Clinical Updates on Antiplatelet Therapy for Secondary Prevention in Acute Ischemic Stroke

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Abstract

Antiplatelet therapy is the first-line management for noncardioembolic transient ischemic attack (TIA) and acute ischemic stroke (IS). Herein, we review the safety and efficacy of antiplatelet therapies in patients with IS and TIA, primarily focusing on the acute stage. We discuss current antiplatelet monotherapy and the factors influencing efficacy and continuation rate according to clinical trial data. Aspirin remains the most commonly used first-line antiplatelet agent for preventing noncardioembolic stroke recurrence, and clopidogrel, cilostazol, and ticagrelor are feasible alternatives. Various short-term dual antiplatelet therapies (including clopidogrel–aspirin and ticagrelor–aspirin combination therapy) for minor stroke and high-risk TIA are also reviewed. For selected patients with specific stroke etiologies, short-term dual antiplatelet therapy with aspirin combined with clopidogrel or ticagrelor can significantly reduce the risk of stroke. However, insufficient evidence supports the benefits of triple antiplatelet therapy for recurrent noncardioembolic stroke prevention, and this treatment substantially increases the rate of bleeding complications.

Keyword: antiplatelet therapy, acute ischemic stroke, secondary prevention, transient ischemic attack

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INTRODUCTION

In 2019, stroke was the second leading cause of death and third leading cause of death or disability worldwide [(1)]. In the United States, approximately 795,000 individuals experience cerebrovascular events annually, and ischemic stroke (IS) constitutes 87% of these events [(2)]. A 5-year follow-up study of the TIAregistry.org project estimated the risk of recurrent stroke following a transient ischemic attack (TIA) or stroke to be 16.8% [(3)]. Lacunar infarcts account for approximately 23% of IS cases, and cardioembolic infarcts account for approximately 35% of the nonlacunar cases [(2)]. As in the United States, the majority of stroke cases in Taiwan are noncardioembolic IS (>70%) [(4)].

Antiplatelets have become a part of a key management strategy for noncardioembolic IS and TIA [(5)]. Antiplatelet treatment has greater benefits in the acute phase, in which it significantly reduces the risk of recurrent stroke [(6)]. Patient selection, treatment agents, and combinations of antiplatelet therapies for secondary stroke prevention are continually refined. This paper reviews the safety and

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efficacy of antiplatelet therapy in patients with IS or TIA. The results of recent clinical trials and published cohort studies and the recommendations of reviews and meta-analyses are discussed.

Early Antiplatelet Therapy for Acute IS or TIA

Antiplatelet Monotherapy in Acute Stage

Aspirin

Aspirin remains the most common agent used for the treatment of both acute IS (AIS) and the long-term prevention of recurrent stroke following noncardioembolic stroke. In 1997, two large randomized controlled trials (the International Stroke Trial and Chinese Acute Stroke Trial) led to the fundamental treatment of early (within 48 hours) aspirin initiation [7, 8]. A 2014 systematic review concluded that initiating aspirin (160 to 300 mg daily) within 48 hours after IS onset reduces the risk of early recurrent IS and improves long-term outcomes [9]. Therefore, the 2019 American Heart Association and American Stroke Association guidelines and 2020 Taiwan Stroke Society guidelines recommend the administration of aspirin within the first 24 to 48 hours after AIS onset for patients who are not candidates for intravenous thrombolysis or have not undergone thrombolysis in the past 24 hours [10, 11].

However, patients with an inadequate aspirin response have an increased likelihood of recurrent vascular events. Two meta-analyses have reported higher odds (odds ratio, 3.8) of future vascular events in such individuals [12, 13]. Numerous mechanisms have been proposed to explain aspirin resistance, including reduced bioavailability and genetic variability [14]. For patients with aspirin resistance with no identifiable cause, the use of an alternative antiplatelet medication is a feasible option. A meta-analysis of five studies with a combined sample of 8,723 patients with AIS or TIA undergoing aspirin monotherapy reported that the addition of or switch to an alternative antiplatelet agent, such as clopidogrel and ticagrelor, was associated with reduced risks of future vascular events, including recurrent stroke (hazard ratio [HR], 0.70; 95% confidence interval [CI], 0.54–0.92) [15].

Clopidogrel

Clopidogrel is a feasible alternative to aspirin for secondary noncardioembolic stroke or TIA prevention. The 1996 CAPRIE trial reported that clopidogrel (75 mg) resulted in a significantly lower risk of AIS, acute coronary syndrome, or peripheral artery disease, compared with aspirin (325 mg) monotherapy (5.3% vs. 5.8% annually, respectively; relative risk reduction, 8.7%; 95% CI, 0.3–16.5) [16].

Clopidogrel is a thienopyridine medication that inhibits adenosine diphosphate–dependent platelet aggregation. Numerous polymorphisms of hepatic enzyme genes (most notably, CYP2C19) are associated with clopidogrel metabolism. Polymorphism of the gene encoding the P2Y12 platelet receptor may prevent platelet aggregation inhibition. In a secondary analysis of the CHANCE trial, dual antiplatelet therapy (DAPT) with clopidogrel and aspirin resulted in a significantly lower stroke rate than did aspiring alone (HR, 0.51; 95% CI, 0.35–0.75), but this result was not observed in those with CYP2C19 loss-of-function (LOF) alleles (HR, 0.93; 95% CI, 0.69–1.26) [17].

Ticagrelor

Ticagrelor is another potential alternative agent for secondary noncardioembolic stroke prevention in the acute stage. In the 2016 SOCRATES trial of over 13,000 participants with high-risk TIA, minor IS, or ipsilateral arterial stenosis, ticagrelor monotherapy did not result in a significant difference in the composite outcomes of stroke, myocardial infarction, or death after 90 days, compared with aspirin monotherapy (HR, 0.89; 95% CI, 0.78–1.01). Furthermore, the discontinuation rate with ticagrelor was higher because of side effects such as dyspnea and minor bleeding [18]. However, this trial also demonstrated that the use of ticagrelor marginally reduced the risk of IS compared with aspirin monotherapy (HR, 0.87; 95% CI, 0.76–1.00).

Compared with clopidogrel, ticagrelor has more rapid onset and a more potent antiplatelet effect [19], and it is not dependent on metabolic activation for its antiplatelet activity. The 2017 PRINCE trial discovered significantly lower platelet reactivity and stroke recurrence at 90 days in the ticagrelor–aspirin group than in the clopidogrel–aspirin group; this result was observed even in patients carrying CYP2C19 LOF alleles. No difference was reported between the arms in the rates of major bleeding events.

Cilostazol

Cilostazol is another antiplatelet monotherapy for secondary stroke prevention tested in several randomized controlled trials and meta-analyses. The results of the 2005 CSPS trial in Japan were promising; cilostazol (100 mg twice daily) provided a significant reduction in recurrent stroke risk(relative risk reduction, 42%; 95% CI, 9.2–62.5). The 2010 CSPS 2 trial compared the efficacy of cilostazol with that of aspirin monotherapy [20, 21]. In total, 2,757 patients with a recent (< 26 weeks) noncardioembolic cerebral infarction were assigned to receive cilostazol (100 mg twice daily) or aspirin (81 mg daily) for 1–5 years. After a mean follow-up of 29 months, the yearly rates of recurrent stroke (infarction or hemorrhage) in the cilostazol and aspirin groups were similar (2.76% vs. 3.71%, respectively; HR, 0.74; 95% CI, 0.56–0.98); this demonstrates that cilostazol is not inferior to aspirin monotherapy for secondary stroke prevention [21]. Notably, the annual rates of intracranial or other hemorrhagic events were lower among patients using cilostazol (0.77%) than among those using aspirin (1.78%; HR, 0.46; 95% CI, 0.30–0.71). However, side effects (e.g., headache, dizziness, diarrhea, palpitation, and tachycardia) were more frequently reported in the cilostazol group, which led to a higher discontinuation rate than that in the aspirin group (20% vs. 12%, respectively).

DAPT in Acute Stage of IS

Minor IS and High-Risk TIA

The 2013 CHANCE trial investigated 5,170 Chinese patients with high-risk TIA (ABCD2 score ≥ 4) or minor IS (National Institutes of Health Stroke Scale [NIHSS] score ≤ 3) within 24 hours of onset; it was the first study to demonstrate the superiority of dual aspirin–clopidogrel therapy (300 mg of clopidogrel initially, then 75 mg daily for 90 days, with 75 mg of aspirin daily for the first 21 days) to aspirin monotherapy (75 mg daily for 90 days; Table 1) [22]. The risk of subsequent stroke was significantly lower in the dual aspirin–clopidogrel group than in the placebo–aspirin group (8.2% vs. 11.7%, respectively; absolute risk reduction, 3.5%; HR, 0.68; 95% CI, 0.57–0.81). Nevertheless, genetic variations of CYP2C19 may affect the efficacy of clopidogrel. The recent CHANCE-2 trial randomly assigned 6,412 Chinese patients with CYP2C19 LOF alleles and high-risk TIA or minor IS to a ticagrelor–aspirin or clopidogrel–aspirin DAPT group for 21 days [23]. After 90 days, the rate of recurrent stroke was lower in the ticagrelor–aspirin group than that in the clopidogrel–aspirin group (6% vs. 7.6%, respectively; HR, 0.77; 95% CI, 0.64–0.94). However, the generalizability of these findings to non-Chinese populations, which may have lower CYP2C19 polymorphism prevalence and higher small-vessel disease prevalence, is unknown.

The 2018 POINT trial randomly assigned 4,881 patients with high-risk TIA (ABCD2 score ≥ 4) or minor IS (NIHSS score ≤ 3) to receive dual aspirin–clopidogrel (600-mg clopidogrel loading, then 75 mg daily for 90 days, with 50–325 mg of aspirin daily for 90 days) or aspirin monotherapy (50 to 325 mg daily for 90 days) within 12 hours of onset at 269 international sites (with 82.8% enrolled in the United States) [24]. At 90 days, the rate of the composite outcome of major ischemic events in the dual aspirin–clopidogrel group was lower than that in the placebo–aspirin group (5.0% vs. 6.5%, respectively; adjusted relative risk, 1.5%; HR, 0.75; 95% CI, 0.59–0.95). Similar to the CHANCE trial, the POINT trial supported the view that DAPT with clopidogrel and aspirin presented a lower risk of recurrent stroke after mild AIS or high-risk TIA, compared with that presented by aspirin monotherapy. However, a higher risk of major hemorrhage was reported in the dual aspirin–clopidogrel group (0.9% vs. 0.4%, respectively; HR, 2.32; 95% CI, 1.10–4.87); consequently, the trial was stopped early after only 84% of the patients had enrolled. A substudy of the POINT trial investigating over 900 patients with CYP2C19 polymorphisms discovered similar rates of stroke or major ischemic events between carriers and noncarriers of CYP2C19 LOF alleles [25]. However, the higher loading dose of clopidogrel (600 mg) in the POINT trial (compared with the 300 mg used in the CHANCE and CHANCE-2 trials) has been suggested to counteract the metabolic differences between carriers or noncarriers of CYP2C19 LOF alleles.

The 2020 THALES trial randomly assigned 11,016 patients with minor noncardioembolic stroke (NIHSS score ≤ 5) or high-risk TIA (ABCD2 score ≥ 6) to DAPT with ticagrelor and aspirin (180-mg ticagrelor loading, then 90 mg twice daily, with 300–325-mg aspirin loading, followed by 75 to 100 mg daily) or to placebo–aspirin (300–325-mg aspirin loading, then 75 to 100 mg daily)

monotherapy for 30 days (Table 1) [19]. The DAPT group demonstrated a lower risk of the composite primary outcome of stroke or death within 30 days compared with that of the aspirin monotherapy group (5.5% vs. 6.6%, respectively; HR, 0.83; 95% CI, 0.71–0.96). A total of 3,314 patients in the THALES trial had an NIHSS score of 4 or 5 (such patients were excluded from the CHANCE and POINT studies), but subgroup analysis demonstrated that the benefit of ticagrelor–aspirin treatment for these patients was similar to that for patients with lower NIHSS scores or with TIA [26]. Although uncommon, major bleeding events were more frequent in the ticagrelor–aspirin group (0.5% vs. 0.1%; HR, 3.99; 95% CI, 1.74–9.14) than they were in the aspirin monotherapy group, resulting in a higher discontinuation rate in the ticagrelor–aspirin group. The results of these three trials suggest that DAPT with aspirin combined with clopidogrel or ticagrelor is a feasible option for patients with minor stroke (NIHSS score ≤5) or high-risk TIA (ABCD2 score ≥4).

Large-Artery Atherosclerosis

DAPT has demonstrated benefits for patients with high-risk intracranial atherosclerotic arterial stenosis. In the 2011 SAMMPRIS trial, 451 patients with recent AIS or TIA attributable to 70%–99% atherosclerosis

Table 1. Randomized control trials assessing the efficacy and safety of early initiation of antiplatelet agents for secondary stroke prevention.

Trial	Patient population	Treatment groups	Follow-up duration	Outcome (P, primary; S, safety)
CHANCE 2013	5,170 patients within 24 hours of minor AIS (NIHSS ≤ 3) or high-risk TIA (ABCD2 ≥ 4)	300 mg clopidogrel loading then 75 mg daily for 90 days + 75–300 mg aspirin loading then 75 mg daily for 21 days vs. 75–300 mg aspirin loading then 75 mg daily for 90 days	90 days	DAPT vs. aspirin **P**: Composite of new stroke events (IS or hemorrhagic stroke)—8.2% vs. 11.7% (HR, 0.68; 95% CI, 0.57–0.81) **S**: Severe bleeding—0.2% vs. 0.2% (HR, 0.94; 95% CI, 0.24–3.79)
POINT 2018	4,881 patients within 12 hours of minor AIS (NIHSS ≤ 3) or high-risk TIA (ABCD2 ≥ 4)	600 mg clopidogrel loading then 75 mg daily for 90 days + 50–325 mg of aspirin daily for 90 days vs. 50–325 mg of aspirin daily for 90 days	90 days	DAPT vs. aspirin P: Composite of IS, MI, or death from vascular cause—5.0% vs. 6.5% (HR, 0.75; 95% CI, 0.59–0.95) S: Major hemorrhage—0.9% vs. 0.4% (HR, 2.32; 95% CI, 1.10–4.87)
THALES 2020	11,016 patients within 24 hours of minor AIS (NIHSS ≤5), high-risk TIA (ABCD2 ≥ 6), or symptomatic intra/extracranial arterial stenosis (≥50%)	180 mg ticagrelor loading then 90 mg twice daily for 30 days + 300–325 mg aspirin loading then 75–100 mg daily for 30 days vs. 300–325 mg aspirin loading then 75–100 mg daily for 30 days	30 days	DAPT vs. aspirin P: Composite of first stroke or death within 30 days—5.5% vs. 6.6% (HR, 0.83; 95% CI, 0.71–0.96) S: First severe bleeding event—0.5% vs. 0.1% (HR, 3.99; 95% CI, 1.74–9.14)
CHANCE-2 2021	6,412 patients with *CYP2C19* LOF alleles within 24 hours of minor AIS (NIHSS ≤ 3) or high-risk TIA (ABCD2 ≥ 4)	180 mg ticagrelor loading then 90 mg twice daily for 90 days + 75–300 mg aspirin loading then 75 mg daily for 21 days vs. 300 mg clopidogrel loading then 75 mg daily for 90 days + 75–300 mg aspirin loading then 75 mg daily for 21 days	90 days	Ticagrelor–aspirin vs. clopidogrel–aspirin P: Composite of new stroke events (IS or hemorrhagic stroke)—6.0% vs. 7.6% (HR, 0.77; 95% CI, 0.64–0.94) S: Severe bleeding—0.3% vs. 0.3% (HR, 0.82; 95% CI, 0.34–1.98)

were randomly assigned to aspirin–clopidogrel DAPT or standard treatment with Wingspan stenting for up to 90 days [27]. The patients undergoing DAPT had a lower rate of the combined stroke and death outcome at 30 days (5.8%) than did those undergoing aggressive treatment with stenting arms (14.7%; P = 0.002). This benefit of DAPT over Wingspan stenting persisted over an extended follow-up [28]. Other studies have supported the efficacy of DAPT for patients with intracranial large-artery atherosclerosis. In a subgroup analysis of the CHANCE trial, 481 (44.2%) patients with 50%–99% intracranial large-artery atherosclerosis had a nonsignificantly lower stroke recurrence rate in the DAPT group (HR, 0.79; 95% CI, 0.47–1.32) [29]. In addition, in the THALES trial, a subgroup analysis of patients with symptomatic ipsilateral atherosclerotic stenosis (≥50% stenosis), the rate of stroke recurrence or death within 30 days was also lower in the dual ticagrelor–aspirin group (HR, 0.73; 95% CI, 0.56–0.96) [30]. However, in the MATCH trial, prolonged DAPT (>90 days) offered no additional benefits over antiplatelet monotherapy but resulted in a substantially higher rate of bleeding complications (after 18 months of treatment) [31].

Triple Antiplatelet Therapy in Acute Stage

Evidence supporting the use of triple antiplatelet therapy for noncardioembolic secondary stroke prevention is insufficient. The 2017 TARDIS was a randomized open-label phase 3 trial that assigned 3,096 patients with noncardioembolic IS or TIA to receive intensive triple antiplatelet therapy (300-mg aspirin loading, then 75 mg twice daily; 300-mg clopidogrel loading, followed by 75 mg daily; 200 mg of dipyridamole twice daily or 100 mg three or four times daily) or guideline-based therapy (either clopidogrel monotherapy or combined aspirin and dipyridamole) within 48 hours of onset [32]. No differences were reported between the incidence rates of recurrent IS or TIA of the intensive and guideline therapy groups (adjusted common odds ratio [cOR], 0.90; 95% CI, 0.67–1.20). However, triple antiplatelet therapy was associated with more major bleeding events (adjusted cOR, 2.54; 95% CI, 2.05–3.16).

CONCLUSIONS

Antiplatelets remain crucial for secondary noncardioembolic stroke prevention. Early administration provides considerably reduces the risk of recurrent stroke. For patients with AIS who are ineligible for intravenous thrombolysis using alteplase or mechanical thrombectomy, antiplatelet agents should be initiated immediately after the confirmation of the TIA or AIS diagnosis. Aspirin is widely available and commonly used as a first-line antiplatelet agent for preventing stroke recurrence. In addition, clopidogrel, cilostazol, and ticagrelor are feasible alternatives for antiplatelet monotherapy, but genetic polymorphisms (e.g., LOF alleles for clopidogrel) or side-effect profiles may be considered. For selected patients with specific stroke etiologies, short-term DAPT with aspirin combined with clopidogrel or ticagrelor significantly reduces the rate of recurrent stroke, specifically for patients with minor noncardioembolic IS, high-risk TIA, or stroke attributable to moderate-to-severe intracranial arterial stenosis. prolonged DAPT (> 90 days) provides no additional benefits over antiplatelet monotherapy but substantially increases the rate of bleeding complications. Nevertheless, the optimal duration, efficacy, and safety of DAPT for patients with other etiologies, such as extracranial large-artery stenosis or atheromatous disease, are not fully understood and require further studies. Finally, triple antiplatelet therapy is not recommended for routine clinical practice because it significantly increases the risk of major bleeding. To optimize secondary stroke prevention for various stroke etiologies, future studies must refine treatment algorithms to determine the appropriate applications of various antiplatelet agents and combination therapies.

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