

# Contemporary antiplatelet therapy for secondary stroke prevention: a narrative review of current literature and guidelines

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## ABSTRACT

Antiplatelet therapy is one of the mainstays for secondary stroke prevention. This narrative review aimed to highlight the current evidence and recommendations of antiplatelet therapy for stroke prevention.

We conducted advanced literature search for antiplatelet therapy. Landmark studies and randomised controlled trials evaluating antiplatelet therapy for secondary stroke prevention are reviewed. Results from Cochrane systematic review, pooled data analysis and meta-analysis are discussed.

Single-antiplatelet therapy (SAPT) with aspirin, aspirin/extended-release dipyridamole or clopidogrel reduces the risk of recurrent ischaemic stroke in patients with non-cardioembolic ischaemic stroke or transient ischaemic attack (TIA). Dual-antiplatelet therapy (DAPT) with aspirin and clopidogrel or ticagrelor for 21–30 days is more effective than SAPT in patients with minor acute noncardioembolic ischaemic stroke or high-risk TIA. Prolonged use of DAPT is associated with higher risk of haemorrhage without reduction in stroke recurrence than SAPT. Compared with placebo, aspirin reduces the relative risk of recurrent stroke by approximately 22%. Aspirin/dipyridamole and cilostazol are superior to aspirin but associated with significant side effects. Cilostazol or ticagrelor might be more effective than aspirin or clopidogrel in patients with intracranial stenosis. SAPT is indicated for secondary stroke prevention in patients with non-cardioembolic ischaemic stroke or TIA. DAPT with aspirin and clopidogrel or ticagrelor for 21–30 days followed by SAPT is recommended for patients with minor acute noncardioembolic stroke or high-risk TIA. Selection of appropriate antiplatelet therapy should also be based on compliance, drug tolerance or resistance.

## INTRODUCTION

Stroke is the second-leading cause of death and the third-leading cause of death and disability combined in 2019 globally.<sup>1</sup> Platelets are activated by collagen, ADP and arachnoid acid metabolite thromboxane A<sub>2</sub>. Activated platelets induce platelet aggregation and blood clot formation, resulting in acute ischaemic stroke (AIS) or transient ischaemic attack (TIA). Antiplatelet agents inhibit platelet aggregation and reduce the risk of AIS or TIA.<sup>2</sup> Aspirin, clopidogrel, dipyridamole/

aspirin, cilostazol and ticagrelor are commonly used antiplatelet agents. In recent years, numerous randomised controlled trials (RCTs), Cochrane systematic reviews and meta-analyses evaluated the efficacy and safety of antiplatelet therapy for secondary stroke prevention.<sup>3–9</sup> Due to the complexity of stroke aetiology and diverse mechanisms of antiplatelet agents (figure 1), it is essential to select optimal antiplatelet therapy in the real-world practice. In this narrative review, we aimed to highlight current evidence and recommendations of the antiplatelet therapy for secondary stroke prevention.<sup>2–10</sup>

## METHODS AND MATERIALS

We conducted a literature search of peer-reviewed English language articles in PubMed and Cochrane Library using the following keywords: antiplatelet therapy AND stroke, antiplatelet therapy AND ischaemic stroke, antiplatelet therapy AND transient ischaemic attack, antiplatelet agent AND stroke, antiplatelet agent AND ischaemic stroke, antiplatelet agent AND transient ischaemic attack. The search was performed for studies published between 1 January 1980 and 15 November 2021. Landmark studies, RCTs, Cochrane systematic review, pooled data analysis and meta-analysis were included for discussion.

## RESULTS

### Single-antiplatelet therapy

#### Aspirin

Aspirin irreversibly inactivates cyclooxygenase 1 (COX1) and inhibits platelet aggregation. In 1994, the Antiplatelet Trialists' Collaboration study evaluated 145 RCTs regarding aspirin in preventing ischaemic stroke, myocardial infarct or vascular death.<sup>11</sup> Aspirin treatment was associated with a 22% relative



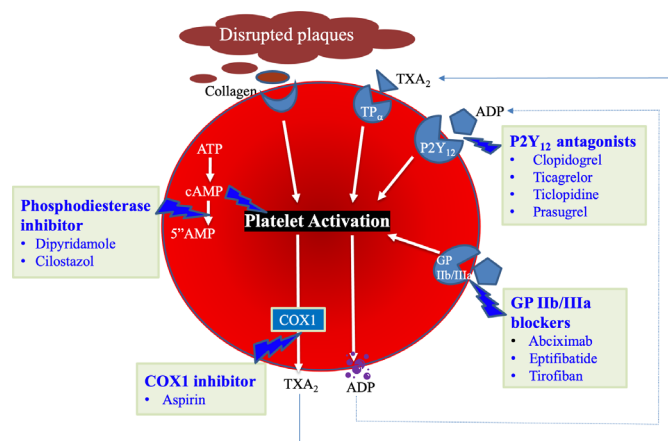
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**Figure 1** The mechanisms of antiplatelet agents. Aspirin irreversibly inhibits cyclooxygenase 1 (COX1) activity. Clopidogrel and ticagrelor blocks ADP receptor. Dipyridamole and cilostazol inhibits phosphodiesterase, thereby increasing cAMP levels and preventing platelet activation. ADP, adenosine diphosphate; COX, cyclooxygenase; GP, glycoprotein; TXA<sub>2</sub>, thromboxane A<sub>2</sub>.

risk reduction of vascular event in patients with history of AIS or TIA.

Table 1 lists the key RCTs of antiplatelet agents for stroke prevention. The International Stroke Trial (IST) randomised patients to aspirin 300 mg daily, subcutaneous heparin, both or neither within 48 hours of ischaemic stroke for up to 2 weeks.<sup>12</sup> The aspirin group had significantly fewer recurrent ischaemic stroke (2.8% vs 3.9%,  $p < 0.001$ ) but equal rates of haemorrhage. The Chinese Acute Stroke Trial was similar in design except for a different aspirin dose (160 mg daily) and duration (4 weeks).<sup>13</sup> There were significantly lower absolute risk of recurrent ischaemic stroke in the aspirin group (1.6% vs 2.1%,  $p = 0.01$ ). In a Cochrane systematic review of 8 RCTs with 41 483 participants on oral antiplatelet therapy for stroke prevention, aspirin 160–300 mg daily, started within 48 hours of stroke onset, reduced the risk of early recurrent ischaemic stroke without significant risk of haemorrhagic complications.<sup>5</sup>

#### Dipyridamole and aspirin/dipyridamole

Dipyridamole inhibits phosphodiesterase and platelet activation.<sup>14</sup> European Stroke Prevention Study (ESPS) randomised patients with either stroke or TIA within 3 months to receive aspirin/dipyridamole (325 mg/75 mg) or placebo three times a day.<sup>15</sup> The treatment group was associated with 33% relative risk reduction in stroke and death. ESPS-2 randomised patients with TIA or ischaemic stroke within 3 months to either aspirin 25 mg two times a day, dipyridamole 200 mg two times a day, aspirin/dipyridamole or placebo.<sup>16</sup> Compared with placebo, relative stroke risk was significantly reduced by 18%, 16% and 37%, respectively, suggesting a synergistic effect from combination therapy.

There was no significant difference in risk of bleeding between aspirin and combination therapy group.

The main side effects of dipyridamole were headache and diarrhoea.

European Stroke Prevention in Reversible Ischaemia Trial randomised patients with TIA or minor stroke within 6 months to either aspirin/dipyridamole or aspirin.<sup>17</sup> The dose of aspirin ranged from 30 to 325 mg, with majority receiving 30 mg daily. Aspirin/dipyridamole therapy was associated with an absolute risk reduction of 1% per year, corresponding to a number needed to treat of 104 to prevent 1 stroke, death or myocardial infarction. Of note, 34% of patients discontinued aspirin/dipyridamole due to side effects, mostly headache.

The Prevention Regimen for Effectively Avoiding Second Strokes trial randomised patients to either aspirin/dipyridamole or clopidogrel.<sup>18</sup> At a mean 2.5 years follow-up, there was no significant difference in recurrent stroke (9% vs 8.8%) between the two groups.

Aspirin/dipyridamole has been rarely used due to high cost and significant side effect.

#### Cilostazol

Cilostazol also inhibits phosphodiesterase and platelet aggregation.<sup>19</sup> CSPS randomised patients with recent stroke to cilostazol 100 mg two times daily or placebo.<sup>19</sup> Cilostazol was associated with a relative stroke risk reduction by 41.7% ( $p = 0.015$ ). In CSPS-2 trial,<sup>20</sup> 2757 patients were randomised to receive cilostazol 100 mg two times daily ( $n = 1379$ ) or aspirin 81 mg daily ( $n = 1378$ ). At mean 29-month follow-up, cilostazol group had a 34% relative risk reduction in cerebral infarction than aspirin group (2.76% vs 3.71%,  $p = 0.0357$ ) and lower haemorrhagic events (0.77% vs 1.78%;  $p = 0.0004$ ).

CSPS.com (CSPS for antiplatelet Combination) evaluated the efficacy of cilostazol and either aspirin or clopidogrel versus either aspirin or clopidogrel monotherapy.<sup>21</sup> Patients with ischaemic stroke within the previous 6 months were eligible for enrolment if at least two vascular risk factors were present and at least 50% stenosis of either an extracranial or intracranial artery. Dual-antiplatelet therapy (DAPT) was found to be superior to single-antiplatelet therapy (SAPT) in annual rate of ischaemic stroke (2.2% vs 4.5%,  $p = 0.001$ ). There was no significant difference in life-threatening bleeding between the two groups. In a systemic review and meta-analysis of RCTs,<sup>22</sup> cilostazol was shown to have lower rates of recurrent ischaemic stroke, haemorrhages or deaths, but higher rates of headache, palpitations and discontinuation than placebo, aspirin or clopidogrel.

Of note, essentially all clinical trials on cilostazol were conducted in Asia and results have not been replicated in other ethnic populations.<sup>22</sup>

#### Ticlopidine

Ticlopidine was the first developed ADP receptor (P2Y<sub>12</sub>) antagonist.<sup>23</sup> However, due to serious adverse effects, including hepatotoxicity and bone marrow suppression, it is not used in clinical practice.

**Table 1** Landmark randomised controlled trials evaluating antiplatelet therapy in secondary stroke prevention

Study	Study population	Trial design	Mean follow-up	Outcomes
IST (1997) <sup>12</sup>	19 435 patients with AIS within 48 hours of symptom onset in 36 countries	Randomised to aspirin 300 mg daily, subcutaneous heparin, both or neither for up to 14 days.	6 months	Rate of dependence at 6 months (aspirin vs no aspirin): 62.2% vs 63.5%, $p=0.07$ . Ischaemic stroke at 14 days (aspirin vs no aspirin): 2.8% vs 3.9%, $p<0.001$ .
CAST (1997) <sup>13</sup>	21 106 patients with AIS were treated within 48 hours of symptom onset in China	Aspirin 160 mg vs placebo for up to 4 weeks	4 weeks	Mortality (aspirin vs placebo): 3.3% vs 3.9%, $p=0.04$ . Recurrent ischaemic stroke (aspirin vs placebo): 1.6% vs 2.1%, $p=0.01$ .
ESPS (1987) <sup>15</sup>	2500 patients with recent ischaemic stroke or TIA in Europe	Dipyridamole 75 mg plus aspirin 325 mg or placebo three times daily	2 years	Stroke and death (dipyridamole/aspirin vs placebo): 33% relative risk reduction ( $p<0.01$ ).
ESPS-2 (1996) <sup>16</sup>	6600 patients with prior stroke or TIA within 3 months in Europe	Aspirin 25 mg two times daily, dipyridamole 200 mg two times daily, dipyridamole/aspirin or placebo	2 years	Relative stroke risk reduction compared with placebo: aspirin 18% ( $p=0.013$ ), dipyridamole 16% ( $p=0.039$ ), combination 37% ( $p \leq 0.001$ )
ESPRIT (2006) <sup>17</sup>	2739 patients with TIA/minor stroke within 6 months	Aspirin 30–325 mg daily plus dipyridamole 200 mg two times daily vs aspirin	3.5 years	The composite of death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction or major bleeding complication (Aspirin/dipyridamole vs aspirin): 12.7% vs 15.7%, HR: 0.80, 95% CI 0.66 to 0.98.
PRoFESS (2008) <sup>18</sup>	20 332 patients with ischaemic stroke within 90 days of randomisation and an age of 50 years or older.	Aspirin/dipyridamole (25/200 mg) two times daily vs clopidogrel 75 mg daily	2.5 years	First recurrence of stroke (aspirin/dipyridamole vs clopidogrel): 9.0% vs 8.8%; $p=NS$ . Risk of major haemorrhage: 4.1% vs 3.6%, $p=NS$ .
CSPS (2000) <sup>19</sup>	1095 with ischaemic stroke within 1–6 months in Japan	Cilostazol 100 mg two times daily vs placebo	1.5 years	Ischaemic stroke relative risk reduction (cilostazol vs placebo): 41.7% (95% CI 9.2% to 62.5%; $p=0.015$ )
CSPS-2 (2010) <sup>20</sup>	2757 patients with a cerebral infarction within previous 26 weeks in Japan	Cilostazol 100 mg two times daily vs aspirin 81 mg	29 months	Recurrence of cerebral infarction (cilostazol vs aspirin): 2.76% vs 3.71%, $p=0.0357$ . Haemorrhage: 0.77% vs 1.78%; $p=0.0004$ .
CSPS.com (2019) <sup>21</sup>	1879 patients with recent ischaemic stroke and either at least 50% stenosis or more than two vascular risk factors	Aspirin 81 mg or clopidogrel 75 mg and cilostazol 100 mg two times daily vs aspirin or clopidogrel	1.4 years	Annual rate of recurrent stroke (DAPT vs SAPT): 2.2% vs 4.5%, HR 0.49 (95% CI 0.31 to 0.76; $p=0.001$ )
CAPRIE (1996) <sup>24</sup>	19 185 patients with either recent ischaemic stroke or myocardial infarction	Clopidogrel 75 mg vs aspirin 325 mg daily	1.9 years	Annual rate of ischaemic stroke, myocardial infarction or cardiovascular death (Clopidogrel vs aspirin): 5.32% vs 5.83%, $p=0.043$ .
SOCRATES (2016) <sup>25</sup>	13 199 patients with recent stroke or high-risk TIA within previous 24 hours	Ticagrelor 90 mg two times daily vs aspirin 100 mg daily	4 months	Rate of recurrent stroke, myocardial infarction or death (Ticagrelor vs aspirin): 6.7% vs 7.5%, $p=0.07$ . Rate of ischaemic stroke: 5.8% vs 6.7%; $p=0.046$ .

AIS, acute ischaemic stroke; CAPRIE, Clopidogrel vs Aspirin in Patients at Risk of Ischaemic Events; CAST, Chinese Acute Stroke Trial; CSPS, Cilostazol stroke prevention study; DAPT, dual-antiplatelet therapy; ESPRIT, European Stroke Prevention in Reversible Ischaemia Trial; ESPS, European Stroke Prevention Study 2; IST, International Stroke Trial; NS, not significant; PRoFESS, Prevention Regimen for Effectively Avoiding Second Strokes; SAPT, single-antiplatelet therapy; SOCRATES, Acute Stroke or Transient Ischaemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes; TIA, transient ischaemic attack.

### Clopidogrel

Clopidogrel is a thienopyridine that blocks ADP receptor P2Y<sub>12</sub> and interferes with platelet cross-linking and aggregation.<sup>23</sup> The Clopidogrel vs Aspirin in Patients at Risk of Ischaemic Events trial randomised patients with stroke, myocardial infarction or peripheral vascular disease to either aspirin 325 mg or clopidogrel 75 mg daily.<sup>24</sup> The clopidogrel group had a significantly lower annual rate of vascular event than the aspirin group (5.32% vs 5.83%,  $p=0.043$ ). Of note, the relative risk reduction in patients with prior stroke was 7.3% and not statistically significant. Haemorrhage risks were similar between the two groups.

Therefore, clopidogrel is considered a good option for secondary stroke prevention.

### Ticagrelor

Ticagrelor is a new generation P2Y<sub>12</sub> receptor antagonist. It is not dependent on hepatic activation and has a more potent antiplatelet effect.<sup>25</sup> The Acute Stroke or Transient Ischaemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes trial randomised patients with minor stroke (National Institutes of Health Stroke Scale (NIHSS) score <5) or high-risk TIA within 24 hours to either ticagrelor 90 mg two times a day or aspirin 100 mg

daily for 90 days.<sup>25</sup> There was no significant difference in the rate of stroke, myocardial infarction or death between the two groups (6.7% vs 7.5%; HR 0.89;  $p=0.07$ ). Haemorrhage risk was also similar. Of note, ticagrelor had a 17.5% discontinuation rate primarily due to dyspnoea and bleeding. A subgroup analysis showed that ticagrelor was superior to aspirin in patients with ipsilateral atherosclerotic stenosis.<sup>26</sup>

### Glycoprotein IIb/IIIa antagonists

Glycoprotein IIb/IIIa receptor antagonists, including abciximab, eptifibatid and tirofiban, represent a unique class of antiplatelet agents. Abciximab is a chimeric mouse/human monoclonal antibody with high affinity for the platelet glycoprotein IIb/IIIa receptor.<sup>27</sup> It was used as an adjunct to thrombolysis or endovascular procedures. Abciximab in Emergency Treatment of Stroke Trial evaluated the efficacy and safety of abciximab in patients with AIS within 5 hours of symptoms onset. It was terminated early after 808 enrolments due to an unfavourable benefit–risk profile.<sup>28</sup> There was significantly higher rate of symptomatic or fatal intracranial haemorrhage in the abciximab group (5.5% vs 0.5%;  $p=0.002$ ) without significant outcome benefit (32% vs 33%;  $p=0.944$ ). Therefore, glycoprotein IIb/IIIa antagonists for patients with AIS is harmful and should not be used for stroke prevention.<sup>10</sup>

### Dual-antiplatelet therapy

The key RCTs investigating the efficacy of DAPT in secondary stroke prevention are listed in [table 2](#). Management of Atherosclerosis with Clopidogrel in High-Risk Patients trial randomised patients with recent ischaemic stroke or TIA to either clopidogrel 75 mg or aspirin 75 mg and clopidogrel 75 mg daily for 18 months.<sup>29</sup> There was a non-significant difference in primary outcomes (15.7% vs 16.7%) but a significantly higher risk of life-threatening bleeding in the DAPT group (2.6% vs 1.3%).

Subsequently, Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilisation, Management and Avoidance and SPS3 (Stroke Prevention of Small Subcortical Strokes) showed no difference in stroke recurrence but higher risk of bleeding in the DAPT group in patients with atherosclerotic risk factors or lacunar stroke, respectively.<sup>30 31</sup>

Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) evaluated DAPT for 21 days in Chinese population with high-risk TIA or minor ischaemic stroke within 24 hours of symptom onset.<sup>32</sup> A total of 5170 patients were randomised to either clopidogrel (300 mg on day 1, followed by 75 mg daily) for 90 days plus aspirin 75 mg daily for the first 21 days or placebo plus aspirin 75 mg daily for 90 days. DAPT group had a significantly lower rate of ischaemic or haemorrhagic stroke at 90 days than aspirin group (8.2% vs 11.7%, HR 0.68;  $p<0.001$ ). The absolute risk reduction was 3.5%. There was no significant difference in the rate of haemorrhage between the two groups. The benefit persisted during 1-year follow-up.<sup>33</sup>

To determine if the results transcend to a broader population, POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischaemic Stroke) trial was conducted in North America, Europe, Australia and New Zealand.<sup>34</sup> It showed a significant risk reduction in recurrent ischaemic events (5.0% vs 6.5%,  $p=0.02$ ) but increased rate of bleeding (0.9% vs 0.4%,  $p=0.02$ ) with DAPT. Of note, there were some differences in the study design between POINT and CHANCE. The POINT trial included a higher loading dose of clopidogrel (600 mg) and longer DAPT duration (90 days). These differences may explain the increased risk of bleeding in the POINT trial.

The (Acute Stroke or Transient Ischaemic Attack Treated with Ticagrelor and ASA for Prevention of Stroke and Death) trial randomised patients with a mild-to-moderate acute noncardioembolic ischaemic stroke (NIHSS score  $\leq 5$ ) or TIA within 24 hours of symptom onset to either ticagrelor plus aspirin or placebo plus aspirin for 30 days.<sup>35</sup> There were significant lower rates of stroke or death (5.5% vs 6.6%, HR, 0.83; 95% CI 0.71 to 0.96;  $p=0.02$ ) and ischaemic stroke (5.0% vs 6.3%, HR, 0.79; 95% CI, 0.68 to 0.93;  $p=0.004$ ), but higher rate of severe bleeding (0.5% vs 0.1%,  $p=0.001$ ) in the DAPT group. Exploratory analysis showed that ticagrelor plus aspirin was associated with lower rate of disabling stroke or death than aspirin alone (4.0% vs 4.7%,  $p=0.001$ ).<sup>36</sup> For every 1000 patients, DAPT would prevent 11 strokes or deaths at the cost of four severe haemorrhages. The number needed to treat to benefit one patient is 143. In subgroup analysis of patients with ipsilateral atherosclerotic stenosis, ticagrelor plus aspirin was associated with lower rate of stroke or death than aspirin alone (8.1% vs 10.9%,  $p=0.023$ ), resulting in a number needed to treat of 34 (95% CI 19 to 171).<sup>37</sup>

Stenting vs Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial compared medical therapy with intracranial stenting.<sup>38</sup> Patients with a TIA or stroke attributed to 70%–99% stenosis of an intracranial artery were randomised to aggressive medical management with aspirin 325 mg and clopidogrel 75 mg daily for 3 months vs angioplasty and stenting plus aggressive medical management. The study was stopped early after enrolment of 450 patients due to a higher 30-day rate of stroke and death in the stenting group (14.7% vs 5.8%,  $p=0.002$ ) primarily due to periprocedural complications. At a median follow-up of 32.4 months, the risk of stroke or death was 23% in the stenting group vs 15% in the medical group.<sup>39</sup> These results supported the use of DAPT for 90 days in patients with symptomatic high-grade intracranial stenosis.<sup>10</sup>

CHANCE-2 trial randomised 6412 patients with a minor ischaemic stroke or TIA and CYP2C19 loss-of-function alleles to aspirin for 21 days plus ticagrelor or clopidogrel for 90 days.<sup>40</sup> The risk of new stroke at 90 days was modestly lower in ticagrelor group (6.0% vs 7.6%,  $p=0.008$ ). There was no difference in rate of severe or moderate bleeding between the two groups (0.3% vs 0.3%), but ticagrelor

**Table 2** Randomised controlled trials evaluating dual-antiplatelet therapy (DAPT) in secondary stroke prevention

Study	Study population	Trial design	Mean follow-up	Outcomes
MATCH (2004) <sup>29</sup>	7599 patients with ischaemic stroke or TIA within 3 months	Aspirin 75 mg daily plus clopidogrel 75 mg daily or placebo plus clopidogrel 75 mg daily	18 months	Rate of primary endpoints (aspirin plus clopidogrel vs clopidogrel): 15.7% vs 16.7%, $p=0.244$ . Rate of life-threatening bleeding: 2.6% vs 1.3%, $p<0.0001$
CHARISMA (2006) <sup>30</sup>	15 603 patients with cerebrovascular disease or multiple risk factors	Aspirin 75–162 mg daily plus clopidogrel 75 mg daily or aspirin 75–162 mg daily plus placebo	2.3 years	Rate of stroke, myocardial infarction or death Aspirin plus clopidogrel vs aspirin): 6.8% vs 7.3%, $p=0.22$ Rate of stroke 1.9% vs 2.4%, $p=0.03$ Rate of moderate bleeding: 2.1% vs 1.3, $p<0.001$
SPS3 (2012) <sup>31</sup>	3020 patients with lacunar infarcts within 180 days (n=3020)	Aspirin 325 mg daily plus clopidogrel 75 mg daily or aspirin 325 mg daily plus placebo	3.4 years	Rate of primary outcome of ischaemic or haemorrhagic stroke: 2.5% (dual) vs 2.7% (aspirin), HR 0.92, 95% CI 0.72 to 1.16, $p=0.48$
CHANCE (2013) <sup>32</sup>	5170 patients with minor ischaemic stroke or high-risk TIA within 24 hours of symptom onset in China.	Clopidogrel 300 mg on day 1 followed by 75 mg daily for 90 days, plus aspirin 75 mg daily for 21 days or placebo plus aspirin 75 mg daily for 90 days.	90 days	Ischaemic or haemorrhagic stroke (Clopidogrel plus aspirin vs aspirin): 8.2% vs 11.7%; HR 0.68, 95% CI 0.57 to 0.81, $p\leq 0.001$ . Severe or moderate bleeding: 0.3% vs 0.3%.
POINT (2018) <sup>34</sup>	4881 patients with minor ischaemic stroke or TIA within 12 hours	Clopidogrel 600 mg loading followed by 75 mg daily for 90 days plus aspirin 50–325 mg daily or placebo plus aspirin daily for 90 days	90 days	Primary outcome of recurrent stroke, death, myocardial infarction (Clopidogrel plus aspirin vs aspirin): 5.0% (dual) vs 6.5% (aspirin), $p=0.02$ Risks of major haemorrhage: 0.9% (dual) vs 0.4% (aspirin), $p=0.02$
THALES (2020) <sup>35</sup>	11 016 patients with mild-to-moderate acute non-cardioembolic ischaemic stroke, with an NIHSS score $\leq 5$ or TIA within 24 hours after symptoms onset	Ticagrelor 180 mg loading dose followed by 90 mg two times daily plus aspirin 300–325 mg on day 1 followed by 75–100 mg daily or matching placebo plus aspirin.	30 days	Primary outcome of stroke or death (Ticagrelor plus aspirin vs aspirin): 5.5% vs 6.6%, $p=0.02$ . Ischaemic stroke: 5.0% vs 6.3%, $p=0.004$ . Incidence of disability: no difference Severe bleeding: 0.5% vs 0.1%, $p=0.001$ .
SAMMPRIS (2011) <sup>38 39</sup>	451 patients with stroke within 30 days due to 70%–99% stenosis of intracranial artery	Aspirin 325 mg daily plus clopidogrel 75 mg daily or stenting plus aspirin and clopidogrel	90 days	Rate of stroke or death within 30 days (DAPT vs stenting plus DAPT): 5.8% vs 14.7%; $p=0.002$ . Ischaemic stroke or death at year 3: 14.9% vs 23.9%, $p=0.0193$ .
CHANCE-2 (2021) <sup>40</sup>	6412 patients with a minor ischaemic stroke or TIA and CYP2C19 loss-of-function alleles within 24 hours of symptom onset.	Ticagrelor 180 mg on day 1 followed by 90 mg two times daily or Clopidogrel 300 mg on day 1 followed by 75 mg daily. Both groups received aspirin 75 mg daily for 21 days.	90 days	New stroke (Ticagrelor plus aspirin vs clopidogrel plus aspirin): 6.0% vs 7.6%; HR 0.77, 95% CI 0.64 to 0.94, $p=0.008$ . Severe or moderate bleeding: 0.3% vs 0.3%.

Continued

Table 2 Continued

Study	Study population	Trial design	Mean follow-up	Outcomes
TARDIS (2018) <sup>41</sup>	3096 patients with ischaemic stroke or TIA within 48 hours after symptom onset	Aspirin (300 mg load, 75 mg daily)+clopidogrel (300 mg load, 75 mg daily)+dipyridamole 200 mg two times daily vs either clopidogrel alone or combined aspirin and dipyridamole).	90 days	The incidence of recurrent stroke or TIA (Triple therapy vs clopidogrel or Aggrenox): 6% vs 7%; adjusted OR 0.90, 95% CI 0.67 to 1.20, p=0.47. Severe bleeding: 3% vs 1%; adjusted OR 2.54, 95% CI 2.05 to 3.16, p<0.0001.

CHANCE-2, Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events; CHARISMA, Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilisation, Management and Avoidance; MATCH, Management of Atherosclerosis with Clopidogrel in High-Risk Patients; NIHSS, National Institutes of Health Stroke Scale; POINT, Platelet-Oriented Inhibition in New TIA; SAMMPRIS, Stenting vs Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis; THALES, Transient Ischaemic Attack Treated with Ticagrelor and ASA for Prevention of Stroke; TIA, transient ischaemic attack; TRADIS, Therapy with Dipyridamole in Patients with Acute Cerebral Ischaemia.

was associated with more total bleeding events (5.3% vs 2.5%).

The Antiplatelet Therapy with Aspirin, Clopidogrel and Dipyridamole vs Clopidogrel Alone or Aspirin-Dipyridamole in Patients with Acute Cerebral Ischaemia trial compared triple antiplatelet therapy versus SAPT.<sup>41</sup> After randomising 3096 patients within 48 hours of AIS or TIA, the trial was stopped early due to significantly more bleeding in the triple therapy group (20% vs 9%, p<0.001) without a decrease in recurrent stroke or TIA within 90 days (6% vs 7%, p=0.47). Therefore, triple antiplatelet therapy is harmful and should not be used for stroke prevention.<sup>10 41</sup>

Cochrane systematic review, pooled data analysis and meta-analysis of RCTs demonstrated that DAPT with aspirin and clopidogrel or ticagrelor for 21–30 days is more effective than SAPT for secondary stroke prevention when initiated early after the onset of minor stroke or high-risk TIA.<sup>3 6–9</sup> However, when initiated later and used longer than 90 days, DAPT increases the risk of bleeding without reduction of stroke recurrence than SAPT.<sup>7–9</sup>

## Recommendations

The current evidence-based recommendations on antiplatelet therapy for secondary stroke prevention are summarised in table 3.<sup>3–10</sup>

## Special considerations

### Antiplatelet therapy after intracerebral haemorrhage

Restart or Stop Antithrombotics Randomised Trial (RESTART) compared starting vs avoiding antiplatelet agent after intracerebral haemorrhage (ICH).<sup>42</sup> At a median 3-year follow-up of 537 participants, there was no significant difference in recurrent ICH (8.2% vs 9.3%, p=0.64) or major vascular events (26.8% vs 32.5%, p=0.14) between two groups.

Restarting antiplatelet therapy after ICH should be considered, particularly in patients with high-risk thromboembolic conditions.

## Antiplatelet resistance

One-third of patients who had a stroke may develop recurrent stroke while on antiplatelet therapy, partly due to aspirin or clopidogrel resistance.<sup>43–45</sup> In the laboratory studies, aspirin resistance is defined as a failure to achieve reduction in TXA<sub>2</sub> formation.<sup>44</sup> Clopidogrel resistance refers to the inability to inhibit ADP-mediated platelet aggregation.<sup>45</sup>

The most common cause of inadequate antiplatelet therapy is non-compliance.<sup>46 47</sup> Approximately 50% of patients either stop taking medication or fail to adhere to the prescribed dose at 1 year.

Potential drug interactions may also result in reduced effect of antiplatelet therapy. Concomitant use of NSAIDs, particularly ibuprofen, offsets the clinical benefit of aspirin.<sup>48</sup> Proton-pump inhibitors (PPIs) inactivates the hepatic enzyme that converts clopidogrel to its active metabolite. Therefore, concomitant use of PPIs may decrease clopidogrel's effect.<sup>49</sup>

Clopidogrel resistance has also been linked to gene polymorphisms.<sup>50</sup> Clopidogrel is a prodrug that requires conversion into active metabolite by hepatic CYP2C19. The prevalence of poor metabolisers (subjects carrying two loss-of-function alleles) is as high as 58.8% among Asians.<sup>51</sup>

## PERSPECTIVES

Many challenges remain for the selection of optimal antiplatelet therapy in the real-world practice. Currently, we are still uncertain about the best antiplatelet therapy in different ethnic populations. For example, is cilostazol equally effective in blacks or whites as in Asians? We also need to know the best dose of medications, best combination and duration of DAPT among patients with diverse comorbidities, multiple vascular risk factors, high body mass index, CYP2C19 loss-of-function gene mutations or stroke recurrence while on antiplatelet therapy.

Ticagrelor does not need hepatic activation and was shown to be more effective than aspirin in patients with

**Table 3** Current guidelines on the use of antiplatelet therapy for secondary stroke prevention<sup>2 10</sup>

Noncardioembolic ischaemic stroke or TIA	<ol style="list-style-type: none"> <li>The use of antiplatelet agents is indicated to reduce the risk of recurrent ischaemic stroke and other cardiovascular events (class 1/Level A).               <ul style="list-style-type: none"> <li>Aspirin 50–325 mg daily (1/A) or aspirin 25 mg/extended-release dipyridamole 200 mg two times daily (1/B)</li> <li>Clopidogrel 75 mg daily (2 a/B).</li> </ul> </li> <li>For patients with minor-to-moderate acute noncardioembolic ischaemic stroke or high-risk TIA, DAPT (aspirin and clopidogrel or ticagrelor in carriers of <i>CYP2C19</i> loss-of-function alleles) should be started within 24 hours for 21–30 days, followed by SAPT (1/A).</li> <li>Long term use of DAPT increases the risk of haemorrhage and is not recommended (3/A)</li> <li>Triple antiplatelet therapy (aspirin +clopidogrel + aspirin/dipyridamole) for secondary stroke prevention is harmful and should not be used (III harm/B-R).</li> </ol>
Intracranial large artery atherosclerosis	<ol style="list-style-type: none"> <li>In patients with AIS or TIA caused by 50% to 99% stenosis of a major intracranial artery, aspirin 325 mg daily is recommended in preference to warfarin to reduce the risk of recurrent ischaemic stroke and vascular death (1/B).<sup>56</sup></li> <li>In patients with 70%–99% stenosis of a major intracranial artery, the addition of clopidogrel 75 mg daily to aspirin for up to 90 days is reasonable (2 a/B).</li> <li>In patients with recent minor stroke or high-risk TIA and concomitant ipsilateral &gt;30% intracranial stenosis, the addition of ticagrelor 90 mg two times a day to aspirin for 30 days might be considered to reduce recurrent stroke risk (2b/B).</li> <li>In patients with stroke or TIA attributable to 50%–99% intracranial stenosis, the addition of cilostazol 200 mg/day to aspirin or clopidogrel might be considered (2b/C).<sup>10 57 58</sup></li> </ol>
Extracranial carotid or vertebral artery stenosis	Aspirin, clopidogrel or aspirin-dipyridamole is recommended indefinitely (1/A). <sup>10 59</sup>
Extracranial carotid or vertebral arterial dissection	In patients with ischaemic stroke or TIA, treatment with antiplatelet or anticoagulation therapy for at least 3 months is indicated to prevent recurrent stroke or TIA (I/ C). <sup>50</sup>
Aortic arch atherosclerosis	In patients with an aortic arch atheroma, antiplatelet therapy is recommended to prevent recurrent stroke (1/C). <sup>10 29 52</sup>
Moyamoya disease	The use of aspirin monotherapy may be reasonable for the prevention of ischaemic stroke or TIA (2b/C).
Carotid web	In patients with carotid web in the distribution of ischaemic stroke and TIA, antiplatelet therapy is recommended to prevent recurrent ischaemic stroke or TIA (1/B)
Dolichoectasia	In patients with vertebrobasilar dolichoectasia, the use of antiplatelet or anticoagulant therapy is reasonable for the prevention of recurrent ischaemic events (2 a/ C).
Fibromuscular dysplasia	In patients with fibromuscular dysplasia (FMD), antiplatelet therapy is recommended for the prevention of future ischaemic events (1/C).
Antiphospholipid syndrome	In patients with isolated antiphospholipid antibody, antiplatelet therapy is recommended to reduce the risk of recurrent stroke (1/B).
Haematologic traits	In patients with prothrombin 20210A mutation, activated protein C resistance, elevated factor VIII levels or deficiencies of protein C, protein S or antithrombin III, antiplatelet therapy is reasonable for prevention of recurrent stroke or TIA (2 a/C)
Embolic stroke of undetermined source (ESUS)	In patients with ESUS, treatment with ticagrelor or direct oral anticoagulants is not recommended to reduce the risk of stroke (3/B)
Atrial fibrillation and CAD	The usefulness of adding antiplatelet therapy to anticoagulation therapy is uncertain for reducing the risk of ischaemic stroke (2b/C).

AF, atrial fibrillation; AIS, acute ischaemic stroke; CAD, coronary artery disease; CAS, carotid artery stenting; CEA, carotid endarterectomy; DAPT, dual-antiplatelet therapy.

aortic arch and intracranial atherosclerotic disease.<sup>26 37 52</sup> However, in patients with high risk of bleeding, cilostazol or aspirin-dipyridamole may be better option.<sup>17 21 22</sup>

A common clinical practice is increasing the dose of aspirin or choosing a different antiplatelet agent after a recurrent TIA or AIS while on aspirin.<sup>53</sup> However, systematic review and meta-analysis did not show effectiveness of increasing the dose of aspirin or changing to another antiplatelet medication.<sup>54</sup>

Selecting of appropriate antiplatelet agent should also be based on compliance, drug tolerance or resistance.

In a systematic review and meta-analysis, *CYP2C19* loss-of-function alleles were found in 25% of white patients and in 60% of Asian patients.<sup>55</sup> Among 15 studies of

4762 patients with stroke or TIA treated with clopidogrel, carriers of *CYP2C19* loss-of-function alleles were at greater risk of stroke in comparison with noncarriers (12.0% vs 5.8%; risk ratio, 1.92, 95% CI 1.57 to 2.35;  $p < 0.001$ ). Therefore, patients with ischaemic stroke or TIA may need *CYP2C19* gene test. In carriers of *CYP2C19* loss-of-function alleles, ticagrelor is preferred to clopidogrel for secondary stroke prevention.<sup>40</sup>

Additional RCTs are warranted to evaluate *CYP2C19* gene testing-based antiplatelet therapy for stroke prevention: (1) Ticagrelor plus aspirin versus clopidogrel plus aspirin for patients with symptomatic intracranial stenosis and (2) Ticagrelor plus aspirin vs ticagrelor in patients

with symptomatic intracranial stenosis or chronic large vessel occlusion.

## CONCLUSION

SAPT is indicated for secondary stroke prevention in most patients with noncardioembolic ischaemic stroke or TIA. DAPT with aspirin and clopidogrel or ticagrelor for 21–30 days is more effective than SAPT for secondary stroke prevention when initiated early after minor noncardioembolic stroke or high-risk TIA. Aspirin is appropriate and cost-effective in antiplatelet naïve patients. Cilostazol, as off-label treatment, would be attractive alternative for patients with high risk for haemorrhage. In patients with intracranial stenosis, the addition of ticagrelor or cilostazol to aspirin for up to 30 days might reduce recurrent stroke risk. Ticagrelor might be preferred to clopidogrel in patients with CYP2C19 loss of function alleles.

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