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Primary Prevention of Ischemic Stroke : A Statement for Healthcare Professionals From the Stroke Council of the American Heart Association

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AHA Scientific Statement

Primary Prevention of Ischemic Stroke

A Statement for Healthcare Professionals From the Stroke Council of the American Heart Association

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Stroke ranks as the third leading cause of death in the United States. It is now estimated that there are more than 700 000 incident strokes annually and 4.4 million stroke survivors.[1,2] The economic burden of stroke was estimated by the American Heart Association to be $51 billion (direct and indirect costs) in 1999.[3] Despite the advent of treatment of selected patients with acute ischemic stroke with tissue plasminogen activator and the promise of other experimental therapies, the best approach to reducing the burden of stroke remains prevention.[4,5] High-risk or stroke-prone individuals can be identified and targeted for specific interventions.[6] This is important because epidemiological data suggest a substantial leveling off of prior declines in stroke-related mortality and a possible increase in stroke incidence.[7,8]

The Stroke Council of the American Heart Association formed an ad hoc writing group to provide a clear and concise overview of the evidence regarding various established and potential stroke risk factors. The writing group was chosen based on expertise in specific subject areas, and it used literature review, reference to previously published guidelines, and expert opinion to summarize existing evidence and formulate recommendations (Table 1).

As given in Tables 2 through 4, risk factors or risk markers for a first stroke were classified according to potential for modification (nonmodifiable, modifiable, or potentially modifiable) and strength of evidence (well documented, less well documented).[5] The tables give the estimated prevalence, population attributable risk, relative risk, and risk reduction with treatment for each factor when known. Population attributable risk reflects the proportion of ischemic strokes in the population that can be attributed to a particular risk factor and is given by the formula $100\times[\text{prevalence(relative risk}-1)/\text{prevalence(relative risk}-1)+1])$.[9] Well-documented modifiable risk factors (Table 3) were considered as those with clear, supportive epidemiological evidence in addition to evidence of risk reduction with modification as documented by randomized trials. Less well-documented or potentially modifiable risk factors were those with either less clear epidemiological evidence or without evidence from randomized trials demonstrating a reduction of stroke risk with modification. Gaps in current knowledge are indicated by question marks in the tables.

Table 5 summarizes guideline or consensus statement management recommendations where available. Other recommendations are indicated in the text. Based primarily on an individual patient's risk assessment profile (the Framingham Heart Study risk profile[6] is an easy-to-use and valuable tool for identifying persons at risk of stroke) and overall medical condition, interventions involving appropriate lifestyle behavior changes and surgical and pharmacological treatments can be implemented to treat, control, or modify specific risk factors with the goal of reducing the risk of a first stroke.

Nonmodifiable Risk Factors

Although these factors are nonmodifiable, they identify individuals at highest risk of stroke and those who may benefit from rigorous prevention or treatment of modifiable risk factors.[5] (See Table 2.)

Age

The cumulative effects of aging on the cardiovascular system and the progressive nature of stroke risk factors over a prolonged period of time substantially increase stroke risk. The risk of stroke doubles in each successive decade after 55 years of age.[8,10]

Sex

Stroke is more prevalent in men than in women.[8] Overall, men also have higher age-specific stroke incidence rates than women.[11] Exceptions are in 35- to 44-year-olds and in those over 85 years of age in whom women have slightly greater age-specific incidence than men.[11] However, stroke-related case-fatality rates are higher in women than men. In 1997, females accounted for 60.8% of stroke fatalities.[2] Overall, 1

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TABLE 1. Levels of Evidence and Grading of Recommendations

Level of evidence	
Level I	Data from randomized trials with low false-positive and low false-negative errors
Level II	Data from randomized trials with high false-positive or high false-negative errors
Level III	Data from nonrandomized concurrent cohort studies
Level IV	Data from nonrandomized cohort studies using historical controls
Level V	Data from anecdotal case series
Strength of recommendation	
Grade A	Supported by Level I evidence
Grade B	Supported by Level II evidence
Grade C	Supported by Level III, IV, or V evidence

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in 6 women will die of stroke, compared with 1 in 25 who will die of breast cancer.[12] Circumstances such as oral contraceptive use and pregnancy uniquely contribute to the risk of stroke in women.[13–15]

Race/Ethnicity

Blacks[1,11,16] and some Hispanic Americans[16,17] have high stroke incidence and mortality rates compared with whites. For example, in the Atherosclerosis Risk In Communities (ARIC) study, blacks had a 38% greater incidence of strokes than whites.[18] Possible reasons for the high incidence and mortality rate of strokes in blacks include a higher prevalence of hypertension, obesity, and diabetes mellitus within the black population.[19–21] However, a higher incidence of these other risk factors does not explain all of the excess risk.[19] Epidemiological studies have also shown an increase in stroke incidence among self-identified Hispanic populations.[22–24] Chinese and Japanese populations generally have high stroke incidence rates as well.[25]

Family History

Both paternal and maternal history of stroke may be associated with increased stroke risk.[26,27] This increased risk could be mediated through a variety of mechanisms, including genetic heritability of stroke risk factors, the inheritance of susceptibility to the effects of such risk factors, familial sharing of cultural/environmental and lifestyle factors, and the interaction between genetic and environmental factors.[28] Studies with twins provide strong data suggesting familial inheritance of stroke. Concordance rates for strokes are markedly higher in monozygotic than in dizygotic twins.[29] There is a nearly 5-fold increase in stroke prevalence among monozygotic versus dizygotic twins.[30]

Well-Documented Modifiable Risk Factors

Several well-documented modifiable risk factors for stroke exist. (See Table 3.)

Hypertension

Hypertension is a major risk factor for both cerebral infarction and intracerebral hemorrhage.[31] The incidence of stroke increases in proportion to both systolic and diastolic blood pressures. This relationship is "direct, continuous, and apparently independent."[32] Blood pressure, particularly systolic blood pressure, increases with age.[33] Elevated systolic pressure, with or without an accompanying elevation in diastolic pressure, has been shown to increase stroke risk. Isolated systolic hypertension is an important risk factor for stroke in the elderly (systolic blood pressure $>$160 mm Hg and diastolic blood pressure $<$90 mm Hg).[34]

There has been compelling evidence for more than 30 years that the control of high blood pressure contributes to the prevention of stroke as well as to the prevention or reduction of other target-organ damage, including congestive heart failure and renal failure.[35,36] A meta-analysis of 18 long-term randomized trials found that both β-blocker therapy (relative risk 0.71; 95% CI 0.59 to 0.86) and treatment with high-dose diuretics (relative risk 0.49; 95% CI 0.39 to 0.62) were effective in preventing stroke.[37] In the past 10 years, the importance of controlling isolated systolic hypertension to prevent stroke in the elderly has been underscored in clinical trials.[38] For example, in the Syst-Eur Trial, 4695 patients with isolated systolic hypertension were randomized to active treatment (nitrendipine and possibly enalapril or hydrochlo-

TABLE 2. Nonmodifiable Risk Factors

Factor	Incidence	Population Attributable Risk	Relative Risk	Risk Reduction With Treatment
Age[8,10]	Doubling of stroke rate each 10 years after age 55	...	...	...
Race[11]	Blacks: 233/100 000 Hispanics: 196/100 000 Whites: 93/100 000	...	...	...
Sex[8]	Men: 174/100 000 Women: 122/100 000 Total: 145/100 000	...	...	...
Family history of stroke/TIA[27]	...	...	RR paternal history: 2.4 (95% CI 0.96–6.03) RR maternal history: 1.4 (95% CI 0.60–3.25)	...

RR indicates relative risk.

TABLE 3. Well-Documented Modifiable Risk Factors

Factor	Prevalence	Population Attributable Risk	Relative Risk	Risk Reduction With Treatment
Hypertension (by age group)[281]				38%
50 y	20%	40%	4.0	
60 y	30%	35%	3.0	
70 y	40%	30%	2.0	
80 y	55%	20%	1.4	
90 y	60%	0	1.0	
Smoking	25%	12–18%	1.8	50% Within 1 year. Baseline after 5 years.[50]
Diabetes	20%[64]	14–58%	1.8–6	Reduction of stroke risk in hypertensive diabetics with blood pressure control. No demonstrated benefit in stroke reduction with tight glycemic control; however, reduction in other complications (see text).
Asymptomatic carotid stenosis	2–8%[66,67,282–287]	2–7%§	2.0[288]	50%[76]
Sickle cell disease	0.25% of blacks[289]	...	200–400†[120]	91%‡[120]
Hyperlipidemia[290]	8–9% adults <35 y[64] 25% men aged 55 y 40% women aged 65 y	25%	1.8 for TC 240–279 mg/dL 2.6 for TC >280 mg/dL	20–30% With statins in patients with known coronary heart disease (see text)
Atrial fibrillation (nonvalvular)[80,87]				
Overall, by age group, risk factor adjusted*				
50–59 y	0.5%	1.5%	4.0	68% (Warfarin)[88]
60–69 y	1.8%	2.8%	2.6	21% (Aspirin)[284]
70–79 y	4.8%	9.9%	3.3	
80–89 y	8.8%	23.5%	4.5	
Risk categories	Annual Event Rate[88]			
<65 y, no risk factors	1.0%			
<65 y, with risk factors	4.9%			
65–75 y, no risk factors	4.3%			
65–75 y, with risk factors	5.7%			
>75 y, no risk factors	3.5%			
>75 y, with risk factors	8.1%			

TC indicates total cholesterol.
*Atrial fibrillation risk factors: hypertension, diabetes, prior TIA/stroke, prosthetic heart valve (may require higher target International Normalized Ratio).
†Relative to stroke risk in children without sickle cell disease.
‡For high-risk patients treated with transfusion.
§Calculated based on referenced data provided in the table or text.

rothiazide to lower systolic blood pressure 20 mm Hg) or to placebo.[38] The trial was stopped when stroke reduction reached 42% in the actively treated group. The Systolic Hypertension in the Elderly Program (SHEP) trial demonstrated a 36% reduction in the incidence of total stroke with antihypertensive treatment (chlorthalidone or atenolol).[39] Despite extensive education efforts, a significant proportion of the population has undiagnosed or inadequately treated hypertension.[34,40,41] This is particularly true in high-risk race/ethnic groups.[42]

Recommendation

Regular screening for hypertension (at least every 2 years in adults) and appropriate management, as summarized in the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, are recommended (Table 5).[34] (Level of Evidence I, Grade A)

Smoking

Active (current) cigarette smoking has been long recognized as a major risk factor for stroke. Pathophysiological effects of smoking are multifactorial, affecting both the systemic vasculature and blood rheology. Smoking causes reduced blood vessel distensibility and compliance by leading to increased arterial wall stiffness.[43] Smoking is also associated with increased fibrinogen levels, increased platelet aggregation, decreased high-density lipoprotein (HDL) cholesterol levels, and increased hematocrit.[44]

TABLE 4. Less Well-Documented or Potentially Modifiable Risk Factors

Factor	Prevalence	Population Attributable Risk	Relative Risk or Odds Ratio	Risk Reduction With Treatment
Obesity	17.9%[291]	12–20%*	1.75–2.37[163,164]	?
Physical inactivity[172]	25%	30%	2.7*	?
Alcohol abuse				
≥5 Drinks/d[196,290]	2–5%	1.2–3.0%	1.6*	?
Not moderate	60%	32%	1.8*	?
Hyperhomocysteinemia	29%, age 40–59, men	26%, age 40–59, men	1.3–2.3[205–207]	?
	21%, age 40–59, women	37%, age 40–59, women		
	43%, age ≥60, men	35%, age ≥60, men		
	47%, age ≥60, women[204]	37%, age ≥60, women[204,206]		
Drug abuse	3–14%[64]	?	?	?
Hypercoagulability				
Antiphospholipid antibody	0–24%[292–295]	0–65%*	0.8–8.83[311–316]	?
Factor V Leiden	0–12%[296–304]	0–17%*	1.0–2.75[317–321]	?
Prothrombin 20210 mutation	0–4.4%[305–308]	0–11%*	1.1–3.8[317,319,322–325]	?
Protein C deficiency	0.145–0.5%[301,309]	?	NS[321,326]	?
Protein S deficiency	0.003–0.007%[303]	?	NS[321]	?
Antithrombin III deficiency	0.02–0.17%[301,310]	?	NS[310,321]	?
Hormone replacement therapy	...	...	0.23–1.46[170,192,227–239]	...
Oral contraceptive use	...	0.06%†[250]	0.6–7.09‡[242–247,250,327]	
Inflammatory processes	...	...	...	...

*Calculated based on referenced data provided in the table or text.

†Calculated assuming a relative risk of 1.93 with 425 total ischemic strokes per year attributable to oral contraceptive use as given in Reference 250.

‡Studies published since 1985.

A meta-analysis of 22 studies indicates an approximate doubling of the relative risk of cerebral infarction among smokers versus nonsmokers.[45] A prospective estimate of a 1.8-fold increase in stroke risk associated with smoking (after control for other stroke risk factors) from the Framingham Heart Study confirms this substantial increase in risk.[46] Currently, 25% of adults are active smokers.[47] Therefore, ≈18% of strokes are attributable to active cigarette smoking. This estimated population attributable risk is only slightly higher than the estimated 12% population attributable risk associated with active smoking in the Rochester, Minn, population.[9]

To the extent that former smoking may also place individuals at increased risk of stroke, efforts to prevent the initiation of smoking are important to the primary prevention of stroke. The relative risk of stroke among former smokers (compared with nonsmokers) was 1.34 in the Nurses' Health Study[48] and 1.26 in the Physicians' Health Study.[49] Currently, the Centers for Disease Control and Prevention estimate that 23% of the adult population are former smokers,[47] implying a population attributable risk for former smoking of 6%. However, the stroke risk associated with former smoking has been shown to substantially decrease with increasing time since cessation. As such, in the Physicians' Health and Nurses' Health studies, the 6% population attributable risk estimate is a function of the distribution of time since quitting. The Framingham Heart Study found stroke risk to be at the level of nonsmokers at 5 years from cessation.[50] A second study reported that stroke risks disappeared from 2 to 4 years after smoking cessation and that the benefits of cessation were independent of the age at starting and the number of cigarettes smoked per day.[48] Wannamethee et al[51] concluded that smoking cessation is associated with a considerable and rapid benefit in decreased risk of stroke, particularly in light smokers (<20 cigarettes/d). However, switching to pipe or cigar smoking confers little benefit, emphasizing the need for complete cessation of smoking.[51]

Avoidance of exposure to environmental tobacco smoke may also play a role in the primary prevention of stroke. Nearly 90% of nonsmokers have been shown to have detectable levels of serum cotinine, assumed to be present through exposure to environmental tobacco smoke.[52] Because of the high population prevalence of exposure, even a small increase in the relative risk of stroke associated with exposure to environmental tobacco smoke may have a substantial population attributable risk. However, the increase in relative risk may not be small. It has been suggested that exposure to environmental tobacco smoke increases the risk for coronary events from 20% to 70%. An estimated 62 000 coronary heart disease deaths in 1985 were attributable to exposure to environmental tobacco smoke.[52]

Because atherosclerosis can lead to both stroke and coronary heart disease, it is reasonable to suspect environmental tobacco smoke as a cause for some strokes. After adjusting for potential confounders (age, sex, history of hypertension, heart disease, and diabetes), Bonita and colleagues[53] found a

TABLE 5. Guideline or Consensus Statement Management Recommendations

Factor	Goal	Recommendations
Hypertension[34]	SBP <140 mm Hg	Measure BP in all adults at least every 2 years.
	DBP <90 mm Hg	Promote lifestyle modification: weight control, physical activity, moderation of alcohol intake, moderate sodium intake. If BP >140/90 mm Hg after 3 months of life habit modification or if initial BP >180/100 mm Hg: add antihypertensive medication; individualize therapy to patient's other requirements and characteristics.
Smoking[64]	Cessation	Strongly encourage patient and family to stop smoking. Provide counseling, nicotine replacement, and formal programs as available.
Diabetes	Improved glucose control; treatment of hypertension	Diet, oral hypoglycemics, insulin. See guidelines and policy statements.[64,65]
Asymptomatic carotid stenosis[328,329]	...	Endarterectomy may be considered in selected patients with >60% and <100% carotid stenosis, performed by surgeon with <3% morbidity/mortality. Careful patient selection guided by comorbid conditions, life expectancy, patient preference, and other individual factors. Patients with asymptomatic stenosis should be fully evaluated for other treatable causes of stroke.
Atrial fibrillation[87]	...	
Age <65 y, no risk factors†		Aspirin
Age <65 y, with risk factors†		Warfarin (target INR 2.5; range 2.0–3.0)
Age 65–75 y, no risk factors†		Aspirin or warfarin
Age 65–75 y, with risk factors†		Warfarin (target INR 2.5; range 2.0–3.0)
Age >75 y, with or without risk factors†		Warfarin (target INR 2.5; range 2.0–3.0)
Lipids[330]		
Initial evaluation (no CHD)		
TC <200 mg/dL and HDL ≥35 mg/dL	General education	Repeat TC and HDL within 5 years or with physical examination
TC <200 mg/dL and HDL <35 mg/dL		Lipoprotein analysis
TC 200–239 mg/dL and HDL ≥35 mg/dL and <2 CHD risk factors*		Dietary modification, reevaluation in 1–2 years
TC 200–239 mg/dL and HDL <35 mg/dL or <2 CHD risk factors*		Lipoprotein analysis
TC ≥240 mg/dL		Lipoprotein analysis
LDL evaluation		
No CHD and <2 CHD risk factors*	LDL <160 mg/dL	6-Month trial of diet modification. Drug therapy if LDL remains ≥190 mg/dL.
No CHD but ≥2 CHD risk factors	LDL <130 mg/dL	6-Month trial of diet modification. Drug therapy if LDL remains ≥160 mg/dL.
Definite CHD or other atherosclerotic disease	LDL <100 mg/dL	6- to 12-Week trial of Step II diet. Drug therapy if LDL remains ≥130 mg/dL.
Physical inactivity[183]	≥30 Min of moderate-intensity activity daily	Moderate exercise (eg, brisk walking, jogging, cycling, or other aerobic activity)
		Medically supervised programs for high-risk patients (eg, cardiac disease) and adaptive programs depending on physical/neurological deficits
Poor diet/nutrition		A diet containing at least 5 servings of fruits and vegetables per day may reduce the risk of stroke.
Alcohol[64]	Moderation	No more than 2 drinks/d for men and 1 drink/d for nonpregnant women
Drug abuse[64]	Cessation	An in-depth history of substance abuse should be included as part of a complete health evaluation for all patients

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; INR, International Normalized Ratio; CHD, coronary heart disease; and TC, total cholesterol.

*CHD risk factors: men ≥45 years, women ≥55 years or early menopause without hormone replacement therapy, family history of premature CHD, smoking, hypertension, HDL <35 mg/dL, diabetes mellitus.

†Atrial fibrillation risk factors: hypertension, diabetes mellitus, poor left ventricular function, rheumatic mitral valve disease, prior TIA/stroke, systemic embolism or stroke, prosthetic heart valve (may require higher target INR).

1.82-fold increase (95% CI 1.34 to 2.49) in the risk of stroke among nonsmokers and long-term ex-smokers exposed to environmental tobacco smoke. The risk was significant in both men and women. An increase of 1.82 is surprisingly large; however, even a more modest 1.20-fold increase in relative risk (the lower limit of the estimated effect on coronary heart disease) is associated with an estimated population attributable risk of 12% (based on a 67.5% population exposure, calculated as 90% prevalence of exposure in the 75% of the nonsmoking population).

In summary, these data suggest that the population attributable risk associated with all forms of exposure to cigarette smoke is substantial, with current smoking contributing to approximately half of the stroke events (population attributable risk of 18% for current smoking, 6% for former smoking, and 12% for exposure to environmental tobacco smoke).

Recommendation

Smoking cessation for all current smokers is recommended (Table 5).[34] (Level of Evidence III, Grade C; note that the evidence level reflects a lack of prospective randomized trials of smokers compared with nonsmokers. However, the data from cohort and epidemiological studies are consistent and overwhelming.)

Diabetes, Hyperinsulinemia, and Insulin Resistance

Insulin-dependent diabetics have both an increased susceptibility to atherosclerosis and an increased prevalence of atherogenic risk factors, notably hypertension, obesity, and abnormal blood lipids. A constellation of metabolic risk factors, termed syndrome X, has also been identified in some type 2 diabetics.[54,55] The main characteristics of syndrome X are hyperinsulinemia and insulin resistance. These result in the secondary features of the syndrome, including hyperglycemia, increased very-low-density lipoprotein cholesterol, decreased HDL cholesterol, and hypertension.

Case-control studies of stroke patients and prospective epidemiological studies have confirmed an independent effect of diabetes on ischemic stroke, with an increased relative risk in diabetics ranging from 1.8- to nearly 6-fold. In the United States, from 1976 to 1980, a history of stroke was 2.5 to 4 times more common in diabetics than in persons with normal glucose tolerance. Among Hawaiian Japanese men in the Honolulu Heart Program, those with diabetes had twice the risk of thromboembolic stroke as nondiabetics, an increase in risk that was independent of other factors.[56] In the Framingham Heart Study, although the impact of diabetes was greatest on peripheral arterial disease with intermittent claudication, for which the relative risk was increased 4-fold, coronary and cerebral artery territories were also affected. For brain infarction, the impact of glucose intolerance was greater in women than men, reaching significance as an independent contributor only in older women. Overall, persons with glucose intolerance have double the risk of brain infarction compared with nondiabetics.[57]

High blood pressure is common in patients with type 2 diabetes, with a prevalence of 40% to 60% in adults. The combination of hyperglycemia and hypertension has long been believed to increase the frequency of diabetic complications, including stroke. Several recent trials examining stroke and other cardiovascular outcomes compared the benefit of tight control of blood glucose and blood pressure in type 2 diabetics with less stringent management.[58] For combined fatal and nonfatal stroke, tight blood pressure control (mean blood pressure achieved 144/82 mm Hg) resulted in a convincing 44% relative risk reduction compared with more liberal control (mean blood pressure achieved 154/87 mm Hg).[59] This 44% benefit in stroke risk reduction is above and beyond the ≥20% risk reduction with antihypertensive treatment found in diabetics in SHEP.[60] However, improved glycemic control did not produce a significant reduction in stroke incidence over 9 years of follow-up.[61]

The conclusion reached from these studies and in a recent review is that tight control of hypertension in diabetics significantly reduces stroke incidence.[62] Current measures to achieve tight glycemic control are less effective for stroke prevention. Nevertheless, intensive therapy to achieve tight control of hyperglycemia with ≥3 doses per day of insulin in patients with recent-onset insulin-dependent (type 1) diabetes mellitus was shown to reduce microvascular complications, nephropathy, and retinopathy, as well as peripheral neuropathy.[59]

The report of the Heart Outcomes Prevention Evaluation (HOPE) study represents an exciting development in prevention of cardiovascular disease. In this placebo-controlled, randomized clinical trial, the addition of the angiotensin-converting enzyme (ACE) ramipril was compared with the current medical regimen of high-risk patients. The substudy of 3577 diabetic patients (of a total population of 9541 participants in the HOPE study) showed a reduction of the primary combined outcome of myocardial infarction, stroke, and cardiovascular death by 25% (95% CI 12% to 36%, $P=0.0004$) and a reduction of stroke by 33% (95% CI 10% to 50%, $P=0.0074$).[63] This benefit was present even after adjustment for the minor decrease in blood pressure in the ramipril group. There was also a reduction in diabetic complications (overt nephropathy, dialysis, or need for laser therapy).

These new reports provide long-sought evidence for stroke prevention in diabetics. Control of hypertension in diabetics and treatment of high-risk diabetic patients with the ACE inhibitor ramipril prevent stroke.

Recommendations

Careful control of hypertension in both type 1 and type 2 diabetics is recommended. (Level of Evidence I, Grade A) Glycemic control is recommended to reduce microvascular complications (Table 5).[64,65]

Asymptomatic Carotid Stenosis

In the Cardiovascular Health Study, carotid stenoses >50% were detected in 7% of the men and 5% of the women ≥65 years of age.[66] Similarly, stenoses of ≥50% were detected in 7% of women and 9% of men aged 66 to 93 years in the Framingham cohort.[67] Therefore, it seems likely between 7% and 10% of men and between 5% and 7% of women above age 65 have carotid stenoses >50%.

Several studies have attempted to identify subgroups of patients with asymptomatic carotid artery stenosis who may be at particularly elevated risk of stroke. The Toronto Asymptomatic Cervical Bruit Study followed a cohort of 500 patients for a mean of 23 months.[68] Overall, cerebral ischemic events (transient ischemic attack [TIA] or stroke) were more frequent in patients with severe (>75%) carotid artery stenosis, progressing carotid artery stenosis, or heart disease and in men. A total of 8 patients (1.6%) had an unheralded stroke; however, only 2 (0.4%) were ipsilateral to a high-grade extracranial carotid artery stenosis as demonstrated by Doppler ultrasonography. In another study, 38 asymptomatic patients with >90% stenosis of the internal carotid artery were followed up for a mean period of 48 months.[69] Each year, 1.7% of the patients had an unheralded ipsilateral stroke. More recently, the NASCET (North American Symptomatic Carotid Endarterectomy Trial) investigators have retrospectively reviewed their data regarding the risk of stroke in the territory of an asymptomatic carotid artery stenosis contralateral to the side of the symptomatic vessel.[70,71] The annual risk of stroke was 3.2% (over 5 years of observation) in patients with 60% to 99% stenosis. The average annual risk of ipsilateral stroke increased from 3.0% for those with 60% to 74% stenosis to 3.7% for those with 75% to 94% stenosis and decreased to 2.9% for those with 95% to 99% stenosis, with a rate of 1.9% for those with complete occlusion. Overall, 45% of ipsilateral strokes in patients with asymptomatic stenosis contralateral to a symptomatic stenosis may be attributable to lacunes or cardioembolism, underscoring the need to fully evaluate these patients for other treatable causes of stroke.

Taken together, these and other observational studies suggest that the rate of unheralded stroke ipsilateral to a hemodynamically significant extracranial carotid artery stenosis is ≈1% to 2% annually. This represents a significant factor on a population basis. Some studies suggest that the rate of stroke may be higher in those patients with progressing stenosis than in those with stable disease and higher in those with more severe stenosis. As with asymptomatic carotid bruit, an asymptomatic stenosis of the carotid artery is an important indicator of concomitant ischemic cardiac disease.[68,69,72]

There have been 4 published randomized controlled trials that were designed to address the benefit of carotid endarterectomy in patients with asymptomatic carotid artery stenosis. The CASANOVA (Carotid Artery Stenosis with Asymptomatic Narrowing: Operation Versus Aspirin) study was inconclusive.[73] The Mayo Clinic Asymptomatic Carotid Endarterectomy (MACE) study included 71 randomized and 87 nonrandomized patients.[74] Surgically treated patients were not given aspirin. There were no major strokes or deaths in either group. However, the study was stopped because myocardial infarction occurred in 26% of those in the surgical arm (no aspirin) versus 9% of those in the aspirin-treated medical arm ($P=0.002$), reflecting the high incidence of concomitant coronary artery disease in patients with asymptomatic carotid artery stenosis.

The Veterans Affairs Cooperative Study of carotid endarterectomy for patients with asymptomatic carotid artery stenosis included 444 men followed up for a mean of 48 months.[75] Two hundred eleven patients received best medical therapy plus carotid endarterectomy, and 233 received medical therapy alone (including 650 mg of aspirin twice daily). Patients had >50% stenosis of the extracranial carotid artery demonstrated by angiography. Combined perioperative and angiographic risk was 4.7%. There was a 38% risk reduction for the combined end points of ipsilateral TIA, transient monocular blindness, and stroke over 2 years ($P<0.001$). Although the rate of fatal and nonfatal stroke was reduced in the surgical group (4.7% versus 9.4%, or 1.2% per year versus 2.4% per year), the difference was not significant ($P=0.08$). However, the study was not powered to detect differences in outcome subgroups.

The Asymptomatic Carotid Atherosclerosis Study (ACAS) was a randomized trial investigating the efficacy of carotid endarterectomy in patients with asymptomatic high-grade (>60% diameter reduction) carotid artery stenosis.[76] Patients (n=1662) were randomized to surgery plus medical therapy (n=828) or to medical therapy without carotid endarterectomy (n=834). There was a 1.2% risk of angiography-related complications among the 424 patients undergoing postrandomization angiograms and a 2.3% aggregate perioperative stroke risk. The study was halted after a median follow-up of 2.7 years (4465 patient-years) because a significant benefit of surgery was found. The aggregate rate of ipsilateral stroke, any perioperative stroke, or death in surgically treated patients was estimated at 5% over 5 years; in medically treated patients, the corresponding rate was 11% (53% risk reduction, 2% per year event rate reduced to 1% per year; $P=0.004$). There was no relationship between benefit and the degree of carotid artery stenosis. Women did not benefit (17% nonsignificant risk reduction in women [95% CI −0.96 to 0.65] versus 66% risk reduction in men [95% CI 0.36 to 0.82]), a difference ascribed to a higher rate of perioperative complications in women (3.6% versus 1.7%). Other studies have also noted an increased risk of perioperative complications after endarterectomy in asymptomatic women compared with men.[77] However, as with the Veterans Affairs trial, the study was not powered to detect differences among subgroups of patients.

It should be noted that the benefit of endarterectomy in the setting of asymptomatic carotid artery stenosis is highly dependent on surgical risk. Yet, most physicians are not aware of the complication rates of the surgeon to whom they refer patients for the operation.[78,79]

Recommendation

Endarterectomy may be considered in patients with high-grade asymptomatic carotid stenosis performed by a surgeon with <3% morbidity/mortality rate. (Level of Evidence I, Grade A) Careful patient selection, guided by comorbid conditions, life expectancy, and patient preference, as well as other individual factors, including sex, and followed by a thorough discussion of the risks and benefits of the procedure, is required. It is important that patients with asymptomatic carotid artery stenosis be fully evaluated for other treatable causes of stroke. (See Table 5.)

Atrial Fibrillation

Atrial fibrillation is a common arrhythmia and an important risk factor for stroke, with established effective therapy for stroke prevention. The annual risk of stroke in unselected patients with nonvalvular atrial fibrillation is 3% to 5%, with the condition responsible for 50% of thromboembolic strokes.[80] It is estimated that approximately two thirds of the strokes that occur in patients with atrial fibrillation are cardioembolic. The median age of patients with atrial fibrillation is 75 years. The Framingham Heart Study noted a dramatic increase in stroke risk associated with atrial fibrillation with advancing age, from 1.5% for those 50 to 59 years of age to 23.5% for those 80 to 89 years of age.[81] In addition, atrial fibrillation was associated with an OR for death of 1.5 (95% CI 1.2 to 1.8) in men and 1.9 (95% CI 1.5 to 2.2) in women after adjustment for other risk factors.

Five placebo-controlled trials investigating the efficacy of warfarin in the primary prevention of thromboembolic stroke included the Copenhagen Atrial Fibrillation Aspirin and Anticoagulation (AFASAK) trial,[82] Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF),[83] Stroke Prevention in Atrial Fibrillation I (SPAF I),[84] Veterans Affairs Stroke Prevention in Atrial Fibrillation trial (SPINAF),[85] and the Canadian Atrial Fibrillation Anticoagulation (CAFA) trial.[86] The efficacy of aspirin was studied in 2 of these trials (AFASAK and SPAF I). Combined analysis of these 5 trials showed that the relative risk of thromboembolic strokes for patients treated with warfarin was reduced by 68%.

An important observation arising from the randomized treatment trials is that there are a limited number of predictors of high stroke risk within the population of patients with atrial fibrillation. The predictors of high risk include advancing age, prior TIA or stroke, systolic hypertension (systolic blood pressure >160 mm Hg), a history of hypertension, impaired left ventricular function, diabetes mellitus, and women over the age of 75 years.[87] Long-term oral anticoagulation of patients with these high-risk features reduces the risk of stroke by 68% based on results of the intention-to-treat analysis of the randomized trials and by as much as 80% when the on-treatment effect is noted.[88]

Recommendation

Antithrombotic therapy (warfarin or aspirin) should be considered for patients with nonvalvular atrial fibrillation based on an assessment of their risk of embolism and risk of bleeding complications (Tables 4 and 5).[87] (Level of Evidence I, Grade A)

Other Cardiac Disease

Other types of cardiac disease that contribute a small yet finite risk to thromboembolic stroke include dilated cardiomyopathy, valvular heart disease (eg, mitral valve prolapse, endocarditis, and prosthetic cardiac valves), and intracardiac congenital defects (eg, patent foramen ovale, atrial septal defect, and atrial septal aneurysm). Overall, an estimated 20% of ischemic strokes are due to cardiogenic embolism. Potential cardiac sources of emboli are associated with up to 40% of cryptogenic strokes in some series involving the younger population.[89]

The presence of cerebrovascular disease is strongly associated with the presence of symptomatic[90–93] and asymptomatic[94–98] cardiac disease. Conversely, based on the Framingham Heart Study, 8% of men and 11% of women will have a stroke within 6 years after acute myocardial infarction. In addition, myocardial infarction is associated with the development of atrial fibrillation and is a common source of cardiogenic emboli.[81] However, acute myocardial infarction is infrequently associated with stroke, occurring in 0.8% of patients.[99–101] The majority of these strokes (in 0.6% of patients) are ischemic.[101]

Perioperative stroke occurs in 1% to 7% of patients undergoing cardiac surgical procedures (predominantly coronary artery bypass procedures and open heart surgery). A history of prior neurological events, increasing age, diabetes, and atrial fibrillation have been identified as risk factors for early and delayed stroke after cardiac surgery.[102–112] Other factors associated with perioperative stroke include duration of cardiopulmonary bypass and the presence of aortic atherosclerosis.[113,114]

Sickle Cell Disease

Sickle cell disease (SCD) is a genetic disorder with autosomal dominant inheritance in which the abnormal gene product is an altered β-chain in the structure of hemoglobin. Although the clinical manifestations are highly variable, typically SCD manifests early in life as a severe hemolytic anemia punctuated by bouts of painful episodes involving the extremities and bones ("vaso-occlusive crises"), bacterial infections, and organ infarctions, including stroke. In addition, there are systemic effects including impaired growth and possibly cognitive developmental retardation.[115]

Stroke prevention is most important for patients with homozygous SS disease. The prevalence of stroke by age 20 in these patients is at least 11%,[116] and a substantial number of patients also have "silent" strokes on brain MRI.[117] The highest stroke rates occur in early childhood. Recent advances in detection of risk with transcranial Doppler have made primary prevention of stroke a high priority in children with SCD.[118,119] The risk of stroke during childhood is ≈1% per year, but patients with transcranial Doppler evidence of high cerebral blood flow velocity rates (time-averaged mean velocity of ≥200 cm/s) have stroke rates in excess of 10% per year.

A recently completed randomized trial (Stroke Prevention Trial in Sickle Cell Anemia; the STOP study) compared periodic blood transfusion with standard care in 130 children with SCD ranging in age from 2 to 16 years (mean 8 years).[120] Blood transfusions were given an average of 14 times per year for >2 years in the treatment group, with a target reduction of Hb S from a baseline of 90% to 95% of total hemoglobin to <30%. The trial was halted 16 months early at the point at which 11 strokes had occurred in the standard-care arm compared with 1 stroke in the transfusion-treated group. The risk of stroke was reduced from 10% per year to <1%. Given these results, a Clinical Alert issued by the National Heart, Lung, and Blood Institute of the National Institutes of Health has recommended screening all children with SCD who have no history of stroke, with consideration

of transfusion for those with 2 abnormal transcranial Doppler studies.

At present, the duration of transfusion needed has not been determined. Long-term transfusion is always associated with iron toxicity that must be treated with chelation.[121] In the STOP study, there was no evidence of transfusion-related infection, but this and alloimmunization remains a transfusion risk.[120] The role of other therapies such as bone marrow transplantation or hydroxyurea, which reduce the number of painful crises but have an uncertain effect on organ damage, including stroke, requires further study.[122,123] The roles of anticoagulation and antiplatelet agents have not been evaluated. The use of methods other than transcranial Doppler, such as MRI or magnetic resonance angiography, to predict stroke sufficient to trigger prophylactic transfusion has not been well studied. There are no systematic data on prevention of stroke in adults with SCD, and improvements in care have increased expected longevity well beyond 40 years of age, making stroke in older SCD patients a more common clinical problem. Preventive therapies other than transfusion and the development of a prevention strategy in adults should be explored.

Recommendation

Children with SCD should be screened with transcranial Doppler ultrasonography at 6-month intervals to determine their level of stroke risk. Those at elevated risk should be considered for transfusion therapy. (Level of Evidence I, Grade A)

Hyperlipidemia

Abnormalities of serum lipids (triglycerides, cholesterol, low-density lipoprotein [LDL], and HDL) have traditionally been regarded as a risk factor for coronary artery disease but not for cerebrovascular disease. However, recent studies have helped clarify the relationship between lipids and stroke, as well as showing that the risk of stroke and amount of carotid atheroma can be reduced with cholesterol-lowering medications.

In a large meta-analysis of 45 prospective observational cohorts involving 450 000 individuals, no association was found between cholesterol and stroke rate.[124] However, these epidemiological studies of the relationship between total cholesterol and stroke are confounded by reports of an inverse association between total cholesterol and cerebral hemorrhage, with a greater mortality from hemorrhagic stroke among those with serum cholesterol levels $<$160 mg/dL.[125–127] In the studies included in the meta-analysis, most of the strokes were fatal, and there was not a clear differentiation between ischemic and hemorrhagic strokes.

For ischemic stroke, some studies have found a weak association between serum cholesterol and an increasing risk of cerebral infarction.[128] For example, the Multiple Risk Factor Intervention Trial demonstrated increased mortality among men with high cholesterol levels.[129] The adjusted risk ratio was 1.8 for those with serum cholesterol 240 to 279 mg/dL and 2.6 for those with cholesterol levels $\geq$280 mg/dL. In the Honolulu Heart Program, there was a continuous and progressive increase in both coronary heart disease and thromboembolic stroke rates with increasing levels of cholesterol. An inverse relationship between HDL and stroke risk was demonstrated in both the Oxfordshire Community Study and the Northern Manhattan Stroke Study.[130–132] More recent studies utilizing ultrasound technology have established an association between lipid levels and extracranial carotid atherosclerosis and intimal-media plaque thickness.[66,67,133–135]

Older clinical trials did not confirm a reduction in stroke risk with the use of lipid-lowering therapies.[136] However, more recent clinical trials using serial ultrasound measurements showed that reductions of elevations of LDL with β-hydroxy-β-methylglutaryl-CoA (HMG-CoA) reductase inhibitors ("statins") can modestly retard the progression of asymptomatic carotid atherosclerosis.[67,137–140]

Trials using these agents have demonstrated consistent benefits in reduction of stroke risk among individuals with coronary artery disease and elevated cholesterol levels, as well as among those with only mild to borderline elevations of cholesterol.[141–146] For example, the Simvastatin Survival Study (4S) evaluated the effects of lowering cholesterol on 4444 patients with elevated total cholesterol levels and coronary heart disease.[141] The simvastatin-treated group experienced 51% and 35% reductions in ischemic nonembolic stroke and TIAs, respectively. In 1998, the Food and Drug Administration (FDA) approved simvastatin to reduce the risk of first stroke or TIA in people with high total cholesterol and coronary heart disease. The West of Scotland Primary Prevention (WOSCOPS) trial found a nonsignificant 11% reduction in stroke in men with coronary heart disease and hypercholesterolemia who were treated with pravastatin.[147] The Cholesterol And Recurrent Events (CARE) study investigated the efficacy of lowering cholesterol with pravastatin in 4159 patients who had suffered a heart attack in the previous 2 years and showed a reduction in stroke or TIA risk by 32%.[148] Pravastatin was also approved by the FDA in 1998 for use in reducing risk of stroke or TIA in patients who have had a heart attack and have normal cholesterol levels (total cholesterol $<$240 mg/dL).

The benefits of statin agents in stroke prevention in patients with coronary heart disease have been supported by several meta-analyses.[146,149,150] Exactly how statins provide stroke protection is uncertain. Although some of the stroke reduction may be due to lipoprotein alterations, statins may also act through mechanisms unrelated to their lipid-lowering properties, such as improved endothelial function, plaque stabilization, and antithrombotic, anti-inflammatory, and neuroprotective properties.[151–155]

Lipoprotein(a) [Lp(a)], an apolipoprotein homologous with plasminogen,[156] is a known risk factor for the development of coronary heart disease.[157,158] A study performed in Japan found that Lp(a) was also an independent risk factor for ischemic stroke, especially in young adults.[159] However, a population-based prospective study in the United States found that Lp(a) was only a weak risk factor for cerebrovascular disease in men and was not a significant predictor of stroke risk in women.[158] One case-control study revealed no relationship between Lp(a) concentrations and either stroke, TIA, or carotid atheromata in men,[160] whereas a second found that serum Lp(a) levels were associated with stroke risk

independent of other factors.[161] There was no association between elevated Lp(a) levels and future stroke risk in a study in which patients with ischemic stroke were compared with matched controls.[162]

Recommendations

Management of patients with elevated cholesterol according to National Cholesterol Education Program II guidelines is recommended (Table 5).[34] Patients with known coronary heart disease and elevated LDL cholesterol levels should be considered for treatment with a statin. (Level of Evidence I, Grade A) Additional data are required to elucidate the role of Lp(a) as an independent risk factor for stroke.

Less Well-Documented or Potentially Modifiable Risk Factors

Less well-documented or potentially modifiable risk factors are given in Table 4.

Obesity

Obesity (defined as a body mass index [BMI] $\geq$30 kg/m^2) predisposes to cardiovascular disease in general and to stroke in particular. However, obesity prevalence increases with advancing age, and obesity is associated with increased blood pressure, blood sugar, and blood lipids. On the basis of these associations alone, it is not surprising that obesity would be related to an increased risk of stroke. However, several large studies suggest abdominal obesity, rather than BMI or general obesity, is more closely related to stroke risk. The age-adjusted relative risk of stroke was 2.33 in a comparison of the extreme quintiles of waist-hip ratios in American men participating in the Health Professionals Follow-Up Study.[163]

In women, obesity was associated with an increased risk of ischemic stroke with increasing levels of BMI. The relative risk ranged from 1.75 (95% CI 1.17 to 2.59) for BMI of 27 to 28.9 kg/m^2, 1.90 (95% CI 1.28 to 2.82) for BMI of 29 to 31.9 kg/m^2, and 2.37 (95% CI, 1.60 to 3.50) for BMI of $\geq$32 kg/m^2. Weight gain after the age of 18 years was also related to ischemic stroke, with increasing weight associated with increasing stroke risk.[164] Thus, recent evidence supports abdominal obesity in men and obesity and weight gain in women as independent risk factors for stroke.

Recommendation

Weight reduction in overweight persons is recommended on the basis of the associated increase in comorbid conditions that can lead to stroke. Reduction in stroke risk with weight loss has not been established on the basis of existing prospective randomized studies. (Level of Evidence IV, Grade C)

Physical Inactivity

Regular physical activity has well-established benefits for reducing the risk of premature death and cardiovascular disease. The beneficial effects of physical activity have also been documented for stroke.[165–173] The Framingham Heart Study, Honolulu Heart Program, and Oslo Study have shown the protective effect of physical activity for men.[166–168] For women, the Nurses' Health Study and Copenhagen City Heart Study demonstrated an inverse association between level of physical activity and stroke incidence.[169,170] The protective effects of leisure-time physical activity have also been found for blacks and Hispanics in the National Health and Nutrition Examination Survey (NHANES) I Follow-Up Study and the Northern Manhattan Stroke Study.[171,172]

Dose-response relationships have sometimes been difficult to demonstrate, with no to deleterious effects of vigorous physical activity compared with lower levels of physical activity.[167,173,174] In the Northern Manhattan Stroke Study, intensive forms of physical activity provided additional benefits compared with light-to-moderate activities. Additional protection was observed with increasing duration of exercise; however, the prevalence of such activities in the elderly was quite low.[172] The protective effect of physical activity may be mediated in part through its role in controlling various known risk factors for stroke, such as hypertension,[175] cardiovascular disease,[176] diabetes,[177] and body weight. Other biological mechanisms are also associated with physical activity, including reductions in plasma fibrinogen and platelet activity, as well as elevations in plasma tissue plasminogen activator activity and HDL concentrations.[178–181]

Currently available data support the benefits of physical activity. Guidelines endorsed by the Centers for Disease Control and Prevention and the National Institutes of Health recommend that Americans should exercise moderately for at least 30 minutes on most, and preferably all, days of the week.[182,183] For stroke, the benefits are apparent even for light-to-moderate activities, such as walking, and the data support additional benefit from increasing the level and duration of one's recreational activity. Physical activity is a modifiable behavior that requires greater emphasis in stroke prevention campaigns.

Recommendation

As per guidelines endorsed by the Centers for Disease Control and Prevention and the National Institutes of Health, regular exercise ($\geq$30 minutes of moderate-intensity activity daily) is part of a healthy lifestyle and helps to reduce comorbid conditions that may lead to stroke (Table 5).[183] (Level of Evidence III, Grade C)

Poor Diet/Nutrition

Data regarding the effects of general nutritional status on stroke risk are limited. There is no evidence that the use of dietary vitamin E or C supplements or the use of specific carotenoids substantially reduces the risk of stroke.[184] There may be a protective relationship between stroke and consumption of fruits and vegetables, especially cruciferous and green leafy vegetables and citrus fruit and juice.[185] An analysis of data from the Nurses' Health Study and the Health Professionals' Follow-Up Study that included individuals free of cardiovascular disease at baseline found that the relative risk of stroke was 0.69 (95% CI 0.52 to 0.92) for persons in the highest quintile of fruit and vegetable intake.[185] An increment of 1 serving per day was associated with a 6% lower risk of stroke. However, it cannot be certain whether the effect was specifically due to diet or a reflection of a generally more healthy lifestyle in these individuals.

Recommendation

A healthy diet containing at least 5 daily servings of fruits and vegetables may decrease the risk of stroke (Table 5). (Level of Evidence III, Grade C)

Alcohol Abuse

The effect of alcohol as a risk factor for ischemic stroke is controversial and likely dose dependent. For hemorrhagic stroke, cohort studies have shown that alcohol consumption has a direct dose-dependent effect.[186–188] For cerebral infarction, chronic heavy drinking and acute intoxication have been associated with an increased risk among young adults.[189] In older adults, risk is increased among heavy-drinking men. No effect is present among men and women after controlling for other confounding risk factors, and there is a protective effect for moderate alcohol consumption.[186,187,190–195]

Some studies have supported a J-shaped dose-response curve between alcohol intake and ischemic stroke risk, with protection for those drinking up to 2 drinks per day and an increased risk for those drinking >5 drinks per day compared with nondrinkers.[196–198] The dose-response relationship between alcohol and stroke is consistent with the observed deleterious and beneficial effects of alcohol. The deleterious effects of alcohol for stroke may occur through various mechanisms, including increasing hypertension, hypercoagulable states, and cardiac arrhythmias and reducing cerebral blood flow. However, there is also evidence that light-to-moderate alcohol intake can reduce the risk of coronary artery disease, increase HDL cholesterol, and increase endogenous tissue plasminogen activator. Although it is difficult to consider recommending alcohol to those who are nondrinkers, elimination of heavy drinking and reduction to moderate levels of alcohol intake (no more than 2 drinks per day) for those who are currently drinking will probably do no harm and may reduce the incidence of stroke.

Recommendation

No more than 2 drinks per day for men and 1 drink per day for nonpregnant women, as reflected in the US Preventive Services Task Force report (Table 5), is recommended.[64] (Level of Evidence IV, Grade C)

Hyperhomocysteinemia

Although the definition of hyperhomocyst(e)inemia has not been standardized across epidemiological studies, fasting plasma levels of homocyst(e)ine between 5 and 15 μmol/L are generally considered normal,[96,199,200] and levels ≥16 μmol/L are generally classified as indicating hyperhomocyst(e)inemia (although the risk is likely continuous).[199,201] In the Framingham Heart Study original cohort (aged 67 to 96 years), Selhub and colleagues[202] found 19% had homocysteine concentrations >16.4 μmol/L. Homocysteine concentrations increase with age, with men having higher levels than women, especially at younger ages.[203] From NHANES III, Selhub and colleagues[204] recently identified population references for total homocysteine concentrations. For men aged 40 to 59 years and those aged ≥60 years, the prevalence of high homocyst(e)ine (defined as >11.4 μmol/L) is 28.6% and 43.2%, respectively. For women aged 40 to 59 years and those aged ≥60 years, the prevalence of high homocyst(e)ine (defined as >10.4 μmol/L) is 21.1% and 46.5%, respectively.[204]

Numerous case-control studies have shown an association between hyperhomocyst(e)inemia and stroke. Based on a change of 5 μmol/L in homocysteine level, a meta-analysis found a summary OR for cerebrovascular disease of 1.5 (95% CI 1.3 to 1.9).[205] From the NHANES III data, the OR comparing the top quartile with the bottom 3 quartiles is ≈2.25 (95% CI 1.59 to 3.18).[206] In the Framingham Study, the relative risk for stroke, comparing the lowest quartile with the highest, was 1.82 (95% CI 1.14 to 2.91).[207] Although the association between plasma homocyst(e)ine and cerebrovascular risk is biologically plausible, it is more consistently present in case-control studies than in prospective studies, so further confirmatory evidence is required.[199,207–210]

The OR from NHANES III, when coupled with the prevalence estimates from Selhub et al,[202] gives a population attributable risk of 26% for men aged 40 to 59 years, 35% for men aged >60 years, 21% for women aged 40 to 59 years, and 37% for women aged >60 years. These population attributable risk estimates must be interpreted with caution, because no data are available that would permit the estimation of population attributable risk after adjustment for other cerebrovascular risk factors that are positively correlated with homocyst(e)ine levels.

Folic acid, together with vitamins B_6 and B_{12}, has been shown to be effective in reducing elevated plasma homocyst(e)ine levels,[211] but no randomized trials have as yet been completed to determine whether lowering elevated homocyst(e)ine levels will subsequently reduce stroke. Secondary prevention trials are in progress.[199,212]

Recommendations

An emphasis should be placed on meeting current recommended daily amounts of folate (400 μg/d), vitamin B_6 (1.7 mg/d), and vitamin B_{12} (2.4 μg/d) by intake of vegetables, fruits, legumes, meats, fish, and fortified grains and cereals (nonpregnant, nonlactating individuals).[201] Specific recommendations regarding treatment of patients without cerebrovascular or cardiovascular disease are deferred pending completion of ongoing clinical trials. In the interim, given their safety and low cost, use of folic acid and B vitamins may be considered for patients with known elevated homocysteine levels. (Level of Evidence IV, Grade C)

Drug Abuse

Illicit drug abuse, particularly involving the use of amphetamines, "crack" cocaine, and heroin, has emerged as a serious public health threat. Although the available data are derived primarily from limited epidemiological studies focusing on minority populations with low socioeconomic status, a consistent increase in the risk of both ischemic and hemorrhagic stroke has been demonstrated.[213–220] Adjusting for other potential stroke risk factors, some studies have found an ≈7-fold increase in stroke risk among drug abusers.[213,220] However, another study[217] found no significant association between illicit drug abuse and stroke. The pathogenesis of stroke in illicit drug abuse is likely multifactorial, possibly involving sudden surges in blood pressure, vasculitis, and

hemostatic and hematologic abnormalities that can result in increased blood viscosity and platelet aggregation.[221,222]

Recommendation
History of illicit drug abuse should be sought during routine medical evaluations and the patient referred for appropriate counseling (US Preventive Services Task Force report; Table 5).[64]

Hypercoagulability

Although the results of certain blood tests have been associated with hypercoagulable states characterized by venous thrombosis, many have not been clearly proven to be associated with cerebrovascular arterial thrombosis. The presence of antiphospholipid antibodies (aPL) has been shown in several case-control studies and one prospective study to be associated with ischemic stroke. The 2 most frequent tests used to detect aPL are anticardiolipin antibodies (more prevalent, but less specific) and lupus anticoagulants (less prevalent, but more specific).

Unfortunately, the definition of a significant positive result on testing for aPL has not been uniformly delineated. For example, the isotype of anticardiolipin antibody (IgG, IgM, or IgA) tested and the definition of a significantly elevated level varies among studies. As a result, it is difficult to give accurate prevalence data or risk of stroke associated with the presence of aPL. Although empirical treatments have been given for secondary stroke prevention in persons with aPL, evidence supporting the efficacy of this approach is limited.[223,224] The Antiphospholipid Antibodies and Stroke Study (APASS) and Warfarin-Aspirin Recurrent Stroke Study (WARSS) results may help to shed light on the best treatment for secondary stroke prevention. However, further studies may then be needed to investigate primary prevention in persons with aPL.

Many case reports and case-control studies have been published related to the association of other coagulation abnormalities and stroke (eg, factor V Leiden, prothrombin 20210 mutation, protein C deficiency, protein S deficiency, and antithrombin III deficiency; Table 3). However, many have been poorly adjusted for other stroke risk factors. More recent case-control and prospective studies of these abnormalities have cast doubt on their importance as independent risk factors for ischemic stroke. Therefore, hypercoagulable states are presently difficult to categorize as targets for primary stroke prevention.

Even if only a small increased risk of ischemic stroke exists with some of these hypercoagulable states, they may be important to consider in the overall risk profile of patients. Because some of the identified factors underlying hypercoagulable states are relatively common, these patients may also have other risk factors for stroke. These disorders may eventually be a target for more aggressive primary stroke prevention; however, further studies are needed to confirm whether these are indeed risk factors for stroke and whether populations who more frequently have these coagulation abnormalities should be targeted for testing and more aggressive primary prevention.

Recommendation
Specific recommendations regarding treatment of patients without cerebrovascular or cardiovascular disease or a history suggestive of a clinical coagulopathy are deferred pending further study.

Hormone Replacement Therapy

The impact of postmenopausal hormone replacement therapy on stroke risk appears to be neutral, but owing to a lack of control studies, definitive conclusions cannot be reached. Since 1980, there have been at least 18 studies published on this subject.[225] With the exception of the Framingham Heart Study, none detected a large increase in stroke risk, and several reported a slight (but often nonsignificant) decrease in risk. The Framingham Heart Study found a 2.60-fold increase in the relative risk of atherothrombotic stroke among women receiving hormone replacement therapy compared with nonusers.[226] In other studies, the relative risk of stroke among hormone replacement therapy users varied from 0.23 to 1.46, with the relative risk of fatal stroke ranging from 0.30 to 1.40.[170,192,227–239] A review indicated a neutral effect of postmenopausal hormone replacement therapy, with a relative risk of 0.96.[240] However, the studies conducted to date have had methodological limitations.[225] These limitations include nonspecific end points, lack of control for prior hormone replacement use or specific regimens, a lack of sufficient numbers of women from minority race-ethnic groups, and possible confounding by a healthy-user effect.[225] The benefits and risks in terms of stroke must also be balanced against other potential effects of hormone replacement, including osteoporosis and breast cancer. Further studies are required to clarify this important issue.

Recommendation
The risk of stroke associated with hormone replacement therapy appears low but requires further study. Until more data are available, the use of hormone replacement therapy should be guided by factors other than stroke risk.

Oral Contraceptive Use

Much of the perceived increased stroke risk associated with the use of oral contraceptives is based on early studies with high-dose preparations[225] (ie, first-generation oral contraceptives containing $\geq$50 μg of estradiol[241–243]). The majority of studies of second-generation oral contraceptives containing lower doses of estrogens did not find an increased risk of stroke.[242–246] However, one study did report an increased risk of stroke in women using first-, second-, or third-generation oral contraceptives.[247] The reasons for this discrepancy are not certain. In addition, women who are cigarette smokers, are hypertensive, or have diabetes, migraine, or prior thromboembolic events may be at increased stroke risk if they use oral contraceptives.[248,249]

A meta-analysis concluded that the risk of ischemic stroke is increased in oral contraceptive users but that the absolute increase in risk would be small because of the low stroke incidence in this population.[250] The increase in risk was present even with the newer low-dose estrogen preparations. Methodological limitations limited definitive conclusions regarding the impact of additional risk factors such as

hypertension and cigarette smoking in oral contraceptive users.

Recommendation

The risk of stroke associated with use of low-dose oral contraceptives in women without additional risk factors appears low. Oral contraceptives should be avoided in women with additional risk factors (eg, cigarette smoking or prior thromboembolic events).

Inflammatory Processes

Atherosclerosis, the most common cause of stroke, is now believed to be a disease of chronic inflammation. Its lesions typically occur at branch points and bifurcations in large and medium-sized elastic and muscular arteries. The extracranial internal carotid artery and the vertebral artery (at its origin and just distal to the posterior inferior cerebellar artery) are the cerebral vessels most commonly affected.

Endothelial cells of normal postcapillary venules express P-selectin, intercellular adhesion molecule-1 (ICAM-1), and E-selectin when exposed to cytokines, peroxides, and other stimuli associated with hypoxic injury. Their appearance mediates leukocyte adhesion and trafficking. The adhesion receptors ICAM-1 and VCAM-1 (vascular cell adhesion molecule-1) are also expressed by endothelium at sites predisposed to atherosclerosis[251] and continue to be expressed during the development of the atheroma. Shear stress and turbulence may contribute to adhesion receptor expression and may explain the localization of atherosclerotic plaques at vessel bifurcations.[252–254]

Monocytes and T cells bind to the expressed adhesion molecules, become activated, and secrete products such as cytokines and proteolytic enzymes that contribute to vessel damage. Markers of inflammation, such as leukocyte adhesion receptors[255] and cytokines,[256] as well as activated T cells and macrophages,[257] are present in carotid endarterectomy specimens of recently symptomatic patients, which suggests that acute inflammatory responses may predispose to plaque destabilization and symptoms. Elevated levels of soluble leukocyte adhesion receptors have been associated with carotid artery atherosclerosis.[258–260]

Chronic infection may underlie atherosclerosis. *Chlamydia pneumoniae*, a Gram-negative obligate intracellular bacterium, has been identified in atherosclerotic carotid plaques[261–265] and localizes to regions of altered plaque morphology.[263,264] The fact that seropositivity to Chlamydia does not seem to correlate to carotid atherosclerosis, as measured by duplex ultrasonography,[265,266] supports the notion that Chlamydia may participate in plaque progression and destabilization as opposed to initiation of atherosclerosis, which may be why there appears to be a relationship between serum antibody titers to *C pneumoniae* and stroke.[267–270] The benefit of eradicating *C pneumoniae* from carotid plaques with antibiotic therapy remains unclear.[271] Data linking infection with other pathogens, such as cytomegalovirus and herpes simplex virus, with atherosclerosis are not as robust as those for *C pneumoniae*.[267,272]

Several observational studies suggest that acute infection may be associated with ischemic stroke. C-reactive protein (CRP) and serum amyloid A, acute-phase reactants produced by the liver, are markers of systemic inflammation. CRP levels are increased in smokers[273,274] and in apparently healthy men with vascular risk factors.[274] There is a significant and positive association between plasma CRP levels and the risk of vascular events, including stroke.[273,275,276]

Data from prospective randomized clinical trials suggest that the efficacy of common preventive agents such as aspirin and HMG-CoA reductase inhibitors may be related, at least in part, to their anti-inflammatory effects. In the Physicians' Health Study, aspirin significantly reduced the risk of vascular events only among men in the highest quartile of CRP levels,[273] although the direct effect of aspirin on CRP is unclear.[277,278] Pravastatin use, which was shown to decrease the risk of vascular events and stroke in the CARE trial, led to a significant decrease in CRP levels over the 5-year follow-up, whereas CRP levels increased in patients who received placebo. This effect of pravastatin appears to be independent of its effect on lowering LDL cholesterol.[154] Whether CRP contributes to vascular disease or is merely a marker of vascular risk is unclear, but an inflammatory environment seems to predispose to the risk of stroke in experimental model studies.[279]

Recommendation

The currently available data do not provide sufficient evidence to support a specific management recommendation.

Management Strategies

Table 5 summarizes strategies for risk factor management based on published guidelines and/or consensus statements. Details of the various recommendations can be found in the original references. Risk factors for which specific guidelines have not been previously adopted have not been included in the Table.[280-330]

Future Research

As can be readily appreciated by inspection of the tables and in the accompanying text, significant gaps exist in current knowledge of the impact of specific factors on stroke risk. Moreover, the possible impact of treatment of many of the potentially modifiable factors on subsequent stroke risk is uncertain. Whether the focus of management of specific risk factors should be modified in different race-ethnic groups requires further study. Additional study is also necessary to develop a fuller understanding of differences in risks between men and women. Despite recent advances in acute stroke management and promising new approaches to improving poststroke recovery, prevention remains the cornerstone of therapy for these devastating diseases.

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