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Review Article

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Antiplatelet Therapy for Secondary Stroke Prevention in Patients with Ischemic Stroke or Transient Ischemic Attack

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Conflict of Interest
The author has no financial conflicts of interest.

ABSTRACT

The risk of stroke recurrence is highest in the acute phase after transient ischemic attack (TIA) or ischemic stroke. Therefore, patients with TIA or ischemic stroke should be treated with antiplatelet medication for stroke prevention. The short-term use of dual antiplatelet therapy between 21 and 90 days may be considered in those with acute minor stroke or TIA and high-risk of recurrence. However, the long-term use of dual antiplatelet therapy is not recommended due to the risk of bleeding. The current stroke guideline does not specify the administration of an antiplatelet for the secondary prevention of ischemic stroke. However, as clinical studies progress, antiplatelet therapy may become a personalized treatment in the future.

Keywords: Ischemic stroke; Platelet aggregation inhibitors; Secondary prevention; Stroke

INTRODUCTION

Stroke is a leading cause of mortality and permanent disability worldwide.[1] Acute cerebral ischemia such as cerebral infarction and transient ischemic attack (TIA), is often followed by recurrent ischemic events, where recurrent stroke or TIA occurs in 12% of cases at 1 year and 16.8% at 5 years after minor stroke or TIA.[2][3] The secondary prevention of recurrent stroke includes the control of risk factors, such as hypertension, diabetes mellitus, and dyslipidemia; lifestyle modification, such as smoking cessation, weight reduction, and regular physical activity; antiplatelet therapy for non-cardioembolic ischemic stroke; and anticoagulation therapy for cardioembolic ischemic stroke.[4] This review will focus on the strategy of antiplatelet therapy administration for the secondary prevention of non-cardioembolic ischemic stroke or TIA in various situations and time points.

ACUTE MINOR STROKE OF HIGH-RISK TIA

A high-risk of recurrent stroke after TIA or minor stroke exists in the early period, with most strokes occurring within the first 2 days[5-8]; therefore, more effective preventive treatment modalities are needed at this time. The secondary preventive effect of antiplatelet therapy after ischemic stroke has been well-established. In the past, secondary stroke prevention

guidelines recommended the use of single antiplatelet (aspirin, clopidogrel) for initial treatment. Although, the combination of aspirin and clopidogrel is more effective than the use of aspirin alone in reducing the risk of ischemic events in patients with acute coronary syndrome,[9] the addition of aspirin to clopidogrel is not recommended for secondary prevention after ischemic stroke or TIA due to the increased risk of bleeding. The MATCH trial randomized patients with a recent TIA or ischemic stroke to clopidogrel plus aspirin versus clopidogrel plus placebo groups. The antiplatelet combination did not reduce major vascular effects, but increased the risk of life threatening events or major bleeding.[10] However, this study did not reflect the prevention of recurrent stroke in the early period after the initial event. The mean time from the qualifying event to randomization was 27 days, and subgroup analysis showed a favorable trend of dual antiplatelet agent in the group with early randomization (within 7 days).

The recent stroke secondary prevention guideline recommends that early initiation of short-term (21–90 days) dual antiplatelet therapy with aspirin and clopidogrel (or ticagrelor), ideally within 12–24 hours, and at least within 7 days after the onset of minor stroke (National Institutes of Health Stroke Scale [NIHSS] ≤ 3, NIHSS ≤ 5 for ticagrelor) or high-risk TIA ($ABCD_2$ score ≥ 4, $ABCD_2$ score ≥ 6 for ticagrelor). This guideline is based on three major randomized controlled trials[11-13] and meta-analyses[14-18] (**Table 1**). The use of dual antiplatelet therapy with aspirin and clopidogrel beyond 90 days after stroke is not recommended due to the increased risk of intracranial hemorrhage and major bleeding[10] (**Figure 1**).

Single antiplatelet therapy is recommended for acute stroke patients who do not meet the dual antiplatelet clinical criteria (minor stroke or high-risk TIA, intracranial or extracranial arterial stenosis). Several antiplatelet agents, including aspirin (50–325 mg daily) and clopidogrel (75 mg daily), or the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily, are recommended for the secondary prevention of ischemic stroke.[19-21]

INTRACRANIAL LARGE ARTERY ATHEROSCLEROSIS

Intracranial atherosclerosis (ICAS) is a common cause of stroke worldwide,[22][23] but is more prevalent in Asian and Black ethnicities than in Caucasians. The annual stroke recurrence rate in patients with ICAS is approximately 4–19%, and it remains as high as 15% in the first year despite optimal medical treatment in several clinical trials comparing the preventive effect of endovascular and medical treatment.[24-27]

Table 1. Clinical trials of dual antiplatelet therapy for secondary stroke prevention in acute minor stroke or transient ischemic attack

Trial	Population	Time window	Antiplatelet intervention	Primary outcome (efficacy & safety)	Key results
CHANCE[12]	5,170 patients of minor ischemic stroke (NIHSS ≤3) or high-risk TIA ($ABCD^2$ score ≥4)	24 hours	Clopidogrel (300 mg load then 75 mg/day) plus aspirin 75 mg/day for 21 days then aspirin only vs. aspirin 75 mg/day	Recurrent stroke at 90 days Moderate to severe bleeding	Reduced recurrent stroke in DAPT (HR, 0.68; p<0.001) No differences in moderate to severe bleeding
POINT[11]	4,881 patients of minor ischemic stroke (NIHSS ≤3) or high-risk TIA ($ABCD^2$ score ≥4)	12 hours	Clopidogrel (600 mg load then 75 mg/day) plus aspirin 50–325 mg/day vs. aspirin 50–325 mg/day for 90 days	Composite of major ischemic event at 90 days Major hemorrhage	Reduced major ischemic event in DAPT (HR, 0.75; p=0.02) Increased major hemorrhage in DAPT (HR, 2.32; p=0.02)
THALES[13]	11,016 patients of minor ischemic stroke (NIHSS ≤5) or high-risk TIA ($ABCD^2$ score ≥6 or symptomatic arterial stenosis)	24 hours	Ticagrelor (180 mg load then 90 mg twice daily) plus aspirin (load 300–325 mg then 75–100 mg/day) vs. aspirin (load 300–325 mg then 75–100 mg/day) for 30 days	Composite of stroke or death at 30 days Severe bleeding	Reduced stroke or death in DAPT (HR, 0.83; p=0.02) Increased severe bleeding in DAPT (HR, 3.99; p=0.001)

DAPT = dual antiplatelet therapy; HR = hazard ratio; NIHSS = National Institutes of Health Stroke Scale.

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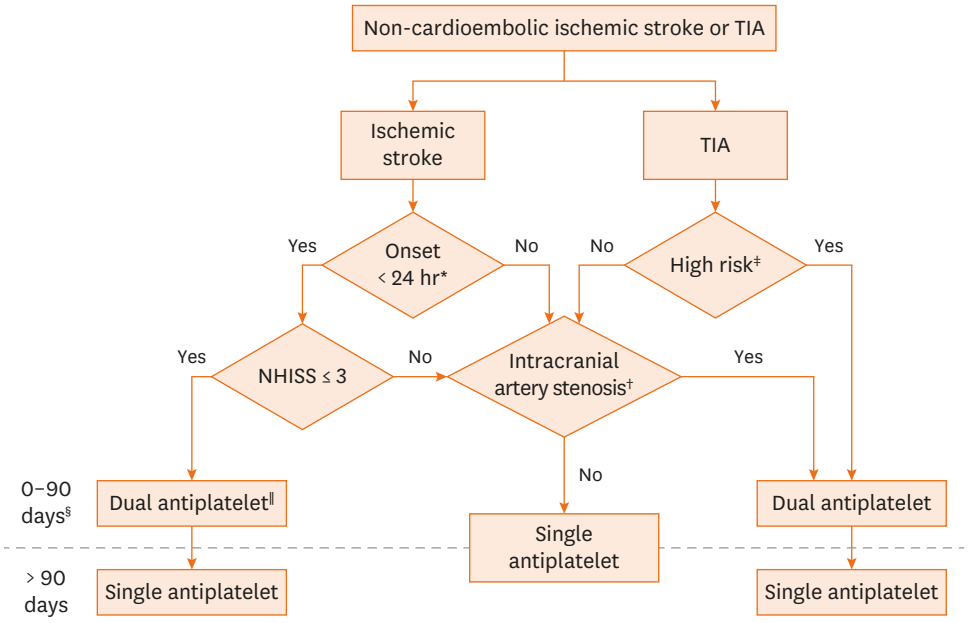

Figure 1. Antiplatelet therapy for non-cardioembolic stroke and transient ischemic attack.
*Dual antiplatelet is ideally initiated within 24 hours of symptom onset but can be given within 7 days of stroke onset; †Intracranial artery stenosis is defined as stenosis >50%; ‡High-risk TIA is defined as an $ABCD_2$ score ≥4; §The benefit of dual antiplatelet therapy was primarily observed during the first 21 days after symptom onset in major clinical trials; ‖Dual antiplatelet means the combination of aspirin and clopidogrel (modified from the Figure of Stroke 2021;52:e364-467[15]).
TIA = transient ischemic attack; NIHSS = National Institutes of Health Stroke Scale.

Several randomized controlled trials have compared percutaneous transluminal angioplasty and stenting (PTAS) with medical therapy for stroke prevention in patients with recent stroke or TIA attributable to severe arterial stenosis. These trials showed a higher rate of cerebrovascular events or death in the PTAS group than in the medical therapy group[25)26)28)29)] (**Table 2**).

The stroke prevention guideline recommends the use of dual antiplatelet medication (addition of clopidogrel 75 mg per day to aspirin for up to 90 days) in patients with recent (within 30 days) stroke or TIA attributable to severe (70–99%) ICAS. Further, the guideline recommends the addition of ticagrelor 90 mg to aspirin twice a day for up to 30 days in

Table 2. Clinical trials of intracranial stent for secondary stroke prevention

Trial	Population	Intervention	Outcome	Follow-up duration	Antiplatelet medication for best medical management	Key results
SAMMPRIS[25)]	451 patients of TIA or nondisabling stroke with 70–99% stenosis of major intracranial artery	Stenting vs. best medical management	Stroke or death	Mean 11.9 months	Aspirin 325 mg per day for entire follow up and clopidogrel 75 mg per day for 90 days	Stenting resulted in more strokes and death
VISSIT[26)]	112 patients of hard TIA or stroke with 70–99% stenosis of major intracranial artery	Stenting vs. best medical management	Stroke or hard TIA	12 months	Aspirin 81–325 mg per day for entire follow up and clopidogrel 75 mg per day for 90 days	Stenting resulted in more strokes and hard TIA
VAST[28)]	115 patients of TIA or minor stroke with at least 50% stenosis of intra or extracranial vertebral artery	Stenting vs. best medical management	Vascular death, MI, stroke	Median 3 years	Not defined Discretion of the treating neurologist	Stenting did not lower the risk of stroke
CASSISS[29)]	380 patients of TIA or stroke with 70–99% stenosis of major intracranial artery	Stenting vs. best medical management	Stroke or death	36 months	Aspirin 100 mg per day for entire follow up and clopidogrel 75 mg per day for 90 days	On going

MI = myocardial infarction; TIA = transient ischemic attack.

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patients with recent (within 24 hours) minor stroke or high-risk TIA and concomitant ipsilateral >30% stenosis of a major intracranial artery. Although the guideline does not recommend long-term dual antiplatelet therapy beyond 3 months, a previous long-term cohort study reported a higher risk of recurrent stroke in patients with severe (50–99%) ICAS than in those without.[30] Additional studies are needed to determine the effect of long-term dual antiplatelet therapy and to establish the specific high-risk subgroup of recurrent stroke in patients with severe symptomatic ICAS.

The medical arm of the SAMMPRIS trial was treated with solely 325 mg aspirin once daily after the first 90 days of dual antiplatelet therapy for the secondary prevention of stroke in severe ICAS, which showed a favorable result compared to interventional arm. The long-term preventive effect of other antiplatelet agents (clopidogrel, cilostazol, ticagrelor, aspirin plus dipyridamole) is not clearly defined and hence should be proven by future studies.

EXTRACRANIAL CAROTID ARTERY STENOSIS

Extracranial carotid artery stenosis is a major risk factor for ischemic stroke. Previous randomized clinical trials have compared carotid endarterectomy (CEA) with optimal medical therapy in patients with recent stroke or TIA.[31-34] The stroke guideline recommends that CEA be used to reduce the risk of future stroke in patients with TIA or non-disabling ischemic stroke and ipsilateral severe (50–99%) carotid artery stenosis. Moreover, carotid artery stenting is considered an option for patients at high-risk of CEA complications.

The intensive medical therapies available for the prevention of stroke recurrence in patients with carotid artery stenosis include antiplatelet therapy, lipid-lowering therapy, and treatment of hypertension. The antiplatelet regimens of ongoing clinical trials in patients with carotid artery stenosis include aspirin 325 mg daily in the CREST-2 trial, and combined aspirin and dipyridamole or clopidogrel in the ECST-2 trial.[35][36]

Dual antiplatelet therapy is not routinely recommended for the secondary prevention of ischemic stroke with symptomatic carotid artery stenosis, unless the symptoms are minor and within the acute period after symptom onset (described above). The CARESS trial demonstrated that combination therapy with clopidogrel and aspirin was more effective than using aspirin alone in reducing asymptomatic embolization in patients with recent (within 3 months) symptomatic carotid stenosis.[37] Although this study used a surrogate marker of microembolic signal instead of clinical outcomes and short duration (7 days) of dual antiplatelet administration, it demonstrated the possible role of dual antiplatelet agent in symptomatic carotid artery stenosis.

LACUNAR INFARCTION

Small subcortical strokes, also known as lacunar infarction, comprise approximately one-fourth of all cerebral infarctions. The Secondary Prevention of Small Subcortical Strokes (SPS3) study was a clinical trial that investigated the prevention of stroke recurrence by comparing aspirin plus placebo versus dual antiplatelet therapy with aspirin and clopidogrel.[38] The addition of clopidogrel to aspirin did not significantly reduce the risk of recurrent stroke but increased the risk of bleeding and death significantly. In the SPS3

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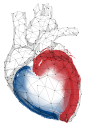

trial, the median time from the date of the qualifying stroke to randomization was 62 days; therefore, the result does not reflect the effect of dual antiplatelet medication in acute stage stroke prevention. Lacunar infarction that is detected within 24 hours of symptom onset and minor symptom (NIHSS ≤3) should be treated with dual antiplatelet as recommended by the guideline. The SPS3 trial subgroup analysis showed that in Caucasians receiving aspirin and clopidogrel, patients with cytochrome P450 2C19 (CYP2C19) intermediate or poor metabolizer status had higher probability of recurrent stroke than those with extensive or ultrarapid metabolizer status.[39] However, this study is limited by the small proportion of Caucasian participants that showed significant results; thus, the results should be interpreted with caution, and a larger clinical trial is necessary to validate the conclusions.

SINGLE ANTIPLATELET AGENT AND ANTIPLATELET RESISTANCE

The American Heart Association stroke guideline recommends antiplatelet therapy in preference to oral anticoagulation to reduce the risk of recurrent ischemic stroke in patients with non-cardioembolic ischemic stroke or TIA.[15] Aspirin 50–325 mg daily, clopidogrel 75 mg, or the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily is recommended for the secondary prevention of ischemic stroke, unless there are specific contraindications, such as minor ischemic stroke, high-risk TIA, or stroke due to large vessel occlusive disease.

The ESPRIT and ESPS2 trials showed that the use of aspirin-dipyridamole is more effective than aspirin alone for the prevention of vascular events.[20][21] Although the CAPRIE trial was not focused strictly on the secondary prevention of ischemic stroke, it showed fewer composite vascular events among patients treated with clopidogrel than those treated with aspirin; however, there was no benefit in stroke reduction among the stroke subgroup.[40] The PRoFESS trial found no significant difference between the use of aspirin-dipyridamole and clopidogrel in terms of secondary stroke prevention after non-cardioembolic stroke.[19]

Clopidogrel is widely used as a single or dual combination antiplatelet for secondary prevention in patients with ischemic stroke. The CYP2C19 genotype differentially affects the liver metabolism of clopidogrel, which may influence the preventive effect. Studies on whether the stroke preventive effect differs by CYP2C19 genotype in ischemic stroke patients have shown controversial results. Previous studies demonstrated that reduced or loss of CYP2C19 function was associated with poorer outcome and increased risk of recurrent stroke in patients with ischemic stroke.[41][42] In contrast, no significant association between CYP2C19 genotype and ischemic events was found in patients with ischemic stroke.[43] In the SPS3 study, there were no significant differences in the occurrence of recurrent stroke by CYP2C19 metabolizer status in the whole study group.[39] Moreover, a meta-analysis showed that carriers of CYP2C19 loss-of-function alleles (*2, *3, and *8) were at a 1.92-fold greater risk of stroke than non-carriers.[44]

Several clinical trials are ongoing to verify the clinical implication of the CYP2C19 genotype on the preventive effect of clopidogrel in ischemic stroke.[45][46]

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CONCLUSION

Antiplatelet agents are used for the secondary prevention of cerebral infarction; however, they do not completely prevent the recurrence of cerebral infarction and may have the disadvantage of bleeding as a side effect. Dual antiplatelet therapy is recommended only for patients with acute mild cerebral infarction and cerebral infarction caused by severe arterial stenosis. However, the long-term effect of dual antiplatelet therapy and its use in other situations have not been completely established.

Further studies are needed on the long-term administration of dual antiplatelet agents in patients with cerebral infarction and cerebral artery stenosis or moderate to severe ischemic damage. The clinical implications of antiplatelet resistance, especially clopidogrel, in ischemic stroke prevention, is another important issue that requires further investigation.

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