Secondary Prevention Strategies in Ischemic Stroke: Identification and Optimal Management of Modifiable Risk Factors

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The identification and treatment of modifiable ischemic stroke risk factors, in addition to appropriate antithrombotic therapy, can reduce the likelihood of first or recurrent stroke, prevent long-term morbidity and mortality after first stroke or transient ischemic attack, and lower health care costs. Long-term morbidity and mortality in patients with ischemic stroke includes patients with coronary artery disease. Therefore, in patients with ischemic stroke (especially those with carotid artery disease and lacunar disease), the goal is to prevent not only recurrent stroke but also coronary artery disease. Neurologists and general practitioners must be aware of the specific risk factors and recommendations for patients with ischemic stroke and apply the information systematically. We review known risk factors for ischemic stroke and current recommendations for treatment, focusing primarily on atherosclerotic risk factors as they apply to patients with stroke. In particular, recent data on hypertension and hyperlipidemia are described. In addition, we discuss the challenges in managing these risk factors and the potential strategies for overcoming them.


ACAS = Asymptomatic Carotid Atherosclerosis Study; ACE = angiotensin-converting enzyme; ACST = Asymptomatic Carotid Surgery Trial; ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial-Lipid-Lowering Trial; ATP = Adult Treatment Panel; CHAMP = Cardiac Hospitalization Atherosclerosis Management Program; CHD = coronary heart disease; CRP = C-reactive protein; HDL = high-density lipoprotein; HOPE = Heart Outcomes Prevention Evaluation; HPS = Heart Protection Study; LDL = low-density lipoprotein; MI = myocardial infarction; PROGRESS = Perindopril Protection against Recurrent Stroke Study; RRR = relative risk reduction; SHEP = Systolic Hypertension in the Elderly Program; TIA = transient ischemic attack

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troke is the third-leading cause of death in the United States and is the leading cause of disability. The identification and treatment of modifiable stroke risk factors can reduce the likelihood of first or recurrent stroke, prevent long-term morbidity and mortality after the first stroke or transient ischemic attack (TIA), and lower health care costs. Despite existing knowledge, there is a lack of systematic assessment, and stroke-prevention strategies are underused, resulting in a gap between existing evidence and actual practice.

EVIDENCE FOR INTERVENTION TO REDUCE STROKE RISK

Definitive and putative stroke risk factors have been established through epidemiological studies (Table 1). For primary stroke prevention, randomized treatment trials have shown value in treating hypertension, hyperlipidemia, atrial fibrillation, asymptomatic carotid disease, and myocardial infarction (MI). Observational and case-control studies have supported treatment of diabetes, smoking cessation, and use of anticoagulation clinics for primary stroke prevention. Antiplatelet agents, including aspirin, ticlopidine, clopidogrel, and extended-release dipyridamole and aspirin have proved valuable in the secondary prevention of ischemic stroke. Also, randomized trial evidence supports secondary prevention strategies for the treatment of hypertension, hyperlipidemia, symptomatic carotid disease, and atrial fibrillation, as well as use of coordinated acute care units. Observational data suggest that control of diabetes and smoking cessation reduce the risk of second stroke or cardiac disease. Additional data are accumulating on the treatment of elevated homocysteine levels, the role of inflammatory conditions and stroke risk, and the value of C-reactive protein (CRP) measurement. Individual stroke risk factors are discussed subsequently in this article.

MEDICAL COMPLICATIONS OF STROKE

Secondary prevention for patients with ischemic stroke obviously includes prevention of recurrent stroke; however, other complications after ischemic stroke often are overlooked. Up to 30% of survivors of ischemic stroke will have a subsequent stroke within the next 5 years, 18% of which will be fatal. However, the risk of MI after cerebral infarction is also high, 5% in the first year and more than 3% annually for the first 10 years, reflecting the importance of recognizing concomitant coronary artery disease in patients presenting with ischemic stroke or TIA. Furthermore, the most frequent causes of death after stroke are cardiovascular and respiratory diseases.

Depression after stroke is common and often underrecognized in patients and their families or caregivers. Recently published reports suggest that nearly 40% of patients with stroke will experience depression during the first year after the event. The highest incidence is often
found in the early phase, that is, within the first 3 months, but may not be present in the acute phase, suggesting the need for ongoing surveillance.\textsuperscript{29} Factors suggested to increase the prevalence of poststroke major depression include left anterior brain injury, female sex, family or previous personal history of mood disorder, younger age, functional impairment, lack of social support, and negative life events.\textsuperscript{29}

Patients who undergo inpatient rehabilitation may receive psychiatric evaluation and treatment; however, depression may be underrecognized in patients with TIA or minor stroke who are discharged directly home from the hospital. Some studies suggest that depression is associated with poor functional outcome. Therefore, early identification and treatment could be helpful for many reasons. Treatment with various antidepressants including tricyclics, selective serotonin reuptake inhibitors, and citalopram have proved successful in the treatment of identified depression and in the prevention of poststroke depression.\textsuperscript{29}

**THE PROBLEM**

The identification and modification of stroke risk factors can reduce first stroke and prevent long-term morbidity and mortality after first stroke or TIA. Despite existing knowledge, there is a lack of systematic assessment, and primary and secondary stroke-prevention strategies are underused.\textsuperscript{5,6}

Data are scant on long-term strategies for intensive cerebrovascular risk management in clinical practice, and results are disappointing.\textsuperscript{6,30} One observational study investigated the assessment and treatment of risk factors (hypertension, atrial fibrillation, prior stroke/TIA) before acute cerebral infarction and compared this with predefined criteria for appropriateness.\textsuperscript{6} A substantial proportion of risk factors were treated inadequately; however, patients with symptomatic vascular disease were more likely to receive appropriate risk management compared with asymptomatic patients (72\% vs 46\%). In another small study of 56 patients treated in a stroke clinic, little improvement was seen in stroke risk factor profiles, despite physicians addressing the issue.\textsuperscript{30} Of note, this study was a small, physician-directed program at a Veterans Administration medical center. Another study revealed that, although hypertension often was treated, only 27\% to 44\% of patients achieved goals set by standard guidelines.\textsuperscript{5} Other studies are similarly disappointing, with risk factors being either underrecognized or undertreated.\textsuperscript{18,31,32}

The gap in evidence and actual practice in prevention of stroke is due to several factors.\textsuperscript{5} Patient factors include lack of knowledge of stroke risk factors and stroke symptoms. In a random telephone survey in Cincinnati, Ohio, only 57\% of people knew 1 stroke symptom.\textsuperscript{33} Another population-based study in Olmsted County, Minnesota,\textsuperscript{34} revealed poor patient knowledge of risk factors, symptoms, and treatment of stroke, even in patients with prior TIA or stroke. Other reasons for underuse of medical care by patients include denial, fear, lack of access, and cost.

Physician factors also may contribute to underuse of stroke-prevention strategies. Systematic risk factor assessment performed during hospitalization is lacking. Furthermore, neurologists who may treat patients with stroke typically are not trained in management of atherosclerosis risk factors or may not consider risk factor modification their responsibility.\textsuperscript{5}

The health care environment may not foster time-consuming stroke-prevention visits and therapies if a return visit is not seen in terms of cost reduction, reduced hospitalizations, or reduction in length of hospital stay.\textsuperscript{5} In the current system, a patient with minor stroke or TIA may be admitted to the hospital and dismissed within 24 to 48 hours, diminishing the importance of the event to the patient and limiting the time available for initiation of preventive strategies by physicians. Often, follow-up is left to the patient’s primary care physician. Patients may not return for follow-up at all or may not be examined for several months. This situation is in contrast to the current system in place for cardiac patients. Cardiac rehabilitation involves an intensive exercise program, aggressive risk factor assessment and treatment within the hospital, support groups, and intensive follow-up, emphasizing the importance of lifestyle management and change. As an increasing number of people are moving into the age of stroke risk, the current system demands preventive services.

The following can be concluded about current stroke-prevention delivery systems. (1) Stroke is the leading cause of disability in the United States, resulting in billions of dollars per year in direct and indirect costs. (2) Public knowledge is lacking on stroke, its risk factors, and treat-
SECONDARY PREVENTION STRATEGIES IN ISCHEMIC STROKE

The goals of a recent trial by Fonarow et al, the Cardiac Hospitalization Atherosclerosis Management Program (CHAMP), included systematic identification of cardiac risk factors and early treatment according to guidelines to achieve a reduction in recurrent MI and 1-year mortality. Compared with conventional guidelines and care, CHAMP was associated with a substantial increase in the use of medications previously shown to reduce mortality. Also, more patients had low-density lipoprotein (LDL) cholesterol levels of 100 mg/dL or lower and improved clinical outcomes after hospitalization for acute MI. Similar programs could be initiated for patients with atherosclerosis.

For long-term surveillance, the physician-directed, nurse-based case management system is a powerful tool. Nurse-based case management has been used in chronic disease prevention for more than 20 years. Physician-directed, nurse-mediated programs for cardiovascular disease prevention have revealed improved clinical outcomes and reduced use of medical resources. The Stanford Coronary Risk Intervention Project randomized patients with angiographically defined coronary artery disease into an intensive multiple risk factor reduction program vs standard care. Treatment consisted of a comprehensive program targeting lifestyle changes and use of medications. After 4 years, patients in the intensive risk factor modification program had improved risk factor status, reduced coronary artery disease on angiography, and fewer hospitalizations. Furthermore, physician-directed, nurse-run clinics with long-term intensive risk factor programs proved practical and effective in secondary prevention of coronary heart disease (CHD). Patient lifestyle modification, and behavioral changes. The effectiveness of such a program in cerebrovascular disease is being evaluated at the Mayo Clinic in Rochester, Minn.

INDIVIDUAL STROKE RISK FACTORS

Hypertension
Hypertension is a risk factor for intracerebral and subarachnoid hemorrhage and for ischemic stroke. Hypertension is a risk factor in nearly all ischemic stroke subtypes by contributing to atherosclerosis, lipohyalinosis associated with small-vessel disease, or cardiac dysfunction. Both systolic and diastolic blood pressures are important because the incidence of stroke increases as they increase. However, it is important to recognize that an elevated systolic blood pressure with or without an elevated diastolic blood pressure is a risk factor. The relationship between blood pressure and risk of ischemic events including stroke and MI is continuous, consistent, and independent of other risk factors. For each increment of 20 mm Hg in systolic blood pressure or 10 mm Hg in diastolic blood pressure, the risk of cardiovascular disease doubles over the entire range, from 115/75 mm Hg to 185/115 mm Hg in patients aged 40 to 70 years.

Treatment of hypertension has been shown to reduce the relative risk of initial stroke in several clinical trials. In the Systolic Hypertension in the Elderly Program (SHEP), blood pressure reduction was associated with a 36% relative risk reduction (RRR) of stroke (30 events per 1000 over 5 years) and a 25% RRR in MI and coronary death within 4.5 years. When separated by stroke subtype, hemorrhagic stroke was reduced by 44% and small-vessel ischemic stroke by 47% when the goal of a systolic blood pressure of less than 160 mm Hg was met. The Heart Outcomes Prevention Evaluation (HOPE) trial evaluated the use of ramipril vs placebo in high-risk patients with vascular disease who had no hypertension and in those whose hypertension was controlled. Stroke risk was reduced by 32% compared with placebo.

Secondary prevention data on the treatment of hypertension are also available. The project collaborators of Individual Data Analysis of Antihypertensive Intervention Trials (INDANA) performed a meta-analysis of randomized...
trials of blood pressure lowering in patients with prior stroke or TIA. The recurrence of stroke was significantly reduced by 28% in active-treatment groups compared with the control group. The Perindopril Protection against Recurrent Stroke Study (PROGRESS) randomized more than 6000 patients with recent stroke or TIA to treatment with perindopril with or without indapamide (a diuretic) or placebo. Combination therapy with perindopril and indapamide produced a significant reduction (43%) in recurrent stroke risk over 4 years, irrespective of initial blood pressure. The average reduction in blood pressure from this combination was 12/5 mm Hg.

Clinical trials have evaluated diuretics, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and other agents. Recent evidence suggests that diuretics should be considered first-line treatment, but special consideration should be given to specific diseases. For instance, patients with coronary artery disease may benefit from a β-blocker and ACE inhibitor. Increasing evidence shows that ACE inhibitors not only lower blood pressure levels but also may reverse endothelial dysfunction, prevent development of congestive heart failure in patients with asymptomatic left ventricular dysfunction, favorably affect the progression of diabetic nephropathy, and reduce albuminuria. The HOPE, PROGRESS, and Losartan Intervention For End point reduction in hypertension (LIFE) trials suggested a benefit of ACE inhibitors or angiotensin receptor blockers for stroke reduction (Table 2). Whether this is an independent effect of the ACE inhibitor or related to lowering of the blood pressure is debatable. In fact, data from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid-Lowering Trial (ALLHAT-LLT) may counter this theory because patients with high-risk vascular disease who were randomized to lisinopril had a slightly higher but statistically significant risk of first stroke compared with those taking chlorthalidone. However, the superiority of diuretics in the ALLHAT trial may be related to the percentage of African American patients in this trial compared with the percentages of those in both the HOPE and PROGRESS trials. In either case, both HOPE and PROGRESS support the use of diuretics, ACE inhibitors, or their combination irrespective of baseline levels of blood pressure once the blood pressure has stabilized after stroke.

The most recent recommendations of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure are a target blood pressure lower than 140/90 mm Hg in most patients or a goal lower than 130/80 mm Hg in patients with diabetes or chronic kidney disease. This may be achieved with lifestyle modifications such as weight control, physical activity, and moderate sodium intake or with lifestyle modifications combined with medications. Selected medications depend on patients’ comorbidities.

### Hyperlipidemia

In a large meta-analysis of 45 prospective cohort studies, no association was found between cholesterol level and stroke rate. However, these studies did not separate pa-

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*ACE = angiotensin-converting enzyme; HOPE = Heart Outcomes Prevention Evaluation; LIFE = Losartan Intervention For End point reduction in hypertension; NA = not applicable; PROGRESS = Perindopril Protection against Recurrent Stroke Study; RRR = relative risk reduction.
patients into subtypes of stroke. When divided into ischemic and hemorrhagic strokes, ischemic strokes were more than twice as likely in patients with total cholesterol levels greater than 240 mg/dL compared with those with levels lower than 240 mg/dL. Furthermore, the strongest association of cholesterol level and stroke was with the carotid artery subtype of ischemic stroke. Studies have suggested an increased risk with high total cholesterol level, high LDL cholesterol level, and low high-density lipoprotein (HDL) cholesterol level.

Data from secondary prevention in patients with known coronary artery disease revealed RRRs of stroke between 20% and 31% over 4 to 5 years with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) or statin lipid-lowering agents. Furthermore, studies of carotid artery disease reported a decrease in progression or even a regression of plaque with the use of statin medications. It is believed that statin lipid-lowering agents stabilize plaque by reducing both cholesterol level and inflammation, both of which predispose the patient to plaque vulnerability.

Guidelines from the National Cholesterol Education Program (Adult Treatment Panel [ATP] III) released in 2001 recommended primarily targeting the LDL cholesterol level. The goal LDL cholesterol level should be lower than 100 mg/dL in patients with prior MI or known diabetes, or in patients whose 10-year risk of coronary artery disease is greater than 20%. This value can be calculated using Framingham data (www.nhlbi.nih.gov/about/framingham/riskabs.htm). This goal would apply to most patients with atherothrombotic ischemic stroke, to patients with known carotid artery disease, or to those with ischemic stroke and a history of coronary artery disease.

Since the ATP III guidelines were published, numerous new clinical trials of statins have been published. The Heart Protection Study (HPS) randomized 20,556 high-risk patients (with prior vascular disease, diabetes, or hypertension) aged 40 to 80 years with initial total cholesterol levels of 135 mg/dL or greater to either simvastatin, 40 mg/d, or to placebo for 5 years. Use of simvastatin was associated with a 24% reduction in major vascular end points. This}

study raises several important points. First, vascular events and mortality were reduced regardless of baseline cholesterol levels, suggesting that there is not necessarily a threshold effect or lower level below which statins are not beneficial. Second, this study included 1820 patients with cerebrovascular disease, thus providing the first look at secondary prevention in stroke; post hoc analysis of this population showed improvement in vascular event rate. Finally, the medication proved safe. The annual excess rate of myopathy in the treatment vs placebo group was approximately 0.01%. A recent analysis of those with cerebrovascular disease at baseline showed no difference in reduction of further stroke but showed significant reduction of future vascular events such as MI (Table 3). Additionally, recent studies in cardiac disease support aggressive lipid lowering, even at levels previously believed to be normal. A recent publication from the Coordinating Committee of the National Cholesterol Education Program has included an optional LDL cholesterol level goal lower than 70 mg/dL in high-risk patients: those with established coronary artery disease plus (1) multiple major risk factors (especially diabetes), (2) severe and poorly controlled risk factors, (3) multiple risk factors of the metabolic syndrome, and/or (4) acute coronary artery syndromes.

Data from the HPS suggest that statin medication should be considered in many patients with TIA or cerebral infarction in whom the total cholesterol level is greater than 135 mg/dL. Data from the ATP III guidelines and the recent National Cholesterol Education Committee suggest a goal LDL cholesterol level lower than 100 mg/dL and lower than 70 mg/dL in high-risk patients. The latter includes patients with diabetes, prior coronary artery disease, and atherosclerotic stroke with poorly controlled risk factors. Ischemic stroke affects a heterogeneous population, including those with atherothrombotic disease, cardioembolic sources, and other pathologies such as dissection and coagulation disorders. Thus, this information should apply primarily to patients with atherothrombotic stroke (large-vessel atherosclerosis, lacunar disease, and cryptogenic stroke in those >55 years) or to patients with established diabetes.

TOBACCO SMOKING

Tobacco use is the single most alterable risk factor contributing to premature morbidity and mortality in the United States, accounting for 430,000 deaths annually. Smoking is an important risk factor for stroke and for the formation of aneurysms and subarachnoid hemorrhage. Physiologically, smoking contributes to atherosclerosis and alters the coagulation systems (increases fibrinogen, increases platelet aggregation, decreases HDL cholesterol level, and decreases hematocrit level). Smoking increases the risk of
stroke nearly 2- to 4-fold and increases the risk of carotid artery disease 5-fold. A recent study revealed a 1.8-fold increase in stroke among nonsmokers exposed to second-hand smoke. Overall, with 25% of the adult population smoking, 18% of strokes are attributable to active cigarette smoking, and 12% of strokes are attributable to second-hand smoke.

Data from observational studies suggest that stroke risk in cigarette smokers is reduced by 60% with smoking cessation. By 5 years after smoking cessation, the stroke risk can be reduced to that of a person who never smoked.

**Diabetes Mellitus**

Patients with diabetes mellitus have both an increased susceptibility to atherosclerosis and a higher prevalence of atherogenic risk factors, notably hypertension, hyperlipidemia, and obesity. Case-control studies and prospective epidemiological studies have shown a 2- to 6-fold increased risk of stroke in patients with diabetes. Patients with glucose intolerance (fasting glucose, 110-125 mg/dL) have a 2-fold increase in risk of stroke. This risk increases as the fasting glucose level increases, and mortality is 3 times higher in patients with diabetes and first ischemic stroke.

Blood pressure levels should be managed carefully in patients with diabetes and associated hypertension. Nearly 40% to 60% of persons with type 2 diabetes mellitus have hypertension, and both the SHEP and the HOPE study reported stroke reduction in patients with diabetes and good hypertension control. Interestingly, in the HOPE study, which evaluated the use of ramipril, an ACE inhibitor, the diabetic subgroup benefited from the medication beyond reduction in blood pressure level. Also, tight glucose control reduces microvascular complications with neuropathy, retinopathy, and nephropathy.

**Atrial Fibrillation**

Atrial fibrillation is a common arrhythmia that is present in 1% of the general population and in up to 10% of persons older than 75 years. Abnormal contraction of the atria may result in thrombus formation. The risk of stroke secondary to thromboembolism related to atrial fibrillation is approximately 3% to 5% per year. In 1 study of primary prevention in patients with atrial fibrillation, the annual risk of stroke was 6.3% with no treatment, 3.6% with aspirin therapy, and 2.3% with warfarin therapy. Factors that increase the risk of thromboembolic events include age older than 75 years, prior thromboembolic event, systolic blood pressure higher than 160 mm Hg or history of hypertension, impaired left ventricular function, and diabetes.

Randomized treatment trial data have shown that anticoagulation with warfarin can reduce the relative risk of stroke by 70% to 80% in the highest-risk groups. Direct thrombin inhibitors may be equally effective in reducing stroke risk, with low risk of hemorrhagic complications and acceptable adverse-effect profiles.

Current recommendations suggest the use of anticoagulation in any patient older than 75 years or with risk factors (including ischemic stroke) barring any contraindications.

**Asymptomatic Carotid Artery Stenosis**

Asymptomatic carotid artery disease is common. In unselected populations, 7% of men and 5% of women older than 65 years have carotid artery stenoses greater than 50%. The risk of stroke with a carotid arterial narrowing greater than 60% is approximately 2% per year; the risk of MI in these patients approaches 5% per year, and the risk of vascular death may be as high as 5% to 9% per year.

The risk of ipsilateral stroke increases with increasing degrees of stenosis, progression of plaque/stenosis, ulceration of plaque, and/or contralateral symptomatic stenosis/occlusion.

Treatment of asymptomatic carotid artery stenosis is controversial. Five studies have evaluated the role of carotid endarterectomy in asymptomatic carotid artery disease; the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACT) have suggested benefit. The ACAS study revealed a 50% RRR in stroke over 5 years. In absolute numbers, this was a reduction from 2% to 1% per year. Patients in this study were highly selected and were not included if they were older than 80 years, had concomitant active heart disease, or had a disease that limited lifespan. The benefit was seen only if the combined surgical and angiographic morbidity and mortality rate was less than 3%. In the ACT, the risks of combined perioperative events and nonperioperative strokes were evaluated over 5 years among 320 asymptomatic patients with at least a 70% carotid stenosis. The 5-year risks were 6.4% in the surgical group and 11.8% in the medical group when considering all strokes. Benefits were noted in both women and men. Therefore, selection of patients for endarterectomy is left to the discretion of the physician and is individualized according to the patient’s risk of stroke and surgical risk.

Since the asymptomatic carotid endarterectomy trials, awareness of other modifiable risk factors has increased, as have new treatment strategies for plaque stability such as statin drugs. It is difficult to say how new medical strategies would compare with endarterectomy.

**Elevated Homocysteine Level**

Homocysteine is an amino acid present in the blood and tissues, which in excess can result in accelerated vascular
disease. Excess homocysteine can damage the vascular endothelium and affect coagulation pathways, thereby leading to an increase in thromboembolic events. Emerging data suggest that modest elevations in homocysteine levels may increase stroke risk, carotid stenosis, and progressive atherosclerosis. Clinical trial data reveal that homocysteine levels can be lowered with folate (400 µg to 1 mg per day), vitamin B₁₂ (10-12.5 mg/d), and vitamin B₆ (500 µg/d). However, no clinical trial data show that lowering homocysteine levels can reduce recurrent stroke event rates. The Vitamin Intervention for Stroke Prevention (VISP) study evaluated the efficacy of high-dose folate, vitamin B₁₂, and vitamin B₆ in stroke prevention after first ischemic stroke in the setting of mildly elevated homocysteine levels. Stroke risk was not reduced with vitamin therapy. However, the mean baseline homocysteine level was minimally elevated, leading to uncertainty regarding the optimal management of elevated homocysteine levels. Considering the safety of the medications, it is reasonable to lower homocysteine levels in patients with elevated levels.

**Obesity**

Obesity can be defined as a body mass index greater than 30 kg/m². Obesity predisposes a person to both coronary artery disease and cerebrovascular diseases, especially if the weight is predominantly abdominal. Furthermore, obesity can be associated with hypertension, hyperlipidemia, and elevated glucose levels. Reduction in stroke risk with weight reduction has not been proved, but weight loss is recommended to reduce comorbid conditions.

**Metabolic Syndrome**

The metabolic syndrome is characterized by a clustering of metabolic risk factors, including abdominal obesity, atherogenic dyslipidemia (generally elevated triglyceride and low HDL cholesterol levels), hypertension, insulin resistance, a proinflammatory state, and a prothrombotic state. The metabolic syndrome has been shown to increase the risk of vascular disease including stroke. Management of the metabolic syndrome emphasizes the importance of lifestyle modification (dietary changes, exercise, weight loss). Treatment of dyslipidemia in these patients is important, especially in those who have had a stroke or are at high risk of stroke.

**Physical Inactivity**

Regular physical activity has been shown to reduce cardiovascular disease. Apparently, stroke incidence can be reduced as well by physical activity. Many cohort studies including the Honolulu Heart Study, the Framingham Study, and the Nurse’s Health Study have shown an inverse association between the level of physical activity and stroke incidence. Physical activity is probably beneficial because of its positive effects on blood pressure, weight, diabetes, and cardiovascular disease. Also, physical activity may reduce plasma fibrinogen and platelet activities, reduce triglyceride levels, and increase HDL cholesterol concentration.

Thirty minutes of moderate-intensity physical activity per day at least 5 days per week is recommended. Recently, resistance training has been shown to have positive effects on vascular health. A recent scientific statement from the American Heart Association’s Scientific Sessions details specific recommendations for patients with stroke including aerobic activity, strength training, and flexibility and neuromuscular exercises.

Given the increased risk of MI in atherothrombotic stroke, consideration of stress testing before implementing an exercise program is important. Specific guidelines have been established by the American College of Sports Medicine, the American Heart Association, and others.

**Alcohol Consumption**

Several studies have found a “j-shaped” curve relationship between alcohol consumption and stroke risk. One to 2 drinks per day may protect against cardiovascular disease and stroke, whereas more than 4 to 5 drinks per day is deleterious. Other studies report different results. It is believed that some studies may be confounded by the associated diet of wine drinkers.

The American Heart Association recommends no more than 2 drinks per day for men and 1 drink per day for women.

**Sleep Apnea**

Obstructive sleep apnea is a common disorder that involves repetitive pharyngeal collapse during sleep. Recent studies have suggested that the consequences of obstructive sleep apnea include an increased risk of hypertension, coronary artery disease, stroke, and congestive heart failure. These sequelae are believed to be due to sustained sympathetic excitation, reduced parasympathetic activity, and release of endothelin.

Although polysomnography is the gold standard for diagnosing obstructive sleep apnea, a thorough history and physical examination can help identify persons at risk. Furthermore, overnight pulse oximetry is extremely specific and may be helpful; however, its sensitivity may range from 50% to 90%. Therefore, with high clinical suspicion and negative oximetry results, a polysomnogram is still needed.

Because sleep apnea is a potentially treatable condition that may cause or be a consequence of stroke,
screening of this patient population for risk factors should be performed. In current practice, sleep apnea is not always identified.

HORMONE REPLACEMENT THERAPY

Prior observational studies of hormone replacement therapy have shown reductions in the risk of CHD and osteoporotic fractures; thus, menopausal women at risk for these conditions were treated with hormones. Subsequently, several randomized trials of estrogen replacement therapy have shown that coronary risk is not decreased; in fact, there may be small increases in the risks of coronary events, stroke, pulmonary embolism, and breast cancer.\textsuperscript{116} Similarly, other studies have shown no benefit in cognition to date\textsuperscript{115} and no change in quality of life.\textsuperscript{117}

Many of the aforementioned studies included primarily patients at high risk for cardiovascular disease; however, other studies have assessed secondary prevention specifically in patients with stroke. The Women’s Estrogen for Stroke Trial (WEST) compared estradiol to placebo in postmenopausal women with a recent history of TIA or ischemic stroke.\textsuperscript{118} In this study, estradiol replacement did not reduce the risk of recurrent stroke or death, and patients randomized to estrogen therapy had a higher risk of fatal stroke relative to placebo. The literature in this area is evolving; however, at this time, patients with stroke should be advised against estrogen use unless there is a compelling indication to continue.

ELEVATED C-REACTIVE PROTEIN LEVEL

C-reactive protein and other inflammatory markers have been studied as possible risk markers or risk factors for vascular disease. High-sensitivity CRP has been shown in multiple cohort studies to be an independent risk factor for future vascular events after adjustment for typical atherosclerotic risk factors.\textsuperscript{114} It has been suggested that CRP be assessed in primary prevention to further stratify patients at risk. However, in secondary prevention, its utility is unclear.\textsuperscript{119} For instance, statins and aspirin have been shown to lower CRP levels but would be indicated anyway in secondary prevention.\textsuperscript{120} Furthermore, normative values for acute ischemic events have not been well established for stroke, bringing into question the meaning of this value at admission.\textsuperscript{121} Future studies are necessary to determine whether CRP can contribute predictive capabilities in secondary prevention.

CONCLUSIONS

Identification and treatment of modifiable stroke risk factors can substantially reduce ischemic stroke and MI and prevent long-term morbidity and mortality after first stroke or TIA. Neurologists and general practitioners must be aware of the specific risk factors and recommendations for patients with stroke and apply this information systematically. In particular, patients with a history of coronary artery disease or atherosclerotic stroke should be considered a “CHD equivalent” and treated to a goal LDL cholesterol level lower than 100 mg/dL; in certain high-risk patients, the goal should be lower than 70 mg/dL. Also, after an acute event resolves, patients without notable intracranial stenoses should be treated aggressively to blood pressure goals consistent with the recommendations of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.\textsuperscript{46} ACE inhibitors (or angiotensin receptor blockers) and diuretics may be preferred, but meeting the blood pressure goal is most important. Smoking cessation should be emphasized, and specialized treatment programs should be made available to patients. The risk reduction of future vascular events with smoking cessation far exceeds the reduction when comparing various antiplatelet agents to each other. Patients with diabetes should control their glucose levels using diet, oral agents, and insulin when necessary. Other factors should be evaluated including homocysteine level, presence of obesity, dietary considerations, physical activity, alcohol use, and potential presence of obstructive sleep apnea. Systematically addressing each additional individual risk factor through a coordinated multidisciplinary team may lead to improved risk factor status and reduced long-term cerebrovascular and cardiovascular morbidity and mortality.

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