

## Antiplatelet strategy for acute ischemic stroke: A mini review

Zhong-He Zhou, Hui-Sheng Chen

Zhong-He Zhou, Hui-Sheng Chen, Department of Neurology, General Hospital of Shen-Yang Military Region, Shenyang 110840, Liaoning Province, China

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Correspondence to: Hui-Sheng Chen, MD, Professor, Department of Neurology, General Hospital of Shen-Yang Military Region, 83 Wenhua Road, Shenyang 110840, Liaoning Province, China. [chszh@aliyun.com](mailto:chszh@aliyun.com)

Telephone: +86-24-28897511 Fax: +86-24-28856448

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**Core tip:** Patients with acute ischemic stroke have a high risk of deterioration in the 48-72 h after symptom onset. Although thrombolysis is an effective method, most patients are excluded due to the limit of strict indications. Early antiplatelets are recommended for most patients. However, the question remains unclear whether another effective and safe antiplatelet strategy for the treatment of acute ischemic stroke exists. Growing evidence shows that combination antiplatelets may be superior to mono antiplatelets in the treatment of acute ischemic stroke.

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### Abstract

Transient ischemic attacks and minor ischemic strokes have a high risk of an unstable clinical course in the initial 48-72 h after symptom onset. Early antiplatelet treatment is recommended to treat most patients with acute ischemic stroke because few patients can be treated with thrombolysis due to the limit of strict indications, such as a time window. Antiplatelets aim to prevent recurrence or deterioration of stroke. The guidelines recommend the use of aspirin in the acute stage based on two clinical trials. However, some patients still developed recurrence or deterioration of stroke despite timely aspirin administration. Thus, the question remains unclear whether another effective and safe antiplatelet strategy for the treatment of acute ischemic stroke exists. Growing evidence shows that combination antiplatelets may be superior to mono antiplatelets in the treatment of acute ischemic stroke.

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**Key words:** Antiplatelet; Acute ischemic stroke

### INTRODUCTION

In the acute stage of ischemic stroke, one of the most important treatment strategies aims to prevent recurrence or deterioration of stroke, because patients with transient ischemic attack (TIA) and minor ischemic stroke have a high risk of an unstable clinical course. Most of these unfavorable events occur in the initial 48-72 h after symptom onset and have obvious effects on the recovery of neurological functions in these patients<sup>[1-4]</sup>. It is well demonstrated that thrombolysis is an effective method to treat acute ischemic stroke. Due to the limit of strict indications, such as a time window, most patients are excluded for thrombolysis. Thus, early antiplatelet treatment is recommended to treat most patients with acute ischemic stroke in the guidelines<sup>[5,6]</sup>. In acute ischemic stroke, 2 mega trials established the efficacy of aspirin<sup>[7,8]</sup>; thus, the guidelines recommend the use of aspirin in the acute stage<sup>[5,6]</sup>. However, some patients develop recurrence or deterioration of stroke despite timely aspirin administration. Thus, the question remains unclear whether another effective and safe

antiplatelet strategy for the treatment of acute ischemic stroke exists.

In this article, we will briefly review the following topics: (1) the action mechanisms of different antiplatelet agents; (2) the evidence for antiplatelet therapy for acute ischemic stroke; and (3) the efficacy and safety of combination antiplatelet agents for acute ischemic stroke.

## ANTIPLATELET DRUGS AND MECHANISMS

Commonly used antiplatelet agents include aspirin, clopidogrel, cilostazol and dipyridamole. These agents act at different sites of the platelet aggregation pathway to inhibit platelet activation. Aspirin is a non-selective and irreversible cyclooxygenase (COX) inhibitor, which selectively acetylates the hydroxyl group of the COX enzyme, thus inhibiting conversion of arachidonate to prostaglandin G<sub>2</sub>/H<sub>2</sub> and thromboxane A<sub>2</sub>. This leads to irreversible inhibition of platelet aggregation<sup>[9]</sup>.

Clopidogrel is a thienopyridine derivative that prevents ADP-induced platelet activation and aggregation by irreversibly inhibiting the binding of adenosine 5-diphosphate to glycoprotein IIb/IIIa, with the result of preventing the binding of fibrinogen to this receptor<sup>[10]</sup>.

Cilostazol is an inhibitor of phosphodiesterase 3 (PDE3) which results in increased concentrations of intracellular cAMP<sup>[11]</sup>. Cilostazol inhibits primary and secondary platelet aggregation and high-shear stress platelet aggregation both *in vivo* and *in vitro*<sup>[12]</sup>.

Dipyridamole is postulated to have multiple mechanisms of action. On one hand, its inhibition of platelet phosphodiesterase produces an increase in intraplatelet cyclic adenosine monophosphate level, resulting in the potentiation of the platelet inhibitory actions of prostacyclin. On the other hand, it also acts by directly releasing eicosanoid from vascular endothelium and inhibiting cellular uptake and metabolism of adenosine. This leads to the inhibition of platelet aggregation again<sup>[13]</sup>.

## ANTIPLATELET THERAPY FOR ACUTE ISCHEMIC STROKE

A lot of studies have investigated the efficacy and safety of antiplatelet treatment in the secondary prevention of ischemic stroke<sup>[14]</sup>; however, only a few studies have investigated the efficacy and safety of antiplatelet treatment in acute ischemic stroke<sup>[7,8,15,16]</sup>. Of these studies, there are two powerful clinical trials: The Chinese Acute Stroke Trial (CAST)<sup>[8]</sup> and the International Stroke Trial (IST)<sup>[7]</sup>. In the CAST, 21,106 patients with acute ischemic stroke were enrolled in the clinical trial. Aspirin treatment (160 mg/d) was started within 48 h of the onset of a suspected acute ischemic stroke and continued in hospital for up to 4 wk. The results showed that aspirin treatment produced a significant reduction in mortality. Also, significantly fewer recurrent ischemic strokes oc-

curred in the aspirin group compared with the placebo-allocated group, but slightly more hemorrhagic strokes. In the IST, 19,435 patients with acute ischemic stroke within 48 h of symptom onset were enrolled. Anti-thrombotic therapy was started as soon as possible after stroke onset. The results showed that aspirin treatment significantly reduced death or recurrent ischemic strokes.

In addition to the two clinical trials, there are some completed clinical trials that investigated the antiplatelet strategy for acute ischemic stroke<sup>[15,16]</sup>. In the FASTER (the fast assessment of stroke and transient ischemic attack to prevent early recurrence) trial, 392 patients with TIA or minor stroke within 24 h of symptom onset were enrolled<sup>[15]</sup>. The trial was designed to investigate the effect of the combination of aspirin + clopidogrel versus aspirin monotherapy (with or without simvastatin) on the risk of recurrent stroke within 90 d after a TIA or minor stroke. The results showed the trend to lower recurrence or deterioration of stroke in the acute stage in the dual therapy group compared with mono antiplatelets. Another EARLY trial compared the safety and efficacy of aspirin + dipyridamole initiated within 24 h of stroke or TIA with that of aspirin + dipyridamole initiated after 7 d of aspirin monotherapy<sup>[16]</sup>. The results showed that early initiation of aspirin plus extended-release dipyridamole did not lead to differing disability at 90 d compared with late initiation, but the proportion of patients in the early initiation group who had no or mild disability on day 90 was higher than that in the late initiation group. There was also no significant difference in the composite adverse event endpoint between the two groups. These studies demonstrated the efficacy and safety of combined antiplatelet treatment in acute ischemic stroke. Furthermore, the proposal also got support from the CLAIR study<sup>[17]</sup>. The study aimed to investigate whether treatment with clopidogrel plus aspirin reduced the number of microembolic signals detected with transcranial doppler ultrasound compared with aspirin alone in patients with recent stroke. The results showed that combination therapy with clopidogrel and aspirin is more effective than aspirin alone in reducing microembolic signals in patients with predominantly intracranial symptomatic stenosis.

In other clinical trials aiming to investigate the secondary prevention for ischemic stroke, antiplatelet treatment was applied to some patients with acute ischemic stroke. For example, The ESPRIT Study compared aspirin with aspirin plus dipyridamole for secondary prevention after an ischemic stroke or transient ischemic attack<sup>[18]</sup>. The study recruited 96 patients during the acute stage of ischemic stroke and TIA. The Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial is designed to compare extended-release dipyridamole plus aspirin *vs* clopidogrel in secondary stroke prevention<sup>[19]</sup>. The study recruited 1360 patients during the acute stage of ischemic stroke. These studies also demonstrated the efficacy and safety of combined antiplatelet treatment. Furthermore, a recent meta-analysis study shows that dual antiplatelet therapy appears to

be safe and effective in reducing stroke recurrence and combined vascular events in patients with acute ischemic stroke or transient ischemic attack compared with monotherapy<sup>[20]</sup>.

One powerful evidence comes from the Clopidogrel in High-risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) study, which was just published in the *New England Journal of Medicine*<sup>[21]</sup>. The study showed that among patients with a TIA or minor stroke who can be treated within 24 h after the onset of symptoms, the combination of clopidogrel and aspirin is superior to aspirin alone for reducing the risk of stroke in the first 90 d and does not increase the risk of hemorrhage.

## BLEEDING EVENTS CAUSED BY ANTI-PLATELETS

When considering using more intensive antiplatelet therapy, the balance between reducing recurrent stroke and increasing major bleeding events needs to be considered. Previous studies found that combination antiplatelet increased the bleeding events compared with mono antiplatelets. For example, the PROfESS study found that aspirin plus extended-release dipyridamole produced more major hemorrhagic events than clopidogrel, including intracranial hemorrhage<sup>[22]</sup>. The MATCH study showed that life-threatening bleeding was higher in the group receiving aspirin and clopidogrel *vs* clopidogrel alone<sup>[23]</sup>. However, some studies found no difference between combination antiplatelets and mono antiplatelets, for example, the EARLY, FASTER and CLAIR trials<sup>[15-17]</sup>. More importantly, the recent CHANCE study also did not find more bleeding events with combined antiplatelets compared with mono antiplatelets<sup>[21]</sup>. The discrepancy could be due to the duration of antiplatelet treatment. Obviously, combination antiplatelets in the long-term trials such as PROfESS and MATCH<sup>[22,23]</sup> produced more bleeding events. Thus, a time window of combination antiplatelets should exist at which risk outweighs benefit. Taken together, the evidence shows that combination antiplatelets in a short-term time window (maybe less than 3 wk) should be safe.

## CONCLUSION

As discussed above, although IST and CAST provided the most elegant evidence for aspirin in the acute stage of ischemic stroke, growing evidence, including CHANCE, points to the superiority of combination antiplatelets over mono antiplatelets. On one hand, due to their different mechanisms of action, it is postulated that combined antiplatelet agents may provide different degrees of vascular protection. On the other hand, the superiority of combination therapy compared to monotherapy may be due to the synergy effects of different antiplatelet mechanisms in reducing vascular events. Thus, combined antiplatelet therapy, such as aspirin and clopidogrel, should be encouraged in the treatment of acute ischemic stroke.

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