Strategies for Primary and Secondary Stroke Prevention

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Summary: Of the 55 million deaths that occur annually, 1 in 10 is attributable to stroke. As a consequence, cerebrovascular disease is the second leading cause of death worldwide, and stroke is among the most devastating consequences of vascular disease, causing long-term disability and incurring high personal, societal, and financial costs. However, stroke is a highly preventable disease in the majority of patients. The goal of stroke prevention strategies is to identify high-risk patients through the presence of modifiable and nonmodifiable risk factors and to target these modifiable risk factors through the use of appropriate pharmacologic and nonpharmacologic interventions. Clinical and epidemiologic studies point toward three major risk-reducing pharmacologic therapies that together may dramatically reduce stroke risk. First, landmark clinical trials have demonstrated that the reduction of blood pressure in persons at risk for cerebrovascular disease significantly reduces stroke risk. Second, ample evidence supports the use of antiplatelet therapy, such as aspirin, in patients at high risk for a cerebrovascular event. Third, an abundance of data suggests that lipid-lowering therapy with a statin reduces stroke risk in most moderate- to high-risk patients regardless of baseline cholesterol levels. Together, these data suggest that intensive therapy with agents from multiple drug classes that target two or more risk factors for cerebrovascular disease may provide additive—or even synergistic—reductions in stroke risk.

Key words: stroke, primary prevention, secondary prevention, pharmacologic therapy

Introduction

Stroke is a heterogeneous disease caused by occlusion or hemorrhage in the blood supply to the central nervous system. Most strokes (~80%) are ischemic, involving a disruption in blood flow; the remainder are hemorrhagic, intracerebral, or subarachnoid.¹

Stroke is the most devastating consequence of vascular disease, causing both death and disability. Worldwide, 1 in 10 of the 55 million deaths that occur annually is attributable to stroke, making cerebrovascular disease the second leading cause of death worldwide.² An additional 15 million persons have nonfatal strokes, 60% of whom have some residual disability.³ With the aging of the population, projections indicate that stroke will remain the second leading cause of death worldwide and that it will become the fourth leading cause of disability worldwide by the year 2020.²

In the United States, stroke is the third leading cause of death, accounting for > 1 of every 15 deaths in 2001. Over 700,000 persons experience a stroke each year, and of these 200,000 are recurrent events. Consistent with global data, stroke is a leading cause of serious, long-term disability in the U.S., and over 20% of patients who survive a stroke require institutional care within 3 months of the event.¹ In addition to long-term disability, the neurological deficits also leave survivors at increased risk for falls, aspiration, deep vein thrombosis, urinary tract infection, constipation, and depression. In addition, observational studies have demonstrated that cerebrovascular disease is strongly associated with the long-term risk for dementia⁴ and cognitive decline.⁵

Although stroke is sometimes referred to as a cerebrovascular accident, it is no accident. It most often occurs after decades of progression of underlying vascular disease and the relentless effects of vascular risk factors. Approximately 75% of strokes in middle-aged men and women can be attributed to an adverse risk factor profile.² Treatment of the major modifiable risk factors has the potential to reduce the incidence of stroke dramatically. Behavioral modification, including smoking cessation, exercise, and weight reduction, has an important role in reducing overall stroke risk. In addition, evidence from epidemiologic and clinical studies indicates that early and aggressive pharmacologic intervention has the potential to reduce the incidence of stroke dramatically.

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Stroke Risk Factors

The goal of stroke prevention is to identify those at risk and treat them in time; this means identifying and treating risk factors. Modifiable risk factors for stroke include hypertension, diabetes mellitus, atrial fibrillation, asymptomatic carotid stenosis, cigarette smoking, physical inactivity, and, potentially, dyslipidemia.⁶⁻⁸

Approximately 25% of individuals who experience stroke do not have any of the commonly cited modifiable risk factors although other (nonmodifiable) risk factors may be in play.² Although some risk factors cannot be treated, they should be used to identify patients at the greatest risk for stroke to target other risk-modifying strategies. Nonmodifiable risk factors for stroke include age, gender, race, and family history. Stroke is age dependent and most strokes occur in patients aged > 65 years.⁷⁻⁹ There are also clear racial and gender disparities in the stroke death rate: stroke mortality in 2001 was 56.5% for white men and 85.4% for black men, and 54.5% for white women and 73.7% for black women. While the stroke incidence is 1.25-fold higher in men than in women because of a longer-life expectancy, just over half of all strokes occur in women, and women account for nearly 60% of stroke-related deaths.¹

Treatment Strategies for Primary and Secondary Stroke Prevention

Hypertension is the most important risk factor for stroke. Persons with systolic blood pressure (SBP) ≥ 160 mmHg or diastolic blood pressure (DBP) ≥ 95 mmHg have a 4-fold higher relative risk for stroke than those with normal BP.¹ Because 35 to 50% of strokes are directly attributable to hypertension, even small improvements in hypertension control could yield a significant reduction in stroke frequency.⁸

In clinical trials of hypertension, stroke is the major clinical outcome. Blood pressure reduction significantly reduces the risk for a first or recurrent stroke. For example, in the Systolic Hypertension in Europe (Syst-Eur) Trial,¹⁰ patients ≥ 60 years old with isolated systolic hypertension (160–219 mmHg) were randomized to treatment with placebo ($n = 2,297$) or the calcium-channel blocker nitrendipine (10 to 40 mg/day), which could be augmented with the angiotensin-converting enzyme (ACE) inhibitor enalapril (5 to 20 mg/day), the diuretic hydrochlorothiazide (12.5 to 25 mg/day), or both ($n = 2,398$). After a median of 2 years of treatment, SBP and DBP were reduced 13.0/2.0 mmHg in the placebo group and 23.0/7.0 mmHg in the active treatment group; the majority of this BP reduction was observed soon after randomization when most patients were still receiving monotherapy with nitrendipine. A 10.7/4.7 mmHg difference between treatment groups at 4 years resulted in a significant ($p = 0.003$) 42% relative risk reduction in the primary endpoint of fatal and nonfatal stroke. Of importance is the fact that the relative stroke risk began to diverge almost immediately after randomization. These data indicate that SBP reduction in high-risk patients is

associated with a rapid reduction in stroke risk. Similar results have been found for young and old, mild or severe hypertension, systolic or diastolic hypertension, and for primary or secondary prevention. Modest reduction in BP can have a profound effect on reducing stroke risk.

Other trials have examined the effect of inhibition of the renin-angiotensin-aldosterone system (RAAS) with ACE inhibitors or angiotensin-receptor blockers (ARBs) and have included both patients with and without hypertension. In the Perindopril Progression Against Recurrent Stroke Study (PROGRESS),¹¹ 6,105 patients with a history of stroke or transient ischemic attack (TIA) within the previous 5 years were randomized to treatment with the ACE inhibitor perindopril 4 mg/day, with or without the diuretic indapamide 2.5 mg/day ($n = 3,051$), or placebo ($n = 3,054$). Although there were no BP inclusion criteria, 48% of the subjects were classified as hypertensive ($> 160/90$ mmHg). Overall, BP was reduced by an average of 9.0/4.0 mmHg in patients receiving active treatment compared with those receiving placebo. The reduction in BP was approximately twice as great in patients receiving combination therapy with perindopril and indapamide (12.3/5.0 mmHg) as in those receiving monotherapy (4.9/2.8 mmHg). During 4 years of follow-up, 307 patients (10%) in the active treatment group and 420 patients (14%) in the placebo group experienced a stroke, a risk reduction of 28% ($p < 0.0001$) in favor of active treatment. Similar reductions in risk were observed regardless of pretreatment BP (even among those not meeting traditional definitions for hypertension). Stratification by treatment regimen demonstrated that this result was driven largely by reductions in stroke risk among patients receiving combination therapy with perindopril plus indapamide. Combination therapy was associated with a 43% stroke risk reduction; in contrast, perindopril alone was not associated with a significant stroke risk reduction. These benefits were observed against the background of nonstudy antihypertensive treatments and antiplatelet therapy, suggesting that the additional BP reductions achieved with combination therapy further reduced stroke risk.

The PROGRESS investigators also examined whether lowering BP reduced the risk for dementia (using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV] criteria) and cognitive decline (defined as a ≥ 3 -point decline in the Mini-Mental State Examination [MMSE] score) among patients with cerebrovascular disease.¹² During the 3.9 years of follow-up, dementia and cognitive decline were detected in 6.4 and 9.1% of active study participants with appropriate baseline measurements, respectively.¹² Active treatment was associated with a 12% dementia risk reduction ($p = 0.2$) and a 19% cognitive decline risk reduction ($p = 0.01$). The risk for the composite endpoints of dementia with recurrent stroke and cognitive decline with recurrent stroke were reduced by 34% ($p = 0.03$) and 45% ($p < 0.001$), respectively, with active treatment. These results emphasize the importance of cognitive decline and dementia in the post-stroke population and describe another powerful reason to be aggressive in BP control following stroke.

Beyond the effects of BP reduction, data from the Heart Outcomes Prevention Evaluation (HOPE)¹³ and the Losartan Intervention For Endpoint reduction in hypertension (LIFE)¹⁴ studies suggest that RAAS inhibition protects against stroke beyond simple BP reduction. The HOPE, a randomized, placebo-controlled trial, studied the effect of 5 years of treatment with ramipril (10 mg/day) or placebo in 9,297 patients at high risk for vascular disease. Patients were ≥ 55 years old with evidence of vascular disease (coronary artery disease, stroke, peripheral arterial disease) or diabetes plus one additional risk factor. The composite primary endpoint was cardiovascular mortality, myocardial infarction (MI), and stroke. Despite only modest BP reductions (3.8/2.8 mmHg), ramipril reduced the relative stroke risk by 32% ($p = 0.0002$). The fatal stroke risk was reduced by 61% and nonfatal stroke by 24%; moreover, there were also reductions in both ischemic and hemorrhagic stroke subtypes (Fig. 1).¹³ The beneficial effects of ramipril were independent of baseline BP and cardiovascular disease (CVD) status, and they were consistent across subgroups of patients receiving aspirin or other antiplatelet medications, antihypertensive drugs from other classes, and/or statins. In addition, among patients who had a stroke endpoint, those randomized to ramipril treatment had less severe strokes and less functional impairment in cognition, motor strength, speech, and swallowing than those receiving placebo treatment.¹³

The effects of the ARB losartan and the beta blocker atenolol were compared in the LIFE study.¹⁴ A total of 9,193 patients with hypertension (BP 160–200/95–115 mmHg) and left ventricular hypertrophy were randomized to losartan ($n = 4,605$) or atenolol ($n = 4,588$) for at least 4 years or until a primary CV event (death, MI, or stroke) occurred. Patients requiring additional BP lowering would have dose escalation and adjunctive hydrochlorothiazide therapy to achieve a target BP $< 140/90$ mmHg. Although mean BP reductions were nearly identical in losartan-treated patients and atenolol-treated patients (SBP: 30.2 vs. 29.1, $p = 0.017$; DBP: 16.8 vs. 16.6 mmHg, $p = 0.37$, respectively), losartan treatment was associated with a significant ($p = 0.021$) 13% reduction in the primary endpoint compared with atenolol treatment. The overall CV risk reduction in this trial was largely driven by a highly significant ($p = 0.001$) 25% stroke reduction in the losartan group.

FIG. 1 Heart Outcomes Prevention Evaluation (HOPE): Stroke risk by subtype. RRR relative risk reduction for ramipril versus placebo. Source: Ref. No. 13.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)¹⁵ was a randomized, double-blind, multicenter clinical trial comparing the effects of three “newer” antihypertensive agents—amlodipine, lisinopril, and doxazosin—with those of the diuretic chlorthalidone in 33,357 patients ≥ 55 years old with hypertension and one or more additional CV risk factors. The doxazosin arm was subsequently discontinued; therefore the final report compared only amlodipine and lisinopril with chlorthalidone. Patients were randomized to treatment with chlorthalidone (12.5 to 25 mg/day), amlodipine (2.5 to 10 mg/day), or lisinopril (10 to 40 mg/day) and followed for 4 to 8 years for the combined primary endpoint of fatal congestive heart disease (CHD) or nonfatal MI; stroke was a secondary endpoint.

Neither amlodipine nor lisinopril was superior to chlorthalidone in preventing major coronary events or increasing survival. After 5 years of follow up, SBPs were 2 and 0.8 mmHg higher in the lisinopril and amlodipine groups, respectively, than in the chlorthalidone group; DBP was 0.8 mmHg lower in the amlodipine group and equivalent to chlorthalidone in the lisinopril group. For the secondary endpoint of stroke, amlodipine and chlorthalidone were equivalent, but the lisinopril group had a 15% higher risk for stroke ($p = 0.02$).¹⁵

It is important to note that 35% of the study’s population was black. In these patients, there was a significant ($p = 0.01$) 1.40-fold higher risk for stroke in those receiving lisinopril; those given chlorthalidone achieved a 4 mmHg greater SBP reduction than those treated with lisinopril. This result may not be surprising, as black patients generally experience greater BP reductions with diuretics than with RAAS-blocking agents.¹⁵ The recently released results of the Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm (ASCOT-BPLA) demonstrates the utility of a calcium-channel blocker antihypertensive regimen versus a standard treatment regimen such as a diuretic and beta blocker. A highly significant risk reduction in fatal and nonfatal stroke (23%; $p = 0.0003$) was observed for hypertensive patients receiving the calcium-channel blocker amlodipine with ACE inhibitor perindopril (as needed) compared with an atenolol beta-blocker regimen.¹⁶ Significant risk reduction was also observed for total CV events (16%; $p < 0.001$), CV mortality (24%; $p = 0.001$), and all-cause mortality (11%; $p = 0.0247$).¹⁶ This study emphasizes the importance of selecting contemporary regimens for battling hypertension and the advantage of combined agents to reach aggressive BP goals.

While the specific regimens used in ALLHAT¹⁵ are no longer used in routine clinical practice, these data, together with data from other trials of antihypertensive agents, demonstrate that BP reduction, regardless of the method used, reduces the risk for CV events in the majority of patients.

Antiplatelet Therapy

Antiplatelet therapy is one of the mainstays of prevention among patients at high risk for ischemic vascular disease. The Antithrombotic Trialists’ Collaboration (ATC)¹⁷ performed a meta-analysis of 287 studies to compare prolonged antiplate-

let therapy with control in 135,000 high-risk patients and to conduct a head-to-head comparison of individual antiplatelet therapies in 77,000 high-risk patients (e.g., those with previous/acute MI, previous/acute stroke, or other high-risk patients). Antiplatelet therapy resulted in a 22% relative risk reduction in fatal and nonfatal stroke, with no significant heterogeneity among the five patient categories studied. Moreover, antiplatelet therapy resulted in 22 and 11% risk reductions, respectively, in vascular events among patients with a previous stroke and those with acute stroke. Addition of dipyridamole to aspirin did not result in significant additional reductions in vascular events compared with aspirin alone.

The ATC¹⁷ failed to detect an overall difference between the benefit of aspirin plus dipyridamole and that of aspirin alone for the combined endpoint of nonfatal stroke, nonfatal MI, and vascular death. The European Stroke Prevention Study 2 (ESPS-2)¹⁸ suggests that combination therapy with extended-release dipyridamole (200 mg b.i.d.) and aspirin (25 mg b.i.d.) was superior to this dose of aspirin alone in preventing recurrent stroke (23.1% relative risk reduction; $p = 0.006$) (Fig. 2).¹⁸ In this study, dipyridamole was not well tolerated, and more patients withdrew from the dipyridamole ($n = 485$) and combination therapy ($n = 479$) groups than from the aspirin group ($n = 366$).

The effects of the antiplatelet clopidogrel on vascular events were tested in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial.¹⁹ A total of 19,185 patients with a history of ischemic stroke, MI, or peripheral vascular disease were randomly assigned to treatment with aspirin 325 mg/day or clopidogrel 75 mg/day and followed for a mean of 1 to 3 years for the combined primary endpoint of ischemic stroke, MI, or vascular death. After a mean follow-up of 1.91 years, compared with placebo, clopidogrel was associated with a significant ($p = 0.043$) 8.7% relative risk reduction in the combined primary endpoint.¹⁹

More recently, the effects of clopidogrel plus aspirin on secondary prevention of stroke were tested directly in the Management of ATHerothrombosis with Clopidogrel in High-risk patients (MATCH) trial.²⁰ A total of 7,599 patients with recent ischemic stroke or TIA and one or more additional risk factors (including hypertension, prior ischemic stroke, MI, angina, diabetes, or symptomatic peripheral arterial disease) were randomized to clopidogrel 75 mg/day with or without aspirin 75 mg/day. The primary composite endpoint was ischemic stroke, MI, vascular death, and rehospitalization for an acute ischemic event. Combination therapy was associated with a nonsignificant 6.4% risk reduction in the composite primary endpoint. Life-threatening hemorrhage was significantly more common among patients randomized to combination therapy than among those who received clopidogrel alone (3 vs. 1%, respectively; $p < 0.001$). Although there was a slight, nonsignificant risk reduction in ischemic events with combination therapy, this was nearly equal in absolute number to the increased risk for serious or life-threatening hemorrhage. This study indicates that the addition of aspirin to clopidogrel therapy is not necessary for the majority of stroke patients.

Nonvalvular atrial fibrillation is associated with a significantly increased (approximately 5-fold) risk for ischemic stroke and systemic embolism.⁶ Warfarin therapy reduces the risk for first and recurrent stroke by up to 75% but is underutilized in the United States. Aspirin, indicated for those at lower risk, reduces the risk for stroke by about 20% but is associated with lower rates of bleeding complications.²¹

Efforts are underway to find more effective, safer, and easier ways to anticoagulate patients with atrial fibrillation. The Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III and V trials compared ximelagatran, an oral direct thrombin inhibitor, with warfarin in the prevention of stroke and systemic embolic events in patients with nonvalvular atrial fibrillation and one or more additional

FIG. 2 European Stroke Prevention Study (ESPS): Risk for stroke and stroke or death in ASA- versus ER-DP-treated groups. ASA = aspirin, ER-DP = extended-release dipyridamole. Adapted from Ref. No. 18 with permission.

risk factors for stroke.²² In SPORTIF III,²³ 3,407 patients were randomized to open label warfarin (adjusted-dose international normalized ratio 2.0 to 3.0) or ximelagatran (fixed-dose, 36 mg b.i.d.). By intent-to-treat analysis, warfarin treatment resulted in a nonsignificant reduction in primary events versus ximelagatran therapy (29% relative risk reduction; $p = 0.10$). Rates of disabling or fatal stroke, mortality, and major bleeding were similar between groups, but combined minor and major hemorrhages were lower with ximelagatran than with warfarin (29.8 vs. 25.8% per patient-year, respectively, for a 14% relative risk reduction; $p = 0.007$). The advantage of ximelagatran and other direct thrombin inhibitors is fixed dose, the lack of interaction with the effects of antibiotics, and the elimination of the need for International Normalized Ratio monitoring.

Lipid-Lowering Therapy

Although vascular disease is the most important contributor to the pathogenesis of stroke, plasma cholesterol levels have not been shown to be consistent in predicting stroke risk. The prospective British Regional Heart Study²⁴ conducted in 7,735 men, 40 to 59 years old, with no history of stroke, found a significant relationship between higher levels of high-density lipoprotein (HDL) cholesterol and stroke risk reductions. However, this study found no strong association between total cholesterol levels and fatal or nonfatal stroke. In contrast, the Atherosclerosis Risk in Communities (ARIC) study,²⁵ a large, 10-year, prospective study of 14,175 men and women, aged 45 to 64 years, with no history of CVD, found only a weak relationship between low-density lipoprotein (LDL) and HDL cholesterol levels and risk for ischemic stroke. The Multiple Risk Factor Intervention Trial (MRFIT)²⁶ found a clear relationship between risk for ischemic stroke and total cholesterol levels in 350,977 men aged 35 to 57 years, with no history of CVD or diabetes. Conversely, the risk for hemorrhagic stroke was significantly highest at the lowest total cholesterol concentrations. The Honolulu Heart Program²⁷ also found a progressive increase in thromboembolic stroke rates with increasing cholesterol levels. In this study, the relative risk for stroke when the highest and lowest serum cholesterol quartiles were compared was 1.4, similar to the 1.7-fold increase in risk for CHD when the same groups were compared. In the Women's Pooling Project,²⁸ which studied 24,343 women aged 30 to 97 years, there was a highly significant relationship between the highest quintile of plasma total cholesterol and ischemic stroke death in women ≤ 55 years old.

In balance, these data suggest that total cholesterol levels may be associated with risk for ischemic stroke and possibly inversely related to risk for hemorrhagic stroke. More important for stroke prevention are the results of clinical trials of statin therapy on the endpoint of stroke.

The Prospective Pravastatin Pooling Project²⁹ reported the results of a prospectively defined pooled analysis of data from three trials that evaluated the effect of pravastatin 40 mg/day on stroke in 19,768 patients, including the West of Scotland Coronary Prevention Study (WOSCOPS),³⁰ the Cholesterol

and Recurrent Events (CARE) trial,³¹ and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial.³² The WOSCOPS was a primary prevention trial involving 6,595 men aged 45 to 64 years, with hypercholesterolemia and no history of MI. The CARE trial was a secondary prevention trial that enrolled 4,159 men and postmenopausal women aged 21 to 75 years, with average lipid levels and a history of MI within 3 to 20 months prior to randomization. The LIPID trial was a secondary prevention study that enrolled 9,014 men and women aged 31 to 75 years, with a wider lipid range than CARE and a history of MI or unstable angina. Subjects enrolled in WOSCOPS, CARE, and LIPID were followed for an average of 4.9, 5.0, and 6.1 years, respectively.²⁹

Of the subjects enrolled in the three trials, 3% (598/19,768) had a stroke. Overall, subjects who were randomized to pravastatin had a 20% stroke risk reduction compared with placebo ($p < 0.01$). Among participants in CARE³¹ and LIPID,³² pravastatin was associated with a 22% stroke risk reduction ($p < 0.01$) and a nonsignificant 25% nonfatal stroke risk reduction. A similar trend toward stroke risk reduction was observed among patients enrolled in WOSCOPS.³⁰ In contrast to the observational data suggesting that lower cholesterol levels are associated with an increased risk for hemorrhagic stroke, there was no difference between the pravastatin and placebo groups in the risk for hemorrhagic stroke.²⁹

Similarly, a 27% stroke risk reduction ($p = 0.02$) was observed in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT),³³ which randomized moderate-risk patients with hypertension and average or near-average total cholesterol levels to atorvastatin 10 mg/day or placebo (Fig. 3).³³ Although this risk reduction was not statistically significant by the study's predefined statistical criteria, it should be noted that the study was ended approximately 2 years early due to significant risk reductions in the primary endpoint among patients randomized to atorvastatin. Had the study continued through the planned 5 years of follow-up, it seems likely that this endpoint would have approached or achieved statistical significance.

In the Heart Protection Study (HPS),³⁴ simvastatin was associated with a significant 24% reduction in the rate of major

FIG. 3 Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT): Stroke risk reduction for atorvastatin versus placebo. Adapted from Ref. No. 33 with permission.

TABLE I Key components of stroke prevention

Diabetes

Diabetes is a potent risk factor for stroke and increases the importance of BP control. All patients with stroke should be screened for diabetes. Those with diabetes should have the control of their diabetes and BP closely monitored.

Revascularization

Among patients with recent carotid territory TIA and stroke, carotid endarterectomy can reduce the risk for recurrent stroke by two-thirds. All patients with carotid territory stroke who are potential surgical candidates should be screened for carotid stenosis. Those with $\geq 70\%$ stenosis should be referred to an experienced surgeon.

Blood pressure

Blood pressure is the most important risk factor for stroke. The older target $\leq 140/90$ mmHg (or $135/85$ mmHg for diabetics) may not be low enough. Recent trial data suggest that BP $> 120/80$ mmHg is associated with an increased risk for first or recurrent stroke. Reduction of BP is the goal. Therapy with a diuretic and an ACE inhibitor is a reasonable starting regimen.

RAAS blockade

Recent studies suggest that RAAS inhibition with an ACE inhibitor or an ARB may provide additional protection above and beyond simple BP reduction. This approach is not specified in national guidelines.

Antithrombotic therapy

Patients at high risk for stroke should be on some form of antithrombotic therapy. For those with atrial fibrillation and additional vascular risk factors, anticoagulation with warfarin is often the preferred therapy.

Statin therapy

Given early benefits in trials of acute coronary syndromes, statin initiation during hospitalization for first ischemic stroke of atherosclerotic origin is probably justified and may increase rates of long-term use. Based on the HPS, simvastatin at 40 mg per day is commonly recommended.³⁴

Smoking cessation

Cigarette smoking is the leading cause of preventable deaths in the United States. The beneficial effects of smoking cessation on stroke risk are evident within the first few years after stopping.

Abbreviations: ACE = angiotensin-converting enzyme, RAAS = renin-angiotensin-aldosterone system, ARB = angiotensin receptor blocker, HPS = Heart Protection Study, BP = blood pressure, TIA = transient ischemic attack.

vascular events compared with placebo ($p < 0.0001$). Treatment with simvastatin 40 mg/day resulted in a significant 25% reduction in first strokes (444 with simvastatin and 585 with placebo; $p < 0.0001$). This reduction is attributable chiefly to a highly significant 30% reduction in ischemic strokes; there was no adverse effect on hemorrhagic stroke. This reduced stroke incidence was evident across strokes of all levels of severity, even when hemorrhagic strokes were included in the analysis.

Risk-Reducing Therapies in Clinical Practice

Although the focus of this article was on medical therapies, surgical therapy (for carotid stenosis) and lifestyle modifications (e.g., smoking cessation) are also important to consider in clinical practice. Stroke is largely preventable. Table I summarizes key components of stroke prevention. Finally, for those who have had a recent stroke, initiation and reinforcement of secondary prevention therapies while in the hospital may result in increased adherence to such therapies and reduced rates of recurrent stroke.^{35–37}

Conclusions

Stroke is a highly preventable disease in the majority of patients. Stroke risk reductions can be achieved through implementation of a two-part strategy. First, patients at high risk for stroke should be identified through careful assessment of modifiable and nonmodifiable risk factors. Second, each modifiable risk factor should be targeted for aggressive treatment with pharmacologic and nonpharmacologic therapy. Intensive risk-reduction therapies with agents from multiple drug classes may provide additive—or even synergistic—reductions in stroke risk.

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