Curr Neurol Neurosci Rep (2013) 13:327
DOI 10.1007/s11910-012-0327-y

STROKE (HP ADAMS JR, SECTION EDITOR)

Aspirin and Clopidogrel for Prevention of Ischemic Stroke

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Published online: 9 January 2013

Abstract This review examines the role of platelets in ischemic stroke, platelet activation mechanisms, aspirin's rise as an antithrombotic agent, clopidogrel's appearance on the stage, a possible role for combination therapy, antiplatelet resistance, practical considerations, and future directions. Reviewed in this chapter are issues central to optimal antiplatelet therapy: efficacy, safety, resistance, and biochemical/laboratory testing. Current guidelines do not recommend combination aspirin and clopidogrel use, however recent research indicates dual antiplatelet therapy with combined aspirin and clopidogrel may have specific roles in secondary prevention of ischemic stroke. A cautious and analytical interpretation of the literature is advised before application of this knowledge to clinical practice. The best recommendation at this time is to follow the published guidelines for secondary prevention of ischemic stroke.

Keywords Thienopyridines · Phosphodiasterase inhibitors · Aspirin · Clopidogrel · Aspirin resistance · Antiplatelet resistance · Clopidogrel resistance · Dipyridamole · CYP2C19 polymorphism · Stroke · Transient ischemic attack

Introduction

The development of antiplatelet therapies to prevent ischemic stroke has been among the most significant advances in vascular neurology. Great effort and resources have been dedicated to expanding our understanding of the pathophysiology of ischemic stroke and the mechanisms of action of the antiplatelet agents used to prevent them, however questions and uncertainty remain. Current ambiguities include whether there is there is a role for dual antiplatelet therapy with the combination of aspirin and clopidogrel in the prevention of stroke and whether antiplatelet resistance is a useful clinical concept. The aim of this chapter is to review foundational and current literature regarding optimal secondary prevention of ischemic stroke with a focus on aspirin and clopidogrel.

This article is part of the Topical Collection on *Stroke*

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The Role of Platelets in Ischemic Stroke

Thrombosis has been recognized as the final step in vascular occlusion and tissue ischemic infarction for centuries. Knowledge of the existence of platelets dates to the late 1800 s. Clinical observation that platelet-fibrin emboli might be involved in transient ocular and cerebral ischemic events was made in the 1950s supporting research on preventing maladaptive thrombosis to ameliorate or prevent ischemic events involving the eye and brain [1]. Cardiology has played a central role in advancing knowledge and development of new management strategies as the issues are shared between heart and brain, however not all lessons are transferable. Anticoagulants were examined as treatment and preventive strategies for ischemic stroke in the 1950s and 1960s, but underpowered trials of heparin and oral anticoagulants failed to demonstrate efficacy [1–3]. By the 1960s, attention was turning to the role of platelets and antithrombotic strategies focusing on blocking platelet aggregation.

The first documented use of aspirin to prevent vascular disease dates back to the late 1950s when a general practitioner noticed that patients for whom he had prescribed a daily aspirin rarely had heart attacks [4]. More direct discovery of the antiplatelet effect of aspirin was coincidentally made when a creative researcher observed that his personal ingestion of aspirin increased his bleeding from razor nicks [5]. This observation was then taken to the laboratory,

resulting in new knowledge of the pharmacologic ability of aspirin to alter the function of blood platelets. Direct evidence implicating the role of platelets in acute arterial thrombosis was established when the infusion of ADP (a potent platelet aggregating agent) into the coronary arteries of pigs was found to result in myocardial ischemia and arrhythmia [6]. The observation of improved clinical outcomes in 2 patients who experienced a reduction in their attacks of amaurosis fugax when treated with aspirin, provided a cerebrovascular spin to the emerging antiplatelet story [7].

Research and experience has since revealed the limits of aspirin's efficacy as well as adverse effects, catalyzing the search for other agents with the ability to block platelet activity. Parallel advancement in biochemistry and the role of platelets in thrombosis facilitated the search for safer and more efficacious agents. The resulting pharmaceutical products included the thienopyridines, phosphodiasterase inhibitors, glycoprotein IIb/IIIa antagonists, and others.

Mechanisms of Action

The pharmacologic mechanisms of several major antiplatelet therapies are illustrated in the Fig. 1. Aspirin inhibits platelet aggregation through blockade of the thromboxane-mediated aggregation pathway [8]. Blockade is accomplished by inhibition of the enzyme cyclooxygenase 1 through acetylation, resulting in reduced production of thromboxane A2, a prostaglandin derivative and promoter of platelet aggregation. It has been postulated that the efficacy of aspirin is explained by a differentially greater inhibition of thromboxane A2 relative to prostacyclin. Thromboxane is a potent vasoconstrictor and platelet activator, whereas prostacyclin is a vasodilator and platelet inhibitor [9].

The thienopyridine derivatives were first demonstrated to have anti-inflammatory effects and to inhibit ADP-induced platelet aggregation when administered to rats in the mid-1970s [10]. This class of drugs has been intensely studied and developed as antiplatelet therapies for use in patients with coronary and cerebrovascular disease and includes the receptor/P2Y12 inhibitors. Most notable are the first generation agent, ticlopidine, and second generation agents, clopidogrel, and prasugrel. Ticagrelor is a non-thienopyridine ADP/P2Y12 receptor blocker [8].

Aspirin

Aspirin's efficacy in secondary stroke prevention was demonstrated in clinical trials in the late 1970s. Subsequent trials have qualified and extended its roles (see Table 1, a chronological listing of literature supporting use of aspirin in stroke prevention) [11, 12]. For example, aspirin was found to be effective for recurrent stroke prevention in doses as low as 30 mg/day, and higher aspirin doses were associated with significantly greater risk of adverse events when compared with lower doses [17]. Data from thousands of patients treated with antiplatelet therapy after TIA or stroke demonstrated a relative risk reduction of 18 % for secondary prevention of ischemic stroke with aspirin [28]. The absolute risk reduction for serious vascular events for pooled antiplatelet agents, mainly aspirin, is 36 per 1,000 events over 2.5 years [25].

The use of long-term oral anticoagulation to prevent recurrent non-cardioembolic ischemic stroke was halted when warfarin was found no more efficacious and more dangerous than aspirin in trials evaluating the safety and efficacy of these 2 agents for the prevention of stroke due to non-cardioembolic mechanisms [22, 30]. Co-administration of warfarin and aspirin for thromboembolism prevention is of proven benefit in patients with some mechanical heart valves and is sometime necessary in those with strong coincident indications for warfarin and arterial stenting [31]. Evidence supporting co-administration in settings such as concurrent atrial fibrillation and coronary disease is, however, lacking, and risk of significant bleeding is significantly increased [32•]. The use of aspirin for management of very early secondary prevention of stroke was investigated in a large clinical trial comparing aspirin with placebo within 48 h of onset. Early initiation results in 9 fewer deaths or non-fatal strokes per 1,000 patients treated in the

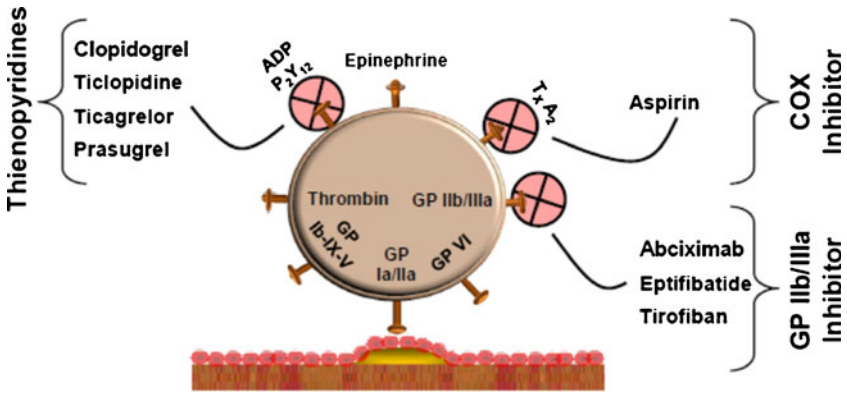

Fig. 1 Pharmacologic mechanisms of commonly used antiplatelet therapies

Table 1 Selected publications influencing the use of aspirin in prevention of ischemic stroke

Trial name	Year	Advance
US aspirin trial	1977	Aspirin superior to placebo in preventing combined end-point of stroke, retinal infarct, TIAs, and death after TIA [11].
Canadian aspirin sufinpyrazone trial	1978	Aspirin superior to placebo in preventing stroke or death in men; sulfinpyrazone no better than placebo after TIA [12].
AICLA	1983	Aspirin superior to placebo in preventing stroke after TIA or stroke; trend for dipyridamole to be superior to placebo; combination superior to placebo [13].
ESPS	1987	Aspirin plus dipyridamole superior to placebo in preventing stroke or death after TIA or stroke [14].
SPAF	1990	Aspirin effective but less so than warfarin in preventing stroke or systemic embolism in atrial fibrillation [15].
UK TIA trial	1991	Lower dose (300 mg) aspirin as effective as higher dose (600 mg) in preventing vascular events after TIA; both superior to placebo [16].
Dutch TIA trial	1991	Low dose (30 mg) aspirin as effective as higher dose (283 mg) in preventing vascular events after TIA [17].
Antiplatelet Trialists' Collaboration	1994	Aspirin superior to placebo in preventing vascular events with 18 % relative risk reduction in both men and women with stroke or TIA; no dose effect found [18].
ESPS II	1996	Aspirin and dipyridamole both superior to placebo in preventing stroke after TIA or stroke; combination better than either one alone [19].
CAST	1997	Aspirin superior to placebo in preventing death or dependency in acute ischemic stroke [20].
IST	1997	Aspirin as effective as parenteral heparin and safer in early prevention of recurrence in acute ischemic stroke [21].
SPIRIT	1997	Aspirin safer than warfarin in preventing vascular events and major bleeding after noncardioembolic stroke [22].
HAEST	2000	Aspirin as effective as low molecular heparin in preventing recurrence en route to anticoagulation with warfarin after atrial fibrillation-related stroke [23].
WARSS	2001	Aspirin as effective as and safer than warfarin in preventing recurrence after noncardioembolic stroke [24].
Antithrombotic Trialists' Collaboration	2002	Aspirin's efficacy in reducing vascular events after TIA or stroke supported with additional data; most data pertaining to dose f 75–150 mg/d [25].
WASID	2005	Aspirin more effective and safer than warfarin in preventing vascular events in medical management of symptomatic intracranial stenosis [26].
Antiplatelet Trialists' Collaboration	2008	Aspirin efficacy in reducing death or dependency in acute stroke with additional data; recommendation for dose of 160–300 mg [27].
Antithrombotic Trialists' Collaboration	2009	Aspirin borderline superior to placebo in reducing ischemic stroke in primary prevention; no advantage detected for all stroke [28].
WARCEF	2012	Aspirin as effective as warfarin in preventing stroke, intracranial hemorrhage or death in low ejection fraction [29••].

first several weeks following stroke [20]. The findings in this study were corroborated and extended by a second acute stroke mega-trial that demonstrated significant benefit at 6 months follow-up for patients who were initiated on aspirin within 48 h of onset [21]. The same trial found medium dose, subcutaneous, unfractionated heparin too dangerous to be of value in the setting of acute stroke. Other trials demonstrated that aspirin was as good, better, or safer than warfarin in stroke prevention settings such as bridging to warfarin anticoagulation in atrial fibrillation [23], symptomatic intracranial stenosis [26], and low cardiac ejection fraction [29••].

There is controversy regarding the level of cardiovascular risk that warrants aspirin antiplatelet therapy. Primary prevention is not completely benign. Use of aspirin in low risk groups, especially women, may lack efficacy and carry increased risk of poor outcomes including death [33–35••]. That aspirin may be protective against colon and other cancers needs to be addressed in future primary prevention analyses [36•].

Aspirin use is associated with risks including, but not limited to bleeding. Non-bleeding side effects include nausea, gastric ulcers, hearing loss, tinnitus, renal effects including interstitial nephritis with renal failure, respiratory effects including bronchospasm, hepatotoxicity, and rare cases of anaphylaxis [37]. Low dose aspirin has been demonstrated to increase the risk of bleeding, however the absolute increase in risk is relatively modest in most patients. Analysis has shown 769 patients would need to be treated with low dose aspirin to cause 1 additional major bleeding event annually [38]. In an analysis of all antiplatelet-related bleeding and adverse events reported to

the U.S. Food and Drug administration, hemorrhage rates were less with aspirin when compared with clopidogrel except for gastrointestinal bleeding, where the rate was higher with aspirin [39]. Patients should always be assessed for the potential of bleeding risks, especially gastrointestinal bleeding, prior to initiation of aspirin.

Clopidogrel

Clopidogrel's efficacy in prevention of ischemic events in patients with documented atherothrombotic disease is proven, and the drug gained U.S. FDA approval for this indication in 1998 (see Table 2, a chronological listing of literature supporting use of clopidogrel in stroke prevention) [40]. Although the CAPRIE trial demonstrated clopidogrel's superiority when compared with aspirin in the secondary prevention of vascular events, the margin was narrow and not statistically significant for those with documented stroke as the index event. Nevertheless clopidogrel along with the combination of aspirin and extended release dipyridamole attracted significant attention, somewhat eclipsing aspirin during the early 2000s (see Tables 1 and 2) [19, 42]. The ProFESS trial demonstrated no difference in efficacy or safety between clopidogrel and aspirin combined with extended release dipyridamole and had the effect of leveling the antiplatelet playing field [46].

Table 2 Selected publications influencing use of clopidogrel in prevention of ischemic stroke

Trial name	Year	Advance
CATS	1989	Ticlopidine, a precursor to clopidogrel, superior to placebo in preventing vascular events after stroke [40].
TASS	1989	Ticlopidine slightly superior to aspirin in preventing stroke or death after stroke [41].
CAPRIE	1996	Clopidogrel slightly superior to aspirin in preventing vascular events in subjects with documented atherosclerotic vascular disease [42].
MATCH	2004	Combination clopidogrel and aspirin, compared with clopidogrel monotherapy, associated with bleeding without offsetting efficacy [43].
CHARISMA	2006	Combination clopidogrel and aspirin not significantly superior to aspirin monotherapy in preventing vascular events in subjects with vascular disease or risk factors [44].
FASTER	2007	Combination aspirin and clopidogrel trended toward benefit compared with aspirin monotherapy in very early secondary stroke prevention [45].
ProFESS	2008	Clopidogrel monotherapy and dual therapy with aspirin and dipyridamole roughly equivalent in preventing recurrent stroke [46].
ACTIVE A	2009	Combination of aspirin and clopidogrel superior to aspirin monotherapy in preventing stroke in atrial fibrillation [47].
SPS3	2012	Combination aspirin and clopidogrel no more efficacious than aspirin monotherapy in preventing recurrent small vessel stroke; unexplained excess all-cause mortality with combination [48].

The most common adverse event associated with clopidogrel administration is bleeding. The rate of bleeding for clopidogrel is similar to that for aspirin although rate of gastrointestinal bleeding is less due to the agent's lower gastrotoxicity [42]. Clopidogrel use has also been associated with thrombotic thrombocytopenic purpura, and rash, although frequency of these complications with clopidogrel is much lower than with ticlopidine, a first generation thienopyridine [49]. It takes 4 to 5 days before clopidogrel reaches maximum antiplatelet effect, prompting interest in loading doses when using the agent in acute cerebral ischemia and in the setting of interventional procedures [50].

Dual Antiplatelet Therapy with Aspirin Plus Clopidogrel

The concept of dual antiplatelet therapy with aspirin combined with clopidogrel is intriguing as there is limited benefit of these agents in monotherapy, alternative combination strategies such as aspirin plus extended release dipyridamole have demonstrated efficacy [51], and there have been clear successes with the combination of aspirin and clopidogrel in the cardiac arena [52]. The merit of aspirin combined with clopidogrel for secondary stroke prevention has been investigated in clinical trials. MATCH enrolled patients with TIA or stroke and concurrent high risk features such as MI, prior stroke, diabetes, angina, or symptomatic peripheral artery disease [43]. This study was terminated early because of safety concerns, but analysis demonstrated that combined therapy did not reduce the risk of major vascular events. Combination therapy was associated with a significant increase in life threatening bleeding complications, including intracranial, and gastrointestinal hemorrhage. Dual therapy was estimated to result in an additional thirteen life threatening hemorrhages per 1,000 patients treated as compared with monotherapy with clopidogrel [43].

CHARISMA enrolled patients with documented cardiovascular disease or multiple atherothrombotic risk factors and randomized them to combination aspirin plus clopidogrel or aspirin monotherapy [44]. The risk of myocardial infarction, stroke of any cause, or death from cardiovascular causes was not significantly reduced by dual antiplatelet therapy compared with aspirin monotherapy (6.8 % vs 7.3 %). Dual therapy was associated with increased risk of

bleeding, with a significant increase in moderate bleeding (2.1 % vs 1.3 %) and a nonsignificant increase in severe bleeding (1.7 % vs 1.3 %) [44].

Increased bleeding is expected with increased antithrombotic effect; the question is whether net benefit is enhanced. Additional research has demonstrated increased major bleeding events associated with combination therapy, particularly gastrointestinal bleeds and bleeding from puncture sites [52]. However, the increased incidence of intracranial hemorrhage and fatal bleeding seen in the MATCH study was not observed [44]. Dual antiplatelet therapy with aspirin and clopidogrel as well as clopidogrel monotherapy is associated with an increase in incidence of perioperative wound hematoma [53]. This finding is of practical importance for neurointerventionists performing groin punctures and using clopidogrel in the perioperative setting. Minor bleeding such as epistaxis, hematuria, and ecchymosis are also increased in patients treated with combined aspirin and clopidogrel therapy [53].

The idea that combined aspirin and clopidogrel might be useful in stroke prevention has survived despite the lackluster MATCH and CHARISMA findings. The strategy is to define specific settings or subgroups of patients who may benefit from combination therapies despite the known increased risks of bleeding. The SPS3 study set out to test 2 secondary prevention interventions in patients with lacunar stroke (see Table 2). Subjects were randomized to aspirin compared with combination aspirin and clopidogrel and also to standard compared with intensive blood pressure control [48]. The antiplatelet trial was terminated on grounds of both futility and safety. There was no reasonable possibility that the preset reduction in outcome event rates would be achieved, and the dual therapy group experienced a higher rate of death from all causes when compared with the aspirin monotherapy group (5.8 % vs 4.1 %) [48]. It appears likely that the excess death rate was a chance finding [48], however the disappointing efficacy results suggest patients with small vessel disease may not benefit from secondary prevention with combined aspirin and clopidogrel.

An attractive target for aspirin plus clopidogrel combination therapy is the setting of acute stroke, the brain counterpart of acute coronary syndrome. Efficacy of combination therapy in acute coronary syndrome was demonstrated in the CURE trial [52]. The prematurely discontinued FASTER trial, which compared combination aspirin and clopidogrel with loading dose to aspirin within 24 h of TIA or minor stroke, suggested that very early dual therapy might reduce early stroke recurrence [45]. The currently enrolling Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke Trial (POINT) aims to determine the efficacy of combined aspirin plus clopidogrel in very early secondary prevention following minor stroke or TIA [54].

Another potential target is active large vessel atherothrombosis. Two phase II trials demonstrated a reduction in the number of microembolic signals detected by transcranial Doppler ultrasound in symptomatic patients with carotid and intracranial stenoses when treated with dual antiplatelet therapy with aspirin and clopidogrel vs aspirin monotherapy [55, 56]. It remains to be seen how this interesting research finding will be applied to clinical practice.

The SAMMPRIS trial demonstrated percutaneous transluminal angioplasty and stenting (PTAS) to prevent recurrent stroke was not superior to aggressive medical management with combination aspirin and clopidogrel in patients with symptomatic intracranial stenosis [57••]. Unfortunately these results have been inappropriately interpreted as evidence supporting the use of combination aspirin and clopidogrel in the setting of high grade intracranial stenosis. The goal of the trial was to evaluate the merit of the neurointerventional procedure and did not test the components of best medical therapy.

Perhaps there is more to be learned about ischemic stroke mechanisms and stroke prevention in general. Speculation might deem those at risk of cardioembolism to be unlikely to benefit from a dual antiplatelet program. Aspirin monotherapy was compared with the combination of clopidogrel and aspirin in subjects with atrial fibrillation at high risk of stroke and in whom warfarin was contraindicated in the ACTIVE A trial [58]. Those randomized to combined therapy showed a 40 % reduction in the primary outcome compared with those on aspirin monotherapy. It is unclear how this interesting result will be applied given the recent advent of direct thrombin and factor Xa inhibitors with lower rates of bleeding and less intrusive management requirements compared with warfarin.

Antiplatelet Resistance

The concept of antiplatelet resistance appeared in the cardiology literature in the 1970s and has been intensely debated ever since. Antiplatelet resistance is defined as a clinical situation in which a patient taking an antiplatelet agent has a recurrent event and/or laboratory phenomenon in which the expected functional or biochemical effect of an antiplatelet agent is not seen. Regarding the latter, it might be theoretically useful to be able to detect that a preventive program such as antiplatelet therapy is at risk of failure by performing a laboratory test. Utility of this practice would depend upon the availability of an antidote or alternative therapy proven to improve outcome in these circumstances. To date, the idea of antiplatelet resistance or failure has not proven useful for prevention of ischemic stroke.

With regard to clinical failure, individuals entering secondary prevention trials of antithrombic agents often had their index stroke while taking an antiplatelet agent, most commonly aspirin, a circumstance referred to as “aspirin

failure". It has been demonstrated that cohorts of these individuals fare no better when randomized to an alternative antiplatelet agent than if randomized back to aspirin [48]. The critical question is whether the original stroke while taking aspirin was due to aspirin's lack of efficacy or to countervailing prothrombotic factors too powerful for the agent to overcome.

Studies investigating the correlation between laboratory evidence of resistance and clinical outcomes have demonstrated variable results, with some correlating aspirin resistance with poor outcomes, and others finding a lack of association [59]. In the world of cardiology, dual resistance to clopidogrel and aspirin has been demonstrated to be a strong predictor of poor outcomes in patients undergoing percutaneous coronary intervention [60]. High rates of poor outcomes associated with laboratory identified antiplatelet resistance have also been reported in the setting of ischemic stroke and TIA [61]. It is not clear, however, whether the association is due to a failing antiplatelet agent or a heightened atherothrombogenic milieu. Platelets are activated under such circumstances, and antiplatelet drug effects may continue but be camouflaged [62]. The tests then are a barometer of atherothrombogenicity as well as an index of medication effect. Atherothrombotic risks such as diabetes and renal failure are associated with antiplatelet activation interpreted in the laboratory setting as resistance [63, 64]. The issue is more than semantic as the appropriate response might actually be a modification of the milieu rather than changing the agent, however the science is inexact at this point.

There are functional and biochemical laboratory tests to detect antiplatelet agent effect. One approach is to measure the response of platelets to activation, for example how well platelets aggregate. Several instruments assessing platelet function in various ways have been developed and are in widespread use. For aspirin, laboratory tests are also available to examine biochemical correlates of platelet aggregation, for example thromboxane in the serum or urine. Levels of these metabolites should be very low with aspirin compliance and efficacy. Their presence indicates platelet resistance or failure, with the caveat that the tests also reflect the platelet activation effects of the milieu. Unfortunately, functional and biochemical test results do not reliably agree with each other in the same individual [62].

Changing antiplatelet therapy is not an evidence-based intervention in the setting of treatment failure, as indicated above. Can better outcomes be achieved using guidance from the laboratory? There has, in fact, been limited success in tailoring antiplatelet therapy based on laboratory evidence of antiplatelet resistance. Favorable outcomes have been demonstrated by using adjuvant glycoprotein IIb/IIIa inhibitors in patients identified as clopidogrel non-responders [65]. In addition, clopidogrel loading dose adjustment based on platelet reactivity monitoring was demonstrated to result in decreased stent thrombosis [66]. A recent meta-analysis of trials of intensified antiplatelet therapy in patients with laboratory resistance demonstrated a significant reduction in short term cardiovascular mortality and myocardial infarction compared with controls treated with standard dose clopidogrel in the setting of a coronary intervention [67]. We are not aware of similar findings for long-term secondary stroke prevention.

What is needed to make the intriguing concept of antiplatelet agent testing useful in the care of patients with ischemic stroke? First, a test of platelet function that is stable, reproducible, and feasible in the clinical setting is required. Ideally the test should reflect or measure a common final indicator of platelet effect relevant to all antiplatelet agents. Second, the test must reliably predict future events. Third, an alternative medical approach that consistently corrects the laboratory failure must be established. Fourth, the alternative approach must be proven to reduce risk of subsequent events, specifically stroke. Although the concept of antiplatelet resistance or failure is not clinically useful for stroke doctors as this time, research continues. For example, a recent report describes glycoprotein VI (GPVI), a key collagen receptor of platelet activation that may be a key diagnostic and prognostic marker of high—risk in patients with symptomatic coronary artery disease and ischemic stroke [68].

Among currently topical antiplatelet resistance issues that may be considered in secondary prevention of stroke are the effects of several concurrent medications on antiplatelet therapy. It has been demonstrated that concomitant use of proton pump inhibitors, prescribed to protect patients from gastrointestinal bleeding associated with antiplatelet therapy, may result in diminished antiplatelet effects for both clopidogrel and aspirin [59]. The interaction with clopidogrel is attributed to competition for the biotransformation enzymes (see also below) leading to the issuance of a black box warning by the FDA [69]. A potential mechanism for aspirin resistance that has received notoriety is use of ibuprofen or other nonsteroidal anti-inflammatory agents (NSAID), which block cyclooxygenase reversibly, just antecedent to taking aspirin, which irreversibly blocks the enzyme [70]. The problem in the sequencing is that the receptors are occupied by the NSAID when aspirin becomes briefly (20- to 30-minute serum half-life) available. A workaround is for the patient to take aspirin before the first dose of NSAID each day.

Pharmacogenomics are thought to impact antiplatelet therapy. Clopidogrel is a prodrug that undergoes biotransformation by a 2-step oxidation process catalyzed by the hepatic cytochrome P450 system [8]. Transformation activates thiol metabolites that bind to P2Y12 receptors on platelets, specifically and irreversibly blocking the activation of the GPIIb/IIIa receptor complex, thereby inhibiting

ADP-mediated platelet activation and aggregation [71, 72]. Studies have associated less active polymorphisms of the enzyme CYP2C19 as a major source for reduced laboratory effect of clopidogrel and demonstrated correlation with clinical outcomes [73]. These findings led to the issuance of a U.S. FDA black box warning informing physicians and patients that an estimated 2 %–14 % of US patients will not have full clopidogrel efficacy due to having a less active genotype of CYP2C19 [74]. The significance of these genetic variations is not clear, as a recent meta-analysis did not corroborate an association between genetic testing results and clinical clopidogrel failure [66, 75]. Aspirin resistance has also been attributed to polymorphisms of the genes encoding for cyclooxygenase and glycoprotein (GP) IIb/IIIa [76].

There have been several other intriguing patient related factors associated with resistance to antiplatelet therapy. Gender, age, race, and diurnal variations in clopidogrel's ability to inhibit platelet aggregation have been shown to have an impact on antiplatelet effects [77–79]. These effects have not been observed in patients treated with aspirin. Although all of these effects are very interesting from a hypothesis generating perspective, they do little to improve our capacity to manage secondary prevention in stroke at this time.

Conclusion

Current guidelines for antithrombotic therapy in secondary prevention of noncardioembolic stroke recommend antiplatelet therapy: aspirin monotherapy, clopidogrel monotherapy, or aspirin combined with dipyridamole. Patient-specific issues are recommended for selection of the specific antiplatelet agent. After considering straightforward issues such as cost, allergies, other sensitivities (eg, history of gastric distress on aspirin), or previous adverse experiences that might exclude or make one of the agents less attractive, one might consider other issues. Evidence does not support the practice of switching to an alternate antiplatelet therapy in the case of clinical failure. Other resistance considerations, such as need for NSAIDS and interaction with aspirin use deserve consideration. Genetic and PPI-related clopidogrel resistance issues are still evolving and more evidence for their utility in selecting among antiplatelet agents or dosing is required.

Current guidelines do not address combination aspirin and clopidogrel use, except to recommend against it. It appears there is still much to be learned in this area. A meta-analysis of combinations of aspirin with dipyridamole and aspirin with clopidogrel showed efficacy and acceptable bleeding rates in secondary stroke prevention [46]. A recent meta-analysis of aspirin plus clopidogrel is encouraging as well [80]. The most recent American Heart Association/American Stroke Association guidelines for primary stroke prevention recommend the use of aspirin for prophylaxis of cardiovascular events including but not limited to stroke. Aspirin 81 mg daily or 100 mg every other day is also recommended for the prevention of first stroke in women with high risk of stroke. Aspirin is not recommended for prevention of first stroke in low risk individuals, nor is it recommended for prevention of first stroke in the setting of diabetes mellitus or diabetes mellitus plus asymptomatic peripheral artery disease. At this point, we recommend adherence to guidelines until research provides us with more definitive knowledge of the issues surrounding antiplatelet therapy as secondary prevention in stroke.

Disclosure No potential conflicts of interest relevant to this article were reported.

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- •• Of major importance

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