

Stroke Prevention in an At Risk Population

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Summary

Strokes are a leading cause of death and disability in the United States. Stroke prevention must target both patients with risk factors who have not yet had a stroke (primary prevention) and patients who have already had an event (secondary prevention). Some risk factors for stroke are not modifiable but many others can be reduced.

Key Points

- For primary prevention ...
 - Screen and treat hypertension according to guidelines.
 - Strongly counsel patients on smoking cessation and to avoid secondary smoke.
 - Strict blood pressure control, with angiotensin converting enzyme inhibitors or an angiotensin receptor blockers and lipid control, are important in patients with diabetes.
 - Patients with asymptomatic carotid stenosis should be aggressively treated medically and only select groups will benefit from surgery.
 - Anticoagulate patients with atrial fibrillation based on concomitant risk factors.
- For secondary prevention ...
 - Blood pressure control is important with the best evidence for diuretic plus angiotensin converting enzyme inhibitor or diuretic alone.
 - Carotid endarterectomy is beneficial with stenosis greater than 70 percent and in selected patients with 50 to 69 percent stenosis.
 - Patients with atrial fibrillation should receive warfarin to prevent a stroke.
 - Consider aspirin, aspirin-dipyridamole, or clopidogrel for secondary prevention in patients with a history of noncardiogenic stroke.

APPROXIMATELY 700,000 STROKES OR cerebrovascular accidents (CVAs) occur in the United States per year. There are about 4.8 million CVA survivors in the United States. The CVA event rate is higher than that of ischemic heart disease or peripheral vascular disease.

CVAs are the third leading cause of death in the United States. Twelve percent of those deaths occur in patients younger than 65. With improvements in care, there was a decrease in mortality by 60 percent from 1968 to 1996. CVAs also result in significant disability, and are the most common cause of disability. About 20 percent of victims are institutionalized at three months after the event, and 15 to 30 percent are disabled. CVAs have psychological impact also. A stroke is viewed by more than 50 percent of patients as worse than death. These events also have financial impact. CVAs account for 2 to 4 percent of health care costs at an estimated total of \$40.9 billion in the United States.

The risk factors for CVAs are nonmodifiable,

modifiable, or potentially modifiable. Exhibit 1 lists these by category.

The increase in risk of stroke with age is probably related to the cumulative effects of aging on the cardiovascular system. The risk of CVA doubles every decade after 55. CVAs are more prevalent in men than in women, except in the 35 to 44 age group related to oral contraceptive use and in those over 85. One in six women die of CVA compared to one in 25 from breast cancer. The incidence of CVA is 38 percent higher in African Americans. The Hispanic American population also is at an increased risk, and genetics also plays a role. Family history and rare genetic disorders increase risk as well.

Primary Prevention

Seventy percent of CVAs are first events. There are published guidelines for preventing a stroke in people with risk factors who have not yet had an event.¹ In certain communities, the incidence of CVAs has dropped secondary to community-based interven-

Exhibit 1: Nonmodifiable Risk Factors

- Age
- Race
- Gender
- Genetics

tions. Oxfordshire in the United Kingdom demonstrated a 40 percent reduction of CVA with preventive treatments and risk factor modifications.

Hypertension is the single most preventable cause of CVA. It is a major risk factor for both infarction and hemorrhage. The higher a patient's blood pressure the greater the risk of CVA. Multiple trials show a consistent 33- to 44-percent reduction in CVA rates with blood pressure lowering. Treating isolated systolic blood pressure and elderly patients also shows consistent benefits in several trials. Trials suggest using beta-blockers as initial therapy may not reduce CVA as much as other agents but the degree of blood pressure lowering may be more important than the specific agents used. It is important to follow current hypertension management guidelines to maximize CVA prevention in all patients. People should be screened yearly for elevated blood pressure.

Smoking is another very important modifiable risk factor. Multiple trials show a doubling of the risk of ischemic CVA and a twofold to fourfold increase in hemorrhagic CVA. Smoking is related to 12 to 14 percent of all CVA deaths. An especially dangerous combination for CVA is smoking and oral contraceptives. Oral contraceptives alone increase stroke risk 1.3 times. Smoking increases risk 2.1 times. The combination increases risk 7.2 fold. Passive smoke exposure is as risky as active smoking. Smoking cessation rapidly reduces risk close to that of nonsmokers. Overall, smoking cessation is important, and so is avoidance of second hand smoke for primary CVA prevention.

Diabetes is an independent risk factor that increases the risk of CVA 1.8 to 6.0 times. Data show that aggressive treatment of blood pressure, lipids, and glucose reduces the risk of stroke in patients with diabetes. Recent data also show aggressive glycemic control alone does not convincingly lower risk of CVA. Interesting data have shown that the use of angiotension converting enzyme inhibitors (ACE-I) reduces the risk of CVA by 33 percent, and the use of angiotension receptor blockers (ARB)

Exhibit 2: Modifiable Risk Factors

- Cardiovascular disease
- Hypertension
- Smoking
- Diabetes
- Asymptomatic carotid stenosis
- Atrial fibrillation
- Dyslipidemia
- Dietary factors
- Obesity
- Postmenopausal hormone therapy

reduces the risk by 21 percent compared to beta-blockers. Statins also are shown to reduce CVA in high-risk diabetic groups by 24 to 48 percent. For patients with diabetes, tight treatment of hypertension with ACE-I or ARB is very important, statins also appear to lower risk, and data with glycemic control alone is lacking.

Atrial fibrillation is another very important aspect of primary stroke prevention but is often under-managed. Currently, many of these patients are not adequately treated to minimize CVA risk. Patients with mechanical heart valves are at very high-risk. Without anticoagulation, the risk of stroke in these patients is 4.4 per 100 patient years and with adequate treatment the rate is 1.0 per 100. All patients with mechanical heart valves should be on warfarin. Patients with valvular heart disease also are high-risk and warfarin is recommended. The majority of patients have nonvalvular atrial fibrillation. In these patients, the decision to provide stroke prophylaxis is based on other risk factors present such as heart failure, hypertension, age greater than 75, diabetes, or history of cerebrovascular event. Generally in these patients, aspirin and warfarin reduce the risk of stroke by 20 percent and 60 percent, respectively.

Only about half of patients with atrial fibrillation who are candidates for anticoagulation receive treatment. Elderly patients are often undertreated though they may get the most benefit. For patients who do receive anticoagulation, hypertension control is very important in reducing risk of bleeding. Health plans can improve their population's risk of

Exhibit 3: Potentially Modifiable Risk Factors

- Metabolic syndrome
- Alcohol abuse
- Drug abuse
- Oral contraceptives
- Sleep apnea
- Migraine
- Hyperhomocysteinemia
- Hypercoagulability
- Inflammation
- Infection

stroke by ensuring that patients with atrial fibrillation who are candidates for anticoagulation actually receive prophylaxis.

Hyperlipidemia is another modifiable risk factor for stroke. Elevated total cholesterol increases the risk of CVA while low high-density lipoprotein cholesterol (HDL-C) is associated with CVA in men. The data are not clear on any association between low HDL-C and CVA in women. Statins reduce CVA rates in high-risk primary prevention patients. They are estimated to prevent 9 CVAs per 1000 high-risk patients treated for five years. The current guidelines for lipid management should be followed to minimize CVA risk in primary prevention patients. There is some evidence that high dose statins may have some benefit over usual dose statins.

Asymptomatic carotid stenosis greater than 50 percent occurs in 5 to 10 percent of patients over 65 years of age. About 1 percent of patients over 65 have greater than 80 percent stenosis. The risk of CVA is 1 to 3.4 percent annually in patients with asymptomatic carotid stenosis of 60 to 99 percent. Patients with higher degrees of stenosis and progressing stenosis may be at higher risk. Treatment can be carotid endarterectomy or medications to reduce atherosclerotic burden. Aspirin is recommended in all patients with asymptomatic carotid stenosis. Surgery should be considered in selected patients age 40 to 75 with stenosis greater than 60

percent. Because the benefits of surgery are modest, patients must be carefully screened regarding life expectancy (>5 years) and comorbid conditions. It is imperative that patients who undergo surgery have low risk of postoperative complications because the risks outweigh the benefits in those with higher risk of postoperative complications. The current guidelines recommend avoiding carotid endarterectomy in asymptomatic women. Improved medical therapy such as the statins may improve outcomes in medically treated patients.

Postmenopausal hormone therapy is controversial. Some trials have shown that it increases the risk of CVA. Postmenopausal hormone therapy should not be used for primary prevention of CVAs.

There are some data to suggest that diet has an impact on CVA risk. Epidemiologic studies show increased intake of fruits and vegetables are associated with a decreased risk of CVA. For each one serving per day increment in fruit and vegetable intake, the risk of CVA is reduced by 6 percent. Higher dietary sodium intake is associated with increased risk, and higher potassium intake is associated with reduced risk. This is probably related to blood pressure lowering.

Data show a protective effect of physical activity in men and women in reducing CVA. Some trials suggest more vigorous activity may have additive benefit. The current recommendations from the National Institutes of Health and the Centers for Disease Control are for everyone to exercise moderately most if not all days of the week. Overall, for CVA prevention, light to moderate exercise appears to reduce risk with additional benefit from more vigorous activities.

Obesity is a major issue in the U.S. population. The risk of CVA increases as weight increases. Abdominal body fat may be a stronger predictor of CVA than weight alone. However, when other CV risk factors are controlled, the predictive value of excessive weight is reduced. There are no clinical trials regarding the effect of weight loss on CVA incidence. Weight loss is shown to reduce blood pressure.

Exhibit 1 lists the potentially modifiable risk factors for CVA. For primary prevention, there are no firm data to establish recommendations for these risk factors.

Aspirin has been used for primary prevention of CVA. There is no evidence aspirin reduces risk of CVA in the general population. Data in men shows reduced cardiovascular events but not CVA. In the Women's Health Study, there was a 17 percent reduction of CVA in 39,876 women given aspirin 100 mg on alternate days compared with placebo.

Aspirin is recommended for cardiovascular disease prophylaxis in patients with a 10-year risk of 6 to 10 percent. It can be used for prevention of CVA in high-risk women but is not recommended for prevention of CVA in men.

Secondary Prevention

Secondary prevention is preventing a stroke in a patient who has already had a stroke or a transient ischemic attack (TIA). Patients with a history of TIA or CVA are at high-risk for having another event. After a TIA, the 90-day risk of CVA is 10.5 percent with the greatest risk occurring within one week of the initial event. Of the 700,000 patients that have a CVA each year, 200,000 are recurrent. Guidelines for management of secondary prevention are available.^{2,3} Secondary prevention risk factor control should occur in all patients with TIA or CVA. All patients with a history of TIA or CVA require blood pressure, blood glucose, and lipid control; smoking cessation; alcohol reduction; weight reduction; and increased physical activity, if indicated.

Regarding blood pressure, systematic reviews of older trials show treatment with antihypertensives reduces recurrent CVA. The evidence is best with a combination of ACE-I and diuretic or diuretic alone. Blood pressure treatment is recommended in patients with ischemic CVA or TIA after the acute period. Benefit has been shown in patients with and without a history of hypertension. The goal values are unclear but benefit is shown with systolic drops of 10 mm of Hg and diastolic of 5 mm.

Fifteen to 33 percent of patients with CVA have diabetes. Approximately 9 percent of recurrent CVAs are related to diabetes. More data are available with primary prevention rather than secondary prevention. Strict blood pressure control less than 130/80 mm Hg with ACE-I and ARB, and lipid control with statins for low density lipoprotein cholesterol (LDL-C) of less than 70 to 100 mg/dL is recommended for secondary prevention patients with diabetes. Data for glycemic control is not clear but treatment should be titrated to achieve a goal hemoglobin A1C of less than 7.0 percent.

When treating a patient with a lipid disorder, intensive lipid lowering therapy with statins is recommended in patients with atherosclerotic ischemic CVA or TIA. The goal is to achieve an LDL-C of less than 70 mg/dL. Because of possible increased bleeding risk, statins should be avoided in patients with a recent hemorrhagic CVA. Statins do not increase bleeding in non-hemorrhagic CVA. Niacin or a fibrate can be considered in patients with low HDL-C and CVA or TIA.

All patients with CVA should quit smoking and

avoid environmental smoke. Light to moderate use of alcohol (one to two drinks a day) has been shown in some studies to have a protective effect against CVA. Greater than five drinks per day has been shown to increase risk of CVA. Heavy drinkers should eliminate or reduce alcohol intake.

There are no prospective trials in secondary prevention of CVA that examine the effects of weight loss. Weight reduction should be encouraged for all overweight and obese patients with CVA or TIA. Exercise should also be prescribed in these patients. Multiple studies show aerobic exercise and strength training improve cardiovascular fitness after a CVA. Studies also show improved mobility, balance, and endurance. Thirty minutes of moderate intensity exercise is recommended the majority of the days of the week. For patients with residual disabilities, a supervised exercise regimen is recommended.

In patients with a recent TIA or CVA and carotid stenosis of more than 70 percent, carotid endarterectomy is recommended if the surgeon's patient's perioperative mortality rate is less than 6 percent. Carotid endarterectomy can be recommended based on patient specific factors in patients with recent TIA or CVA and carotid stenosis of 50 to 69 percent. When a patient has stenosis of less than 50 percent, carotid endarterectomy is not recommended. Surgery is recommended within two weeks of the initial event. Patients with a stenosis greater than 70 percent who are poor candidates for surgery can be considered for carotid stents.

Approximately 20 percent of ischemic CVAs occur secondary to a cardiogenic embolism. Nonvalvular atrial fibrillation accounts for 50 percent of cases of CVA secondary to cardiogenic embolism, valvular heart disease 25 percent, and left ventricular (LV) thrombus 25 percent. Sixty percent of the LV thrombus-related CVAs are associated with an acute myocardial infarction. Patients with a LV thrombus and CVA or TIA should be treated with warfarin. Heart failure increases risk of CVA by two to three times and is associated with about 10 percent of ischemic CVAs. Treatment with warfarin in patients with CVA or TIA and dilated cardiomyopathy should be considered.

Seventy five thousand CVAs a year occur in patients with atrial fibrillation. The risk of CVA is 5.9 percent per year in patients with atrial fibrillation. A TIA or CVA is a strong indication for warfarin treatment in these patients. Warfarin is preferred over aspirin but aspirin can be used in those patients who cannot take warfarin.

The three possible antiplatelet regimens for secondary prophylaxis of CVA in patients with a noncardiogenic CVA are aspirin, aspirin and di-

pyridamole, and clopidogrel. Aspirin is the least expensive agent but updated guidelines recommend considering the combination of aspirin and dipyridamole before aspirin alone. The combination may not be as well tolerated secondary to a high rate of headache and twice a day dosing. Clopidogrel should not be used in combination with aspirin for secondary CVA prophylaxis.

Conclusion

Reducing the risk of CVA in high-risk populations has to target modifiable risk factors. Health plans can reduce the risk of CVA in their populations by ensuring that at risk patients are managed based on current guidelines. JMCM

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