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Current Status of Antiplatelet Agents to Prevent Stroke

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Abstract

Stroke is one of the leading causes of disability; most are due to atherothrombotic mechanisms. About one third of ischemic strokes are preceded by other stroke or transient ischemic attacks. Stroke survivors are at high risk for vascular events (i.e., cerebrovascular and cardiovascular). Prevention of recurrent stroke and other major vascular events can be accomplished by control of risk factors. Nonetheless, the use of antiplatelet agents remains the fundamental component of secondary stroke prevention strategy in patients with noncardioembolic disease. Currently, the uses of aspirin, clopidogrel, or aspirin plus extended-release dipyridamole are valid alternatives for stroke or transient ischemic attack patients. To maximize the beneficial effects of these agents, the treatment should be initiated as early as possible and continue on a lifelong basis.

Keywords

Stroke; TIA; Antiplatelet; Prevention; Aspirin; Clopidogrel; Dipyridamole; Warfarin; Trial; Aspirin failure; Clopidogrel resistance; Cardioembolic

Introduction

Stroke is the second leading cause of death worldwide. The global occurrence of stroke is fifteen million annually, and only 5 million of these patients achieve favorable functional recovery [1•]. The majority (~80%) of these strokes are ischemic. Of the 800,000 cerebrovascular events that happen annually in the United States, almost one third are recurrent [2]. People who had an ischemic stroke or transient ischemic attack (TIA) are at significantly higher risk of stroke and other major ischemic events. Prospective studies have shown that the early risk of stroke post TIA is much higher than previously thought—18% at 90 days. More importantly, most of the recurrent strokes happened within the first 2 days after the index event [3•, 4•]. After 1 year the risk falls at about 5% per year, with about 3% per year in the incidence of myocardial infarction (MI) [5].

Secondary stroke prevention can be divided into early (prevention of early recurrence) and long-term prevention (late recurrence). Ischemic stroke is a heterogeneous syndrome that is

comprised of the following categories according the underlying mechanism: atherothrombotic (30%), cardioembolic (20%), penetrating artery disease (25%), and cryptogenic (25%). Elucidating the mechanism of stroke is crucial to select the most appropriate therapeutic strategy to prevent further events. Antiplatelet agents are the cornerstone for secondary prevention of ischemic events in patients with noncardioembolic disease.

Commonly used antiplatelet drugs are aspirin, dipyridamole, and clopidogrel. Aspirin is an irreversible inhibitor of cyclooxygenase-1, which in turn inhibits the formation of thromboxane A₂. Dipyridamole increases cyclic AMP by inhibiting platelet phosphodiesterase E5. Clopidogrel is a thienopyridine P2Y₁₂ adenosine diphosphate receptor blocker.

Antiplatelet Agents for Secondary Prevention of Noncardioembolic Stroke

Antiplatelets Versus Oral Anticoagulation

To date, large trials have failed to show the superiority of warfarin over aspirin in secondary prevention of non-cardioembolic stroke with various International Normalized Ratio (INR) targets investigated. In addition, patients assigned to anticoagulants had an excess of hemorrhagic complications (Table 1).

The SPIRIT trial compared 30 mg daily aspirin against warfarin (INR target 3.0–4.5) in an open randomized trial of stroke patients (1,316) on sinus rhythm. Due to a high rate of hemorrhagic complications in the anticoagulation group the study was terminated prematurely. Major systemic and intracranial hemorrhage rates were 8% in the warfarin group versus 1% in the aspirin group (hazard ratio [HR], 9.3; 95% CI, 4.0–22). The occurrence of ischemic events was similar in both groups (4.1% in both groups; HR, 1.03; 95% CI, 0.6–1.75) including vascular death, nonfatal ischemic stroke, and nonfatal MI [6].

More conservative INR targets have also failed to establish an advantage of warfarin over aspirin as demonstrated by the WARSS trial, which tested INRs between 1.4 and 2.8. Patients with noncardioembolic stroke (2,206) were included in this trial. The results show similarity in stroke recurrence and death in both groups, with an excess of systemic bleeds in those allocated to warfarin [7].

The ESPRIT trial randomized 1,068 patients with prior stroke or TIA to warfarin (INR target 2.0–3.0) or aspirin, 30–325 mg, per day. Treatment was randomized but open; outcome event assessment was blinded. The median INR was 2.5 and 70% of the time patients were in assigned range. The study was terminated prematurely due to the fact that randomization to the aspirin or aspirin plus dipyridamole intervention was determined to be superior. There were no significant differences in terms of primary outcome (stroke, MI, vascular death, or major bleeds) in the aspirin group compared with warfarin, with an 18% event rate in the aspirin and 19% in the warfarin group (HR, 1.02; 95% CI, 0.77–1.35). There was a nonsignificant trend toward a lower rate of ischemic stroke in the warfarin group (7.6% vs. 10.0%; HR, 0.76; 95% CI, 0.51–1.15), which was offset by a significantly higher rate of major bleeding in this group (8.4% vs. 3.4%; HR, 2.56; 95% CI, 1.48–4.43) [8].

The WASID trial compared high-dose aspirin (1,300 mg/d) to dose-adjusted warfarin with target INR between 2.0 to 3.0 in patients with prior stroke and proven intracranial stenosis. Five hundred sixty-nine patients with 50% stenosis were enrolled. There was no significant difference in recurrent stroke rate, with 22% recurrence over 1.8 years of follow-up in the aspirin group and 22% in the warfarin group (HR, 1.04; 95% CI, 0.73–1.48). Enrollment

was stopped early due to high rates of adverse events among the patients receiving warfarin, including death (4.3% in the aspirin group vs. 10% in the warfarin group; HR, 0.46; 95% CI, 0.23–0.90; $P=0.02$), major hemorrhage (3% vs. 8%; HR, 0.39; 95% CI, 0.18–0.84; $P=0.01$), and MI and sudden death (3% vs. 7%; HR, 0.40; 95% CI, 0.18–0.91; $P=0.02$) [9].

Antiplatelet Agents: Monotherapy and Combination of Agents for Secondary Stroke Prevention in Patients on Sinus Rhythm (Table 2)

Aspirin—Aspirin is the most commonly used antiplatelet agent for prevention of vascular events. In a meta-analysis by the Antithrombotic Trialist Collaboration, aspirin was associated with a 23% reduction in the combined events of stroke, MI, and vascular death in patients with prior cerebrovascular events. Aspirin was associated with a 22% reduction in stroke in secondary prevention trials (2.08% vs. 2.54% per year; relative risk [RR], 0.78; 95% CI, 0.61–0.99; $P=0.002$). There was a nonsignificant increase in hemorrhagic stroke in the aspirin group [10].

Aspirin has been shown to be effective in secondary prevention of ischemic events in doses from 30 to 1,300 mg daily [11–15]. Higher doses cause an increased rate of gastrointestinal upset and gastrointestinal bleeds.

Aspirin Plus Dipyridamole—The ESPS-2 trial randomized patients with prior ischemic stroke or TIA into one of four groups with twice-daily dosing within 3 months after their index event: placebo, acetylsalicylic acid (ASA) 25 mg, extended-release dipyridamole (ERDP) 200 mg, or combination aspirin and dipyridamole (ASA-ERDP, same dose and formulation). Six thousand sixty-two patients were followed with a mean follow-up of 2 years. The stroke rate in the placebo group was 16%. Both aspirin and ERDP showed a superiority over placebo with a reduced rate of stroke (13%; OR, 0.79; 95% CI, 0.65–0.97; 13%; OR, 0.81; 95% CI, 0.67–0.99, respectively); the benefits were greater with combination therapy (9.9%; OR, 0.59; 95% CI, 0.48–0.73), with a 23% RR reduction and 3% absolute risk reduction in stroke between the aspirin monotherapy and the combination group over 2 years of follow-up [14].

Aspirin monotherapy was compared with combination aspirin and ERDP in the ESPRIT trial, the results of which echoed that of ESPS-2. Patients were randomized to ASA 30–325 mg daily with or without ERDP 200 mg twice daily within 6 months of stroke or TIA. Two thousand seven hundred thirty-nine patients were followed for over 3.5 years. Almost half of the participants received a daily 30-mg dosage of aspirin and the rest 75 mg. The percent of major ischemic events (vascular death, nonfatal ischemic stroke, and nonfatal MI) was 13% in the aspirin group and 10% in the combination group with an absolute risk reduction of 7%. There was no significant difference in the proportion of major bleeds between the two groups (RR, 1.03; 95% CI, 0.84–1.25), although a larger proportion (34%) of the combination group discontinued therapy, mostly due to headache [16].

Clopidogrel—The CAPRIE trial investigated the effects of clopidogrel in 19,185 patients with a history of stroke, MI, or peripheral vascular disease. Participants were randomized to daily clopidogrel 75 mg or aspirin 325 mg. Over a mean follow-up of 1.9 years, the annual rate of nonfatal stroke, nonfatal MI, and vascular death was 5.83% in the aspirin group and 5.32% in the clopidogrel group (RR reduction, 0.087; 95% CI, 0.003–0.165; $P=0.043$) with an absolute risk reduction of 0.5%. In the stroke population, there were no differences in events between both groups. There was no significant difference in major hemorrhage rates between groups, and clopidogrel had fewer gastric side effects [17].

Aspirin Plus Dipyridamole Versus Clopidogrel—The PROfESS study was designed as a noninferiority trial to test the efficacy of aspirin-EDRP against clopidogrel for stroke prevention. In a factorial design, 20,332 patients with prior stroke were enrolled. Patients were allocated to 75 mg daily clopidogrel or twice-daily aspirin-EDRP 25–200 mg in combination with telmisartan or placebo. Mean follow up was 2.5 years. This large study showed that the rate of recurrent stroke was similar in both groups (9% of patients in the aspirin-EDRP vs. 8.8% in the clopidogrel group; HR, 1.01; 95% CI, 0.92–1.11). The rate of major systemic hemorrhage, including intracranial, was higher in the aspirin-EDRP group (HR, 1.15; 95% CI, 1.00–1.32). Rates of discontinuation were higher in aspirin-EDRP than clopidogrel (29% vs. 23%; 7% difference; 95% CI, 5.3–7.7), most often due to headache [18].

Combination Therapy: Aspirin Plus Clopidogrel—Favorable results of combination aspirin and clopidogrel for prevention of vascular events in patients with percutaneous coronary intervention in the PCI-CURE (a substudy of the CURE) [19] and acute MI in the CURE [20] and CREDO [21] trials prompted an interest in investigating this combination in patients with prior cerebrovascular disease.

The MATCH trial compared clopidogrel 75 mg per day alone to clopidogrel 75 mg per day plus aspirin 75 mg per day in 7,599 patients with a recent ischemic stroke or TIA. About 70% of the participants were diabetics. Patients assigned to combination therapy had a nonsignificant reduction of primary outcome of 6% ($P=0.24$). There was an excess of non—central nervous system life-threatening hemorrhages among those receiving combination therapy (absolute increase of 0.5% per year; $P<0.05$). In short, MATCH did not show a benefit of adding aspirin to clopidogrel in this cohort [22].

The CHARISMA study compared aspirin alone (75–162 mg/d) to aspirin plus clopidogrel (75 mg/d) in 15,603 patients with symptomatic vascular disease (80%, including prior stroke, MI, or peripheral vascular disease) or multiple vascular risk factors (asymptomatic). The overall results showed no significant difference in primary outcome in both groups (RR, 0.93; 95% CI, 0.83–1.05; $P=0.22$). There was a trend in favor of combination therapy in the symptomatic patients (RR, 0.88; 95% CI, 0.77–0.998; $P=0.046$) and a 20% reduction in nonfatal stroke (RR, 0.80; 95% CI, 0.65–0.997; $P=0.05$) among all participants. Compared with MATCH, which demonstrated an increase in intracerebral hemorrhage (ICH), CHARISMA did not show this same safety concern. CHARISMA reported no differences in ICH (26 vs. 27; P = not significant) or in major bleeding (130 vs. 104; $P=0.09$), although moderate bleeding was increased in the combination group ($P<0.001$) [23].

Based on the results of MATCH and CHARISMA trial, the combination of aspirin plus clopidogrel should not be routinely indicated for secondary stroke prevention. The ongoing National Institutes of Health (NIH)—National Institute of Neurological Disorders and Stroke (NINDS) SPS3 (<http://www.sps3.org>) trial (<http://clinicaltrials.gov>) is investigating whether daily combination ASA-clopidogrel 325/75 mg is superior to ASA monotherapy for reducing stroke, cognitive decline, and major vascular events in 3,000 patients with lacunar stroke. Patients are also being randomized in a two-by-two factorial design to two blood pressure control target groups: “usual” (systolic 130–149 mm Hg) or “intensive” (<130 mm Hg). At present, the study has enrolled 2,856 participants with the final results anticipated by mid 2012.

Prevention of Early Stroke Recurrence: Aspirin Plus Clopidogrel—Data from the MATCH and CARESS trials suggest a possible short-term benefit of combination aspirin and clopidogrel in those patients enrolled within 24 h of their event. The FASTER trial was a randomized, double-blinded pilot trial that allocated 392 patients within 24 h of TIA or

minor ischemic stroke to clopidogrel 300-mg loading dose, then 75 mg daily or placebo and simvastatin 40 mg daily. All patients took ASA 81 mg and received a loading dose of 162 mg if they were aspirin-naïve prior to their qualifying event. Primary outcome was the occurrence of any new stroke at 3 months. The trial was terminated prematurely due to low recruitment. Stroke rates were 11% in the placebo group and 7% in the clopidogrel group (RR, 0.7; 95% CI, 0.3–1.2; $P=0.19$). There were two intracranial hemorrhages, both in the clopidogrel group (absolute risk increase 1.0%; 95% CI, –0.4 to 2.4; $P=0.5$). Although the results of FASTER are encouraging, the early termination and lack of statistical power preclude change in current practice. Further research is warranted in this field [24].

Two trials, the POINT and CHANCE studies, are currently investigating prevention of early recurrence of stroke. The ongoing NIH-NINDS–sponsored POINT trial (NCT00991029) plans to enroll 5,000 patients with minor stroke (NIH Stroke Scale < 3) or high-risk TIA (ABCD2 > 4). This study may further clarify the benefit of short-term combined antiplatelet therapy. Patients receiving aspirin 50–325 mg daily are being randomized within 12 h of symptom onset to clopidogrel 600-mg loading dose, then 75 mg daily, or placebo. Primary outcome is a composite of ischemic stroke, MI, or vascular death at 90 days. The trial began enrollment in early 2010 and is anticipated to be completed by 2016 (<http://clinicaltrials.gov>). The CHANCE study has similar design to the POINT and is being conducted in China; it has enrolled about 2,500 patients with an anticipated completion date by late 2011 (<http://clinicaltrials.gov>).

Early Stroke Prevention: ASA Plus Dipyridamole Plus Clopidogrel—The TARDIS trial is investigating whether the triple combination aspirin-EDRP and clopidogrel, initiated within 48 h of the index event, is superior to aspirin-EDRP alone in preventing recurrent stroke and TIA at 35 and 90 days (<http://clinicaltrials.gov>).

Other Antiplatelet Agents—Current data suggest that triflusal, cilostazol, and sarpogrelate have shown equal efficacy to aspirin, although their performance in phase 3 trials has yet to be verified.

A meta-analysis of five trials comparing aspirin 325 mg daily to triflusal for secondary prevention of stroke and TIA (four trials, 2,944 patients; follow-up 6–47 months) or MI (one trial, 2,275 patients; follow-up 35 days) showed no significant difference in the number of major vascular events between treatment groups (odds ratio [OR], 1.04; 95% CI, 0.87–1.23). Triflusal-treated patients had a lower risk of major (OR for aspirin 2.34; 95% CI, 1.58–3.46) and minor hemorrhage (OR for aspirin 1.60; 95% CI, 1.31–1.95) but experienced more nonhemorrhagic adverse gastrointestinal events than aspirin (OR for ASA 0.84; 95% CI, 0.75–0.95) [25].

Cilostazol has been investigated in two trials for secondary stroke prevention. The first, which randomized 1,067 patients with ischemic stroke, compared cilostazol with placebo and found a 41.7% reduction in ischemic stroke (3.37%/y in cilostazol, 5.78% in placebo; 95% CI, 10.3–62.9; $P=0.0127$) [26]. The second, which compared 100 mg daily ASA with 100 mg twice-daily cilostazol, enrolled 720 patients in a pilot study within 1–6 months of their index event and were followed for 12–18 months. There was no significant difference in rates of recurrent stroke (HR, 0.62; 95% CI, 0.30–1.26; $P=0.185$) between the treatment groups. There were more intracranial hemorrhages in patients who were taking ASA (7 ASA vs. 1 cilostazol; $P=0.034$) [27].

Sarpogrelate was investigated in the S-ACCESS trial, which randomized 1,510 stroke patients within 1 week to 6 months after their event. Patients received sarpogrelate 100 mg three times a day or daily aspirin 81 mg and were followed for a mean of 1.59 years. There

was no significant difference in the number of strokes (6.09%/y sarpogrelate, 4.86%/y aspirin; HR, 1.25; 95% CI, 0.89–1.77; $P=0.19$) or vascular events in either group (7.61%/y sarpogrelate, 7.12%/y aspirin; HR, 1.07; 95% CI, 0.80–1.44; $P=0.65$). There were fewer hemorrhagic events in the sarpogrelate group (11.9% sarpogrelate, 17.3% ASA; $P<0.01$) [28].

Antiplatelet Agents in Secondary Prevention of Cardioembolic Stroke

Oral anticoagulants remain the treatment of choice for secondary prevention of cardioembolic stroke. However, antiplatelet therapy provides an alternative when oral anticoagulation is contraindicated or when patient choice or compliance limits choice of therapy.

The superiority of warfarin over combination antiplatelet therapy for stroke prevention in nonvalvular atrial fibrillation has been shown in several trials. A meta-analysis of 29 trials with 28,044 patients showed a 64% reduction in stroke in the warfarin group compared with 22% (95% CI, 0.49–0.74) in the antiplatelet groups (95% CI, 0.06–0.35) for a RR reduction of 39% (95% CI, 0.22–0.52) [29].

The ACTIVE-W trial compared warfarin to combination aspirin plus clopidogrel in 6,706 patients; it was terminated early due to a clear benefit in the warfarin group, who had a 4% annual event rate versus 6% in the combination group (RR, 1.44; 95% CI, 1.18–1.76; $P=0.0003$) [30].

The ACTIVE-A trial enrolled patients with cardioembolic stroke deemed unsuitable for warfarin therapy, either due to risk of bleeding, physician judgment, or patient preference. The effects of combination aspirin and clopidogrel versus aspirin and placebo on secondary stroke prevention were compared in 7,554 patients over a mean follow-up period of 3.6 years. Only 13% of participants had history of stroke or TIA. The clopidogrel group experienced major vascular events at a rate of 6.8% per year, compared with 7.6% per year in the control group (RR, 0.89; 95% CI, 0.81–0.98). The risk reduction was largely due to a significant reduction of ischemic strokes, with rates of 1.9% versus 2.8% per year in the clopidogrel and control groups, respectively (RR, 0.68; 95% CI, 0.57–0.80). However, this therapeutic benefit was hampered by a high incidence of systemic and intracranial hemorrhage. Annual rates of any major bleeding in the clopidogrel and control groups, respectively, were 2.0% versus 1.3% (RR, 1.57; 95% CI, 1.29–1.92) and rates of intracranial bleeding were 0.4% versus 0.2% (RR, 1.87; 95% CI, 1.19–2.94) [31].

Aspirin Resistance and “Failure”

In spite of the well-reported efficacy of aspirin in the secondary prevention of cardiovascular disease [32–35], recurrent vascular events are not uncommon in patients on aspirin. The recurrence of vascular events under prescription of a regular therapeutic dose of aspirin characterizes what is known as clinical aspirin resistance or aspirin treatment failure. This may or may not be accompanied by biochemical evidence of aspirin resistance, a phenomenon of persistent platelet activation measured by platelet function tests [36]. The incidence of clinical aspirin resistance varies from 11% to 17.3% depending on the definition adopted [35], whereas the incidence of biochemical resistance ranges from as little as 5% to as much as 60% depending primarily on the platelet function assay used [37–39]. At present, no standardized definition or test can be used to quantify either type of aspirin resistance. A few studies have attempted to quantify both clinical and pharmacologic resistance but the reported data are hampered by internal and external validity concerns including small sample sizes, lack of agreement between different platelet function tests, different dose regimens and non-adherence, and insufficient information about measurement

stability over time. Moreover, none of the available platelet aggregation assays have convincingly been shown to correlate with recurrence of clinical events (ischemic stroke or MI) and the results between different assays have also been discordant. Because aspirin resistance is a poorly defined phenomenon and it is likely to be multifactorial, there is no consensus regarding how to treat patients with so-called “aspirin resistance or aspirin failure.” Consequently, currently there is no indication to screen patients for “aspirin resistance.”

Clopidogrel Resistance

The concept of clopidogrel resistance has emerged as a possible explanation for the continued occurrence of ischemic events despite the adequate dosage of the antiplatelet agent and proper compliance. The prevalence of clopidogrel nonresponse in different populations has been described as between 4% and 30%. The reason for the response variability among different studies depends on the technique used to evaluate platelet aggregation [40, 41]. There are several potential mechanisms of clopidogrel resistance, which can be divided into two main groups: 1) extrinsic mechanisms (i.e., drug interactions involving CYP3A4) and 2) intrinsic mechanisms (i.e., polymorphisms of P2Y₁₂ receptor and CYP3As).

In regard to drug interactions, any medication that interacts with (either inhibiting or increasing) CYP3A4 can potentially block the conversion of clopidogrel into its active metabolite. Among these drugs, statins, except for pravastatin, might interfere with clopidogrel metabolism. The antiplatelet activity has also been shown to be reduced in persons receiving omeprazole, which is a CYP2C19 inhibitor. However, other studies have not confirmed this observation.

Recently, several reports indicate that certain polymorphisms in the hepatic cytochrome p450 system are associated with an excess of vascular events. Patients who are carriers of a loss of function of CYP2C19 allele (including the *2 and *3 alleles) might have a reduced rate in the conversion to an active metabolite, therefore resulting in a decreased inhibition of platelets. Carriers of loss-of-function alleles compared with noncarriers showed a significant increase in the risk of major vascular events [42]. A recent analysis of data among 5,059 patients with acute coronary syndromes or atrial fibrillation showed that the response to clopidogrel compared with placebo was consistent, irrespective of CYP2C19 loss-of-function carrier status [43]. Therefore, it is possible that loss-of-function variants do not directly alter the efficacy and safety of clopidogrel. Consequently, clopidogrel should be used regardless of the carrier status until further studies can elucidate this paradox.

Currently, the management of clopidogrel resistance is a challenge and there are no standardized guidelines. Until new data are available, it seems prudent to avoid interactions of drugs with a well-known effect on the hepatic cytochrome p450 that might affect the metabolism of clopidogrel.

Antiplatelet Agents and Cerebral Microbleeds

Although the benefit of antiplatelet agents for the secondary prevention of stroke has been clearly demonstrated, there is also solid evidence that the benefit can be negated by the increased risk of hemorrhagic complications, including ICHs. Cerebral microbleeds (CMBs) are deposits of hemosiderin easily identified in T2*-weighted gradient-echo MRI sequences as they are residues of small hemorrhages [44]. CMBs are currently regarded as evidence of cerebral small artery disease [45] and therefore are associated with leukoaraiosis and lacunar and hemorrhagic strokes [46]. There is considerable debate concerning the potential

increased risk of ICH in patients with CMBs who are on antiplatelet therapy. The prevalence of CMBs in patients with ICH is high, particularly in those with lobar hematomas.

Prospective studies have shown that there is an increased risk for developing ICH in patients with CMBs on basal MRI [47, 48]. A case-control study investigated whether asymptomatic CMBs were a risk factor for ICH among aspirin users [49]. Twenty-one patients with ICH and 21 controls with no ICH were compared. CMBs were present in 19 (90%) patients with ICH, whereas only seven patients (33%) in the control group were found to have CMBs ($P<0.001$). Moreover, the number of CMBs was also significantly higher in the group of patients with ICH (mean number of microbleeds, 13 vs. 0.2; $P<0.001$). Conversely, patients with CMBs have an excess risk for ischemic stroke when compared to those without CMBs [46]. Based on the present evidence, the use of antithrombotic therapy should not be based on the presence or absence of CMBs. Therefore, screening for CMB is not justified.

Conclusions

Antiplatelet drugs are the gold standard for secondary prevention of noncardioembolic stroke of presumed thrombotic etiology. There is no proven indication for the use of anticoagulants in this stroke population. Current guidelines favor the use of aspirin, aspirin-ERDP, or clopidogrel in stroke or TIA patients [50••]. Aspirin dosages between 50 to 325 mg per day are commonly used because of their lower cost, although clopidogrel and ASA-ERDP are also acceptable options. Clopidogrel is better tolerated than aspirin and offers greater benefit on noncerebrovascular events. Aspirin-ERDP is superior to aspirin in preventing stroke recurrence; however, it is not as well tolerated as aspirin and clopidogrel. In particular, many patients cannot tolerate the headaches that may accompany the use of aspirin-ERDP. There is no current indication for long-term combination aspirin-EDRP plus clopidogrel or aspirin plus clopidogrel in atherothrombotic stroke, although the use of combination aspirin and clopidogrel is under investigation for short-term use and long-term secondary prevention in patients with lacunar stroke.

Tests for resistance to aspirin and clopidogrel are not standardized and their results are not currently validated. Therefore, selection of an antiplatelet agent should not be based on the results of these tests. Oral anticoagulants are the gold standard for secondary prevention of cardioembolic stroke, although aspirin plus clopidogrel confers additional protection over aspirin alone in patients with nonvalvular atrial fibrillation who are not suitable for anticoagulation.

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Clinical Trial Acronyms

ACTIVE	Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events
CAPRIE	Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events
CHANCE	Clopidogrel in High-risk Patients with Acute Non-disabling Cerebrovascular Events
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization. Management and Avoidance
CREDO	Clopidogrel for the Reduction of Events During Observation
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events
ESPRIT	European/Australasian Stroke Prevention in Reversible Ischaemia Trial
ESPS-2	European Stroke Prevention Study 2
FASTER	Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence
MATCH	Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attacks or Ischemic Stroke
POINT	Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke

PRoFESS	Prevention Regimen for Effectively Avoiding Second Strokes
S-ACCESS	Sarpogrelate-Aspirin Comparative Clinical Study for Efficacy and Safety in Secondary Prevention of Cerebral Infarction
SPIRIT	Stroke Prevention in Reversible Ischemia Trial
SPS3	Secondary Prevention of Small Subcortical Strokes
TARDIS	Triple Antiplatelets for Reducing Dependency After Ischaemic Stroke
WARSS	Warfarin-Aspirin Recurrent Stroke Study
WASID	Warfarin-Aspirin Symptomatic Intracranial Disease

Table 1
Randomized trials comparing warfarin to aspirin for secondary prevention in noncardioembolic stroke

Trial	Year	Patient population, n	Follow-up	Comparison	Primary outcome	Efficacy	Safety
SPRIT	1997s	1,316 with stroke or TIA	14 months	ASA 30 mg/d Warfarin target INR 3.0–4.5	Vascular death, nonfatal stroke, nonfatal MI, or nonfatal major bleeding	4.1% in both groups (HR, 1.03; 95% CI, 0.6–1.75)	Major hemorrhage 8.1% warfarin and 1.0% ASA (HR, 9.3; 95% CI, 4.0–22)
WARSS	2001	2,206 with ischemic stroke	2 years	ASA 325 mg/d Warfarin target INR 1.4–2.8	Recurrent ischemic stroke or death	17.8% warfarin, 16.0% ASA (HR, 1.13; 95% CI, 0.92–1.38)	No significant difference in major hemorrhage: 2.22/100,000 patient-years warfarin, 1.49 ASA (rate ratio 1.48; 95% CI, 0.93–2.44; $P<0.10$)
WASID	2005	569 with stroke or TIA and intracranial stenosis 50% to 99%	1.8 years	ASA 1,300 mg/d Warfarin target INR 2.0–3.0	Ischemic and hemorrhagic stroke, vascular death	22.1% ASA, 21.8% warfarin (HR, 1.04; 95% CI, 0.73–1.48)	Major hemorrhage 3.2% ASA, 8.3% warfarin (HR, 0.39; 95% CI, 0.18–0.84); MI and sudden death 2.9% ASA, 7.3% warfarin (HR, 0.40; 95% CI, 0.18–0.91)
ESPRIT	2007	1,068 with recent stroke or TIA	Mean 4.6 years (SD 2.2)	ASA 30–325 mg/d Warfarin target INR 2.0–3.0	Vascular death, nonfatal stroke, nonfatal MI, or major bleeding complication	18% ASA, 19% warfarin (HR, 1.02; 95% CI, 0.77–1.35)	Major bleeding 8.4% warfarin, 3.4% ASA (HR, 2.56; 95% CI, 1.48–4.43)
Post hoc ASA-ERDP vs. warfarin (HR, 1.31; 95% CI, 0.98–1.75)							

ASA acetylsalicylic acid, ERDP extended-release dipyridamole, ESPRIT European/Australasian Stroke Prevention in Reversible Ischaemia Trial, HR hazard ratio, INR International Normalized Ratio, MI myocardial infarction, SD standard deviation, SPRIT Stroke Prevention in Reversible Ischemia Trial, TIA transient ischemic attack, WARSS Warfarin-Aspirin Recurrent Stroke Study, WASID Warfarin-Aspirin Symptomatic Intracranial Disease

Table 2

Randomized trials for secondary stroke prevention testing antiplatelet agents

Trial	Year	Patient population, n	Comparison (doses in mg)	Primary end point	Follow-up	Efficacy	Major safety and adverse events
ESPS-2	1996	6,602 with prior ischemic stroke or TIA	Placebo vs. ASA 25 bid vs. ERDP 200 bid vs. ASA-ERDP 25/200 bid	Stroke, death, and stroke or death together	2 years	ASA-ERDP vs. placebo: 24.4% RRR (95% CI $\pm 5.3\%$) stroke or death ASA-ERDP vs. ASA: 12.9% ($\pm 6.0\%$) 20% hazard reduction (95% CI, 2–34)	Rates of discontinuation due to bleeding highest in ASA (absolute rate, any bleeding: 1.2%) and ASA-ERDP (1.3%) Rates of discontinuation due to headache highest in ERDP (8.0%) and ASA-ERDP (8.1%)
ESPRIT	2006	2,739 with recent stroke or TIA	ASA 30–325 ASA/ERDP 30–325/200 bid	All-cause vascular death, nonfatal stroke, nonfatal MI, major bleed	Mean 3.5 years (SD 2.0)		No significant difference in major bleeding, 34% in combination group discontinued treatment due to headache
CAPRIE	1996	19,185 with history of stroke, MI, or PVD	ASA 325 Clopidogrel 75	Ischemic stroke, MI, or vascular death	Mean 1.91 years	All patients: 8.7% RRR (95% CI, 0.3–16.5) Subgroup with history of stroke: 7.3% (-5.7 to 18.7)	No significant difference in major hemorrhage
MATCH	2004	7,599 with recent ischemic stroke or TIA and at least one additional vascular risk factor who were already taking daily clopidogrel	Clopidogrel 75 ASA-C 75/75	Ischemic stroke, MI, vascular death, or rehospitalization for acute ischemia	18 months	6.4% RRR (95% CI, -4.6 to 16.3) Ischemic stroke: 7.1% (-8.5 to 20.4)	1.3% absolute risk increase (1.3% vs. 2.6%, 95% CI, 0.6–1.9) in major and life-threatening bleeding in combination group, no difference in fatal bleeding
CHARISMA	2006	15,603 with clinically evident cardiovascular disease or multiple vascular risk factors	ASA 75–162 7.1% RRR (95% CI, -4.5 to 17.5) ASA-C 75–162/75	MI, stroke, or death from cardiovascular causes	28 months		Nonsignificant increase in severe and fatal bleeding, significant increase in moderate bleeding in combination group (1.3% vs. 2.1%, RR, 1.62; 95% CI, 1.27–2.08)
PRoFESS	2008	20,332	ASA-ERDP 25–200 bid Clopidogrel 75	First recurrence of stroke	Mean 2.5 years	1% hazard reduction (95% CI, -8 to 11)	Major hemorrhage increased in DP group (HR, 1.15; 95% CI, 1.00–1.32), rates of discontinuation higher in DP group (6.5% absolute

Trial	Year	Patient population, n	Comparison (doses in mg)	Primary end point	Follow-up	Efficacy	Major safety and adverse events
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difference; 95% CI, 5.3–7.7), mostly due to headache
 ASA acetylsalicylic acid, ASA-C acetylsalicylic acid–clopidogrel, *bid* twice a day, CAPRIE Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events, CHARISMA Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance, DP dipyridamole, ERDP extended-release dipyridamole, ESPRIT European/Australasian Stroke Prevention in Reversible Ischaemia Trial, ESPS-2 European Stroke Prevention Study 2, HR hazard ratio, INR International Normalized Ratio, MATCH Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attacks or Ischemic Stroke, MI myocardial infarction, PROFESS Prevention Regimen for Effectively Avoiding Second Strokes, PVD peripheral vascular disease, RR relative risk, RRR relative risk reduction, SD standard deviation, TIA transient ischemic attack