

# WAPRACTICE *Matters*

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## PRIMARY STROKE PREVENTION

- *Approximately 600,000 Americans have a stroke each year; it is the third leading cause of death in the United States and a leading cause of disability, resulting in an approximated annual cost of \$30 billion.*
- *Approximately 15,000 veterans are annually hospitalized for stroke, requiring 5% of VHA resources.*
- *Antihypertensive agents can reduce stroke incidence by 40%.*
- *For eligible patients with atrial fibrillation, warfarin can reduce the risk of stroke by 60%.*
- *Carotid endarterectomy is effective in reducing stroke in selected high-risk patients in centers where complication rates for surgery are less than 3% for asymptomatic patients and less than 6% for symptomatic patients.*
- *Specific cholesterol reducing agents (HMG-CoA) can reduce stroke incidence by 30% in patients with known coronary artery disease.*
- *Lifestyle modifications that focus on diet and exercise can reduce the risk of stroke and heart disease.*

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## BACKGROUND

Prevention practices are the optimal clinical approach to reducing the risk of stroke. In this issue of *VA Practice Matters* we highlight important recent developments of research on stroke prevention aimed at helping the practicing physician.

## PREVENTION AND TREATMENT GOALS

### Hypertension

In the United States, hypertension is the most prevalent and treatable risk factor for stroke. Due to national educational initiatives, the percentage of Americans aware of their hypertension has increased from 51% in 1976 to over 70% in 1994, and treatment has increased from 31% to 55%. Over this same period, death from stroke declined by 59%. However, 75% of all Americans with hypertension are not achieving acceptable blood pressure levels (less than 140/90 mm Hg).

Hypertension is more common among the elderly, who are also at higher risk of cardiovascular comorbidity. A number of lifestyle modifications have been associated with decreased hypertension: increased dietary calcium, magnesium and potassium; reduced saturated fat, cholesterol, sodium, alcohol consumption and cigarette smoking; weight reduction; increased aerobic activity; and stress reduction.

### Atrial fibrillation

Patients with atrial fibrillation (AF) have a five-fold increased risk of stroke, with approximately 80,000 strokes in the United States attributable to AF each year. Both the prevalence of AF, as well as the risk of stroke among persons with AF, increases dramatically with age, hence AF treatment is particularly important to health care systems that care for older patients. Cost-effectiveness analyses suggest that stroke prevention among persons with AF is likely to be not only cost-effective, but cost-saving.

Well-managed anticoagulation with warfarin reduces the risk of stroke by approximately 65-70% in patients with AF. The corresponding risk reduction of aspirin therapy is approximately 20-35%. On average, 25% of patients will have absolute

contraindications to warfarin therapy, 25% will have relative contraindications, and 50% will have no contraindications. Accordingly, up to 50-75% of all AF patients should be receiving warfarin, but several studies have shown that only half of eligible patients receive it. Some subgroups of patients with AF are at low risk and may do well with aspirin alone, but many elders with AF have risk factors (e.g. left ventricular hypertrophy, hypertension, diabetes) that place them at higher risk for stroke. In these patients, well-controlled warfarin anticoagulation is most effective in reducing stroke rates and averting hospitalization costs.

### Carotid artery stenosis

In the Cardiovascular Health Study some degree of carotid stenosis was detectable in 75% of men and 62% of women over 65, and this percentage increased with age. However, less than 10% of people had more than 50% stenosis. This relationship between prevalence and severity suggests that general screening programs may not be the best approach.

Several recent randomized trials have helped define important indications for carotid endarterectomy (CE). When performed by surgeons at institutions that achieve low complication rates, CE can reduce stroke risk in symptomatic and asymptomatic patients by at least 50%. Several patient groups appear to benefit most: those with ipsilateral carotid artery distribution, transient ischemic attack (TIA), or minor, non-disabling stroke, and proven stenosis of 70% or more, but less than 100%. The benefit of CE in patients with moderate stenosis (50-69%) is less dramatic, but the identification of subgroups of patients who may be at particularly high risk is important. In addition, the overall CE complication rates are generally higher than experienced by patients enrolled in the efficacy trials of the 1990s. Therefore, to benefit from CE, patients must have a high degree of stenosis and receive surgery at institutions with low complication rates.

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## EXPERT OPINION

Observational epidemiological studies have led to risk factor profiles for stroke. Experimental epidemiological studies (randomized controlled clinical trials) have proven that modification and treatment of various precursor conditions can effectively reduce the risk of ischemic stroke.

Much of current attention should focus on controlling modifiable risk factors for stroke. These include hypertension, cardiac disease, atrial fibrillation, diabetes, hyperlipidemia, asymptomatic carotid stenosis, physical inactivity, cigarette smoking and alcohol abuse. Exciting findings suggest additional risk factors: new cardiac risk factors (patent foramen ovale, left atrial enlargement, and valve strands), elevated homocysteine, anticardiolipin antibodies, chronic infections or inflammatory conditions (chlamydia, periodontal disease), and markers of subclinical disease (white matter hyperintensities, aortic arch atheroma, and carotid intimal-medial plaque thickness).

This issue of *VA Practice Matters* highlights the latest knowledge on modifiable stroke risk factors. Evidence through well-controlled, randomized clinical trials shows that proper treatment of hypertension, atrial fibrillation, carotid artery stenosis, and hypercholesterolemia can reduce stroke risk. Multiple studies, however, have documented less than adequate control of many of these conditions in the community. As health care providers, it is our duty to try to reduce the risk of stroke just as efficiently as has been done in clinical trials. Any improvement in our awareness and treatment of these risk factors should lead to a substantial reduction in the number of persons killed or disabled by stroke each year.

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## RECOMMENDATIONS

Research evidence indicates key areas of emphasis for physicians in primary stroke prevention and treatment are to:

- Identify patients with hypertension and control BP to levels of 140/90 by a combination of lifestyle modifications and medication.
- Address full spectrum of lifestyle and risk factor modifications (e.g. smoking, diet, physical activity).
- Screen patients for atrial fibrillation, assess risk for bleeding, provide well-monitored anti-coagulation for those at acceptable risk (50-75% of those with AF) and provide aspirin for the remaining cohort.
- Identify carotid artery stenosis for patients with symptoms of anterior circulation ischemia (TIA or minor stroke) and refer for CE if factors related to surgery are favorable (<3% complication rates in institutions).
- Educate patients to recognize symptoms of stroke and TIA, and take appropriate steps upon symptoms of recurrent stroke.

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## PREVENTION AND TREATMENT GOALS

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### Cholesterol

The National Cholesterol Education Program indicates that blood cholesterol levels below 200 mg/dl are “desirable”, whereas levels above 240 mg/dl are “high.” More than half of Americans have blood cholesterol levels over 200 mg/dl and a quarter have levels over 240 mg/dl. Recent studies have shown that HMG-CoA reductase inhibitors (statins) lower lipid levels and are associated with a 30% relative reduction in risk of stroke in patients with known coronary artery disease. This benefit is similar to the benefit statins confer on reducing myocardial infarctions (MI) in asymptomatic patients. Despite these promising findings, hypercholesterolemia has not been confirmed as an independent risk factor for stroke in those older than 70, and further research needs to establish the effectiveness of statins for the elderly. Furthermore, there are no studies of statins and stroke risk in patients with elevated serum cholesterol levels but no known coronary artery disease.

Physicians need to be aware of the patient’s total cholesterol level, and levels of both low and high density lipoprotein (LDL and HDL) cholesterol and triglycerides. Moreover, concomitant risk factors such as hypertension, age, and family history of coronary artery disease should be considered.

### Lifestyle

Targeting modifiable risk factors can reduce the risk of stroke. Research evidence indicates decreased risk with cessation of cigarette smoking, reducing hypercholesterolemia and obesity, and increasing physical activity. Moderate alcohol consumption (two drinks per day) appears to confer a lower risk for first stroke compared to either no or heavy alcohol intake.

Previous research has found a relationship between high homocysteine levels in the blood with heart disease and associated stroke events. For example, patients with vascular disease had significantly higher levels of homocysteine than normal subjects. Recent findings suggest that folate supplements can reduce homocysteine levels, and are associated with lower rates of heart disease and stroke events. However, more research is needed to elucidate safe, effective levels of folate supplementation for homocysteine reduction, and whether or not it leads to reduced cardiovascular and cerebrovascular events.

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# Evidence Chart for Primary Stroke Prevention

Reference	Participants or Type of Study	Observations/ Interventions	Outcomes
<b>Hypertension</b>			
Psaty BM. Health outcomes associated with antihypertensive therapies. <i>JAMA</i> 1997; 277(9): 739-45.	Meta-analysis of 18 randomized trials.	Association between administration of diuretics or beta blockers and subsequent stroke rate.	High dose beta-blocker therapy prevented stroke (relative risk [RR], 0.71) and congestive heart failure (RR, 0.58). High dose diuretic therapy prevented stroke (RR, 0.49) and congestive heart failure (RR, 0.17).
<b>Atrial Fibrillation</b>			
Atrial Fibrillation Investigators. The efficacy of aspirin in patients with atrial fibrillation. <i>Arch Int Med</i> 1997;157(11):1237-40.	Meta-analysis of 3 randomized trials. 1,985 patient-years assigned to the aspirin and 1,867 patient-years assigned to the placebo group.	Association between aspirin and stroke risk reduction.	Relative stroke risk reduction of 21% in patients with AF.
Hart RG. Prevention of stroke in patients with nonvalvular atrial fibrillation. <i>Neurology</i> 1998;51:674-81.	Review of 13 randomized trials of antithrombotic therapy.	Patients with atrial fibrillation (AF) who received antithrombotic therapy.	Stroke risk for patients with AF averages 5%/y, with wide variation as a function of coexistent thromboembolic risk factors. Low risk = about 1%/y, Moderate = about 3%/y, and High = about 6%/y. Prior stroke or transient ischemic attack are highest risk = about 12%/y. Well-monitored adjusted-dose warfarin (INR 2-3) = 70% stroke risk reduction. Aspirin = 20% stroke risk reduction.
<b>Carotid Artery Stenosis</b>			
Goldstein LB. Comparison and meta-analysis of randomized trials of endarterectomy for symptomatic carotid artery stenosis. <i>Neurology</i> 1995;45(11): 1965-70.	Meta-analysis of NASCET, ECST and VACS.	Compared rates of nonfatal stroke, nonfatal MI, or death for surgically or medically treated patients in the perioperative period (30 days).	Event rates after 30 days for medically treated patients = .20 versus 0.08 for NASCET; 0.12 versus 0.07 for ECST; and 0.15 versus 0.07 for VACS.
Wennberg DE. Variation in carotid endarterectomy mortality in the Medicare population: trial hospitals, volume, and patient characteristics. <i>JAMA</i> 1998;279:1278-1281.	"Trial" hospitals in NASCET and ACAS n=86 patients, and Medicare "non-trial" hospitals n=2613 patients.	Mortality rates in patients undergoing CE in trial hospitals and non-trial hospitals.	Mortality risk reduction in patients at trial hospitals compared with high volume non-trial hospitals was 15%, compared with average-volume hospitals was 25%, compared with low-volume hospitals was 43%.
<b>Cholesterol</b>			
Blauw GJ. Stroke, statins, and cholesterol. <i>Stroke</i> 1997; 28(5): 946-50.	Meta-analysis of 13 trials.	Stroke rate in middle-aged patients receiving HMG-CoA reductase inhibitor compared to patients receiving placebo.	Treatment with an HMG-CoA reductase inhibitor led to an overall risk reduction of 31%.
Hebert PR. Cholesterol lowering with statin drugs, risk of stroke and total mortality. <i>JAMA</i> 1997;278:313-21.	Meta-analysis of 16 trials.	29,000 patients receiving statins with averaged 3.3 year follow up.	Average reductions in total and low-density lipoprotein cholesterol were 22% and 30%, respectively. Reductions in risks of stroke of 29% and total mortality of 22%.
Crouse JR. HMG-CoA reductase inhibitor therapy and stroke risk reduction. <i>Atherosclerosis</i> 1998;138:11-24.	Meta-analysis of primary and secondary prevention trials.	HMG-CoA reductase inhibitors effect on reducing cholesterol levels and coronary heart disease.	30% stroke reduction and CHD in secondary prevention.
<b>Lifestyle</b>			
Shinton R. Lifelong exposures and the potential for stroke prevention: the contribution of cigarette smoking, exercise, and body fat. <i>Jl of Epidemiol Community Health</i> 1997;51(2):138-43.	125 men and women who had just had their first stroke and were aged 35-74 and 198 controls matched for age and sex.	Stroke and concomitant risk factors.	Cigarette smoking was estimated to have caused 49% of the strokes. Cigarette smoking combined with lack of exercise caused 62% and smoking combined with obesity caused 72%.
Perry IJ. Prospective study of serum total homocysteine concentration and risk of stroke in middle-aged British men: <i>Lancet</i> 1995;346(8987):1395-8.	107 men with stroke and 118 control men.	Association between serum total homocysteine (tHcy) concentration taken between 1978-1980 and subsequent first stroke.	tHcy concentrations were significantly higher in cases than controls (p = 0.004). Relative risk of stroke increased in the second, third and fourth quarters of the tHcy distribution relative to the first (trend p = 0.005).

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### REFERENCES

- Blauw GJ, Lagaay AM, Smelt AH, et al. Stroke, statins, and cholesterol. A meta-analysis of randomized, placebo-controlled, double-blind trials with HMG-CoA reductase inhibitors. *Stroke* 1997;28(5):946-50.
- Boushey CJ, Beresford SA, Omenn GS, et al. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. *JAMA* 1995;274:1049-1057.
- Cebul RD, Snow RJ, Pine R, et al. Indications, outcomes and provider volumes for carotid endarterectomy. *JAMA* 1998;279:1282-7.
- Clarke R, Daly L, Robinson K, et al. Hyperhomocysteinemia: an independent risk factor for vascular disease. *New England Journal of Medicine* 1991;324(17):1149-55.
- Deveraj S, Vega G, Lange R, et al. Remnant-like particle cholesterol levels in patients with dysbetalipoproteinemia or coronary artery disease. *American Journal of Medicine* 1998;104(5):445-5.
- Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. *JAMA* 1998;279(20):1615-22.
- Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA* 1995;273:1421-28.
- Feinberg WM. Primary and secondary stroke prevention. *Current Opinion in Neurology* 1996;9(1):46-52.
- Gorelick PB. Stroke prevention. *Archives of Neurology* 1995;52(4):347-55.
- Herbert PR, Gaziano JM, Chan KS, et al. Cholesterol lowering with statin drugs, risk of stroke, and total mortality. An overview of randomized trials. *JAMA* 1997;278(4):313-21.
- National Cholesterol Education Program. *Second Report of the Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II)*. NHLBI. NIH Publication 93-3096, September, 1993, Updated 1996.
- North American Symptomatic Carotid Endarterectomy Trial Collaborators (NASCET). Beneficial effect of carotid endarterectomy in symptomatic patients with high grade carotid stenosis. *New England Journal of Medicine* 1991;325:445-53.
- Matchar DB. Should we just let the Anticoagulation Clinic Service do it? *Journal of General Internal Medicine* 1996;11:768-70.
- Matchar DB, Oddone EZ, McCrory DC, et al. Influence of projected complication rates on estimated appropriate use rates for carotid endarterectomy. *Health Services Research* 1997;32:325-343.
- Moser M. Why are physicians not prescribing diuretics more frequently in the management of hypertension? *JAMA* 279(22):1813-6, 1998.
- Mulrow C, Lau J, Cornell J, Brand M. Antihypertensive drug therapy in the elderly (Cochrane Review). In: *The Cochrane Library*, Issue 1, 1999.
- O'Leary DH, Polak JF, Kronmal RA, et al. Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study. The CHS Collaborative Research Group. *Stroke* 1992; 23(12):1752-60.
- Rich MW. Epidemiology, pathophysiology, and etiology of congestive heart failure in older adults. *Journal of the American Geriatrics Society* 1997;45(8):968-74.
- Sacco RL. Identifying patient populations at high risk for stroke. *Neurology* 1998;51(3Suppl 3):S27-30.
- Sacco RL, Roberts JK, Jacobs BS. Homocysteine as a risk factor for ischemic stroke: an epidemiological story in evolution. *Neuroepidemiology* 1998;17(4):167-73.
- Selhub J, Jacques PF, Bostom AG, et al. Association between plasma homocysteine concentrations and extracranial carotid-artery stenosis. *New England Journal of Medicine* 1995;332(5):286-91.
- Shepherd J. Profiling risk and new therapeutic interventions: looking ahead (review). *American Journal of Medicine* 1998;104(2A):19S-22S.
- Sixth Report of the Joint National Committee on *Prevention, Detection and Treatment of High Blood Pressure*. NHLBI. NIH Publication, 98-4080, November, 1997.
- The SPAF III Writing Committee for the Stroke Prevention in Atrial Fibrillation Investigators. Patients with nonvalvular atrial fibrillation at low risk of stroke during treatment with aspirin. *JAMA* 1998;279:1273-77.
- Welch GN, Loscalzo J. Mechanisms of disease: homocysteine and atherothrombosis. *New England Journal of Medicine* 1998;338(15):1042-50.
- Wennberg DE, Lucas FL, Birkmeyer JD, et al. Variation in carotid endarterectomy mortality in the Medicare population. *JAMA* 1998;279:1278-81.
- Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly: The Framingham Study. *Archives of Internal Medicine* 1987;147:1561-4.



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