Stroke Prevention: Update on Antiplatelet Therapy

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Substantial advances have been made in recent decades in understanding the mechanisms of stroke and its risk factors and in developing therapies.² Because thrombosis plays an important role in the pathogenesis of ischemic stroke, drugs that interfere with hemostasis and clot formation, such as anticoagulants and platelet aggregation inhibitors, commonly are used to manage cerebrovascular disease.

In this article, we review the efficacy and safety of aspirin, ticlopidine, clopidogrel, and aspirin/extended-release dipyridamole in the secondary prevention of atherothrombotic stroke.

PRIMARY STROKE PREVENTION

Primary stroke prevention requires a comprehensive multidisciplinary approach. The first objective is to identify and modify stroke risk factors, including hypertension; diabetes mellitus; myocardial infarction (MI); hyperlipidemia; atrial fibrillation; asymptomatic carotid stenosis; and lifestyle factors, such as smoking, alcohol use, and sedentary lifestyle.³ In addition to risk factor modification, attention has recently focused on the role of aspirin in primary stroke prevention, given its well-established efficacy in the primary prevention of MI⁴ (specifically, the American Heart Association guidelines recommend aspirin at a dosage of 75 mg/d for cardiovascular prophylaxis for persons whose 10-year risk of a coronary event is 10% or greater).⁵

In persons at low risk for vascular disease, the data supporting the role of aspirin in primary stroke prevention are scant. A meta-analysis of 5 randomized trials, which included more than 50,000 participants, revealed no difference in the incidence of stroke between low-risk patients randomized to receive aspirin and those randomized to receive placebo during an average follow-up of 4.6 years. Regular use of aspirin significantly increased the rate of intracranial hemorrhage by a relative risk of 1.35.⁶

In the Women's Health Study, 39,876 asymptomatic women older than 44 years were randomized to receive 100 mg of aspirin or placebo on alternate days and then followed up for 10 years for a first major vascular event (nonfatal MI, nonfatal stroke, or cardiovascular death).⁷ Investigators found a nonsignificant 9% reduction for the primary end point but a significant 17% relative risk reduction for ischemic stroke. The most consistent benefit was for women aged 65 years or older, among whom the risk of major cardiovascular events was reduced by 26%, including a 30% relative risk reduction in ischemic stroke. There was, however, only a trend in the relative reduction of the overall risk of ischemic and hemorrhagic stroke because of an increased risk of brain hemorrhage in these elderly women.

At present, no evidence supports the use of aspirin to prevent stroke in low-risk asymptomatic persons.⁶,⁸,⁹ Recent guidelines from the American Heart Association/American Stroke Association Stroke Council state that aspirin can be useful for cardiovascular (including but not specific to stroke) prophylaxis in high-risk patients and for prevention of a first stroke among women whose risk is sufficiently high to outweigh the risks associated with treatment.³

Secondary Prevention of Stroke

The goal of therapy in patients who have sustained a stroke or transient ischemic attack (TIA) is to prevent recurrent cerebrovascular events. Longitudinal studies of patients with a history of ischemic...
stroke show that the rate of stroke recurrence ranges from 5% to 14% in the first year, and from 25% to 40% within 5 years, after the initial event. The risk of mortality also increases over time.

The approach to secondary prevention includes risk factor modification, medical therapy, and surgery, if appropriate. The most effective approach depends on the cause of the first cerebral ischemic event. Patients at high risk for recurrent cardioembolic stroke (ie, those with atrial fibrillation) are best managed with warfarin, barring any medical contraindications. Patients who are not candidates for anticoagulation and who do not have surgically correctable cerebrovascular disease may benefit from antiplatelet therapy.

Antiplatelet agents. The use of these agents to treat TIA and stroke has become widespread. Studies support the efficacy of aspirin, ticlopidine, clopidogrel, and dipyridamole. The selection of an agent is based on relative efficacy, availability, cost, and adverse effects (Table).

Aspirin. This is the most widely used and studied antiplatelet agent. It inhibits platelet aggregation by irreversibly blocking cyclooxygenase, essential for the synthesis of thromboxane A2, which promotes vasoconstriction and platelet activation.

Several trials support the benefits of aspirin in patients at risk for stroke. The Swedish Aspirin Low Dose Trial, in which 1360 patients with minor stroke or TIA were randomized to receive either aspirin, 75 mg/d, or placebo, demonstrated a statistically significant 18% reduction in stroke and death in the aspirin group. A meta-analysis of 21 trials that compared aspirin with placebo for the prevention of vascular events in 18,270 patients with previous stroke or TIA found an overall significant relative risk reduction of 28% in nonfatal strokes and of 16% in fatal strokes. To prevent 1 vascular event during 2 years of therapy, 36 patients needed to be treated with aspirin. The most effective dosage of aspirin required for stroke prevention has been the subject of extensive debate. No clear evidence favors one dose over another. The United Kingdom Transient Ischaemic Attack (UK-TIA) study found no differences in vascular events between patients who received 300 mg/d of aspirin and those who received 1200 mg/d. Similarly, the Dutch TIA Trial, which included 3131 patients with minor stroke, found no differences between groups receiving 30 mg/d and 283 mg/d. A meta-analysis by the Antiplatelet Trialists’ Collaboration showed high- (500 to 1500 mg/d) and medium-dose (75 to 325 mg/d) aspirin were equally effective in preventing the composite end point of nonfatal MI, nonfatal stroke, or vascular death. Another meta-analysis also found no dose-dependent relationship for the efficacy of aspirin in patients with previous stroke or TIA. The results of these studies and others suggest that there are no important differences in dosages between 50 mg/d and 1200 mg/d for stroke prevention and only modest differences in dose-related toxicity.

Until further data become available, the American Heart Association/American Stroke Association Council on Stroke recommends aspirin in a dosage of 50 to 325 mg/d for secondary prevention of ischemic stroke. There is no evidence that increasing the dosage benefits patients who have an ischemic event while taking aspirin, an occurrence commonly referred to as "aspirin failure." The usual practice is to prescribe a different antiplatelet agent for these patients.

Ticlopidine. This agent inhibits adenosine diphosphate (ADP), which participates in platelet aggregation and fibrinogen binding to the glycoprotein IIb/IIIa receptor. In the Ticlopidine Aspirin Stroke Study, a 21% greater relative risk reduction for fatal and nonfatal stroke was seen in patients who took ticlopidine, 250 mg bid, compared with those who took aspirin, 650 mg bid. The reduction in the risk of the combined outcome of stroke, MI, or vascular death was nonsignificant, however. Moreover, the African American Antiplatelet Stroke Prevention Study, which randomized 1800 African Americans to the same treatment regimen, also found no difference in the risk of stroke, MI, or vascular death at 2 years.

The most common adverse effects of ticlopidine are diarrhea and rash. Neutropenia, which is severe in fewer than 1% of patients, also occurs. Thrombotic thrombocytopenic purpura has been reported. Because of the potential for serious adverse effects, ticlopidine is now rarely used in clinical practice.
Clopidogrel. This newer ADP inhibitor belongs to the same chemical family as ticlopidine. The Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study of 19,185 patients with previous ischemic stroke, MI, or atherosclerotic peripheral arterial disease compared clopidogrel, 75 mg/d, with aspirin, 325 mg/d.23 Efficacy was determined by the subsequent occurrence of ischemic stroke, MI, or vascular death.

The incidence of any one of these outcomes was 5.32% per year in the clopidogrel group compared with 5.83% per year in the aspirin group, a small but statistically significant difference. A total of 196 patients would need to be treated with clopidogrel to prevent 1 more vascular event than in another group of patients who received aspirin. However, this benefit was driven primarily by results found in the subgroup of patients with peripheral arterial disease. For the stroke subgroup of 6431 patients, no significant advantage was found for clopidogrel over aspirin. These results suggest that clopidogrel is at least as effective as aspirin in the prevention of secondary thromboembolic events.

The CAPRIE trial also showed that clopidogrel has a mild adverse-effect profile. In the clopidogrel-treated group, the incidence of neutropenia was 0.1% and the incidence of thrombocytopenia was 0.26%. No differences in this regard were observed between clopidogrel and aspirin. With respect to other adverse effects, more episodes of rash and diarrhea were reported with clopidogrel, whereas aspirin was associated with more episodes of upper GI discomfort and GI hemorrhage. More recently, clopidogrel-related thrombotic thrombocytopenic purpura has been reported.24 Based on existing data, there is no clear indication to prescribe clopidogrel rather than aspirin.19 Aspirin and dipyridamole. The fixed-dose formulation of aspirin (25 mg)/extended-release dipyridamole (200 mg) combines 2 antiplatelet agents with different mechanisms of action. Dipyridamole inhibits platelet aggregation by inhibiting the uptake of adenosine and phosphodiesterase and can also cause vasodilation.

In the European Stroke Prevention Study 2 (ESPS-2), which included 6602 patients with previous ischemic stroke or TIA, aspirin/dipyridamole was twice as effective as either agent alone in the prevention of a second ischemic event after 2 years.18 Dipyridamole (200 mg bid) and aspirin (25 mg bid) separately led to significant reductions in stroke recurrence: 16% and 18%, respectively, compared with placebo.

The combination of dipyridamole and aspirin had an additive effect of 37% risk reduction, lowering the relative risk of stroke over aspirin alone by 23%. The absolute risk reduction of the combination used in ESPS-2 was 3% at the end of 2 years. Compared with a group of patients who received aspirin, 33 patients would need to be treated with aspirin/extended-release dipyridamole to prevent 1 additional vascular event. A post hoc subgroup analysis of ESPS-2 has shown that treatment was particularly beneficial among patients with a history of hypertension, MI, TIA, or stroke, or any cardiovascular disease as well as patients who were smokers at baseline.25

Overall, bleeding events were similar in patients treated with aspirin/extended-release dipyridamole (8.7%) and in those who received aspirin alone (8.2%). However, the incidence of headache was higher in the aspirin/extended-release dipyridamole group (8.1%) than in the aspirin group (1.9%), leading to premature cessation of the study medication.

Almost a decade after ESPS-2, the results of the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) were published.26 ESPRIT was a 14-country, randomized trial that included 2739 patients with a history of TIA or ischemic stroke who received aspirin (30 to 325 mg) with or without dipyridamole (200 mg bid). The primary outcome event was a composite of death from all vascular causes, stroke, MI, or major bleeding complication, whichever occurred first. Participants were followed up for 3.5 years.

A primary event occurred in 13% of the patients who received combined treatment and in 16% of those who took aspirin alone. The absolute risk reduction was 1% per year for the combined treatment, confirming the results of ESPS-2. Patients who received the combination treatment had fewer major bleeding complications than those who took aspirin alone; however, this difference was not significant, and the authors attributed it to a chance finding. ESPRIT also showed that long-term
therapy with dipyridamole and aspirin is difficult to maintain: 34% of patients discontinued treatment, mainly because of adverse effects. Twenty-six percent reported headache as one of the reasons.

No large clinical trial is perfect in all aspects, and ESPRIT is no exception. The trial was not blinded. An open design might at least in theory influence the investigators’ interpretation of potential end points and their vigor in the use of other secondary preventive measures. However, the replication of results in 2 large independent trials reaffirmed the beneficial effect of the combination therapy.

Currently, it is recommended that the aspirin/extended-release di-pyridamole combination be considered when the primary treatment goal is prevention of recurrent stroke rather than MI; however, its cost and adverse-effect profile may limit its use as initial therapy.

Aspirin and clopidogrel. Results of randomized controlled trials in patients with coronary manifestations of atherothrombosis have shown the sustained benefit of clopidogrel when added to aspirin.27,28 These trials provided the rationale for further investigation to determine whether the combination of aspirin and clopidogrel can reduce the risk of recurrent ischemic vascular events in patients who have sustained a TIA or ischemic stroke.

The Management of Atherothrombosis With Clopidogrel in High-Risk Patients (MATCH) study compared clopidogrel monotherapy (75 mg) with clopidogrel and aspirin (75 mg) in patients who have had a recent stroke or TIA.29 The primary end point was a composite of stroke, acute MI, vascular death, or rehospitalization for an acute ischemic event during the 18-month treatment period. The study showed that clopidogrel-aspirin combination therapy did not produce a significantly greater reduction in major vascular events than clopidogrel alone. Of more concern was a significant increase in life-threatening hemorrhage—up to a 1.3% absolute risk increase—in patients who took the clopidogrel-aspirin combination (2.6% vs 1.3% in the clopidogrel-alone group).

This study was followed by the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial.30 A total of 15,603 patients with either clinically evident cardiovascular disease or multiple cardiovascular risk factors received clopidogrel (75 mg) in combination with low-dose aspirin (75 to 162 mg) or low-dose aspirin alone over a 28-month period. There was no overall difference in the primary end point of MI, stroke, or death from cardiovascular causes, and there was a significant increased risk of moderate to severe bleeding in the group who received aspirin-clopidogrel combination (3.8%) compared with the group who received aspirin alone (2.6%).

Both the CHARISMA and MATCH trials suggest that the combination of clopidogrel and aspirin does not provide greater benefit than aspirin or clopidogrel alone and increases the risk of bleeding. Thus, the combination is not recommended at this time.

A final caveat. In clinical practice, strategies intended to prevent recurrent stroke are far from ideal.31 Antiplatelet therapy is not the sole preventive measure; equal emphasis should be given to risk factor and lifestyle modification.

**References:** REFERENCES:
5. Pearson TA, Blair SN, Daniels SR, et al. AHA Guidelines for Primary Prevention of Cardiovascular


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