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Secondary Prevention of Stroke and Transient Ischemic Attack:

Is More Platelet Inhibition the Answer?

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Abstract

Background—Recurrent cerebrovascular events constitute an estimated 200 000 of the 700 000 strokes reported annually in the United States, which makes secondary stroke prevention an important goal in the management of disease among patients who have experienced stroke or transient ischemic attack.

Methods and Results—Various pharmacological approaches have been advocated, but the relative efficacy and safety of these regimens has remained the subject of much debate. The results of recent clinical trials on the use of antiplatelet therapy suggest that patients with a history of stroke or transient ischemic attack may constitute a population distinct from patients with coronary or peripheral vascular disease. This may be caused, in part, by the differing etiologies of stroke and the increased vulnerability of cerebral vessels to bleeding. Indeed, dual antiplatelet therapy, which has been found to be beneficial for the treatment of acute coronary syndromes and percutaneous coronary interventions, does not confer secondary stroke protection. The emerging paradigm is that some level of platelet inhibition is required for secondary stroke protection; a level beyond which increased risk of bleeding arises.

Conclusion—Because the vast majority of patients with ischemic stroke have recurrent stroke or transient ischemic attack, rather than myocardial infarction, as their next event, antiplatelet therapies for these patients should be administered according to what has been shown to be efficacious for secondary stroke protection rather than for myocardial protection. Combination therapies, which provide optimal platelet inhibition as well as vascular protection, may offer the best strategy for secondary stroke protection.

Keywords

platelets; stroke; prevention

Recurrent cerebrovascular events constitute an estimated 200 000 of the 700 000 strokes reported annually in the United States.¹ The consequent morbidity and mortality, as well as the healthcare costs associated with disability from strokes, make the prevention of these events an extremely high public health priority.¹ Because the majority of strokes in the United States are noncardioembolic ischemic strokes, treatment with antiplatelet agents is the current recommended first-line therapy for secondary stroke prevention in these patients.²

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Presently, only 4 antiplatelet regimens have been approved by the US Food and Drug Administration for secondary stroke prevention: monotherapy with aspirin, ticlopidine, clopidogrel, and the combination of aspirin plus extended-release dipyridamole (ER-DP).² What has emerged from recent clinical trials with antiplatelet agents is that, in contrast to symptomatic coronary and peripheral vascular disease, more platelet inhibition is not necessarily better for secondary stroke protection. These results suggest that the pathogenesis of cerebrovascular events may differ from other manifestations of atherothrombotic disease, and that cerebral vessels may be more vulnerable to bleeding caused by antiplatelet therapy than vessels from other vascular beds.

Differences Between Recurrent Cerebrovascular and Coronary Events

Atherothrombotic vascular disease most frequently manifests as a cerebrovascular event (stroke or transient ischemic attack [TIA]), coronary event (myocardial infarction [MI]), or event associated with peripheral arterial disease (PAD) (eg, intermittent claudication, ischemic limb). The predominant risk factors for these events are broadly similar, and they include diabetes mellitus or impaired glucose tolerance, obesity, dyslipidemia, hypertension, and cigarette smoking.²⁻⁴ The commonality of risk factors reflects the systemic nature of atherothrombotic vascular disease. However, the observed differences between risk factors associated with specific types of cardiovascular disease suggest some degree of divergence in the underlying pathophysiological processes. For example, dyslipidemia is a major risk factor for coronary artery disease, but its role in stroke is equivocal.^{3,5} The notion of divergent etiologic pathways for stroke and coronary heart disease (CHD) has also been supported by data from epidemiologic studies and therapeutic clinical trials, with respect to patterns of recurrent events and response to therapy among patients with symptomatic cerebrovascular disease and symptomatic CHD.

One key differentiator between CHD and stroke is the degree to which local atherothrombosis is implicated as a direct causative factor. Whereas most CHD events are caused by plaque rupture from coronary atherosclerosis, atherosclerotic disease contributes only to an estimated 20% of large-vessel ischemic strokes.^{6,7} Although another 20% to 25% of ischemic strokes are caused by small vessel disease (ie, lacunar strokes), it is not entirely clear that the etiology of small vessel disease is caused by atherosclerosis. Thus the remaining types of stroke for which atherosclerosis may not be a major contributing factor include hemorrhagic, lacunar, and cryptogenic strokes. The therapeutic options for CHD and ischemic stroke, therefore, may not overlap for the majority of strokes.

A study of event recurrence patterns in 2 large cohorts of patients with symptomatic cardiovascular disease showed that 77% to 79% of recurrent events among patients with an initial stroke were stroke, whereas only about 20% had an MI. Conversely, among patients with initial MI, 76% to 84% had a recurrent MI, whereas only 13% to 18% had a stroke.⁸ In a study of cardiovascular events among Michigan Medicare patients after stroke or TIA, the 2-year incidence of stroke was 11.8%, whereas the incidence of cardiac events (such as PCI and coronary bypass procedures, as well as MI) was 7.7%.⁹ Another study of recurrent events after first ischemic stroke among elderly patients enrolled in the Heart Protection Study (age 65 years or older) found that the 1-year rate of recurrent stroke was nearly twice that of cardiac events (105.4 versus 59.3 per thousand person-years, respectively).¹⁰ Similar patterns of recurrent events have also been described in clinical intervention studies. During the Clopidogrel versus Aspirin in Patients at Risk of Recurrent Ischemic Events (CAPRIE) study, which evaluated secondary events among patients with a history of either stroke, MI, or PAD, patients with an index stroke had 7 times more strokes than MIs. In contrast, among patients with an index MI, there were nearly 4 times more recurrent MIs than strokes.^{11,12}

The suggestion that patients are especially “fragile” (susceptible to recurrent stroke) after stroke or TIA has been borne out by several recent studies. As noted previously, the 1-year risk of recurrent stroke after ischemic stroke in elderly patients is >10%.¹⁰ Risk of recurrent stroke appears to be strongly weighted toward early occurrence. In 1 study, the 90-day stroke risk after initial TIA was 10.5%, but half of the recurrent events occurred within 2 days of the TIA.¹³ Consistent with these results, another study found that the risk of stroke 7 days and 30 days after onset of first TIA was 8.6% and 12.0%, respectively.¹⁴ Poststroke patients also appear to differ from post-MI patients with regard to safety outcomes. In the Stroke Prevention in Reversible Ischemia Trial (SPIRIT), for example, warfarin treatment of stroke patients at an anticoagulation intensity (international normalized ratio, 3.0 to 4.5) known to be well tolerated by patients with coronary artery disease, resulted in premature suspension of the study as a result of a high rate of severe bleeding complications.^{12,15} These results suggest that patients with a history of stroke or TIA may constitute a population distinct from those with symptomatic CHD or PAD. This may have important clinical implications in terms of therapy, especially if the therapeutic approach for secondary strokes differs from that for other cardiovascular diseases. The differences between the cerebral vasculature and other vascular beds, and the need for a more comprehensive understanding of the developmental and physiological interactions between neural and vascular tissues in the brain, have been implicitly acknowledged by the inception of a National Heart, Blood, and Lung Institute initiative to coordinate research activity in this area.¹⁶

Antiplatelet Therapy in Stroke Prevention

Aspirin

With irreversible inhibition of platelet cyclooxygenase and a decrease of thromboxane A₂ production, aspirin was the first agent to demonstrate significant benefit in prevention of recurrent stroke (Table 1).^{17–21} Most studies of aspirin treatment after ischemic stroke or TIA have suggested a placebo-controlled relative risk reduction (RRR) in the range of 10% to 15% with aspirin doses as low as 50 mg/d. The relatively small magnitude of the benefit derived from aspirin has spurred the search for more effective antiplatelet agents or regimens.²¹ However, the consistency of the observed risk reduction associated with aspirin treatment and its low cost have led to the use of aspirin as the standard of care compared with newer agents.

Ticlopidine

Ticlopidine is a thienopyridine derivative that inhibits adenosine diphosphate–induced platelet aggregation. In the Canadian American Ticlopidine Study (CATS), 250 mg ticlopidine twice daily, compared with placebo, reduced the risk for the combined end points of stroke, MI, or vascular death in patients with recent atherothrombotic or lacunar stroke (RRR, 30.2%; $P=0.006$).²² Similarly, in the Ticlopidine Aspirin Stroke Study (TASS), ticlopidine was more effective than aspirin in the reduction of risk for secondary stroke among patients with a history of TIA or minor stroke (RRR, 21%; $P=0.024$).²³ However, in the African-American Antiplatelet Stroke Prevention Study (AAASPS), ticlopidine did not demonstrate greater efficacy in the reduction of the incidence of the composite vascular outcome (recurrent stroke, MI, or vascular death) compared with aspirin.²⁴ Moreover, use of ticlopidine was associated with a 1% risk for severe neutropenia and an increased risk of thrombotic thrombocytopenia purpura.⁷ Because of these safety concerns, ticlopidine is rarely used in secondary stroke prevention.

Clopidogrel

Clopidogrel is another thienopyridine-derived antiplatelet agent. Its broad efficacy as monotherapy in the prevention of cardiovascular events was assessed in the CAPRIE study. In this study, 19 195 patients with symptomatic cardiovascular disease, which included those

with recent ischemic stroke, recent MI, and symptomatic PAD, were randomized to receive either aspirin (325 mg/d) or clopidogrel (75 mg/d) for a mean treatment period of 1.9 years. Compared with aspirin, clopidogrel treatment was associated with a significant reduction in the incidence of the primary composite end points of ischemic stroke, MI, or vascular death (5.32% versus 5.83%; RRR, 8.7%; $P=0.043$).¹¹ However, the relative benefits of clopidogrel were not equally realized across the index event–defined subgroups. The comparative benefit versus aspirin was greatest in the PAD subgroup, in which the RRR for the primary outcome was 23.8% ($P=0.0028$). In the stroke subgroup, the RRR for the primary outcome versus aspirin was not significant ($P=0.26$), whereas in the MI subgroup there was a tendency for the incidence of the primary end point to be higher in clopidogrel-treated patients (RRR, -3.7% ; $P=0.66$). Therefore, the overall benefits of clopidogrel observed in CAPRIE were derived predominantly from the PAD subgroup.

Cilostazol

Cilostazol is an inhibitor of phosphodiesterase type III that possesses both antiplatelet and vasodilatory effects. Although cilostazol is approved in the United States for treatment of intermittent claudication associated with PAD, its efficacy in secondary stroke prevention was evaluated in the Cilostazol Stroke Prevention Study, which randomized 1095 Japanese patients with recent stroke or TIA to treatment with cilostazol or placebo. Cilostazol reduced the incidence of secondary stroke by 41.7% compared with placebo ($P=0.015$); the greatest risk reduction (43.4%) was among patients enrolled after lacunar stroke.²⁵ These clinical benefits were not associated with adverse events relative to placebo.²⁵ However, despite the magnitude of the observed risk reduction, the lack of an active comparator arm with aspirin (the standard of care at the time of the study) makes it impossible to compare the efficacy of cilostazol to that of aspirin.²⁶ Because phosphor-diesterase III inhibitors have been shown to cause decreased survival in patients with class III to IV congestive heart failure, cilostazol is contraindicated in patients with any degree of congestive heart failure.²⁷ A new study to determine the efficacy and safety of cilostazol compared with aspirin in secondary stroke prevention (Cilostazol in Stroke Prevention 2) is currently in subject recruitment. Thus, further clinical studies are warranted to assess cilostazol's efficacy in stroke patients compared with aspirin, especially in a mixed-race population.

Combination Therapy

Aspirin Plus Clopidogrel—In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study, which assessed antiplatelet treatment in patients with acute coronary syndromes without ST-segment elevation, the addition of clopidogrel (initial 300-mg dose followed by 75 mg/d) to aspirin treatment was associated with a RRR of 20% ($P<0.001$) in the primary composite outcome (cardiovascular death, nonfatal MI, or nonfatal stroke) compared with aspirin alone.²⁸ However, such a strategy may not apply to secondary prevention of ischemic strokes. The elevation in incidence of hemorrhagic stroke observed with higher doses of aspirin in the CAST study suggests that the degree of platelet inhibition may need to be carefully calibrated in patients with ischemic stroke between a reduction of recurrent ischemic event risk on the one hand and an increase in hemorrhagic event risk on the other. Indeed, in the CURE study, the clopidogrel plus aspirin combination was associated with a higher incidence of major bleeding episodes (3.7% versus 2.7%; $P=0.001$) than aspirin alone, but the between-group difference in the incidence of life-threatening bleeding episodes was not significant (2.1% versus 1.8%; $P=0.13$).²⁸ It should be emphasized that the CURE study was not a stroke trial, but instead was an acute coronary syndrome trial that showed the efficacy of clopidogrel and aspirin in the reduction of recurrent events in this patient population. Unfortunately, there were insufficient numbers of stroke or TIA to assess effectiveness for secondary stroke prevention. Nonetheless, the desire to reduce recurrent strokes has spurred many subsequent clinical trials to investigate combined antiplatelet therapies.

In contrast to the CURE study, the Management of Athero-thrombosis With Clopidogrel in High-Risk Patients (MATCH) was a stroke trial that investigated the efficacy of the clopidogrel plus aspirin combination compared with clopidogrel alone. A total of 7599 patients with recent stroke or TIA and at least 1 additional cardiovascular risk factor were randomized to treatment with clopidogrel alone (75 mg/d) or clopidogrel plus aspirin (75 mg/d) for 18 months. Although MATCH was a stroke trial, a composite cluster (ischemic stroke, MI, vascular death, or rehospitalization for acute ischemia) was used as the primary end point. Despite this, the combination of clopidogrel plus aspirin treatment did not reduce the incidence of the primary end point compared with clopidogrel alone (15.7% versus 16.7%; RRR 6.4%; 95% CI, -4.6% to 16.3%; $P=0.244$).²⁹ The combination therapy, however, doubled the rate of life-threatening bleeding episodes (defined as any fatal bleeding event, a drop in hemoglobin ≥ 50 g/L, hemorrhagic shock, symptomatic intracranial bleeding, or transfusion of ≥ 4 U of red blood cells or whole-blood equivalent [2.6% versus 1.3%; $P<0.0001$]), and substantially increased the rate of major bleeding episodes (defined as significantly disabling intraocular bleeding with significant vision loss, or transfusion of ≥ 3 U of red blood cells or whole-blood equivalent [1.9% versus 0.6%; $P<0.0001$]). The observation that the increased number of life-threatening bleeding episodes associated with combination treatment (47 episodes) exceeded the number of prevented outcome events (40 events) was of great concern.²⁹

Although the addition of aspirin to clopidogrel was not beneficial compared with clopidogrel alone, it was suggested that perhaps the addition of clopidogrel to aspirin could be more effective than aspirin alone. This concept was tested in the Clopidogrel for High Atherothrombosis Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study, in which 15 603 patients with symptomatic (80% of subjects) and asymptomatic (20% of subjects) cardiovascular disease or multiple risk factors were randomized to treatment with aspirin alone or with aspirin plus clopidogrel for a median follow-up of 28 months (primary prevention cohort $n=3284$; secondary prevention cohort $n=12 153$). Within the secondary prevention cohort, 4320 patients had experienced a documented cerebrovascular event (ischemic stroke or TIA) within the previous 5 years. The primary end point was a composite of MI, stroke, or vascular death.³⁰ Surprisingly, the combination of clopidogrel and aspirin did not decrease the incidence of the primary end point compared with aspirin alone (6.8% versus 7.3%; RRR, 7%; $P=0.22$). When analyzed according to baseline status, the benefit of combination therapy in the secondary prevention cohort was marginally significant (6.9% versus 7.9%; RRR, 12%; $P=0.046$), whereas results from the primary prevention cohort actually showed a trend that favored aspirin mono-therapy (6.6% versus 5.5%; RRR, -20%; $P=0.20$).³⁰ Indeed, in asymptomatic patients with multiple risk factors for atherothrombosis, the relative risk of overall and cardiovascular mortality was increased by 42% and 77% with the combination of clopidogrel and aspirin compared with that of aspirin alone ($P<0.04$ and $P<0.01$, respectively).

A prespecified CHARISMA substudy compared clopidogrel and aspirin versus aspirin alone among patients enrolled into the secondary prevention cohort after stroke or TIA. Although there was a slight trend toward increased benefit with the combination of clopidogrel and aspirin among patients who began treatment within 30 days of the index event ($P>0.05$), no between-group differences were observed among patients whose treatment was initiated >30 days after the index event.³¹ As in the MATCH study, the combination of clopidogrel and aspirin was associated with higher bleeding complications. The incidence of moderate bleeding (defined as bleeding that required transfusion but did not otherwise meet criteria for severe bleeding) was 2.1% versus 1.3% (relative risk, 1.62; $P<0.001$). Given these findings, the addition of clopidogrel to aspirin is not recommended for prevention of cardiovascular events in patients with ischemic stroke or asymptomatic CHD. However, because stroke patients have a lifetime CHD risk of 10% or more, stroke or TIA could be considered a CHD equivalent.

Indeed, antiplatelet therapy with aspirin and clopidogrel was found to be marginally beneficial in the secondary prevention of CHD.^{11,30}

Aspirin Plus ER-DP—Dipyridamole is a phosphodiesterase inhibitor, which increases intracellular levels of cAMP and cGMP. At higher concentrations, dipyridamole can also inhibit the cellular uptake of adenosine. In some early studies of secondary stroke prevention, the addition of immediate-release dipyridamole to low-dose aspirin did not appear to increase the efficacy of stroke reduction compared with aspirin alone.^{32–35} However, in the first European Stroke Prevention Study (ESPS-1), the combination of high-dose aspirin plus immediate-release dipyridamole (330 mg plus 75 mg, respectively, 3 times daily) demonstrated a 33.5% reduction versus placebo ($P<0.001$) in all-cause death after 2 years of treatment in 2500 patients with recent stroke or TIA. However, ESPS did not include an aspirin-alone arm, which makes it impossible to assess the additive effects of these 2 agents compared with aspirin alone.³⁶

In the Second European Stroke Prevention Study (ESPS-2), immediate-release dipyridamole was replaced by an extended-release formulation (200 mg) combined with low-dose aspirin (25 mg) in a twice-daily dosage form (aspirin plus ER-DP). The extended-release formulation of dipyridamole was used for better gastrointestinal absorption, and because the plasma concentration of the immediate-release formulation declines rapidly (half-life of 40 minutes). ESPS-2 incorporated 4 treatment arms (monotherapy with each agent, the aspirin plus ER-DP combination, and placebo) to permit comparison of each monotherapy arm with placebo and combination therapy. A total of 6602 patients with prior stroke or TIA were randomized to 1 of the 4 treatment arms for 2 years.³⁷ At follow-up, aspirin monotherapy and ER-DP monotherapy demonstrated comparable reductions in the risk of stroke versus placebo (RRR aspirin monotherapy, 18%; $P=0.013$; RRR ER-DP monotherapy, 16%; $P=0.039$). Similar trends were observed for the end point of stroke plus death ($P=0.02$ for each). The aspirin plus ER-DP combination, however, produced not only substantial reduction of stroke risk versus placebo (RRR, 37%; $P<0.001$), but also significant reduction versus each of the monotherapy arms (23% RRR versus aspirin monotherapy, $P=0.006$; 25% RRR versus ER-DP monotherapy, $P=0.002$). The incidence of bleeding events associated with the aspirin plus ER-DP combination in ESPS-2 was similar to that in the aspirin monotherapy arm.³⁷ Overall, the pattern of adverse events for aspirin plus ER-DP reflected patterns of the most prominent adverse events observed in the monotherapy arms. The incidence of headache, the most common adverse event associated with dipyridamole, was 37% for ER-DP monotherapy and 38% for aspirin plus ER-DP, compared with 33% for aspirin monotherapy and 32% for placebo.³⁷ The bleeding complications associated with aspirin plus ER-DP were similar to that of aspirin alone.

A subsequent analysis of the results of ESPS-2 was conducted to investigate possible adverse effects on cardiac ischemia. Each of the ESPS-2 treatment arms included comparable proportions of patients ($\approx 50\%$) with a history of MI or symptomatic CHD. The analysis showed that there was no increase in risk for MI, angina, or mortality among cardiac patients who received dipyridamole compared with those who received aspirin alone or placebo, which alleviated concerns about dipyridamole as a cause of coronary steal phenomena in patients with existing CHD.³⁸ However, other concerns about the findings of ESPS-2, which precluded translation of its findings into clinical practice, include: 1) the fact that it was only 1 prospective trial to show a benefit of aspirin and ER-DP versus aspirin alone; 2) the trial was conducted more than a decade ago, when the standard of care for patients with cardiovascular disease might have been suboptimal compared with the present (ie, relatively low statin, angiotensin-converting enzyme inhibitor, and angiotensin receptor blocker usage); and 3) the relatively low dose of aspirin (50 mg/d) used as the comparative arm.

Recently, the findings of ESPS-2 were essentially confirmed in the European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT), in which 2739 patients with recent TIA or nondisabling ischemic stroke were randomized to aspirin alone (dose range between 30 and 325 mg/d, determined by the treating physician; median dose during the study was 75 mg/d in all groups that received aspirin) or to aspirin plus 200 mg dipyridamole twice daily (either as a fixed combination or separately; 83% of patients in this group used the ER-DP formulation). After a mean follow-up of 3.5 years, the incidence of the primary outcome cluster of vascular death, nonfatal MI, nonfatal stroke, or major bleeding event on an intent-to-treat basis was 13% in the aspirin plus dipyridamole group, versus 16% in the aspirin monotherapy group (RRR, 20%; 95% CI, 2% to 34%). When analyzed according to an on-treatment basis, the RRR was 18%, with a 95% CI of -2% to 34%.³⁹ Unexpectedly, there were fewer major bleeding events in the combination therapy group than in the aspirin monotherapy group (35 versus 53 events, respectively), primarily as a result of fewer nonfatal intracranial and extracranial bleeding episodes (30 versus 49). The incidence of minor bleeding events was similar between groups (171 versus 168 events). However, more patients discontinued treatment in the combination therapy group than in the aspirin monotherapy group (470 versus 184 patients), with headaches as the most significant reason for discontinuation. The findings of ESPRIT, therefore, confirm the additive benefits of dipyridamole plus aspirin versus aspirin alone in secondary prevention of stroke that were demonstrated in ESPS-2. Indeed, a revised meta-analysis, which incorporated all studies to date that compared dipyridamole plus aspirin with aspirin alone, showed that the addition of dipyridamole to aspirin treatment is associated with a RRR of 18% (95% CI 9% to 26%) compared with aspirin mono-therapy.³⁹ It should be noted that the combination of dipyridamole and aspirin has not been shown to prevent CHD.

Potential Mechanisms That Underlie the Benefits of Secondary Stroke Protection in Antiplatelet Clinical Trials

Review of the clinical trials of antiplatelet therapy in secondary stroke prevention inspires the question: Why does the addition of clopidogrel to aspirin yield no clinical benefit, but cause greater bleeding complications compared with that of aspirin or clopidogrel alone (CHARISMA and MATCH), whereas the addition of ER-DP to aspirin is more efficacious than aspirin or ER-DP alone (ESPS-2 and ESPRIT)? These findings suggest that additional platelet inhibition, at least as provided by the aspirin and clopidogrel combination, yields no additional protection against recurrent cerebrovascular events, but instead increases adverse bleeding events. Indeed, the CHARISMA results suggest that little or no protection is provided by adjunctive clopidogrel across a wide range of symptomatic cardiovascular disease and cardiovascular risk factors. However, aggressive platelet inhibition with the combination of aspirin and clopidogrel is warranted in patients with acute coronary syndromes without ST-segment elevation and after PCI.^{40,41}

The mechanism by which dipyridamole, especially the extended release formulation, could reduce the risks for secondary strokes without excess bleeding may be caused by some of its effects beyond platelet inhibition on the vascular wall. By an increase of intracellular levels of cGMP, dipyridamole could augment many of the downstream signaling pathways of nitric oxide (NO). Loss of endothelial-derived NO activity that leads to a reduction in intracellular cGMP levels contributes to impaired vascular responses,⁴² enhanced platelet aggregation,⁴³ and vascular smooth muscle proliferation.⁴⁴ Inhibition of endothelial NO production by the endothelial NO synthase inhibitor, *N* ω -monomethyl-L-arginine, causes vasoconstriction⁴⁵ and vascular inflammation by promotion of endothelial leukocyte adhesion.⁴⁶ Indeed, lower vascular cGMP levels in mutant mice that lack endothelial NO synthase are associated with systemic and pulmonary hypertension,⁴⁷ greater propensity for intimal smooth muscle proliferation in response to vascular cuff injury,⁴⁸ and larger stroke sizes in response to cerebral ischemia.⁴⁹ These findings suggest that dipyridamole may protect against stroke in part

through a platelet-independent mechanism, and in conjunction with the antiplatelet effects of aspirin may confer greater secondary stroke protection than either one alone. Similar mechanisms may occur with other cardiovascular agents such as statins (Stroke Prevention by Aggressive Reduction in Cholesterol Levels [SPARCL] trial), angiotensin-converting enzyme inhibitors (Heart Outcomes Prevention Evaluation [HOPE]), and angiotensin receptor blockers (Losartan Intervention for Endpoint Reduction [LIFE] study), which protect the vascular wall and confer stroke protection without any direct effects on platelet aggregation. However, it should be kept in mind that the clinical studies described did not formally assess changes in platelet aggregation, nor did they evaluate aspirin resistance. Therefore, it is not possible ascribe the effects of treatment with these agents (positive and negative) to antiplatelet effects per se.

Summary

The comparative benefits of clopidogrel and aspirin plus ER-DP in secondary stroke prevention are under evaluation in the ongoing Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) study, which has enrolled >20 000 patients with a recent history of ischemic stroke randomized to either the combination of ER-DP plus aspirin or clopidogrel monotherapy. With results expected in 2008, the PROFESS study should help further clarify the roles of these antiplatelet therapies in the secondary prevention of ischemic stroke.

Accumulating evidence from randomized clinical studies suggests that aspirin monotherapy, clopidogrel monotherapy, and ER-DP monotherapy provide comparable benefit for the prevention of recurrent stroke after stroke or TIA. Dual antiplatelet therapy for secondary stroke protection, especially with aspirin and clopidogrel, has not been shown to be beneficial versus aspirin alone, and could result in greater bleeding complications. Currently, the only therapy that has been shown to be better than aspirin alone for the prevention of recurrent stroke is the combination of aspirin plus ER-DP. Because patients who present with ischemic stroke or TIA tend to have recurrent stroke or TIA as their next event, antiplatelet therapy in these patients should be tailored to what has been shown for secondary stroke protection rather than for myocardial protection.

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Studies of Secondary Stroke Prevention With Aspirin Monotherapy

Study Name	Inclusion Criteria	Comparison(s)	N	Study Duration	Outcomes	Adverse Events
UK-TIA ¹⁷	Recent (≤ 3 months) TIA or minor ischemic stroke	Placebo vs 300 mg/d ("low-dose") aspirin vs 1200 mg/d ("high-dose") aspirin	2435	Mean follow-up 4 years (range 1 to 7 years)	RRR (aspirin vs placebo) of 15% for composite outcome (vascular death, nonfatal MI, or nonfatal stroke); no difference between aspirin doses	Incidence of upper GI symptoms/GI hemorrhage: placebo, 26%/1%; low-dose aspirin, 31%/3%; high-dose aspirin, 41%/5%
SALT (Swedish Aspirin Low-Dose Trial) ¹⁸	Recent (≤ 3 months) TIA or minor ischemic stroke	Placebo vs 75 mg/d aspirin	1360	Median follow-up 32 months	RRR (aspirin vs placebo) of 18% for composite primary outcome (stroke or death); RRR of 16 to 20% for secondary outcomes	Incidence of severe bleeding: placebo, 1.3%; aspirin, 3.0% Incidence of nonbleeding GI AE: placebo, 10.7%; aspirin, 12.5%
Dutch TIA Trial ¹⁹	Recent (≤ 3 months) TIA or minor ischemic stroke	30 mg/d Aspirin vs 283 mg/d aspirin	3131	Mean follow-up 2.6 years	Similar incidence of composite outcome (vascular death, nonfatal stroke, nonfatal MI)	Major/minor bleeding episodes: 30 mg/d, 40/49; 283 mg/d, 53/84
CAST (Chinese Acute Stroke Trial) ^{20*}	Acute ischemic stroke	Placebo vs 160 mg/d aspirin; both initiated within 48 hours of stroke onset and continued for 4 weeks	21 106	4 weeks	RRR (aspirin vs placebo) of 14% for death and 24% for ischemic stroke	Trend toward increased incidence of hemorrhagic stroke: aspirin, 1.1%; placebo, 0.9%

AE indicates adverse event; GI, gastrointestinal.

*The CAST study was a short-term study of immediate treatment after stroke; it is included here because of the high risk of recurrent events immediately after TIA or stroke.