Preventing ischemic stroke in the older adult

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ABSTRACT

Stroke is a deadly and disabling disease that preferentially afflicts older adults. It shares common risk factors with myocardial infarction (MI), such as hypertension, diabetes, and hyperlipidemia. Blood pressure control, cholesterol reduction with statins, and glucose control reduce the risk for both stroke and MI. Additionally, management of atrial fibrillation with warfarin reduces stroke risk. Beyond risk factor reduction, antiplatelet therapy is an effective option for lowering the likelihood of stroke in at-risk patients. Among antiplatelet agents, aspirin has been shown effective for secondary stroke prevention as well as primary and secondary MI prevention; clopidogrel for secondary stroke and MI prevention; and both ticlodipine and dipyridamole for secondary stroke prevention. Combining antiplatelet agents is rational. Carotid endarterectomy should be considered for stroke prevention in patients with ischemic symptoms; for patients with asymptomatic stenosis, potential benefit must be balanced against surgical risk.

KEY POINTS

In older patients, stroke and myocardial infarction (MI) are causally linked and treatments that effectively reduce risk for one also reduce risk for the other.

Prior stroke increases the risk of MI threefold, and prior MI increases the risk of stroke threefold. Death in stroke patients is due largely to the coexisting relationship of stroke with heart failure.

Hypertension increases the risk of stroke sevenfold. Reducing blood pressure lowers the risk for first stroke by 30% to 45%, and perhaps by 55% to 60% if normotension is attained.

In elderly patients, blood pressure reduction must be gradual to maintain normalized cerebral blood flow and reduce the risk of ischemic injury.

Although antiplatelet therapy substantially lowers the incidence of stroke and MI in at-risk patients, fewer than 50% of patients who stand to benefit from antiplatelet therapy receive it.

The utility of carotid endarterectomy for stroke prevention in at-risk patients is highly dependent on whether the patient has ischemic symptoms, the degree of stenosis, and the surgeon's perioperative complication rate.

Cerebral infarction (stroke) and myocardial infarction (MI) are critically important diseases. This is particularly true among the elderly. Alone, stroke is the third leading cause of death and disability among adults. The incidence of stroke has continued to increase since the mid-1960s, with up to 700,000 new cases reported in the United States each year.[1,2] Although significant advances have been made in our understanding and treatment of this disease, it remains a scourge. However, the close relationship of stroke and MI means that comprehensive risk factor management, proper antiplatelet therapy, and appropriate surgical intervention can greatly reduce the risk for both.

STROKE CLASSIFICATION AND PATHOGENESIS

There are two main stroke categories of etiologic importance: ischemic stroke, accounting for about 83% of cases, and hemorrhagic stroke.[3] The ischemic strokes are attributable to arterial thrombosis (20%), embolism (25%), small-vessel disease (25%), and cryptogenic causes (30%). Hemorrhagic strokes are further subcategorized as intraparenchymal (60%) or subarachnoid hemorrhage (40%). As ischemic stroke is the cause of significant morbidity and mortality in the elderly, its

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prevention will be the focus of this article.

In older adults, the predominant process leading to the development of stroke is progressive atherosclerosis (Figure 1).[4,5] Temporal arteritis and amyloid angiopathy, although infrequent, disproportionately afflict older adults and also result in stroke. Some recently identified diseases such as homocysteinemia may prove to increase the risk for stroke in the elderly, but their roles are uncertain, as are specific intervention strategies.

The sidebar on page S16 provides an overview of stroke pathogenesis.[4–7]

Similarities with ischemic heart disease

Ischemic brain disease and ischemic heart disease share pathogenesis and risk factors, and it is not surprising that these diseases often coexist. Nearly 60% of patients over age 60 presenting with ischemic stroke have evidence of coronary artery occlusion.[8] A review of leading secondary stroke prevention trials reveals that 30% to 35% of these patients also have significant coronary artery disease.[9–12] This pattern of coexistence is consistent across diverse ethnic backgrounds.[13] The high prevalence of acute coronary syndromes has stimulated extensive research on ameliorating this disease. Neurologists and neuro-interventionalists have adopted clinical strategies developed by cardiologists for managing heart disease. Antihypertensive and lipid-lowering agents, glucose management, antiplatelet therapy, surgical management, reperfusion treatments, and endovascular interventions are all being used.

SEQUELAE AND COMPLICATIONS OF STROKE

With a 5-year mortality of greater than 50%, stroke is a deadly disease that ranks with serious cancers such as hepatic carcinoma and invasive bladder cancer.

A 2003 analysis of the Perth Community Stroke Study database showed that 60% of stroke patients die within 5 years and 80% within 10 years.[14,15] The risk of death among 1-year survivors remains fairly consistent at 10% per year, and the annual case fatality rate is 5% per year.[14,15] A 2003 analysis of a Connecticut Medicare database likewise found that 60% of patients who suffer ischemic stroke die within 5 years.[16] Survival after transient ischemic attack (TIA) is also poor, with 49.6% mortality at 5 years.[16] Furthermore, patients who have survived one stroke are at nine times greater risk for subsequent stroke,[17] with incident stroke as the leading cause of death in the first 6 months following the index stroke.[18,19]

The coexistence of stroke and MI has profound prognostic significance. Patients who have had a stroke are at three times greater risk for MI compared with patients sharing a similar risk factor burden who have not had a stroke.[20] Conversely, patients who have had an MI are at three times greater risk for stroke than patients who have not had an MI. Any history of nonacute cardiac disease also dramatically increases the risk for stroke. History of congestive heart failure increases stroke risk fourfold, and this is further doubled if the patient has atrial fibrillation.[18]

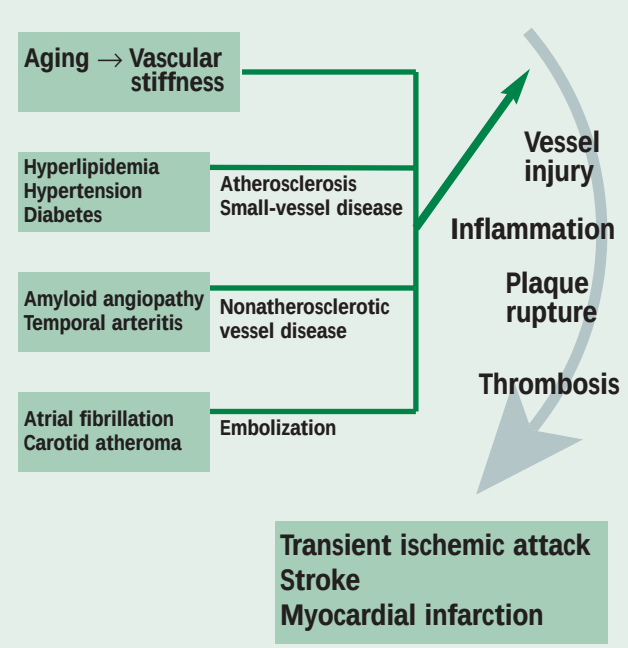

FIGURE 1. Schematic showing contributors to and progression toward stroke and myocardial infarction.

Coexisting heart disease is major driver of mortality

Death in stroke patients is due largely to the coexisting relationship with heart disease. A 1993 analysis from the Oxfordshire Community Stroke Project found that 35% of patients with stroke die from cardiovascular causes during the first 6 years after the initial event.[21] This is twice the number of deaths due to stroke (17%).[21] The Northern Manhattan Stroke Study confirmed these results in 2001, finding 29% of deaths to be attributable to cardiac events compared with 8% to incident stroke.[19] In 2003, the Perth Community Stroke Study yielded similar results, finding incident stroke to be the leading cause of death in the first 6 months after the index stroke, with death chiefly attributable to cardiac events thereafter.[15] During years 1 to 10 after the index stroke, cardiac events accounted for 41% of deaths and recurrent stroke for only 5% of deaths.[15]

Stroke pathogenesis at a glance

Stroke starts with endothelial damage to intracranial cerebrovasculature or extracranial conductive vessels to the brain (eg, the aortic arch, the carotid or vertebral arteries). In general, damage is induced by underlying conditions such as hypertension or diabetes. The ensuing lesion initiates an inflammatory response that is mediated by macrophages. In a hyperlipidemic state, macrophages filled with lipid are known as "foam cells." These foam cells respond to the injured endothelium and give rise to a connective tissue–protein matrix that becomes, in turn, the atheromatous plaque. Over time, the endothelium is reinjured and the cycle repeats.

As the plaque increases in size, the blood vessel lumen narrows, which eventually can compromise blood flow. If this process is not mitigated, lumen occlusion develops, resulting in ischemia "downstream" of the occlusion, particularly if the occlusion develops rapidly. This may be the case during plaque rupture. If a plaque fractures, platelets are recruited to stop the bleeding. Activated platelets form a fibrin clot that will stop the plaque bleeding. If there is significant vessel stenosis, the aggregation of platelets may be large enough to acutely occlude the blood vessel. The structures supplied by this vessel become ischemic. The clinical result is a stroke.[4,5] Gradual vessel occlusion may allow sufficient time for collateral blood flow to develop, in which case the consequences of vessel occlusion may be clinically insignificant.

The atheromatous plaques most prone to fracture and bleeding are unstable plaques. These are believed to pose a particularly high risk. Efforts are under way to elucidate the mechanisms leading to instability, as well as methods to identify those plaques that are most prone to fracture.[6,7]

The coexistence of cardiac disease also has functional significance for stroke survivors, as it further complicates rehabilitative management following stroke. Cardiac disease and stroke independently result in disability and together may broaden the functional limitations of either alone.

RISK FACTOR MODIFICATION

Over the past 2 decades, remarkable advances have been made in both preventing and treating stroke. Beginning in the 1960s, a number of epidemiologic studies have identified risk factors for stroke, some of which are now targets of medical intervention (Table 1). These include hypertension, nonrheumatic atrial fibrillation, hypercholesterolemia, diabetes, and cigarette smoking. Advanced age is the leading nonmodifiable risk factor. The risk factors associated with stroke are similar to those associated with coronary artery disease. Reducing risk factors for myocardial ischemia also reduces the risk of stroke.

Hypertension

Of the known risk factors for stroke, hypertension is the most significant, as it is associated with a sevenfold increase in stroke risk.[22]

Reducing blood pressure reduces the risk for first stroke by approximately 30% to 45%, and perhaps by as much as 55% to 60% if normotension is achieved.[23,24] The 1,627-patient Swedish Trial in Old Patients With Hypertension found that antihypertensive treatment with either beta-blockers or thiazide diuretics reduced systolic blood pressure (SBP) by 20 mm Hg, reduced diastolic blood pressure (DBP) by 5 mm Hg, and reduced stroke incidence by 45%.[25] In a meta-analysis of 14 antihypertensive trials encompassing 37,000 patients with a mean treatment duration of 5 years, Collins and colleagues[26] found that a DBP reduction of 5 mm Hg corresponded with a 42% reduction in risk for stroke. Risk for cardiovascular disease and vascular death were also reduced.[26] Similar findings were reported from the Systolic Hypertension in the Elderly Program (SHEP), a double-blind, randomized, placebo-controlled trial of chlorthalidone and atenolol in 4,736 patients age 60 or older (mean, 72 years).[27] After 5 years, a reduction in SBP of 10 mm Hg (to 143 mm Hg) was associated with a 36% improvement in stroke risk.[27]

More recently, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) compared the thiazide diuretic chlorthalidone, the calcium channel blocker amlodipine, and the ACE inhibitor lisinopril in 33,357 patients with hypertension and multiple risk factors for coronary heart disease.[28] Whereas chlorthalidone and amlodipine comparably reduced the risk for MI, stroke, and death, lisinopril was less effective. However, the doses were not adjusted among the three drugs to produce the same blood pressure reduction, which may in part explain some of the differences observed.[28] The Losartan Intervention for Endpoint reduction in hypertension study (LIFE) compared the angiotensin receptor blocker losartan with the beta-blocker atenolol in 9,193 patients.[23] In addition to the study drugs, many patients were also taking other agents, such as the diuretic hydrochlorothiazide. Overall, the two agents provided similar blood pressure control, but

TABLE 1
Stroke risk factors and corresponding therapeutic interventions

Risk factor	Treatment	Relative risk reduction for stroke	References
Hypertension	Antihypertensive therapy to a goal SBP < 140 mm Hg and a goal DBP < 90 mm Hg	Primary prevention, 30%–45% Second prevention, 43%	24, 33
Hyperlipidemia	Cholesterol reduction to a goal LDL < 70–100 mg/dL	Primary prevention, 19%–26%	61, 62
Atrial fibrillation	*High risk*: warfarin *Moderate risk*: warfarin or aspirin (325 mg/day) *Low risk*: aspirin (325 mg/day)	Primary prevention, 80% Secondary prevention, 33% (warfarin) Secondary prevention, 25% (aspirin)	52, 53
Diabetes	Metformin, glucose control	Primary prevention, 40%	42

SBP = systolic blood pressure; DBP = diastolic blood pressure; LDL = low-density lipoprotein

losartan reduced stroke risk by 25% relative to atenolol, a statistically significant reduction. Losartan was also associated with better MI and survival outcomes. Interestingly, black patients responded better to atenolol.[23] Other data suggest that blacks may also benefit from ACE inhibitors (eg, ramipril).[29]

There is speculation that antihypertensive medications may impart other beneficial effects, such as vascular protection, arterial remodeling (ACE inhibitors, angiotensin receptor blockers, calcium channel blockers), or neuroprotection (calcium channel blockers, thiazide diuretics).[30,31] This has not been clearly proven. From a practical standpoint, however, it is more likely that specific antihypertensive agents are selected for use on the basis of coexisting conditions such as renal disease, diabetes, or congestive heart failure.

Antihypertensive therapy for secondary stroke prevention. Treatment of hypertension is also beneficial in patients who have already suffered a stroke. The Post-Stroke Antihypertension Treatment Study (PATS), a placebo-controlled trial of the diuretic indapamide in 5,665 stroke patients in China, found that indapamide use resulted in a 29% reduction in stroke rate at the end of 3 years.[32] In the Perindopril Protection Against Recurrence of Stroke Study (PROGRESS), 6,105 patients in Europe and Asia received the ACE inhibitor perindopril alone, perindopril combined with indapamide, or placebo.[33] After 4 years of treatment, the combination of perindopril–indapamide reduced blood pressure by 12/5 mm Hg and stroke risk by 43%. Perindopril alone was not effective in reducing stroke. Interestingly, benefits were achieved in both hypertensive and normotensive patients.[33] These studies demonstrate that blood pressure management after stroke, like that before stroke, is effective in reducing risk for subsequent stroke.

Caution needed when lowering blood pressure in the elderly. Although evidence clearly supports treatment of hypertension regardless of patient age,[34] blood pressure should be reduced cautiously in older adults.[35] Using data from the Rotterdam Study, Voko and colleagues[36] described a J-shaped relationship between blood pressure and stroke. Risk for stroke increased directly with increases in blood pressure in untreated patients, but risk also increased when SBP was less than 130 mm Hg and DBP was less than 65 mm Hg.[36] Similar observations were reported from the Cardiovascular Health Study.[37]

A shift in the cerebral autoregulatory curve, which describes the relation between cerebral perfusion pressure and cerebral blood flow, is thought to be the basis of this phenomenon. Cerebral perfusion pressures that are adequate in normotensive patients are inadequate in those with chronic hypertension. As a result, rapid reduction in blood pressure, even to a range normally tolerated by normotensive patients, may compromise cerebral blood flow and perfusion in a hypertensive patient, and ischemic injury may ensue. Thus, reduction of blood pressure to the normotensive range reduces stroke risk but must be gradual to allow normalization of cerebral autoregulation.[36]

Diabetes mellitus

Diabetes is a risk factor for both stroke and MI, increasing the risk of stroke threefold beyond that which can be accounted for by smoking, hypertension, and dyslipidemia.[38] The UK Prospective Diabetes Study (UKPDS) is a unique study comprising 5,102 patients with newly diagnosed type 2 diabetes mellitus who have been followed longitudinally for up to 17 years for vari-

ous macrovascular and microvascular outcomes, including stroke.[39] Among 3,776 patients in the UKPDS without known cardiovascular disease, 99 (2.6%) had a stroke over the initial 8 years of observation; significant risk factors for stroke were age greater than 60 years, male sex, and hypertension.[40] In the subset of 3,728 patients with electrocardiographic data at entry, atrial fibrillation increased the risk of stroke eightfold.[40]

Two parallel substudies of the UKPDS have examined the effect of intensive blood glucose control on cardiovascular complications. UKPDS 33, conducted in a subcohort of patients with ideal body weight, found that intensive blood glucose control with a sulphonylurea or insulin to a target fasting glucose level of less than 6 mmol/L (n = 2,729) reduced the rate of microvascular complications, but not of strokes, compared with conventional treatment (diet) to a target fasting glucose level of less than 15 mmol/L (n = 1,138).[41] UKPDS 34, conducted in a subcohort of 1,704 overweight patients, randomized patients to metformin (n = 342), diet therapy alone (n = 411), or intensive glucose control achieved by chlorpropamide, glibenclamide, or insulin (n = 951) after an initial 3 months of diet therapy.[42] In these overweight diet-treated patients, metformin significantly reduced the risk of diabetes-associated cardiovascular events, including stroke, compared with diet alone and compared with chlorpropamide, glibenclamide, or insulin.[42] However, because comparable benefits were not observed in nonoverweight metformin-treated patients,[41] it remains uncertain whether the benefits with metformin were attributable to tight glucose control, blood pressure reduction, or modification of some other risk factor.[43,44]

Another UKPDS substudy assessed the effectiveness of tight blood pressure control along with glucose control in a sample of 1,148 hypertensive patients with diabetes.[45] It found a highly significant 44% reduction in stroke risk in patients under tight blood pressure control (mean, 144/87 mm Hg) compared with those under less-tight control (mean, 154/87 mm Hg).

Nonvalvular atrial fibrillation

Atrial fibrillation increases stroke risk fivefold.[46] Treating atrial fibrillation with warfarin reduces stroke risk. The Stroke Prevention in Atrial Fibrillation (SPAF) trials showed that warfarin, dosed to achieve an international normalized ratio (INR) of 2 to 3, reduced the risk of first stroke by close to 80% and of subsequent stroke by 33%.[47–49] Aspirin (325 mg/day orally) is also effective and imparts a 25% relative risk reduction compared with placebo.[47–49] Hylek and colleagues[50,51] provided evidence that a target INR of 2 to 3 is optimal. Compared with an INR of 2, risk for stroke is two times higher with an INR of 1.7, three times higher with an INR of 1.5, and seven times higher with an INR of 1.3. No additional benefit is seen with INR levels above 3, even when extrapolated to an INR of 7, although bleeding risk increases dramatically with an INR above 4.[50,51]

Recently, Hart and colleagues from the SPAF investigators group further compared warfarin and aspirin in the context of a treatment algorithm for atrial fibrillation that incorporated comorbidities such as advanced age, heart disease, and hypertension.[52–55] For patients who have suffered a stroke or TIA, warfarin should be used with a target INR of 2 to 3. Patients age 75 or older who have multiple risk factors but have not yet suffered a stroke also should receive warfarin. Patients between ages 65 and 75 with a single risk factor (considered to be at moderate risk) may be treated with either aspirin (325 mg/day) or warfarin. Patients over age 55 with no risk factors (other than atrial fibrillation) are at low risk for stroke and may be treated with aspirin only.[52–55]

Unfortunately, warfarin and aspirin are underused in spite of the clear evidence of their effectiveness in reducing stroke in patients with atrial fibrillation. Only one third of patients who should be treated are receiving warfarin. Although there is a reasonable concern about the risk of bleeding, fewer than half of patients not receiving anticoagulant therapy are receiving antiplatelet medication. This is especially true among the elderly, who have the highest risk for stroke.[56–59]

Hyperlipidemia

Cholesterol-lowering therapy with statins (HMG-CoA reductase inhibitors) reduces risk for stroke. This was first demonstrated as a secondary outcome in the Cholesterol and Recurrent Events (CARE) trial, which found pravastatin to reduce stroke incidence by 31% relative to placebo over 5 years of follow-up among 4,159 patients with a previous MI.[60] This protective effect against stroke has been confirmed by subsequent meta-analyses of statin trials that included stroke as an outcome.[61,62] One such analysis, which included 28 statin trials encompassing more than 106,000 patients with coronary artery disease, including some with prior stroke or TIA, demonstrated a 19% reduction in stroke risk with statin therapy.[61] Another analysis, which comprised 38 studies with more than 81,000 patients, showed a 26% reduction in stroke risk with statin therapy.[62]

The recent PROVE IT–TIMI 22 study examined the effect of intensive vs moderate lowering of low-density lipoprotein (LDL) cholesterol in 4,162 patients with recent acute coronary syndromes.[63] It

found that, after 2 years, intensive reduction of LDL cholesterol (ie, to a mean of 62 mg/dL) was associated with a 16% reduction in the combined risk for MI, stroke, or vascular death compared with moderate LDL reduction (ie, to a mean of 95 mg/dL). This study suggests that more aggressive reduction of LDL cholesterol—ie, to less than 70 mg/dL rather than the usual target of less than 100 mg/dL—might provide additional benefit in patients at high risk for cardiovascular events, including stroke.[63]

Aging

Finally, advanced age has been a common element in all studies of stroke prevention. Age was an independent predictor of death in the Connecticut Medicare database analysis discussed above[16] and was the most robust predictor of death (even more robust than cardiac failure) in the Perth Community Stroke Study.[14] In the latter study, age was also a predictor of recurrent stroke and hemorrhagic stroke.[14] Age greater than 65 is a predictor of ischemic stroke and age older than 75 of hemorrhagic stroke.[64]

Although age itself is not a modifiable risk factor, studies are investigating the contributions of age-associated vascular stiffening and thickening of the intimal media to stroke and other cardiovascular events.

BEYOND RISK FACTORS: ANTIPLATELET THERAPY

In addition to reducing risk factors, clinicians may also consider antiplatelet therapy to reduce the chance of ischemic events in at-risk patients (Table 2).

Aspirin

Acetylsalicylic acid (aspirin) is the most widely used antiplatelet drug. It is an irreversible cyclo-oxygenase inhibitor that prevents thromboxane A_2 production, thereby inhibiting platelet aggregation. Precedence for aspirin therapy was first established in primary and secondary MI prevention studies, which showed nearly reductions of nearly 50% in ischemic cardiac events.[65–67] The American Heart Association recommends an aspirin dosage of at least 75 mg/day orally for these purposes.[68]

Aspirin has also been proved effective for secondary prevention of stroke in high-risk patients. The most recent work of the Antiplatelet Trialists Collaboration is a collaborative meta-analysis of 287 studies involving 212,000 patients, of whom 187,000 were enrolled in placebo-controlled trials.[69] This analysis showed that aspirin use reduced the risk of subsequent stroke by 25% and effectively reduced the risk of other serious vascular events, such as MI (by 34%) and vascular death.[69] Although there is no definitive evidence on the most effective dosage of aspirin for secondary stroke prevention, 75 to 150 mg/day is recommended by the Antiplatelet Trialists Collaboration and 75 mg/day or more by the American Heart Association.[68,69]

Thienopyridines

A new class of oral platelet inhibitors, the thienopyridines, was introduced in 1989.

Ticlopidine is the prototype of this class of agents, which prevent platelet aggregation by blocking the adenosine diphosphate site. Two large clinical trials showed the efficacy of ticlopidine for stroke prevention.[9,10] In one, ticlopidine reduced recurrent stroke risk by 33% relative to placebo.[9] In the other, ticlopidine reduced the risk of nonfatal stroke at 3 years by 12% relative to aspirin and reduced the risk of all strokes (fatal and nonfatal) by 22% vs aspirin.[10] However, because of a 2.4% incidence of neutropenia associated with ticlopidine use,[70] the US Food and Drug Administration requires monitoring of complete blood counts every other week for the first 3 months of therapy.

In a cohort of 1,809 black patients, ticlopidine (500 mg/day) was compared with aspirin (650 mg/day) for reducing recurrent stroke, MI, or vascular death.[71] There were trends favoring aspirin with respect to both efficacy and adverse effects (neutropenia and thrombotic thrombocytopenic purpura), but neither reached statistical significance. Thus, for blacks, the results suggest that high-dose aspirin imparts the same benefit as ticlopidine.

Other important side effects of ticlopidine are diarrhea, rash, and gastrointestinal distress. The incidence of thrombotic thrombocytopenic purpura with ticlopidine use is 1 case per 5,000 patients.[72]

Clopidogrel, another thienopyridine, was introduced in 1996. Clopidogrel was compared directly with aspirin in a randomized, double-blind trial in 19,185 patients with known symptomatic atherosclerotic disease, defined as a history of MI, stroke, or symptomatic peripheral vascular disease.[12] After 2 years of therapy with either aspirin (325 mg/day) or clopidogrel (75 mg/day), the rate of cardiovascular events (MI, stroke, or vascular death) was 8.7% lower in the clopidogrel group than in the aspirin group. For stroke alone, clopidogrel was associated with a 7.2% relative risk reduction compared with aspirin, but this difference was not statistically significant.

Dipyridamole

Dipyridamole, a phosphodiesterase inhibitor and nitric oxide carrier, represents another class of antiplatelet agent. This oral therapy has been studied as monotherapy in a large number of clinical trials,

TABLE 2
Interventions for stroke prevention: profiles of antiplatelet therapies and carotid endarterectomy

Intervention	Treatment/dosage	Relative risk reduction	References
Aspirin	75–325 mg/day	Secondary stroke prevention, 25% Primary MI prevention, 50% Secondary MI prevention, 34%	66, 67, 69
Ticlopidine	250 mg twice daily	Secondary stroke prevention, 33%*	9
Clopidogrel	75 mg/day	Secondary stroke prevention, 25%–30% Secondary MI prevention, 19%	12, 86
Dipyridamole-ER	200 mg/day	Secondary stroke prevention, 16% MI prevention, 0%†	11
Aspirin/dipyridamole-ER	30 mg/200 mg twice daily	Secondary stroke prevention, 36%	11
Aspirin/clopidogrel	75 mg/75 mg daily	Secondary stroke prevention, 25%–30%‡ Secondary MI prevention, 55%–70%	75, 84, 85, 113
CEA (symptomatic)	Lesion >70%: CEA + aspirin (325 mg/day)	Secondary stroke prevention, 70%	99
CEA (asymptomatic)	Lesion >60%: CEA + aspirin (325 mg/day)	Secondary stroke prevention, 53%§	102,103

* Not yet fully tested for secondary MI prevention.
† MI data are in stroke patients only; other MI data are in cardiac patients, but only for immediate-release preparation.
‡ In patients already taking aspirin when index event occurred.
§ Only if surgical risk is < 3%.
MI = myocardial infarction; ER = extended-release; CEA = carotid endarterectomy

most recently in the second European Stroke Prevention Study (ESPS-2).[11] Although treatment with dipyridamole reduces the stroke rate by approximately 16% when compared with placebo,[11] the protective effect is less than that with aspirin. Thus, dipyridamole is not recommended for use as a sole agent for preventing stroke.

Combination antiplatelet therapy

Combining drugs that exert the same effect by different mechanisms can result in "effect summation," ie, greater benefit with fewer side effects. This is the pharmacologic basis for the combinations of aspirin, dipyridamole, and clopidogrel that have been studied to date.

Aspirin plus dipyridamole. The ESPS-2 evaluated the combination of aspirin and extended-release dipyridamole (dipyridamole-ER) for secondary prevention of stroke.[11] It randomized 6,602 patients with recent stroke to either placebo, aspirin alone (25 mg twice daily), dipyridamole-ER alone (200 mg twice daily), or aspirin combined with dipyridamole-ER. Aspirin alone was 18% more effective at preventing a second stroke than placebo, dipyridamole-ER was 16% more effective, and aspirin plus dipyridamole-ER was 36% more effective.

Aspirin plus a thienopyridine. Combining aspirin with a thienopyridine should yield additive effects.[73] Used alone, ticlopidine has achieved a 33% reduction in stroke risk relative to placebo. Because placebo-controlled trials are unethical when a known effective therapy exists, no corresponding placebo-controlled data on stroke risk reduction are available for clopidogrel, but we can infer that clopidogrel lowers stroke risk by approximately 30% relative to placebo based on data from the aspirin-controlled Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events study.[73,74] Thus, combining either ticlopidine or clopidogrel with aspirin should provide additive benefit. However, ticlopidine's unfavorable toxicity profile limits its usefulness.

The Management of Atherothrombosis with Clopidogrel in High-risk Patients (MATCH) trial evaluated the addition of aspirin to clopidogrel for reduction of secondary stroke risk in 7,599 patients who had suffered a stroke or TIA in the prior 3 months.[75] All patients were at high risk for further events, defined as having one or more risk factors such as diabetes or hypertension. Interestingly, 80% of patients were already taking aspirin at enrollment. All patients were treated with clopidogrel 75 mg/day, to which either aspirin 75 mg/day (n = 3,797) or placebo (n = 3,802) was added. After 18 months, the addition of aspirin to clopidogrel did not achieve greater reduction of stroke risk but did double the rate

of hemorrhagic complications (mostly in the gastrointestinal tract), to 2.6% from 1.3% with clopidogrel alone. The investigators attributed this disappointing finding to the high prevalence of diabetes (75%) or small-vessel disease.

Aspirin dosing in combination regimens. An alternative explanation for the disappointing result in the MATCH trial is aspirin resistance, which in prior studies was estimated to affect up to 40% of aspirin users.[76–78] For patients who suffer a stroke while taking aspirin, clinicians must question whether continued aspirin therapy will provide any protective benefit against stroke.[78]

The optimal aspirin dose for stroke prevention is highly controversial, and it is further complicated when combination therapy is considered. If a patient is taking 325 mg/day of aspirin and experiences a cerebrovascular event, is it prudent to reduce the dose when adding a second agent? This is a dilemma clinicians face regularly. In light of concerns over additional adverse effects, such as hemorrhage, decreasing the aspirin dose seems reasonable. However, higher doses could be more effective in some subsets of patients.[79–81] The technology of quantifying platelet aggregation is evolving[82] and may be useful as a pharmacodynamic response that could serve as a convenient surrogate for future cerebrovascular events.

It may simply be that continuation of aspirin in patients who suffer stroke despite adequate aspirin therapy would be rational only if there were another compelling reason, such as reducing MI risk.[76,77,83]

Combination therapy for MI prevention. Because MI is the leading cause of death in stroke survivors, optimizing MI prevention is important. Two clinical trials conducted in high-risk patients, the Clopidogrel for Reduction of Events (CURE) and Percutaneous Coronary Intervention from CURE (PCI-CURE) studies, showed an added benefit from combining aspirin with clopidogrel in reducing MI and death.[84,85] The incremental 21% benefit over aspirin alone compared favorably with the 19% benefit in the CAPRIE trial.[86] In the CURE and PCI-CURE trials, combination therapy with aspirin plus clopidogrel reduced the MI rate by approximately 55% to 70% relative to no therapy.[84,85]

Dipyridamole had not been previously shown to reduce acute coronary syndromes.[11,87–91] Thus, adding dipyridamole to aspirin would not be expected to impart additional protection against MI. The ESPS-2 trial showed a 13% reduction in MI incidence among patients with stroke, but only in its aspirin arm, with no additional protection against MI observed when aspirin was combined with dipyridamole.[11]

Drug interactions relevant to antiplatelet therapy

The interaction between aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs),[92] such as ibuprofen, is clinically important in the context of stroke prevention, since many elderly patients suffer from arthritis and other painful conditions. For such patients, NSAIDs are critical in maintaining quality of life. The problem is that NSAIDs may interfere with aspirin's ability to protect against MI and stroke. Both classes of drugs act to inhibit cyclo-oxygenase; aspirin binds irreversibly, whereas ibuprofen attaches reversibly but at different sites that are in close proximity. If taken with aspirin, ibuprofen interferes with aspirin binding. Because aspirin is rapidly metabolized in blood, it will be degraded before it can attach and produce its beneficial effects. Since NSAIDs have not been shown to protect against MI (although naproxen may), patients may be left without protection against MI and stroke.[93,94] Some studies have suggested, however, that this effect may not be clinically relevant.[95,96]

A practical solution is to instruct patients to take aspirin 30 minutes or so before taking an NSAID.

NO ROLE FOR ANTICOAGULATION IN ABSENCE OF ATRIAL FIBRILLATION

Despite the protective effects observed in patients with nonvalvular atrial fibrillation, anticoagulation with warfarin to ameliorate secondary stroke risk has been disappointing. The Stroke Prevention in Reversible Ischemia Trial (SPIRIT), conducted in Europe, compared warfarin (INR 3 to 4.5) with aspirin (30 mg/day) in 1,316 patients.[97] The results favored aspirin, as the warfarin group suffered 37% more strokes, almost 2.5 times more deaths, and 100 times more bleeding episodes.[97] More recently, the Warfarin for Reduction of Recurrent Stroke (WARRS) trial compared aspirin (325 mg/day) with warfarin dosed to a lower INR goal (1.5 to 3) among 2,206 patients.[98] Warfarin provided no improvement over aspirin in stroke rate but imparted a 50% relative increase in minor bleeding.[98]

SURGICAL INTERVENTIONS FOR STROKE PREVENTION

Surgical intervention with carotid endarterectomy (CEA) is also an option for stroke prevention (Table 2).

Carotid endarterectomy in symptomatic patients

CEA is effective in patients with extracranial internal carotid artery stenosis of 70% or greater and ischemic symptoms referable to that stenosis.

The North American Symptomatic Carotid Endarterectomy Trial (NASCET), conducted in 659 patients who presented within 4 months of symptomatic carotid stenosis, demonstrated a 55% reduction in stroke risk following CEA plus aspirin therapy (325 mg/day) as opposed to aspirin therapy alone.[99] The surgical risk in this study was approximately 6.5%, which is comparable to the perioperative risk of CEA in similar trials.[99,100]

Tu and colleagues[101] reported an increase in CEA procedures following publication of the NASCET results. Many centers reported a 30-day death rate greater than 2%,[101] which is much higher than the 0.6% rate in NASCET and the 0.1% rate in the Asymptomatic Carotid Atherosclerosis Study (ACAS).[102] The perioperative complication rate of the surgeon performing the procedure must be comparable to or better than that of the study surgeons if an overall benefit is to be realized.

Carotid endarterectomy in asymptomatic patients

The role of CEA in asymptomatic patients is less certain.

The ACAS investigators randomized 1,662 asymptomatic patients to CEA plus aspirin (325 mg/day) or aspirin alone.[102] Subjects qualified if they had carotid stenosis of 60% or greater but had not yet suffered a cerebrovascular ischemic event. CEA imparted an overall 53% reduction in stroke risk relative to aspirin alone. Enrolled patients were highly selected, which might in part account for the good results.[103] Additionally, the surgeons in this study had overall perioperative morbidity and mortality rates of less than 3%. This is substantially less than the 6.5% rate for surgeons performing CEA in other trials[101]—an absolute difference of about 3.5 percentage points. When added to the absolute stroke rate of 5.8% in the group treated with CEA plus aspirin, the result is 9.3%. This is close to the absolute stroke rate of 11% in the group receiving aspirin alone. Thus, unless the surgeon has a perioperative complication rate of less than 3%, the benefit of undergoing this procedure will be negated by the surgical risk.

Notably, men were the primary beneficiaries of CEA in ACAS: within the CEA-treated group, men obtained a relative risk reduction of 69%, whereas the reduction was only 16% for women.[102]

In an analysis of patients with asymptomatic internal carotid artery stenosis from the NASCET database, Inzitari and colleagues[104] found that the 5-year risk for stroke from asymptomatic carotid lesions with stenosis of at least 60% was double that from lesions with stenosis of less than 60%. The risk for large-artery stroke was highest with the greatest stenosis (ie, 95% to 99% stenosis). Patients with asymptomatic carotid lesions with stenosis of at least 60% had a 5-year risk for stroke of 10%. These same patients also were at risk for stroke from other etiologies, including a 6% risk for lacunar stroke and a 2% risk for cardioembolic infarctions. Thus, close to half of the overall stroke risk in these patients could be attributed to lesions not associated with the carotid artery, for which CEA would not be ameliorative.[104]

Some experts believe that a more comprehensive evaluation should be done before surgery to determine the source of the greatest risk for stroke. If it is from the carotid lesion, surgical intervention should be considered if the patient is male and the surgeon has a perioperative complication rate below 3%. However, if there is other evidence of cardiac risk for stroke (eg, patent foramen ovale, atrial fibrillation), small-vessel disease, or intracranial carotid disease, CEA will probably not provide substantial benefit.[105] It must be emphasized that we have no evidence that such an evaluation strategy is effective.

Intra-arterial interventions

An evolving area of therapy is intra-arterial intervention. Stents and angioplasty have been used successfully in managing occlusive coronary disease. These technologies are now being applied to the management of cerebrovascular disease and stroke. The Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial was a randomized study that compared stenting with surgical CEA in 334 patients with carotid occlusive disease determined to be at high risk for complications from CEA.[106] The stenosis criteria were 50% if the patient was symptomatic and 80% if asymptomatic. The results showed no difference between the two procedures in stroke, death, or MI at 30 days or in stroke and death at 1 year. However, the long-term effectiveness of these procedures is still under investigation.[107–109]

BARRIERS TO EFFECTIVE STROKE PREVENTION

A frequently encountered barrier to effective stroke prevention is the persistent belief that stroke is either unpreventable or does not warrant aggressive management. Compared with the cost of cancer therapy, the penny-a-day cost of aspirin is an extraordinary bargain. In spite of this, there is evidence that fewer than 50% of patients needing antiplatelet therapy receive it.[110–112] It is even less commonly used among

the elderly, who are at the highest risk for stroke, MI, and vascular death.

The diagnosis and management of comorbid illnesses presents an additional management challenge in older patients. The overlap between two of the three deadliest diseases (ie, stroke and MI) cannot be ignored. Fortunately, these two diseases are etiologically linked and treatments that effectively reduce risk for one also reduce risk for the other. This is not the case with other comorbid illnesses that may require treatment with medications that either worsen stroke-risk profiles (drug-disease interaction) or interfere with drug efficacy or tolerability (drug-drug interaction).

CONCLUSIONS

Stroke remains a life-threatening disease that results in substantial disability in those who survive it. Risk factor modification can protect against initial and recurrent stroke, with additional roles for antiplatelet therapy and surgical interventions such as CEA. When applied appropriately, these strategies can greatly reduce stroke risk. Their implementation requires coordination between neurologists and primary care physicians, especially for older adult patients, who are at greatest risk for stroke and are likely to also have comorbidities that require management. Although current therapy simultaneously improves cerebrovascular and cardiovascular outcomes, it is important to remember the differences between the cerebrovascular and cardiovascular systems. Future research is likely to identify important differences between stroke and MI that will guide future brain-specific treatments.

Disclaimer

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