. The level of significance was set at a value of p less than .05. All statistical analyses were performed using SPSS for windows version 16.0 (IBM, Armonk, NY).

### Results

Baseline characteristic of this study are summarized in Table1. A total of 178 acute ischemic stroke or transient ischemic attack patients with tandem carotid artery stenosis or carotid artery occlusion (108 men and 70 women) with mean age of 67.8 years were included in this study. All of patients received antiplatelet drug, no any patients received anticoagulant drug. The proportion of underlying disease such as hypertension, diabetes mellitus, hypercholesterolemia, chronic kidney disease, liver disease, coronary artery disease and congestive heart failure were 74.7%, 65.7%, 59.0%, 5.0%, 1.1%, 25.3 and 1.7%, respectively. The average mean of low density lipoprotein level (LDL) was 81.5 mg/dl. Baseline NIH stroke scale (p=0.048), proportion of large infarction (p<0.001) were statically significance in univariate analysis model (Table1).

**Table 1. Demographic data of study populations**

Characteristic	Total (N=178)	Dual antiplatelet group (N=84)	Single antiplatelet group (N=94)	p value
Male gender	108(60.7%)	50(60%)	58(61.7%)	0.434
Age, years	67.8(10.3)	67.1(10.2)	68.4(10.5)	0.855*
Type of antiplatelet				-
Aspirin with Clopidogrel	74(41.6%)	74(88.1%)	-	
Aspirin with Cilostazol	6(3.4%)	6(7.1%)	-	
Clopidogrel with Cilostazol	4(2.2%)	4(4.8%)	-	
Aspirin alone	54(30.3%)	-	54(57.4%)	
Clopidogrel alone	40(22.5%)	-	40(42.6%)	
Duration of therapy, months	11.7 (11.3–11.9)	11.6(10.9–11.9)	11.8(11.4–12.0)	0.841*
Hypertension	133(74.7%)	64(76.2%)	69(73.4%)	0.758
Diabetes mellitus	117(65.7%)	55(65.5%)	62(65.6%)	0.556
Hypercholesterolemia	105(59.0%)	49(58.3%)	56(59.6%)	0.535
Chronic kidney disease	9(5.0%)	4(4.8%)	5(5.3%)	0.822
Liver disease	2(1.1%)	0	2(2.1%)	-
Heart disease				
Coronary artery disease	45(25.3%)	20(23.8%)	25(26.6%)	0.922
Congestive heart failure	3(1.7%)	0	3(3.2%)	-
LDL, mg/dl	81.5(18.8)	78.1(20.4)	84.6(18.2)	0.159*
Type of lipid lowering agent				0.352
High intensity statin	167(93.8%)	80(95.2%)	87(92.6%)	
Moderate intensity statin	8(4.5%)	3(3.6%)	5(5.3%)	
Non-statin or low intensity statin	3(1.7%)	1(1.2%)	2(2.0%)	
Baseline NIHSS	12(8–15)	9(7–11)	14(9–16)	0.048*
large infarction	68(38.2%)	23(27.4%)	45(47.9%)	<0.001
Type of carotid artery lesion				0.714
Tandem carotid stenosis	107(60.1%)	49(58.3%)	58(61.7%)	
Carotid occlusion	71(39.9%)	35(41.7%)	36(38.3%)	

Data are N (%), mean (SD), or median (IQR).

NIHSS=National Institutes of Health Stroke Scale.

\* Continuous variables were analyzed using Mann-Whitney U test.

Table 2 showed outcomes of antiplatelet therapy in ischemic stroke or transient ischemic attack patients with tandem carotid artery stenosis or carotid artery occlusion. Patients who received single antiplatelet therapy had higher risk of composite event of ischemic stroke, transient ischemic attack and death than patients who received dual antiplatelet therapy (odd ratio (OR), 0.78; confidence interval (95%CI), 0.42–0.89; p=0.034), and had higher risk of recurrent

ischemic stroke or transient ischemic attack event at 12-months follow-up (OR, 0.67; 95%CI, 0.26–0.98; p=0.029), but not significance in number of death (OR, 0.86; 95%CI, 0.32–39.49; p=0.556). The rate of extracranial bleeding events was higher in dual antiplatelet group than in single antiplatelet group (10.7% versus 5.3% (OR, 3.33; 95%CI, 1.88–5.80; p=<0.001)), but bleeding event occurred just minor bleeding.

**Table 2.** Outcomes of dual antiplatelet therapy in ischemic stroke or transient ischemic attack patients with tandem carotid artery stenosis or carotid artery occlusion

	Dual antiplatelet group (N=84)	Single antiplatelet group (N=94)	p value	Adjusted OR (95%CI)*
Composite of ischemic stroke, transient ischemic attack and death	14(16.7%)	24(25.5%)	0.034	0.78 (0.42–0.89)
Bleeding events				
Intracranial bleeding	0	0	–	–
Extracranial bleeding	9(10.7%)	5(5.3%)	<0.001	3.33 (1.88–5.80)
Major bleeding <sup>++</sup>	1(1.2%)	0	–	–
Minor bleeding	8(9.5%)	5(5.3%)	<0.001	2.98 (1.56–4.60)
Recurrence ischemic stroke or transient ischemic attack	13(15.5%)	22((23.4%)	0.029	0.67 (0.26–0.98)
Death	1(1.2%)	2(2.1%)	0.556	0.86 (0.32–39.49)

Data are N (%).

\*Adjusted for baseline NIHSS and large infarction.

<sup>++</sup>Major bleeding defined by: life threatening bleeding or bleeding that required blood transfusion or bleeding in vital organs.

## Discussion

The results of this study suggested that dual antiplatelet therapy in ischemic stroke or transient ischemic attack patients with tandem carotid artery stenosis or carotid artery occlusion have potential clinical benefit to prevent composite event of ischemic stroke, transient ischemic attack and death (OR, 0.78; 95%CI, 0.42–0.89;  $p=0.034$ ). From previous study, Dual Antiplatelet Therapy With Clopidogrel and Aspirin in Symptomatic Carotid Stenosis Evaluated Using Doppler Embolic Signal Detection (CARESS study group)<sup>14</sup>, a randomized, double-blind study in subjects with recently symptomatic more than 50% carotid artery stenosis revealed a significant reduction in the primary end point: 43.8% of dual-therapy patients were MES (micro-embolic signals) positive on day 7, as compared with 72.7% of monotherapy patients (relative risk reduction 39.8%; 95% CI, 13.8 to 58.0;  $p=0.0046$ ) but primary end point of this study was surrogate outcome and no data about dual antiplatelet therapy in patients with tandem carotid artery stenosis or carotid artery occlusion.

Using dual antiplatelet therapy is associated with increased risk of bleeding event. From previous study, Dual Antiplatelet Therapy With Clopidogrel and Aspirin in Symptomatic Carotid Stenosis Evaluated Using Doppler Embolic Signal Detection (CARESS study group) had increased event rate of minor bleeding in dual antiplatelet group but no significant difference in bleeding between the 2 groups, with no episodes of life-threatening, major, or intracerebral hemorrhage in either group. From previous study, Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack (CHANCE study group)<sup>15</sup> showed that the

combination of clopidogrel and aspirin was superior to aspirin alone for reducing the risk of stroke in the first 90 days and did not increase the risk of hemorrhage. However, this previous study followed up enrolled patients within 3 months and no data of outcomes by using dual antiplatelet therapy beyond 3 months. From previous study, Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA (POINT study group)<sup>16</sup>, the trial was halted after 84% of the anticipated number of patients had been enrolled because the data and safety monitoring board had determined that the combination of clopidogrel and aspirin was associated with both a lower risk of major ischemic events and a higher risk of major hemorrhage than aspirin alone at 90 days. Trial protocol that difference from any previous study due to 600 mg loading dose for clopidogrel in dual antiplatelet arm. However, this trial not directly studied for dual antiplatelet therapy in ischemic stroke patient with tandem carotid artery stenosis or occlusion.

In this study, ischemic stroke patients who received single antiplatelet therapy had higher proportion of large infarction and baseline NIHSS in compared with patients who received dual antiplatelet therapy. This finding might be because this study was an observational study, thus, attending physician tended to prescribed dual antiplatelet for some selected patients who had low risk of bleeding complication such as patients who had small infarction size or had minor neurological deficits.

Symptomatic carotid artery disease is associated with a high risk of recurrent cerebral ischemia. The mechanism of ischemic stroke from tandem carotid artery stenosis or occlusion include cerebral hypoperfusion<sup>17,18</sup>, artery-to-artery embolization<sup>19,20</sup> and a complementary interaction

between the 2 via reduced perfusion, limiting the ability of the bloodstream to wash out emboli lodged in distal vessels<sup>21,22</sup>. Among patients with carotid artery occlusion, emboli from the distal portion of the occluded vessel<sup>23</sup>, the proximal portion of the occlusion through external carotid artery collaterals (the original stump emboli hypothesis)<sup>24</sup>, or vasculature contralateral to the occlusion have all been reported<sup>25</sup>.

Clarifying the pathophysiology of cerebral ischemia in symptomatic carotid artery occlusion has the potential to guide treatment decisions. Whereas interventions to improve cerebral perfusion such as liberalizing blood pressure goals may be useful if hypoperfusion is the underlying mechanism of ischemia, aggressive antithrombotic therapy may be of greater benefit if embolization is the primary mechanism. Some studies have indeed suggested improved outcome among symptomatic carotid artery occlusion patients treated with anticoagulation<sup>26</sup>.

This study has some limitations. Several mechanisms can cause carotid artery disease such as post-radiation carotid artery disease, carotid artery dissection. This study included patients with atherosclerotic risk and excluded patients with asymptomatic carotid artery disease or patients with history of cancer to minimize the risk of enrolling patients with carotid artery disease not from atherosclerosis mechanism. In addition, enrollment of transient ischemic attack patients has some limitations, because ischemic events can occur from posterior circulation vessels.

### **Conclusion**

Ischemic stroke or transient ischemic attack patients with tandem carotid artery stenosis or carotid artery occlusion have potential clinical benefit from dual antiplatelet therapy with

increase in the risk of minor extracranial bleeding.

### **Originality and body of knowledge**

Long-term use of double antiplatelet therapy had clinical benefit in patients with high risk of recurrent ischemic stroke, especially in patients with tandem carotid artery stenosis or carotid artery occlusion.

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