REVIEW

Dual Antiplatelet Therapy of Clopidogrel and Aspirin in Secondary Prevention of Ischemic Stroke: Evidence and Indications

Ya Su, Xin Cheng & Qiang Dong

Department of Neurology, Huashan Hospital, State Key Laboratory of Medical Neurobiology, Fudan University, Shanghai, China

Keywords

Aspirin; Clopidogrel; Dual antiplatelet therapy; Ischemic stroke.

Correspondence

Xin Cheng, M.D., Ph.D. and Qiang Dong, M.D., Ph.D., Department of Neurology, Huashan Hospital, State Key Laboratory of Medical Neurobiology, Fudan University, 12 Wulumuqi Zhong Road, Shanghai 200040, China.

Tel.: +86-21-52887140;

Fax: +86-21-62481088;

E-mails: chengxincn@hotmail.com,

qiang_dong163@163.com

Received 25 March 2015; revision 18 May

2015; accepted 19 May 2015

SUMMARY

Nowadays the dual antiplatelet therapy (DAPT) becomes more widely used in patients with ischemic stroke. Nevertheless, controversies exist for indications of DAPT. In view of evidence-based medicine analysis, patients with high-risk transient ischemic attack and minor stroke, severe symptomatic intracranial artery stenosis, symptomatic intracranial and extracranial artery stenosis causing artery-to-artery embolism, ischemic stroke attributed to aortic arch plaques, high-risk atrial fibrillation not suitable for oral anticoagulants, intracranial and extracranial stent implantation, and ischemic stroke with acute coronary syndrome may gain great benefit from DAPT of clopidogrel and aspirin. In clinical practice, individualized antiplatelet therapy strategies should be taken by weighing risks of ischemia and hemorrhage.

doi: 10.1111/cns.12419

Introduction and Background

Stroke ranked the second most common cause of death (10%) and the third of disability-adjusted life-years (4%) worldwide according to the findings from the Global Burden of Disease Study 2010 [1], 90% of which was ischemic stroke [2]. Arterial atherosclerosis accounts for the majority of ischemic stroke, in which the process of platelet activation and aggregation is considered to be a key point [3]. Antiplatelet drugs block various links in the thrombotic cascade and decrease the risk of vascular events in high-risk patients [4]. The Chinese Acute Stroke Trial (CAST) and International Stroke Trial (IST) have demonstrated a significant decrease in the rate of recurrence and mortality and no significant increase in the risk of hemorrhage with the use of aspirin within 48 h during the acute phase in ischemic stroke [5–7]. In the CAPRIE (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events) study, compared with aspirin, clopidogrel, one of the platelet purinergic receptor P2Y₁₂ inhibitors, greatly reduced the risk of the composite outcome of ischemic stroke, myocardial infarction (MI) or vascular deaths and the risk of nonfatal intracranial hemorrhage or hemorrhagic deaths in patients with symptomatic arterial atherothrombotic disease [8].

The secondary prevention strategy with one single antiplatelet drug of clopidogrel or aspirin does reduce, but not abolish, further events such as recurrent ischemic stroke. This “resistance phenomenon” suggests that blocking one target is far from cutting off the whole thrombotic process [9,10]. Dual antiplatelet drugs working on various thrombotic targets show higher antithrombotic efficacy. The combination therapy with clopidogrel and aspirin is the main drug used worldwide and provides definite clinical benefit, which has been the standard practice for acute coronary syndrome (ACS) [11].

Aims of the Review

Recently, some large randomized controlled trials (RCTs) that assess the effectiveness and safety of DAPT in specific populations with ischemic stroke have shown positive results. The aims of this review are to analyze the reasons for negative findings of some previous DAPT trials and list the proper patient population with ischemic stroke who may gain benefit from DAPT of clopidogrel and aspirin and their evidence-based medicine, in accordance with these RCTs, meta-analyses, and newest guidelines up to March 2015.

Reasons for Negative Results of Previous DAPT Trials

A meta-analysis included six RCTs, which were CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance), ESPRIT (European/Australasian Stroke Prevention in Reversible Ischaemia Trial), JASAP (Japanese Aggrenox Stroke Prevention vs. Aspirin Programme), MATCH (Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischaemic Attack or Ischaemic Stroke), PROFESS (Prevention Regimen for Effectively Avoiding Second Strokes), and SPS3 (Secondary Prevention of Small Subcortical Strokes). It showed no significantly reduced risks of recurrent stroke, but dramatically high risks of severe hemorrhage for long-term administration (more than 1 year) of DAPT with clopidogrel and aspirin versus monotherapy initiated within 1 week to 5 years in patients with ischemic stroke or transient ischemic attack (TIA) [12]. Oppositely, another meta-analysis consisted of 14 RCTs up to November 2012 and 9012 patients with acute noncardioembolic ischemic stroke or TIA who were treated with antiplatelet therapy within 3 days of ictus. There have been significant reductions in risks of stroke recurrence (relative risk [RR] 0.69, 95% confidence interval [CI] 0.60–0.80) and in the combined risks of stroke, TIA, ACS, or all deaths (RR 0.71, 95% CI 0.63–0.81), without a significant increase in risks of major bleeding (RR 1.35, 95% CI 0.70–2.59) for dual versus monotherapy [13].

By comparing the two analyses containing different types of population, we come to a conclusion that patients with ischemic stroke or TIA in the acute phase when the risk of recurrence is greatest benefit from DAPT, while those in the nonacute phase or with long-period administration may be not suitable for DAPT.

Patients with Noncardioembolic Ischemic Stroke

High-Risk TIA and Minor Stroke

Transient ischemic attack is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction [14]. High-risk TIA is ABCD² score of 4 or more, and minor ischemic stroke is NIHSS score of 3 or less [15]. Both of them are associated with extremely high risks of stroke recurrence especially in the initial 48 h after symptom onset, where early secondary prevention is supposed to be crucial and effective [16,17].

The Fast Assessment of Stroke and TIA to prevent Early Recurrence (FASTER) trial was a randomized controlled pilot trial of patients with minor stroke or TIA within 24 h of onset. A total of 392 patients were given clopidogrel 75 mg/day with a loading dose of 300 mg plus aspirin 81 mg/day or aspirin alone, and simvastatin 40 mg/day or placebo for 90 days. The rate of recurrent stroke was 7.1% for the combination therapy and 10.8% for aspirin with an absolute risk reduction (ARR) of –3.8% (95% CI –9.4 to 1.9, $P = 0.19$), and there was no significant difference in intracranial hemorrhage between groups ($P = 0.5$). This trial was stopped earlier due to the low rate of recruitment, but suggested

that for patients with TIA or minor stroke, there might be a net benefit for DAPT compared with monotherapy and simvastatin use acutely after stroke might attenuate the antiplatelet effect [18].

The results of Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial greatly favored short-course DAPT in the acute phase. A total of 5170 patients with high-risk TIA or minor stroke were randomized to receive either clopidogrel (300 mg loading dose plus 75 mg/day, for 90 days) and aspirin (75 mg/day, for 21 days) or aspirin (75 mg/day, for 90 days) in the initial 24 h since symptoms started. After 90 days' follow-up, a significant relative risk reduction (RRR) of 32% (hazard ratio [HR] 0.68, 95% CI 0.57–0.81, $P < 0.001$) in stroke recurrence was seen in the group of DAPT as compared with aspirin alone, without an increase in risks of severe or moderate hemorrhage ($P = 0.73$) or intracranial hemorrhage ($P = 0.98$) [19]. The meta-analysis combining the CHANCE study with 13 previous studies of other populations in the world showed consistent conclusions [13]. Later, glycated albumin level below the cut point of 15.5% implied an additional benefit of DAPT versus monotherapy, with a significant reduction in risks of stroke recurrence (adjusted HR 0.40, 95% CI 0.26–0.61, $P < 0.001$) and combined vascular events (adjusted HR 0.39, 95% CI 0.26–0.60, $P < 0.001$) and a nonelevated risk of bleeding (adjusted HR 1.87, 95% CI 0.71–4.92, $P = 0.204$) in a subgroup analysis of the CHANCE study with total 3044 patients [20]. This study showed that the level of glycated albumin could be a new biomarker in antiplatelet decision-making.

Unlike what had been found in ACS, both the results of 1 year of follow-up in CHANCE trial [21] and the other previous study [22] demonstrated that there was no transient rebound increase in the risk of recurrent stroke after discontinuation of a short-term course of clopidogrel in acute TIA or minor stroke. A pooled analysis based on EXPRESS (Early use of Existing Preventive Strategies for Stroke) and FASTER studies found that even on a 30- to 90-day course of antiplatelet therapy acutely after TIA or minor stroke, the major or life-threatening bleeding caused by DAPT was much more common than that by monotherapy in aspirin-naïve patients (4/137 vs. 0/273, $P = 0.01$), while the similar result was not seen in prior-aspirin patients (1/110 vs. 1/113, $P = 0.98$) [23]. The difference was partly due to the fact that the gastric mucosa in aspirin-naïve patients was much more susceptible to the impairment of prostaglandin E₂ and the anti-angiogenic activities of clopidogrel exacerbated the mucosal damage. However, the event rates of moderate or severe hemorrhage in CHANCE trial were much lower in both arms (7/2584 in the clopidogrel–aspirin group vs. 8/2586 in the aspirin group, $P = 0.73$) compared with those in EXPRESS and FASTER [19,23]. Although CHANCE investigators provided no information regarding the rate of bleeding event in aspirin-naïve patients, it would be advisable to recommend a shorter course of DAPT treatment (21 days) in high-risk TIA and minor stroke in order to minimize the risk of bleeding.

Severe Symptomatic Intracranial Artery Stenosis (sICAS)

Severe intracranial artery atherosclerosis (especially 70–99% stenosis of a major intracranial artery) is an important cause for

ischemic stroke and also a high-risk factor for stroke recurrence in TIA or ischemic stroke [24]. However, in the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial, the combined risk of stroke and intracranial hemorrhage or vascular deaths at 2 years were 22.1% and 21.8%, respectively, in patients with TIA or ischemic stroke attributed to angiographically verified 50–99% stenosis of a major intracranial artery who were treated with aspirin or warfarin, similar but extremely high [25].

Recent results of the Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) trial have provided new evidence for DAPT in this high-risk disease. This study was a randomized, multicenter clinical trial, recruiting 451 patients with TIA or nondisabling stroke within 30 days caused by angiographically verified 70–99% stenosis of a major intracranial artery. Two strategies emerged for the treatment: the aggressive medical group (clopidogrel 75 mg/day plus aspirin 325 mg/day for 90 days) and the aggressive medical therapy plus percutaneous transluminal angioplasty and stenting (PTAS) group, both with management of risk factors including systolic blood pressure <140 mmHg (<130 mmHg in patients with diabetes) and LDL-C < 1.81 mmol/L and lifestyle modification (control of the level of blood glucose and non-HDL, improvement of smoking, excess weight, and insufficient exercise). After a median follow-up of 2.7 years, the combined risks of stroke or death within 30 days, stroke in the territory of the qualifying artery beyond 30 days, or a revascularization procedure for the qualifying lesion during the follow-up period at 30 days, 1 year, and 3 years are 5.8%, 12.2%, and 14.9% for the aggressive medical group and 14.7%, 20.0%, and 23.9% for the PTAS group, all with significant differences ($P_1 = 0.002$, $P_2 = 0.009$, $P_3 = 0.0193$). And the aggressive medical group showed a decrease in risks of symptomatic intracranial hemorrhage at 30 days and in risks of major hemorrhagic events at 1 and 3 years ($P < 0.05$) [26,27]. By comparing patients in the SAMMPRIS trial with those in the WASID trial who matched the same inclusion criteria of SAMMPRIS trial, we found that the combination therapy strategy of DAPT, blood pressure control, intensified blood lipid reduction, and lifestyle improvement proved beneficial by greatly lowering risks of stroke or death from 25.0% to 12.2% at 1 year [27].

Symptomatic Intracranial and Extracranial Artery Stenosis Causing Artery-to-Artery Embolism

The artery-to-artery emboli caused by atherosclerotic plaque rupture and detachment contribute to noticeably elevated risks of ischemic stroke in patients with intracranial and extracranial artery stenosis. One prospective study conducted by Gao S has proved microembolic signals (MES) detected with transcranial Doppler (TCD) as an independent predictor for stroke recurrence [28]. As a noninvasive, *in vivo* surrogate marker, MES were applied to evaluate the effectiveness of antithrombotic drugs in many clinical trials [29,30].

The Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic carotid Stenosis (CARESS) trial recruited 107 patients with $\geq 50\%$ extracranial carotid stenosis, ipsilateral carotid territory TIA, or stroke and ≥ 1 MES identified with TCD. DAPT with clopidogrel and aspirin was superior to aspirin monotherapy in

significantly reducing the proportion of patients with MES positive (RRR 39.8%, $P = 0.0046$) and MES frequency per hour (RRR 61.4%, $P = 0.0013$) on day 7, while no significant difference was proved in the risk of recurrent stroke between two groups [31].

In the CLOpidogrel plus Aspirin for Infarction Reduction in acute stroke or transient ischemic attack patients with large artery stenosis and microembolic signals (CLAIR) trial, 100 patients with TIA or ischemic stroke in the initial 7 days of symptom onset, symptomatic large cerebral or carotid artery stenosis, and positive MES were treated with the combination of clopidogrel and aspirin or aspirin alone for 7 days. A total of 29.8% of patients in the DAPT group were detected MES positive with no stroke event, and 50.9% in the mono group were MES positive with two stroke events at day 2 (RRR 42.4%, $P = 0.025$). The incidence of ischemic stroke recurrence is too low to show differences. Side effects in two groups were similar with no severe intracranial or systemic hemorrhage [32].

One meta-analysis of the CARESS and CLAIR trials suggested that DAPT significantly decreased the number of patients with ≥ 1 MES at day 2 (RR 0.68, 95% CI 0.53–0.89) and day 7 (RR 0.54, 95% CI 0.40–0.75), compared with monotherapy. It was worth noting that the combination of both studies showed a significant reduction in risks of recurrent stroke by 6% ($P = 0.03$), which was not seen separately [32]. So for patients with intracranial and extracranial artery stenosis and positive MES, DAPT for 1 week was more beneficial than aspirin alone.

Ischemic Stroke Attributed to Aortic Arch Plaques

One of the most common sources of cerebral emboli is atherosclerosis in the aortic arch. It has been reported that the risk of recurrent stroke in patients with ischemic stroke and ≥ 4 mm atherosclerotic plaques is triple to quadruple higher than that in others [33]; however, high risks of recurrence were observed with single antiplatelet therapy [34].

Evidence to support the medication of DAPT comes exclusively from the recent Aortic Arch Related Cerebral Hazard (ARCH) trial. It compared DAPT of clopidogrel (75 mg/day) plus aspirin (75–150 mg/day) with warfarin (adjusted international normalized ratio [INR] 2.0–3.0) in 349 patients with nondisabling ischemic stroke, TIA, or peripheral embolism within 6 months and >4 mm plaques in the thoracic aorta without other identified embolic sources. After a median follow-up of 3.4 years, there was no significant difference in the primary endpoint of a composite of stroke, MI, peripheral embolism, vascular deaths, or intracranial hemorrhage, and only the risk of vascular death was proved significantly decreased ($P = 0.013$) in the DAPT versus warfarin therapy. There were similar risks of major hemorrhage between both groups. Because of 33 primary outcomes below expectations and long duration of recruitment (8.25 years), this trial lacked statistical power [35]. But in consideration of increasing risks of vascular deaths with well-conducted warfarin therapy and the complexity of INR-adjusted dosing, the antiplatelet strategy of DAPT for 90 days and clopidogrel monotherapy for long-term use may be more advisable in clinical practice.

Patients with Cardioembolic Ischemic Stroke

Atrial fibrillation (AF) tends to develop mural thrombi in the left atrium, increasing risks of vascular events especially ischemic stroke as the principal adverse consequence. As one choice of treatment for AF patients, oral anticoagulation therapy reduced the risk by 45% in stroke and 29% in cardiovascular events, with an elevated risk of major hemorrhage by 70%, compared with aspirin alone [36].

The Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE) W study enrolled 6706 AF patients plus at least one risk factor for stroke, trying to demonstrate the noninferiority of DAPT with clopidogrel (75 mg/day) and aspirin (75–100 mg/day) to warfarin (target INR of 2.0–3.0). It failed and was stopped earlier after a median time of 1.2 years, with a clear net benefit (primary outcome events of stroke, non-central nervous system systemic embolus, MI, and vascular deaths plus major hemorrhage) favoring oral anticoagulation therapy (RR 1.41, 95% CI 1.19–1.67, $P < 0.0001$). The occurrence of major and severe hemorrhage was similar between DAPT and warfarin groups [37].

Later, the ACTIVE A trial focused on the patient population with AF and high risks of stroke, but not suitable for oral anticoagulation therapy of a vitamin K antagonist. A total of 7554 patients were randomized to receive clopidogrel (75 mg/day) plus aspirin (75–150 mg/day) or aspirin for a median treatment time of 3.6 years. Compared with monotherapy, the DAPT provided an 11% RRR ($P = 0.01$) in a composite of major vascular events, primarily attributed to the decreased RR of stroke recurrence by 28% ($P < 0.001$), at a high cost of major bleeding complications (58%, $P < 0.001$) [38]. The differences of major bleedings between groups are mainly from the gastrointestinal sites, perhaps because of the effect of long-term administration of DAPT on the gastric mucosa. Therefore, for patients with AF and increased risks of stroke in whom oral anticoagulation therapy is contraindicated, the addition of clopidogrel to aspirin therapy is reasonable for the prevention of ischemic stroke, where risks of hemorrhage need to be taken into consideration for individualized therapy.

Special Types of Patients

Intracranial and Extracranial Stent Implantation

Several trials including the PCI-CURE (Percutaneous Coronary Intervention-Clopidogrel in Unstable Angina to Prevent Recurrent Events) and CREDO (Clopidogrel for the Reduction of Events During Observation) trials have proved that long-term use of DAPT greatly lowered the risk of recurrent cardiovascular events among patients treated with percutaneous coronary intervention (PCI) [39,40], leading to a recommendation of the DAPT with the P2Y₁₂ inhibitor and aspirin for at least 12 months after PCI by 2011 ACCF/AHA/SCAI guidelines for PCI [41].

The 12 or 30 months of Dual Antiplatelet Therapy after Drug-Eluting Stents (DAPT) trial published recently enrolled 9961 patients treated with a coronary drug-eluting stent procedure to assess the benefits and risks of DAPT beyond 1 year. It showed a reduced rate of stent thrombosis (0.4% vs. 1.4%,

$P < 0.001$) and a composite of death, MI, or stroke (4.3% vs. 5.9%, $P < 0.001$), but an increased rate of moderate or severe bleeding (2.5% vs. 1.6%, $P = 0.001$) with no significant difference of severe or fatal bleeding (0.8% vs. 0.6%, $P = 0.15$) for 30 months versus 12 months of DAPT [42]. While the probable benefit was not seen in 1687 patients after bare metal stents, there were no significant differences in the rate of stent thrombosis, the composite of vascular events and moderate or severe bleeding between 30 and 12 months of DAPT [43]. These trials provided new ideas for extended DAPT treatment in patients after PCI procedure.

The procedure of percutaneous transluminal angioplasty and stenting (PTAS) recanalizes occluded arteries and restores blood flow to salvage potentially reversible ischemic penumbra tissue during acute cerebral ischemia, which has been proved efficacious particularly in acute ischemic stroke caused by a proximal intracranial arterial occlusion [44]. Medical management in the peri-operative period is closely related to the prognosis, while no guideline covers this field. According to the experiences from several RCTs and multiple centers worldwide, the strategy of DAPT with clopidogrel 300 mg plus aspirin 300 mg initiated before PTAS and clopidogrel 75 mg/day plus aspirin 100–300 mg/day for continuation for 1–3 months is recommended [45,46].

Ischemic Stroke with ACS

In the subgroup analysis of the CHARISMA trial, there was a marginally significant reduction (RR 0.88, $P = 0.046$) in a composite of ischemic vascular events and no significant increase in severe bleeding with DAPT versus aspirin alone in 12,153 patients with documented symptomatic atherothrombosis [47], coming to a conclusion that DAPT showed greater benefit in the population with higher risks of recurrent cardio-cerebrovascular disorders.

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial might reveal a net benefit of DAPT in patients with ACS. The combination therapy greatly reduced the risks of stroke, MI, and vascular death ($P < 0.001$) and significantly increased the risks of major hemorrhage ($P < 0.01$) with no difference in the risk of life-threatening hemorrhage compared with aspirin [48]. Another recent trial named the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) indicated similar results with the DAPT of a novel P2Y₁₂ receptor antagonist of ticagrelor and aspirin [49]. These trials greatly favored the use of DAPT in patients with ischemic stroke and ACS but relatively low risks of hemorrhage.

Gene Polymorphisms Associated with Diverse Responses to Antiplatelet Drugs

Groups of genes were found related to different ischemic stroke subtypes according to the TOAST classification [50]. Even with the same subtype of ischemic stroke and the same medical strategy, patients' reactivity to antiplatelet drugs differs a lot. Till now, it has been reported that polymorphisms of genes encoding for

Table 1 Recommendations of DAPT in secondary prevention of ischemic stroke

Populations	Recommendations	Clinical trials	Clinical guidelines	Classification of recommendations/level of evidence
High-risk TIA/minor ischemic stroke	DAPT of aspirin and clopidogrel initiated within 24 h after symptom and for continuation for 21 days	FASTER, CHANCE	2014 AHA/ASA guideline	IIb/B (new recommendation)
Stroke or TIA attributable to severe stenosis (70–99%) of a major intracranial artery	The addition of clopidogrel 75 mg/day to aspirin for 90 days initiated within 30 days	WASID, SAMMPRIS	2014 AHA/ASA guideline	IIb/B (new recommendation)
Symptomatic intracranial and extracranial artery stenosis and MES	Clopidogrel (a loading dose of 300 mg, then 75 mg/day) plus aspirin, for 7 days	CARESS, CLAIR	NA	Preliminary evidence
Ischemic stroke or TIA and evidence of aortic arch atheroma	Antiplatelet therapy	ARCH	2014 AHA/ASA guideline	I/A (new recommendation)
	The combination of clopidogrel 75 mg/day and aspirin for 90 days	ARCH	NA	Preliminary evidence
Ischemic stroke or TIA and AF, not suitable for oral anticoagulants	Aspirin alone	SPAF	2014 AHA/ASA guideline	I/A
	The addition of clopidogrel to aspirin therapy	ACTIVE W, ACTIVE A	2014 AHA/ASA guideline	IIb/B (revised recommendation)
Ischemic stroke and PTAS	Clopidogrel 75 mg/day plus aspirin 100–300 mg/day for 1 to 3 months after PTAS	NA	NA	NA
PCI	DAPT with clopidogrel and aspirin for at least 12 months after stent implantation	PCI-CURE, CREDO, DAPT	2011 ACCF/AHA/SCAI guideline for PCI	I/B
	The combination with clopidogrel and aspirin	CURES	2012 ACCF/AHA guideline	I/A
Ischemic stroke and ACS	The combination of oral anticoagulation with antiplatelet therapy	NA	2014 AHA/ASA guideline	IIb/C (new recommendation)

DAPT, dual antiplatelet therapy; TIA, transient ischemic attack; MES, microembolic signals; AF, atrial fibrillation; PTAS, percutaneous transluminal angioplasty and stenting; PCI, percutaneous coronary intervention; ACS, acute coronary syndromes; NA, not applicable. FASTER, The Fast Assessment of Stroke and TIA to prevent Early Recurrence [18]; CHANCE, Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events [19]; WASID, Warfarin-Aspirin Symptomatic Intracranial Disease [25]; SAMMPRIS, Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis [26]; CARESS, Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic carotid Stenosis [31]; CLAIR, Clopidogrel plus Aspirin for Infarction Reduction in acute stroke or transient ischemic attack patients with large artery stenosis and microembolic signals [32]; ARCH, Aortic Arch Related Cerebral Hazard [35]; SPAF, Stroke Prevention in Atrial Fibrillation [59]; ACTIVE, Atrial fibrillation Clopidogrel Trial with Ibuprofen for prevention of Vascular Events [37,38]; PCI-CURE, Percutaneous Coronary Intervention-Clopidogrel in Unstable Angina to Prevent Recurrent Events [39]; CREDO, Clopidogrel for the Reduction of Events During Observation [40]; DAPT, 12 or 30 months of Dual Antiplatelet Therapy after Drug-Eluting Stents [42]; CURES, Clopidogrel in Unstable Angina to Prevent Recurrent Events [48]; 2014 AHA/ASA guideline, 2014 American Heart Association/American Stroke Association guidelines for the prevention of stroke in patients with stroke and transient ischemic stroke [15]; 2011 ACCF/AHA/SCAI guideline for PCI, 2011 American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions guideline for percutaneous coronary intervention [41]; 2012 ACCF/AHA guideline, 2012 American College of Cardiology Foundation/American Heart Association focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction [11].

platelet receptors such as GP IIIa, GP Ia, P2Y1, P2Y12, and COX-1 enzyme correlate with poor responses to aspirin and polymorphisms of CYP2C19 (cytochrome P450 family two subfamily C polypeptide 19), CYP3A4, ABCB1, PON1, and PEAR1 are associated with clopidogrel response [51]. However, many of these genes were studied not only *in vitro* but found conflicted results in different clinical trials, which meant further investigations were in need for the clinical relevance.

Of these, the study of CYP2C19 variants, which greatly contributes to the biotransformation of clopidogrel into its active form, is well established. Cayla et al. [52] identified CYP2C19 polymorphisms, and its loading dose was independently associated with early stent thrombosis. Furthermore, patients with the CYP2C19*2 variant were more likely to have an ischemic event or death during 1 year of follow-up [53]. Mega et al. [54] published a meta-analysis of nine studies evaluating CYP2C19 genotype and cardiovascular outcomes in 9685 patients treated with clopidogrel. There was a trend toward increased risk of nonfatal ischemic stroke associated with carriers of ≥ 1 reduced-function allele; however, because of the low rate of recurrent stroke events in the study cohort, this was not statically significant. Studies revealed that the CYP2C19*2 genotype was associated with diminished clopidogrel response [52–54]; however, whether the diminished response in stroke patients was correlated with more recurrent ischemic events was unknown. A trial of 259 patients with acute ischemic stroke found that there were decreased effectiveness of clopidogrel on adenosine diphosphate-induced platelet aggregation ($P = 0.024$) and worse NIHSS and mRS scores at 3 and 6 months after clopidogrel ($P < 0.05$) in CYP2C19 loss-of-function versus normal genotype [55]. The scores could well demonstrate the improvement of neurological function but are hardly correlated with the effect of clopidogrel treatment. We assume that because of the small number of patients recruited and short time of follow-up, they might be unable to find significant differences in stroke recurrence among different CYP2C19 polymorphisms [56]. The same group later reported a retrospective analysis of 90 patients with vertebral artery stent treatment; CYP2C19 impotency significantly increased the rate of in-stent restenosis ($P = 0.008$) and recurrent ischemic stroke ($P = 0.042$) [57], which needs to be verified in multicenter randomized and long-term trials.

Currently, there is no definitive evidence linking *ex vivo* platelet aggregation measurements to clinical outcomes in ischemic stroke patients. Furthermore, it is unclear how patients should be managed based on these test results.

References

1. Feigin VL, Forouzanfar MH, Krishnamurthi R, et al. Global and regional burden of stroke during 1990–2010: Findings from the Global Burden of Disease Study 2010. *Lancet* 2014;**383**:245–254.
2. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics-2015 update: A report from the American Heart Association. *Circulation* 2015;**131**:e29–e322.
3. Steinhilb SR, Moliterno DJ. The role of the platelet in the pathogenesis of atherothrombosis. *Am J Cardiovasc Drugs* 2005;**5**:399–408.
4. Antithrombotic Trialists Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;**324**:71–86.
5. Chen ZM, Collins R, Liu LS, et al. CAST: Randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. CAST (Chinese Acute Stroke Trial) Collaborative Group. *Lancet* 1997;**349**:1641–1649.
6. Peter S, Rory C, Carl C, et al. The International Stroke Trial (IST): A randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. *Lancet* 1997;**349**:1569–1581.
7. Chen ZM, Sandercock P, Pan HC, et al. Indications for early aspirin use in acute ischemic stroke: A combined analysis of 40 000 randomized patients from the Chinese acute stroke trial and the international stroke trial. On behalf of the CAST and IST collaborative groups. *Stroke* 2000;**31**:1240–1249.
8. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet* 1996;**348**:1329–1339.
9. Mijajlovic MD, Shulga O, Bloch S, Covickovic-Sternic N, Aleksic V, Bornstein NM. Clinical consequences of aspirin and clopidogrel resistance: An overview. *Acta Neurol Scand* 2013;**128**:213–219.
10. Agayeva N, Gungor L, Topcuoglu MA, Arsava EM. Pathophysiologic, rather than laboratory-defined

New Clinical Trials for the Combined Antiplatelet Therapy

Recently, several trials that are trying to gain more insight into the efficacy and safety of the combined antiplatelet therapy in patients with ischemic stroke or TIA are in progress. The COMBination of Clopidogrel and Aspirin for Prevention of Early REcurrence in Acute Atherothrombotic Stroke (COMPRESS) trial regards any recurrent stroke lesion confirmed by neuroimaging within 30 days as the primary endpoint in patients with ischemic stroke, to improve the sensitivity of judging a stroke recurrence [58]. The aim of the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial is to test whether there is excess benefit of DAPT used within 12 h of new ischemic symptoms for 90 days in patients with TIA or minor stroke compared with monotherapy [58]. The Triple Antiplatelets for Reducing Dependency after Ischemic Stroke (TARDIS) trial assesses the tolerability and feasibility of the triple antiplatelet therapy (clopidogrel, aspirin, and dipyridamole) versus the guideline therapy (aspirin plus dipyridamole or clopidogrel) for 1 month in patients with very recent ischemic stroke or TIA, with the primary outcome of ordinal stroke severity at day 90 [58]. All these trials will provide clinicians with new ideas on the use of antiplatelet combination therapy in secondary prevention of ischemic stroke.

Conclusion

In summary, DAPT with clopidogrel and aspirin may be an effective strategy to further reduce the risk of recurrence in patients with ischemic stroke or TIA, but not for all populations. It is of vital importance for clinicians to weigh the risk of ischemia and hemorrhage for an individualized antithrombotic therapy. On the evidence so far, the proper patient population, treatment regimen, and evidence-based medicine for DAPT are listed in Table 1.

Acknowledgments

This work was supported by grants from the Science and Technology Commission of Shanghai Municipality China 1241119a8100 (X.C.) and 15QA1400900 (X.C.).

Conflict of Interest

The authors declare no conflict of interest.

- resistance drives aspirin failure in ischemic stroke. *J Stroke Cerebrovasc Dis* 2015;**24**:745–750.
11. Jneid H, Anderson JL, Wright RS, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/Non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2012;**126**:875–910.
 12. Lee M, Saver JL, Hong KS, Rao NM, Wu YL, Ovbiagele B. Risk-benefit profile of long-term dual- versus single-antiplatelet therapy among patients with ischemic stroke: A systematic review and meta-analysis. *Ann Intern Med* 2013;**159**:463–470.
 13. Wong KS, Wang Y, Leng X, et al. Early dual versus mono antiplatelet therapy for acute non-cardioembolic ischemic stroke or transient ischemic attack: An updated systematic review and meta-analysis. *Circulation* 2013;**128**:1656–1666.
 14. Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: A scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke* 2009;**40**:2276–2293.
 15. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;**45**:2160–2236.
 16. Coull AJ, Lovett JK, Rothwell PM. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: Implications for public education and organisation of services. *BMJ* 2004;**328**:326.
 17. Chatzikonstantinou A, Willmann O, Jager T, Szabo K, Hennerici MG. Transient ischemic attack patients with fluctuations are at highest risk for early stroke. *Cerebrovasc Dis* 2009;**27**:594–598.
 18. Kennedy J, Hill MD, Ryckborst KJ, et al. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): A randomised controlled pilot trial. *Lancet Neurol* 2007;**6**:961–969.
 19. Wang Y, Wang Y, Zhao X, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med* 2013;**369**:11–19.
 20. Li J, Wang Y, Wang D, et al. Glycated albumin predicts the effect of dual and single antiplatelet therapy on recurrent stroke. *Neurology* 2015;**84**:1–6.
 21. Wang Y, Pan Y, Zhao X, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack (CHANCE): 1-year outcomes. *Circulation* 2015. DOI: 10.1161/CIRCULATIONAHA.114.014791 [Epub ahead of print].
 22. Geraghty OC, Paul NL, Chandratheva A, Rothwell PM. Low risk of rebound events after a short course of clopidogrel in acute TIA or minor stroke. *Neurology* 2010;**74**:1891–1896.
 23. Geraghty OC, Kennedy J, Chandratheva A, Marquardt L, Buchan AM, Rothwell PM. Preliminary evidence of a high risk of bleeding on aspirin plus clopidogrel in aspirin-naïve patients in the acute phase after TIA or minor ischaemic stroke. *Cerebrovasc Dis* 2010;**29**:460–467.
 24. Arenillas JF. Intracranial atherosclerosis: Current concepts. *Stroke* 2011;**42**:S20–S23.
 25. Chimowitz MI, Lynn MJ, Howlett-Smith H, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med* 2005;**352**:1305–1316.
 26. Chimowitz MI, Lynn MJ, Derdeyn CP, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med* 2011;**365**:993–1003.
 27. Derdeyn CP, Chimowitz MI, Lynn MJ, et al. Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): The final results of a randomised trial. *Lancet* 2014;**383**:333–341.
 28. Gao S, Wong KS, Hansberg T, Lam WW, Droste DW, Ringelstein EB. Microembolic signal predicts recurrent cerebral ischemic events in acute stroke patients with middle cerebral artery stenosis. *Stroke* 2004;**35**:2832–2836.
 29. Wong KS. Is the measurement of cerebral microembolic signals a good surrogate marker for evaluating the efficacy of antiplatelet agents in the prevention of stroke? *Eur Neurol* 2005;**53**:132–139.
 30. Hao Q, Leung WH, Leung C, et al. The significance of microembolic signals and new cerebral infarcts on the progression of neurological deficit in acute stroke patients with large artery stenosis. *Cerebrovasc Dis* 2010;**29**:424–430.
 31. Markus HS, Droste DW, Kaps M, et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using Doppler embolic signal detection: The clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial. *Circulation* 2005;**111**:2233–2240.
 32. Wong KS, Chen C, Fu J, et al. Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR study): A randomised, open-label, blinded-endpoint trial. *Lancet Neurol* 2010;**9**:489–497.
 33. Macleod MR, Amarencio P, Davis SM, Donnan GA. Atheroma of the aortic arch: An important and poorly recognised factor in the aetiology of stroke. *Lancet Neurol* 2004;**3**:408–414.
 34. Heinzl O, Cohen A, Amarencio P. An update on aortic causes of ischemic stroke. *Curr Opin Neurol* 1997;**10**:64–72.
 35. Amarencio P, Davis S, Jones EF, et al. Clopidogrel plus aspirin versus warfarin in patients with stroke and aortic arch plaques. *Stroke* 2014;**45**:1248–1257.
 36. van Walraven C, Hart RG, Singer DE, et al. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: An individual patient meta-analysis. *JAMA* 2002;**288**:2441–2448.
 37. Connolly S, Pogue J, Hart R, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): A randomised controlled trial. *Lancet* 2006;**367**:1903–1912.
 38. Connolly SJ, Pogue J, Hart RG, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med* 2009;**360**:2066–2078.
 39. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: The PCI-CURE study. *Lancet* 2001;**358**:527–533.
 40. Steinhubl SR, Berger PB, Mann JT 3rd, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: A randomized controlled trial. *JAMA* 2002;**288**:2411–2420.
 41. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for percutaneous coronary intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol* 2011;**58**:e44–e122.
 42. Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 2014;**371**:2155–2166.
 43. Kereiakes DJ, Yeh RW, Massaro JM, et al. Antiplatelet therapy duration following bare metal or drug-eluting coronary stents: The dual antiplatelet therapy randomized clinical trial. *JAMA* 2015;**313**:1113–1121.
 44. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015;**372**:11–20.
 45. Meyers PM, Schumacher HC, Higashida RT, et al. Indications for the performance of intracranial endovascular neurointerventional procedures: A scientific statement from the American Heart Association Council on Cardiovascular Radiology and Intervention, Stroke Council, Council on Cardiovascular Surgery and Anesthesia, Interdisciplinary Council on Peripheral Vascular Disease, and Interdisciplinary Council on Quality of Care and Outcomes Research. *Circulation* 2009;**119**:2235–2249.
 46. Blackham KA, Meyers PM, Abruzzo TA, et al. Endovascular therapy of acute ischemic stroke: Report of the Standards of Practice Committee of the Society of NeuroInterventional Surgery. *J Neurointerv Surg* 2012;**4**:87–93.
 47. Bhatt DL, Flather MD, Hacke W, et al. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. *J Am Coll Cardiol* 2007;**49**:1982–1988.
 48. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;**345**:494–502.
 49. Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med* 2015;**372**:1791–1800.
 50. Munshi A, Das S, Kaul S. Genetic determinants in ischaemic stroke subtypes: Seven year findings and a review. *Gene* 2015;**555**:250–259.
 51. Thomas MR, Storey RF. Genetics of response to antiplatelet therapy. *Prog Mol Biol Transl Sci* 2014;**124**:123–153.
 52. Cayla G, Hulot JS, O'Connor SA, et al. Clinical, angiographic, and genetic factors associated with early coronary stent thrombosis. *JAMA* 2011;**306**:1765–1774.
 53. Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *JAMA* 2009;**302**:849–857.
 54. Mega JL, Simon T, Collet JP, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: A meta-analysis. *JAMA* 2010;**304**:1821–1830.
 55. Jia DM, Chen ZB, Zhang MJ, et al. CYP2C19 polymorphisms and antiplatelet effects of clopidogrel in acute ischemic stroke in China. *Stroke* 2013;**44**:1717–1719.
 56. Dong Y, Cheng X, Dong Q. Letter by Dong et al. regarding article, "CYP2C19 Polymorphisms and antiplatelet effects of clopidogrel in acute ischemic stroke in China". *Stroke* 2013;**44**:e107.
 57. Lin YJ, Li JW, Zhang MJ, et al. The association between CYP2C19 genotype and of in-stent restenosis among patients with vertebral artery stent treatment. *CNS Neurosci Ther* 2014;**20**:125–130.
 58. "The Internet Stroke Center: Stroke Trials Directory", March 2015, <http://www.strokecenter.org/trials>.
 59. Hart RG, Pearce LA, McBride R, Rothbart RM, Asinger RW. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: Analysis of 2012 participants in the SPAF I-III clinical trials. The Stroke Prevention in Atrial Fibrillation (SPAF) Investigators. *Stroke* 1999;**30**:1223–1229.