

Guidelines for the Primary Prevention of Stroke A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.

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Vascular Disease, and Interdisciplinary Council on Quality of Care and Outcomes Research

Background and Purpose—This guideline provides an overview of the evidence on established and emerging risk factors for stroke to provide evidence-based recommendations for the reduction of risk of a first stroke.

Methods—Writing group members were nominated by the committee chair on the basis of their previous work in relevant topic areas and were approved by the American Heart Association (AHA) Stroke Council Scientific Statement Oversight Committee and the AHA Manuscript Oversight Committee. The writing group used systematic literature reviews (covering the time since the last review was published in 2006 up to April 2009), reference to previously published guidelines, personal files, and expert opinion to summarize existing evidence, indicate gaps in current knowledge, and when appropriate, formulate recommendations using standard AHA criteria (Tables 1 and 2). All members of the writing group had the opportunity to comment on the recommendations and approved the final version of this document. The guideline underwent extensive peer review by the Stroke Council leadership and the AHA scientific statements oversight committees before consideration and approval by the AHA Science Advisory and Coordinating Committee.

Results—Schemes for assessing a person's risk of a first stroke were evaluated. 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 or less well documented). Nonmodifiable risk factors include age, sex, low birth weight, race/ethnicity, and genetic predisposition. Well-documented and modifiable risk factors include hypertension, exposure to cigarette smoke, diabetes, atrial fibrillation and certain other cardiac conditions, dyslipidemia, carotid artery stenosis, sickle cell disease, postmenopausal hormone therapy, poor diet, physical inactivity, and obesity and body fat

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distribution. Less well-documented or potentially modifiable risk factors include the metabolic syndrome, excessive alcohol consumption, drug abuse, use of oral contraceptives, sleep-disordered breathing, migraine, hyperhomocysteinemia, elevated lipoprotein(a), hypercoagulability, inflammation, and infection. Data on the use of aspirin for primary stroke prevention are reviewed.

Conclusion—Extensive evidence identifies a variety of specific factors that increase the risk of a first stroke and that provide strategies for reducing that risk. (*Stroke*. 2011;42:517-584.)

Key Words: AHA Scientific Statements ■ stroke ■ risk factors ■ primary prevention

Stroke remains a major healthcare problem. Its human and economic toll is staggering. Approximately 795 000 people in the United States have a stroke each year, of which about 610 000 are a first attack; and 6.4 million Americans are stroke survivors.¹ Stroke is also estimated to result in 134 000 deaths annually and is the third leading cause of death in the nation behind heart disease and cancer.¹ Progress has been made in reducing deaths from stroke. Along with other healthcare organizations, the American Heart Association (AHA) set the goal of decreasing cardiovascular and stroke mortality by 25% over 10 years.¹ Between 1996 and 2006 the death rate for stroke fell by 33.5%, with the total number of stroke deaths declining by 18.4%.¹ The goal of a 25% reduction was exceeded in 2008. The declines in stroke death rates, however, were greater in men than in women (age-adjusted male-to-female ratio decreasing from 1.11 to 1.03).¹ Despite overall declines in stroke deaths, stroke incidence may be increasing.² From 1988 to 1997 the age-adjusted stroke hospitalization rate grew 18.6% (from 560 to 664 per 10 000), while the total number of stroke hospitalizations increased 38.6% (from 592 811 to 821 760 annually).³ In 2010, the cost of stroke is estimated at \$73.7 billion (direct and indirect costs),¹ with a mean lifetime cost estimated at \$140 048.¹

Stroke is also a leading cause of functional impairments, with 20% of survivors requiring institutional care after 3 months and 15% to 30% being permanently disabled.¹ Stroke is a life-changing event that affects not only stroke patients themselves but their family members and caregivers as well. Utility analyses show that a major stroke is viewed by more than half of those at risk as being worse than death.⁴ Despite the advent of treatment of selected patients with acute ischemic stroke with intravenous tissue-type plasminogen activator and the promise of other acute therapies, effective prevention remains the best approach for reducing the burden of stroke.⁵⁻⁷ Primary prevention is particularly important because >77% of strokes are first events.¹ The age-specific incidence of major stroke in Oxfordshire, United Kingdom, fell by 40% over a 20-year period with increased use of preventive treatments and general reductions in risk factors.⁹ Those who practice a healthy lifestyle have an 80% lower risk of a first stroke compared with those who do not.⁸ As discussed in detail in the sections that follow, persons at high risk for or prone to stroke can now be identified and targeted for specific interventions.

This guideline provides an overview of the evidence on various established and emerging stroke risk factors and represents a complete revision of the 2006 statement on this topic.⁹ One important change is the broader scope of this new guideline.

Whereas the 2006 statement focused on ischemic stroke, because of the overlap of risk factors and prevention strategies, this guideline also addresses hemorrhagic stroke, primarily focusing on an individual patient-oriented approach to stroke prevention. This contrasts with a population-based approach in which "...the entire distribution of risk factors in the population is shifted to lower levels through population-wide interventions" and is reflected in the AHA statement on improving cardiovascular health at the community level.¹⁰

Writing group members were nominated by the committee chair on the basis of their previous work in relevant topic areas and were approved by the AHA Stroke Council Scientific Statement Oversight Committee and the AHA Manuscript Oversight Committee. The writing group used systematic literature reviews covering the time since the last statement was published in 2006 up to April 2009, reference to previously published guidelines, personal files, and expert opinion to summarize existing evidence, indicate gaps in current knowledge, and when appropriate, formulate recommendations using standard AHA criteria. All members of the writing group had the opportunity to comment on the recommendations and approved the final version of the document. The guideline underwent extensive peer review by the AHA Stroke Council leadership and the AHA Manuscript Oversight Committee before consideration and approval by the AHA Science Advisory and Coordinating Committee (Tables 1 and 2). Because of the diverse nature of the topics, it was not possible to provide a systematic, uniform summary of the magnitude of the effect associated with each recommendation. As with all therapeutic recommendations, patient preferences must be considered. As seen in Tables 3 through 5, risk factors (directly increase disease probability or, if absent or removed, reduce disease probability) or risk markers (attribute or exposure associated with increased probability of disease, but relationship is not necessarily causal)¹¹ of a first stroke were classified according to their potential for modification (nonmodifiable, modifiable, or potentially modifiable) and strength of evidence (well documented, less well documented).⁷ Although this classification system is somewhat subjective, for well-documented and modifiable risk factors (Table 4) there was clear, supportive epidemiological evidence in addition to evidence of risk reduction with modification as documented by randomized trials. For less well-documented or potentially modifiable risk factors (Table 5), the epidemiological evidence was less clear or evidence was lacking from randomized trials that demonstrated reduction of stroke risk with modification. The tables give the estimated

Table 1. Applying Classification of Recommendations and Level of Evidence

		SIZE OF TREATMENT EFFECT ➔			
		CLASS I <i>Benefit >>> Risk</i> Procedure/Treatment SHOULD be performed/administered	CLASS IIa <i>Benefit >> Risk</i> <i>Additional studies with focused objectives needed</i> IT IS REASONABLE to perform procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> <i>Additional studies with broad objectives needed; additional registry data would be helpful</i> Procedure/Treatment MAY BE CONSIDERED	CLASS III <i>Risk ≥ Benefit</i> Procedure/Treatment should NOT be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL
ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none"> ■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> ■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> ■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> ■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
	LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	<ul style="list-style-type: none"> ■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> ■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> ■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> ■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
	LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	<ul style="list-style-type: none"> ■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> ■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> ■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> ■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations†		should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	is not recommended is not indicated should not is not useful/effective/beneficial may be harmful

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as gender, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

†For recommendations (Class I and IIa; Level of Evidence A and B only) regarding the comparative effectiveness of one treatment with respect to another, these words or phrases may be accompanied by the additional terms “in preference to” or “to choose” to indicate the favored intervention. For example, “Treatment A is recommended in preference to Treatment B for. . .” or “It is reasonable to choose Treatment A over Treatment B for. . .” Studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

prevalence, population-attributable risk (ie, the proportion of ischemic stroke in the population that can be attributed to a particular risk factor, given by the formula $100 \times ([\text{Prevalence} \times (\text{Relative Risk} - 1)] / [\text{Prevalence} \times (\text{Relative Risk} - 1) + 1])$,¹² relative risk, and risk reduction with treatment for each factor when known. Gaps in current knowledge are indicated by question marks. When referring to these data, it should be noted that comparisons of relative risks and population-attributable risks between different studies should be made with caution because of differences in study designs and patient populations. Precise estimates of attributable risk for factors such as hormone replacement therapy are not available because of variations in estimates of risk and changes in prevalence.

Other tables summarize endorsed guideline or consensus statements on management recommendations as available. Recommendations are indicated in the text and tables.

Generally Nonmodifiable Risk Factors

These factors are generally not modifiable but identify persons who are at increased risk of stroke and who may benefit from rigorous prevention or treatment of other modifiable risk factors (Table 3). In addition, although genetic predisposition itself is not modifiable, treatments for specific genetic conditions are available.

Age

Stroke is thought of as a disease of the elderly, but incidence rates for pediatric strokes have increased in recent years.^{13,14} Although younger age groups (25 to 44 years) are at lower stroke risk,¹⁵ the public health burden is high in these populations because of a relatively greater loss of productivity and wage-earning years. The cumulative effects of aging on the cardiovascular system and the progressive nature of stroke risk factors over a prolonged period substantially

Table 2. Definition of Classes and Levels of Evidence Used in AHA Stroke Council Recommendations

Class I	Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective.
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
Class IIa	The weight of evidence or opinion is in favor of the procedure or treatment.
Class IIb	Usefulness/efficacy is less well established by evidence or opinion.
Class III	Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful.
<i>Therapeutic recommendations</i>	
Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of Evidence B	Data derived from a single randomized trial or nonrandomized studies
Level of Evidence C	Consensus opinion of experts, case studies, or standard of care
<i>Diagnostic recommendations</i>	
Level of Evidence A	Data derived from multiple prospective cohort studies using a reference standard applied by a masked evaluator
Level of Evidence B	Data derived from a single grade A study, or ≥ 1 case-control studies, or studies using a reference standard applied by an unmasked evaluator
Level of Evidence C	Consensus opinion of experts

increase the risks of both ischemic stroke and intracerebral hemorrhage (ICH). The risk of ischemic stroke and ICH doubles for each successive decade after age 55.^{2,16–20}

Sex

Stroke is more prevalent in men than in women.^{2,21} Men also generally have higher age-specific stroke incidence rates than women have (based on age-specific rates calculated from strata defined by race/ethnicity), and this is true for ischemic as well as hemorrhagic stroke.^{2,16–20,22,23} The exceptions are those 35 to 44 years of age and those >85 years of age.^{23,24}

Factors such as use of oral contraceptives (OCs) and pregnancy contribute to the increased risk of stroke in young women.^{25–27} The earlier cardiac-related deaths (ie, competing causes of death) of men with cardiovascular disease (CVD) may contribute to the relatively greater risk of stroke in older women. Women accounted for 60.6% of US stroke deaths in 2005.²⁸ Overall, 1 in 6 women die of stroke, compared with 1 in 25 who die of breast cancer.²⁹ In 2005 age-adjusted stroke mortality rates were 44.0 per 100 000 among white women and 60.7 per 100 000 among black women, versus rates of 44.7 and 70.5 per 100 000 among white and black men, respectively.²⁸

Low Birth Weight

Stroke mortality rates among adults in England and Wales are higher among people with lower birth weights.³⁰ The mothers of these low-birth-weight babies were typically poor, were malnourished, had poor overall health, and were generally socially disadvantaged.³⁰ A similar study compared a group of South Carolina Medicaid beneficiaries <50 years of age who had stroke with population controls.³¹ The odds of stroke were more than double for those with birth weights of <2500 g compared with those weighing 4000 g (with a significant linear trend for intermediate birth weights). Regional differences in birth weight may partially underlie geographic differences in stroke-related mortality, which is also associated with birthplace.³² The potential reasons for these relationships remain uncertain, and statistical association alone does not prove causality.

Race/Ethnicity

Race/ethnic effects on disease risk can be difficult to consider separately. Blacks^{23,24,33} and some Hispanic/Latino Americans^{23,34–36} have a higher incidence of all stroke types and higher mortality rates compared with whites. This is particularly true for young and middle-aged blacks, who have a substantially higher risk of subarachnoid hemorrhage (SAH) and ICH than whites of the same age.^{24,33} In the Atherosclerosis Risk In Communities (ARIC) Study, blacks had an incidence of all stroke types that was 38% higher [95% confidence interval (CI), 1.01 to 1.89] than that of whites.²² Possible reasons for the higher incidence and mortality rate of stroke in blacks are a higher prevalence of hypertension, obesity, and diabetes.^{37–40} Higher prevalence of these risk factors, however, does not explain all of the excess risk.³⁷ Data from the Strong Heart Study (SHS) show that American Indians had a higher incidence of stroke compared with African-American and white cohorts.⁴¹

Genetic Factors

A meta-analysis of cohort studies showed that a positive family history of stroke increases risk of stroke by approximately 30% [odds ratio (OR), 1.3; 95% CI, 1.2 to 1.5, $P < 0.00001$].⁴² The odds of both monozygotic twins having strokes are 1.65-fold higher than those for dizygotic twins.⁴² Cardioembolic stroke appears to be the least heritable type of stroke compared with other ischemic stroke subtypes.⁴³ Women with stroke are more likely than men to have a parental history of stroke.⁴⁴ The increased risk of stroke imparted by a positive family history could be mediated through a variety of mechanisms, including (1) genetic heritability of stroke risk factors, (2) inheritance of susceptibility to the effects of such risk factors, (3) familial sharing of cultural/environmental and lifestyle factors, and (4) interaction between genetic and environmental factors.

Genetic influences on stroke risk can be considered on the basis of individual risk factors, genetics of common stroke types, and uncommon or rare familial stroke types. Many of the established and emerging risk factors described in the sections that follow, such as hypertension, diabetes, and hyperlipidemia, have both genetic and environmental/behavioral components.^{45–47} Elevations of blood homocysteine occur with 1

Table 3. Generally Nonmodifiable Risk Factors and Risk Assessment

Factor	Incidence/Prevalence	Relative Risk
Age, y ²¹	Prevalence of first stroke (percent per 100 000)	...
18–44	0.5	
45–64	2.4	
65–74	7.6	
75+	11.2	
	Incidence of first stroke (per 1000) ^{1†}	
	White men White women Black Men Black women	
45–54	1.4 1.0 3.5* 2.9	
55–64	2.9 1.6 4.9 4.6	
65–74	7.7 4.2 10.4 9.8	
75–84	13.5 11.3 23.3* 13.5	
85+	32.1 16.5 24.7* 21.8	
Sex (age adjusted) ²¹	Prevalence (percent per 100 000)	...
	Men: 2.9	
	Women: 2.3	
	Total: 2.6	
Low birth weight ^{30,31}	...	≈2 for birth weight <2500 g vs >4000 g
Race/ethnicity (age adjusted) ²¹	Prevalence (percent per 100 000)	...
	Asian: 1.8	
	Blacks: 4.6	
	Hispanics: 1.9	
	Whites: 2.4	
Family history of stroke/TIA ⁷²⁵	...	RR, paternal history: 2.4 (95% CI, 0.96–6.03) RR, maternal history 1.4 (95% CI, 0.60–3.25)

CI indicates confidence interval; RR, relative risk; and TIA, transient ischemic attack.

*Incidence rates for black men and women 45 to 54 y of age and black men >75 y of age are considered unreliable.

†Unpublished data from the Greater Cincinnati/Northern Kentucky Stroke Study.

or more copies of the C677T allele of the methylenetetrahydrofolate reductase gene.⁴⁸ Many coagulopathies are inherited as autosomal dominant traits.⁴⁹ These disorders, including protein C and S deficiencies, factor V Leiden mutations, and various other factor deficiencies, can lead to an increased risk of venous thrombosis.^{50–53} As discussed below, there has not been a strong association between several of these disorders and arterial events, such as myocardial infarction (MI) and stroke.^{54,55} Some apparently acquired coagulopathies, such as the presence of a lupus anticoagulant or anticardiolipin antibody, can be familial in approximately 10% of cases.^{56,57} Inherited disorders of various clotting factors (ie, factors V, VII, X, XI, and XIII) are autosomal recessive traits and can lead to cerebral hemorrhage in childhood or the neonatal period.⁵⁰ Arterial dissections, moyamoya disease, and fibromuscular dysplasia have a familial component in 10% to 20% of cases.^{58,59}

Common variants on chromosome 9p21 adjacent to the tumor suppressor genes *CDKN2A* and *CDKN2B*, which were initially found to be associated with MI,^{60–62} have been found to be associated with ischemic stroke as well.⁶³ Common variants on 4q25 adjacent to the *PITX2* gene involved in cardiac development were first shown to be

associated with atrial fibrillation.⁶⁴ This locus was subsequently associated with ischemic stroke, particularly cardioembolic stroke.⁶⁵ Although commercially available tests exist for the 9p21 and 4q25 risk loci, studies have yet to show that knowledge of genotypes at these loci leads to an improvement in risk prediction or measurable and cost-effective improvements in patient care.

Several rare genetic disorders have been associated with stroke. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is characterized by subcortical infarcts, dementia, and migraine headaches.⁶⁶ CADASIL can be caused by any of a series of mutations in the Notch3 gene.^{66,67} Marfan syndrome (caused by mutations in the fibrillin gene) and neurofibromatosis types I and II are associated with an increased risk of ischemic stroke. Gene transfer therapy has been attempted to correct the genetic defect in Marfan syndrome.⁶⁸

Fabry disease is a rare inherited disorder that can also lead to ischemic stroke. It is caused by lysosomal α -galactosidase A deficiency, which causes a progressive accumulation of globotriaosylceramide and related glycosphingolipids.⁶⁹ Deposition affects mostly small vessels in the brain and other

Table 4. Well-Documented and Modifiable Risk Factors

Factor	Prevalence, %		Population-Attributable Risk, %¶		Relative Risk	Risk Reduction With Treatment
Cigarette smoking						
Overall	19.8 ⁷²⁶		12–14* ^{124,125}		1.9 (ischemic stroke) 2.9 (SAH)	50% within 1 y; baseline after 5 y
Men	22.3					
Women	17.4					
Hypertension						
Age, y	Men	Women	Men	Women†		
20–34	13.4	6.2	99	98	8 ⁷²⁸	32% ¹⁰⁰
35–44	23.2	16.5	99	106		
45–54	36.2	35.9	100	103		
55–64	53.7	55.8	100	102		
65–74	64.7	69.6	100	101		
75+	64.1	76.4	100	101		
Diabetes	7.3		5–27		1.8–6.0	Reduction of stroke risk in hypertensive diabetics with BP control. No demonstrated benefit in stroke reduction with tight glycemic control; however, reduction in other complications (see text). Reduction of stroke with statins (see text).
High total cholesterol	Data calculated for highest quintile (20%) vs lowest quintile		9.1 (5.7–13.8)		1.5 (95% CI 1.3–1.8)	0.81 (95% CI, 0.75–0.87)
	Continuous risk for ischemic stroke		...		1.25/1 mmol/L (38.7 mg/dL) increase	
Low HDL cholesterol:						
<40 mg/dL						
Men	35					
Women	15					
	Data calculated for highest quintile (20%) vs lowest quintile		23.7		0.4	
<35 mg/dL						
	26 (NOMASS)		20.6 (10.1–30.7)		2.00 (95% CI, 1.43–2.70)	
	Continuous risk for ischemic stroke				≈0.5–0.6 for each 1 mmol/L increase	
Atrial fibrillation (nonvalvular)^{235,236,252}						
						Adjusted-dose warfarin vs control: 64% (CI, 49%–74%); 6 trials, 2900 patients Aspirin vs placebo: 19% (CI, –1% to 35%); 7 trials, 3990 patients Adjusted-dose warfarin vs aspirin: 39% (CI, 19% to 53%); 9 trials, 4620 patients
Overall age, y						
50–59	0.5		1.5		4.0	
60–69	1.8		2.8		2.6	
70–79	4.8		9.9		3.3	
80–89	8.8		23.5		4.5	

(Continued)

Table 4. Continued

Factor	Prevalence, %	Population-Attributable Risk, %¶	Relative Risk	Risk Reduction With Treatment
Asymptomatic carotid stenosis	2–8	2–7‡	2.0	≈50% reduction with endarterectomy (see text). Aggressive management of other identifiable vascular risk factors (see text).
SCD	0.25 (of blacks)	...	200–400§	91% with transfusion therapy (see text).
Postmenopausal hormone therapy	25 (women 50–74 y) ^{372,729,730}	9	1.4 ³⁷⁷	Treatment increases risk.
OC use	13 (women 25–44 y) ⁷³¹	9.4	2.3 ^{25,389,390}	None; may increase risk.
Dietary-nutrition				Observational studies show 8% reduction in stroke mortality from a 3 mm Hg reduction in SBP. Extent of SBP reduction from reduced Na and increased K can exceed 3 mm Hg depending on baseline intake levels and other factors.
Na intake >2300 mg	75–90	??	??	
K intake <4700 mg	90–99	??	??	
Physical inactivity ¹	25	30	2.7	N/A
Obesity			1.39 stroke death per increase of 5 kg/m ² ⁴⁴²	N/A
Men	33.3			
Women	35.3 ⁷³³			
Other CVD, CHD#				Overlap with risk factors for first stroke; see text.
Men	8.4	5.8	1.73 (1.68–1.78) 1.55 (1.17–2.07)	
Women	5.6	3.9¶¶		
Other CVD, heart failure				
Men	2.6	1.4	1.1¶¶¶	
Women	2.1	1.1¶¶¶		
Other CVD, PAD	4.9	3.0¶¶¶		

CHD indicates coronary heart disease; N/A, not applicable; NOMASS, Northern Manhattan Stroke Study; PAD, peripheral artery disease; and PAR, population-attributable risk.

*PAR is for stroke deaths, not ischemic stroke incidence.^{120,124,125}

†PAR = 100⁷²⁷ ((prevalence (RR-1)) / (prevalence (RR-1) + 1)).

‡Calculated based on referenced data provided in table or text.

§Relative to stroke risk in children without SCD.

||For high-risk patients treated with transfusion.

#CVD includes CHD, cardiac failure, and PAD. PFO is discussed in text.

¶PAR is proportion of ischemic stroke in population that can be attributed to a particular risk factor (see text for formula).

¶¶¶Calculated based on point estimates of referenced data provided in table; PAD calculation based on average relative risk for men and women.

organs, although involvement of the larger vessels has been reported. Two prospective randomized studies using human recombinant lysosomal α-galactosidase A found a reduction in microvascular deposits as well as reduced plasma levels of globotriaosylceramide.^{70–72} These studies had short follow-up periods, and no effects on stroke incidence were found. Enzyme replacement therapy also appears to improve cerebral vessel function.⁷³ Agalsidase alpha and agalsidase beta given at the same dose of 0.2 mg/kg have similar short-term effects in reducing left ventricular mass.⁷⁴ With the exception of sickle cell

disease (discussed later), no treatment based specifically on genetic factors has yet been shown to reduce incident stroke.

Intracranial aneurysms tend to be more common within families.^{75–78} One study using historical controls found that persons with a familial history of unruptured intracranial aneurysms had a 17-fold higher risk of rupture than persons with sporadic aneurysms of comparable size and location.⁷⁹ One study calls into question anticipation.⁸⁰

Intracranial aneurysms are a feature of certain Mendelian disorders, including autosomal dominant polycystic kidney

Table 5. Less Well-Documented or Potentially Modifiable Risk Factors

Factor	Prevalence, %	Population-Attributable Risk, %	Relative Risk or Odds Ratios	Risk Reduction With Treatment
Migraine with aura	5.2 ⁴⁵¹	3.5	1.7 ⁴⁵¹	Unknown
Metabolic syndrome	23.7 ⁴⁸⁸
Alcohol consumption ≥5 drinks per day		6.9	1.6	Unknown
Drug abuse	8	7.4–24	2.03–4.95	Unknown
SDB		Unknown	HR, 1.97; 95% CI, 1.12–3.48; <i>P</i> =0.01 (adjusted for age, sex, race, smoking status, alcohol consumption status, BMI, and presence or absence of diabetes mellitus, hyperlipidemia, atrial fibrillation, and hypertension) ⁵⁴¹ HR in the elderly, 2.52 (95% CI, 1.04–6.01; <i>P</i> =0.04) ⁵⁴² 3.08; 95% CI, 0.74–12.81; <i>P</i> =0.12 ⁵⁴³ 1.2%/y	Unknown
Men	4			
Women	2			
Hyperhomocysteinemia	Data calculated for highest quartile (25%; >14.24 μmol/L) vs lowest quartile	17.0 (3.4–32.3)	1.82 (1.14–2.91)	Not established with B-vitamin therapy
	Continuous risk for ischemic stroke		1.59 (95% CI, 1.29–1.96) per 5 μmol/L increase	
High Lp(a)	Data calculated for highest (33%) vs lowest tertile	6.8 (95% CI, 1.3–12.4)	1.22 (95% CI, 1.04–1.43)	Unknown
Hypercoagulability				
aCL antibody				
Men	9.7	6	1.3 (0.7–2.3)*	0.99 (0.69–1.41)† Warfarin
Women	17.6	14	1.9 (1.1–3.5)*	
Women 15–44 y	26.9	11	1.9 (1.24–2.83)†	
LA				
Women 15–44 y	2.8	9	1.80 (1.06–3.06)	0.78 (0.50–1.21)† 1.47 (0.91–2.36)† (aCL/LA)
aPL ⁶¹⁷		HR, 1.04 (0.69–1.56) for aspirin (81 mg/d) vs placebo in asymptomatic subjects
Factor V Leiden	7.7	0	0.92 (0.56–1.53)	Unknown
Prothrombin 20210 mutation	3.7 ⁶³¹	3	1.9 (0.5–6.2)	Unknown
Protein C deficiency	2.0	0	0.7 (0.2–3.1)	Unknown
Protein S deficiency	1.0	0	0.9 (0.1–6.7)	Unknown
Antithrombin III deficiency	4.1	1	1.3 (0.5–3.3)	Unknown
Inflammatory processes				
Periodontal disease		16	2.11 (1.30–3.42)	Effects of medical therapy on periodontal disease remain to be studied.
Age				
25–74 y	16.8			
60–64 y	15			
≥65 y	45			

(Continued)

Table 5. Continued

Factor	Prevalence, %	Population-Attributable Risk, %	Relative Risk or Odds Ratios	Risk Reduction With Treatment
<i>Chlamydia pneumoniae</i>		72–78 85–88	IgA 1:16 4.51 (1.44–14.06) IgG 1:512 and/or IgA 1:64; 8:58 (1.1–68.8) Adult men ⁷³⁵	Trials of antibiotics for general cardiovascular event reduction negative; insufficient power for stroke end points.
Age				
65 y	75–100 IgA			
<5 y	0–5			
5–20 y	50			
Cytomegalovirus				
Adults	69	82		See text.
Men	62.5		OR, 1.04; 95% CI, 0.68–1.58	
Women	72.8		OR, 7.6; 95% CI, 3.21–17.96	
<i>Helicobacter pylori</i> CagA seropositivity				
Adults with vascular disease: IgG Ab >40 AU	65.7		Atherothrombotic stroke: OR, 1.97; CI, 1.33–2.91 Carotid plaque irregularities OR, 8.42; CI, 1.58–44.84 IR, 3.19; CI, 2.81–3.62	
Acute infection: Systemic respiratory infection			Days 1–3 IR, 1.27; CI, 1.15–1.41 Days 29–91 IR, 1.65 (CI, 1.19–2.28)	
Acute infection: Urinary tract infection			Days 1–3 IR, 1.16 (CI, 1.04–1.28) Days 19–91	
CD 40 ligand (CD 54)	6% Females free of CVD >3.71 ng/mL	12	3.3 (CI, 1.2–8.6), stroke, MI, acute coronary syndrome deaths	
IL-18 Upper tertile (>235 pg/mL)			Adjusted RR for coronary events, 1.82; (CI, 1.30–2.55)	
Elevated hs-CRP CRP >3 mg/L	28.1 (women ≥45 y)		RR, 3.0; <i>P</i> <0.001, women ≥45 y for cardiovascular and cerebrovascular events combined (highest vs lowest quartile) RR, 2.0 (CI, 1.10–3.79), men age adjusted for first ischemic stroke and TIA (highest vs lowest quartile) RR, 2.7 (CI, 1.59–4.79), women age adjusted for first ischemic stroke and TIA (highest vs lowest quartile)	

aCL indicates anticardiolipin antibody; aPL, antiphospholipid antibody; BP, blood pressure; CR, C-reactive protein; hs-CRP, high-sensitivity C-reactive protein; IgA, immunoglobulin A; IgG, immunoglobulin G; IL, interleukin; IR, incidence rate/ratio; LA, lupus anticoagulant; Lp(a), lipoprotein(a); and SDB, sleep-disordered breathing.

*Adjusted for age, prior CVD, SBP, diabetes, smoking, plasma CRP, and serum total and high-density lipoprotein cholesterol.

†Adjusted for age, smoking, hypertension, diabetes, angina, race/ethnicity, BMI, and high-density lipoprotein cholesterol.

disease (ADPKD) and Ehlers-Danlos type IV (EDS-IV) syndrome (so-called vascular Ehlers-Danlos). Intracranial aneurysms occur in about 8% of individuals with ADPKD and 7% with cervical fibromuscular dysplasia.^{81,82} EDS-IV is associated with dissection of vertebral and carotid arteries, carotid-cavernous fistulae, and intracranial aneurysms.⁸³

Personalized medicine through the use of genetic testing has the potential to improve the safety of primary prevention

pharmacotherapies. For example, genetic variability in the cytochrome P450 2C9 (*CYP2C9*), vitamin K oxide reductase complex 1 (*VKORC1*), and rare missense mutations in the factor IX propeptide affect sensitivity to vitamin K antagonists. Until randomized trials prove that genomic approaches to dosing are clinically advantageous, such testing does not replace close monitoring of the level of anticoagulation as reflected by the international normalized ratio (INR).⁸⁴ A

genomewide association study of persons taking 80 mg of simvastatin identified common variants on *SLCO1B1* that are associated with myopathy.⁸⁵ This may prove useful in screening patients being considered for statin therapy, although randomized validation studies demonstrating the clinical effectiveness and cost-effectiveness of its use are lacking. Clopidogrel is a prodrug that requires metabolism by the cytochrome P450 enzyme complex for activation. Several studies show that polymorphisms modulating metabolic activation of clopidogrel (particularly *CYP2C19*) result in a greater risk of cardiovascular complications following acute coronary syndrome in patients treated with the drug.^{86–88}

Summary and Gaps

Additional studies are required to better establish the relationship between low birth weight and stroke risk. Genetic factors could arguably be classified as potentially modifiable, but because specific gene therapy is not presently available, these have been placed in the “nonmodifiable” section. It should be recognized that treatments are available for some factors with a genetic predisposition or cause (eg, Fabry disease).

Recommendations

1. **Obtaining a family history can be useful to help identify persons who may be at increased risk of stroke (Class IIa; Level of Evidence A).**
2. **Genetic screening of the general population for prevention of a first stroke is not recommended (Class III; Level of Evidence C).**
3. **Referral for genetic counseling may be considered for patients with rare genetic causes of stroke (Class IIb; Level of Evidence C).**
4. **Treatment for certain genetic conditions that predispose to stroke (eg, Fabry disease and enzyme replacement therapy) might be reasonable but has not been shown to reduce risk of stroke, and its effectiveness is unknown (Class IIb; Level of Evidence C).**
5. **Screening of patients at risk for myopathy in the setting of statin use is not recommended when considering initiation of statin therapy at this time (Class III; Level of Evidence C).**
6. **Noninvasive screening for unruptured intracranial aneurysms in patients with 1 relative with SAH or intracranial aneurysms is not recommended (Class III; Level of Evidence C).**
7. **Noninvasive screening for unruptured intracranial aneurysms in patients with ≥ 2 first-degree relatives with SAH or intracranial aneurysms might be reasonable (Class IIb; Level of Evidence C).⁸⁹**
8. **Universal screening for intracranial aneurysms in carriers of mutations for Mendelian disorders associated with aneurysm is not recommended (Class III; Level of Evidence C).**
9. **Noninvasive screening for unruptured intracranial aneurysms in patients with ADPKD and ≥ 1 relatives with ADPKD and SAH or intracranial aneurysm may be considered (Class IIb; Level of Evidence C).**
10. **Noninvasive screening for unruptured intracranial aneurysms in patients with cervical fibromuscular dysplasia may be considered (Class IIb; Level of Evidence C).**

11. **Dosing with vitamin K antagonists on the basis of pharmacogenetics is not recommended at this time (Class III; Level of Evidence C).**

Well-Documented and Modifiable Risk Factors

Hypertension

Hypertension is a major risk factor for both cerebral infarction and ICH (Table 4). The relationship between blood pressure (BP) and stroke risk is strong, continuous, graded, consistent, independent, predictive, and etiologically significant.⁹⁰ Throughout the usual range of BPs, including the nonhypertensive range, the higher the BP, the greater the risk of stroke.⁹¹ The risk of stroke increases progressively with increasing BP, and a substantial number of individuals have a BP level below the current drug treatment thresholds recommended in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).⁹⁰ For these reasons, nondrug or lifestyle approaches are recommended as a means of reducing BP in nonhypertensive individuals with elevated BP (ie, “prehypertension,” 120 mm Hg to 139 mm Hg systolic or 80 mm Hg to 89 mm Hg diastolic).⁹²

The prevalence of hypertension is high and increasing. On the basis of national survey data from 1999 to 2000, it was estimated that hypertension affected at least 65 million persons in the United States.^{93,94} The prevalence of hypertension is increasing, in part as a result of the increasing prevalence of overweight and obesity.^{95,96} BP, particularly systolic BP, rises with increasing age, both in children⁹⁷ and adults.⁹⁸ Persons who are normotensive at 55 years of age have a 90% lifetime risk of developing hypertension.⁹⁹ More than two thirds of persons ≥ 65 years of age are hypertensive.⁹⁰

Behavioral lifestyle changes are recommended in the JNC 7 as part of a comprehensive treatment strategy.⁹⁰ A compelling body of evidence from the results of >40 years of clinical trials has documented that drug treatment of hypertension prevents stroke as well as other BP-related target-organ damage, including heart failure, coronary heart disease, and renal failure.⁹⁰ In a meta-analysis of 23 randomized trials with stroke outcomes, antihypertensive drug treatment reduced risk of stroke by 32% (95% CI, 24% to 39%; $P=0.004$) in comparison with no drug treatment.¹⁰⁰ Several meta-analyses have evaluated whether specific classes of antihypertensive agents offer special protection against stroke beyond their BP-lowering effects.^{100–103} One of these meta-analyses evaluated different classes of agents used as first-line therapy in subjects with a baseline BP $>140/90$ mm Hg. Thiazide diuretics [risk ratio (RR) 0.63; 95% CI, 0.57 to 0.71], β -blockers (RR, 0.83; 95% CI, 0.72 to 0.97), angiotensin-converting enzyme inhibitors (ACEIs; RR, 0.65; 95% CI, 0.52 to 0.82), and calcium channel blockers (RR, 0.58; 95% CI, 0.41 to 0.84) each reduced risk of stroke compared with placebo or no treatment.¹⁰³ Another meta-analysis found that diuretic therapy was superior to ACEI therapy.¹⁰⁰ Subgroup analyses from 1 major trial suggest that the benefit of diuretic therapy over ACEI therapy is especially prominent in blacks.¹⁰⁴ Therefore, although the benefits of lowering BP as a means to prevent stroke are undisputed, there is no

Table 6. Classification and Treatment of Blood Pressure (JNC 7)

Classification	SBP, mm Hg	DBP, mm Hg	No Compelling Indication*	With Compelling Indication*
Normal	<120 and	<80	No antihypertensive drug	No antihypertensive drug
Prehypertension	120–139 or	80–89	No antihypertensive drug	Drugs for compelling indication
Stage 1 hypertension	140–159 or	90–99	Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination.	Drugs for compelling indication. Other drugs (diuretics, ACEI, ARB, BB, CCB) as needed.
Stage 2 hypertension	≥160 or	≥100	Two-drug combination for most† (usually thiazide-type diuretic and ACEI or ARB or BB or CCB).	Drugs for compelling indication. Other drugs (diuretics, ACEI, ARB, BB, CCB) as needed.

ACEI indicates ACE inhibitor; ARB, angiotensin receptor blocker; BB, β -adrenergic receptor blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; EtOH, alcohol; and SBP, systolic blood pressure.

Compelling indications are (1) congestive heart failure, (2) myocardial infarction, (3) diabetes, (4) chronic renal failure, and (5) prior stroke.

*Lifestyle modifications are encouraged for all and include (1) weight reduction if overweight; (2) limitation of EtOH intake; (3) increased aerobic physical activity (30–45 minutes daily); (4) reduction of sodium intake (<2.34 g); (5) maintenance of adequate dietary potassium (>120 mmol/d); (6) smoking cessation; and (7) DASH diet (rich in fruits, vegetables, and low-fat dairy products and reduced in saturated and total fat).

†Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.

definitive evidence that that any class of antihypertensive agents offers special protection against stroke.

Current guidelines recommend a systolic/diastolic BP goal of <140/90 mm Hg in the general population and <130/80 mm Hg in persons with diabetes.⁹⁰ Whether a lower target BP has further benefits is uncertain. One meta-analysis that compared trials with more-intensive goals with those with less-intensive goals found a 23% reduced risk of stroke with more-intensive therapy, as well as a pattern of greater reduction in stroke risk with greater BP reduction.¹⁰¹ In most trials, however, the less-intensive therapy did not test a goal <140/90 mm Hg. There was no difference in rates of stroke among groups of hypertensive persons who achieved mean diastolic BPs of 85.2 mm Hg, 83.2 mm Hg, or 81.1 mm Hg in the largest trial that evaluated different BP goals.¹⁰⁵

Controlling isolated systolic hypertension (systolic BP \geq 160 mm Hg and diastolic BP <90 mm Hg) in the elderly is also important. The Systolic Hypertension in Europe (Syst-Eur) Trial randomized 4695 patients with isolated systolic hypertension to active treatment with a calcium channel blocker or placebo and found a 42% risk reduction (95% CI, 18% to 60%; $P=0.02$) in the actively treated group.¹⁰⁶ The Systolic Hypertension in the Elderly Program (SHEP) Trial found a 36% reduction in the incidence of stroke (95% CI, 18% to 50%; $P=0.003$) from a diuretic-based regimen.¹⁰⁷ No trial has focused on persons with lesser degrees of isolated systolic hypertension (systolic BP between 140 mm Hg and 159 mm Hg with diastolic BP <90 mm Hg). Of considerable importance is a trial that documented the benefit of BP therapy in elderly hypertensive adults (\geq 80 years of age), a group excluded from most other trials of antihypertensive therapy.¹⁰⁶

Despite the efficacy of antihypertensive therapy and the ease of diagnosis and monitoring, a large proportion of the population still has undiagnosed or inadequately treated hypertension.¹⁰⁸ Trend data suggest a modest improvement.⁹⁵ According to the most recent national data, 72% of hypertensive persons were aware of their diagnosis, 61% received treatment, and 35% had BP that was controlled (<140/90 mm Hg). Still, it is well documented that BP control can be achieved in most patients, but the majority require therapy with \geq 2 drugs.^{109,110} Lack of diagnosis and inadequate

treatment are particularly evident in minority populations and the elderly.^{90,111}

The JNC 7 report provides a comprehensive, evidence-based approach to the classification and treatment of hypertension.⁹⁰ JNC 7 classifies persons into 1 of 4 groups on the basis of BP, and treatment recommendations are based on this classification scheme (Table 6). Systolic BP should be treated to a goal of <140 mm Hg and diastolic BP to <90 mm Hg, because these levels are associated with a lower risk of stroke and cardiovascular events. In hypertensive patients with diabetes or renal disease, the BP goal is <130/80 mm Hg (also see section on diabetes).⁹⁰

Summary and Gaps

Hypertension remains the most important well-documented, modifiable risk factor for stroke, and treatment of hypertension is among the most effective strategies for preventing both ischemic and hemorrhagic stroke. Across the spectrum of age groups, including adults \geq 80 years of age, the benefit of hypertension treatment in preventing stroke is clear. Reduction in BP is generally more important than the specific agents used to achieve this goal. Hypertension remains undertreated in the community, and additional programs to improve treatment compliance need to be developed, tested, and implemented.

Recommendations

- 1. In agreement with the JNC 7 report, regular BP screening and appropriate treatment, including both lifestyle modification and pharmacological therapy, are recommended (Class I; Level of Evidence A) (Table 6).**
- 2. Systolic BP should be treated to a goal of <140 mm Hg and diastolic BP to <90 mm Hg because these levels are associated with a lower risk of stroke and cardiovascular events (Class I; Level of Evidence A). In patients with hypertension with diabetes or renal disease, the BP goal is <130/80 mm Hg (also see section on diabetes) (Class I; Level of Evidence A).**

Cigarette Smoking

Virtually every multivariable assessment of stroke risk factors (eg, Framingham,¹¹² Cardiovascular Health Study

[CHS],¹⁸ and the Honolulu Heart Study¹¹³) has identified cigarette smoking as a potent risk factor for ischemic stroke (Table 4), associated with an approximate doubling of risk for ischemic stroke (after adjustment for other risk factors). Data from studies largely conducted in older age groups also provide evidence of a dose-response relationship, and this has been extended to young women from an ethnically diverse cohort.¹¹⁴ Smoking is also associated with a 2- to 4-fold increased risk for SAH.^{115–118} The data for ICH, however, are inconsistent. A multicenter case-control study found an adjusted odds ratio of 1.58 (95% CI, 1.02 to 2.44)¹¹⁹ for ICH and analyses from the Physicians' Health Study¹¹⁸ and Women's Health Study (WHS)¹¹⁷ also found such an association. But other individual studies, including a pooled analysis of the ARIC and CHS cohorts, found no relationship between smoking and risk of ICH.^{16,19,120,121} A meta-analysis of 32 studies estimated the relative risk for ischemic stroke to be 1.9 (95% CI, 1.7 to 2.2) for smokers versus nonsmokers; for SAH, 2.9 (95% CI, 2.5 to 3.5); and for ICH, 0.74 (95% CI, 0.56 to 0.98).¹²⁰

There is a definite relationship between smoking and both ischemic and hemorrhagic stroke, particularly at young ages.^{122,123} The annual number of stroke deaths attributed to smoking in the United States is estimated to be between 21 400 (without adjustment for potential confounding factors) and 17 800 (after adjustment), which suggests that smoking contributes to 12% to 14% of all stroke deaths.¹²⁴ On the basis of data available from the National Health Interview Survey and death certificate data for 2000 to 2004, the Centers for Disease Control and Prevention (CDC) reports that smoking resulted in an estimated average of 61 616 stroke deaths among men and 97 681 stroke deaths among women.¹²⁵

Cigarette smoking may also potentiate the effects of other stroke risk factors, including systolic BP,¹²⁶ vital exhaustion (unusual fatigue, irritability, and feelings of demoralization),¹²⁷ and oral contraceptives (OCs).^{128,129} For example, there is a synergistic effect between the use of OCs and smoking on the risk of cerebral infarction. When nonsmoking, non-OC users were the reference group, the odds of cerebral infarction were 1.3 times greater (95% CI, 0.7 to 2.1) for women who smoked but did not use OCs, 2.1 times greater (95% CI, 1.0 to 4.5) for nonsmokers who used OCs, but 7.2 times greater (95% CI, 3.2 to 16.1) for smokers who used OCs (note that the "expected" odds ratio in the absence of interaction for smokers who used OCs is 2.7).¹²⁸ There was also a synergistic effect of smoking and OC use on hemorrhagic stroke risk. With nonsmoking, non-OC users as the reference group, the odds of hemorrhagic stroke were 1.6 times greater (95% CI, 1.2 to 2.0) for smokers who did not use OCs, 1.5 times greater (95% CI, 1.1 to 2.1) for nonsmokers who used OCs, and 3.7 times greater (95% CI, 2.4 to 5.7) for smokers who used OCs (note that the expected odds ratio in the absence of interaction for the smokers who used OCs was 2.4).¹²⁹ The effect of cigarette smoking on ischemic stroke risk may be higher in young adults who carry the apolipoprotein E ϵ 4 allele.¹³⁰

Exposure to environmental tobacco smoke (passive cigarette smoke or "secondhand" tobacco smoke) is an established risk factor for heart disease.^{131,132} Several studies

provide evidence that exposure to environmental tobacco smoke is also a substantial risk factor for stroke, with risk approaching the doubling of that found for active smoking,^{133–138} although 1 study found no association.¹³⁹ Because the dose of exposure to environmental tobacco smoke is substantially lower than for active smoking, the magnitude of the risk associated with environmental tobacco smoke seems surprising. The lack of an apparent dose-response relationship between the level of exposure and risk may in part be explained by physiological studies suggesting that there is a tobacco smoke exposure "threshold" rather than a linear dose-effect relationship.¹⁴⁰

Smoking likely contributes to increased stroke risk through both acute effects on the risk of thrombus generation in atherosclerotic arteries and chronic effects related to increased atherosclerosis.¹⁴¹ Smoking just 1 cigarette increases heart rate, mean BP, and cardiac index and decreases arterial distensibility.^{142,143} Beyond the immediate effects of smoking, both active and passive exposure to cigarette smoke is associated with the development of atherosclerosis.¹⁴⁴ In addition to placing persons at increased risk for both thrombotic and embolic stroke, cigarette smoking approximately triples the risk of cryptogenic stroke among persons with a low atherosclerotic burden and no evidence of a cardiac source of emboli.¹⁴⁵

Although the most effective preventive measures are to never smoke and to minimize exposure to environmental tobacco smoke, risk is reduced with smoking cessation. Smoking cessation is associated with a rapid reduction in risk of stroke and other cardiovascular events to a level that approaches but does not reach that of those who never smoked.^{141,146–148}

Although sustained smoking cessation is difficult to achieve, effective behavioral and pharmacological treatments for nicotine dependence are available.^{149–151} Comprehensive reviews and recommendations for smoking cessation are provided in the 2004 Surgeon General's report¹⁴⁹ and the 2009 recommendation from the US Preventive Services Task Force.¹⁵² The latter reiterates that the combination of counseling and medications is more effective than either therapy alone.

Summary and Gaps

Cigarette smoking increases the risk of ischemic stroke and SAH, but the data on ICH are inconclusive. Epidemiological studies show a reduction in stroke risk with smoking cessation. Although effective programs to facilitate smoking cessation exist, data showing that participation in these programs leads to a long-term reduction in stroke are lacking. General measures are given in Table 7.

Recommendations

- 1. Abstention from cigarette smoking by nonsmokers and smoking cessation by current smokers are recommended based on epidemiological studies showing a consistent and overwhelming relationship between smoking and both ischemic stroke and SAH (Class I; Level of Evidence B).**
- 2. Although data are lacking that avoidance of environmental tobacco smoke reduces incident stroke, on the basis of epidemiological data showing in-**

Table 7. General Measures

Factor	Goal	Recommendations
Cigarette smoking	Stop smoking. Avoid environmental tobacco smoke.	Strongly encourage patient and family to stop smoking. Provide counseling, nicotine replacement, and formal programs as available.
Diabetes	Improve glucose control. Treat hypertension. Consider use of a statin.	See guidelines and policy statements for recommendations on diet, oral hypoglycemics, and insulin.
SCD	Monitor children with SCD with TCD for development of vasculopathy (see text).	Provide transfusion therapy for children who develop evidence of sickle cell vasculopathy (see text).
OC use	Avoid OCs if risk of stroke is high.	Inform patients about stroke risk and encourage alternative forms of birth control for women who smoke cigarettes, have migraines (especially with older age or smoking), are >35 y of age, or have had prior thromboembolic events.
Poor diet/nutrition	Eat a well-balanced diet.	Encourage consumption of a diet containing at least 5 servings of fruits and vegetables per day, which may reduce stroke risk.
Physical inactivity	Engage in ≥ 30 minutes of moderate intensity activity daily.	Encourage moderate exercise (eg, brisk walking, jogging, cycling, or other aerobic activity). Recommend medically supervised programs for high-risk patients (eg, cardiac disease) and adaptive programs depending on physical/neurologic deficits.
Alcohol consumption	Limit alcohol consumption.	Inform patients that they should limit their alcohol consumption to no more than 2 drinks per day for men and no more than 1 drink per day for nonpregnant women.
Drug abuse	Stop drug abuse.	Include an in-depth history of substance abuse as part of a complete health evaluation for all patients.
SDB	Treat SDB.	Recommend sleep laboratory evaluation for patients with snoring, excessive sleepiness, and vascular risk factors, particularly with BMI >30 kg/m ² and drug-resistant hypertension.

BMI indicates body mass index; SCD, sickle cell disease; SDB, sleep-disordered breathing; and TCD, transcranial Doppler imaging. Refer to text for Class and Level of Evidence.

creased stroke risk and the effects of avoidance on risk of other cardiovascular events, avoidance of exposure to environmental tobacco smoke is reasonable (Class IIa; Level of Evidence C).

- 3. The use of multimodal techniques, including counseling, nicotine replacement, and oral smoking-cessation medications, can be useful as part of an overall smoking-cessation strategy. Status of tobacco use should be addressed at every patient encounter (Class I; Level of Evidence B).**

Diabetes

Persons with diabetes have both an increased susceptibility to atherosclerosis and an increased prevalence of proatherogenic risk factors, notably hypertension and abnormal blood lipids. In 2007, 17.9 million, or 5.9%, of Americans had diabetes, and an estimated additional 5.7 million had undiagnosed disease.¹⁵³ Together this amounted to 10.7% of the US population.

Both case-control studies of stroke patients and prospective epidemiological studies have confirmed that diabetes independently increases risk of ischemic stroke with a relative risk ranging from 1.8-fold to nearly 6-fold.¹⁵⁴ Data from the CDC from 1997 to 2003 showed the age-adjusted prevalence of self-reported stroke was 9% among persons with diabetes aged ≥ 35 years.¹⁵⁵

In the Greater Cincinnati/Northern Kentucky Stroke Study, ischemic stroke patients with diabetes were younger, more likely to be black, and more likely to have hypertension, MI, and high cholesterol than patients without diabetes.¹⁵⁶ Age-specific incidence rates and rate ratios showed that diabetes increased incidence of ischemic stroke for all ages, but that

the risk was most prominent before age 55 in blacks and before age 65 in whites. Although Mexican Americans had a substantially greater incidence of ischemic stroke and ICH than non-Hispanic whites,³⁵ there is insufficient evidence that the presence of diabetes or other forms of glucose intolerance influenced this rate. In the Strong Heart Study, 6.8% of 4549 Native American participants aged 45 to 74 years at baseline without prior stroke had a first stroke over 12 to 15 years, and diabetes and impaired glucose tolerance increased the hazard ratio (HR) to 2.05.⁴¹

Stroke risk can be reduced in patients with diabetes. In the Steno-2 Study, 160 patients with type 2 diabetes and persistent microalbuminuria were assigned to receive either intensive therapy, including behavioral risk factor modification and a statin, ACEI, angiotensin II receptor blocker (ARB), or an antiplatelet drug as appropriate, or conventional therapy with a mean treatment period of 7.8 years.¹⁵⁷ Patients were subsequently followed up for an average of 5.5 years. The primary end point was time to death from any cause. The risk of cardiovascular events was reduced by 60% (HR, 0.41; 95% CI, 0.25 to 0.67; $P < 0.001$) with intensive treatment versus conventional therapy, and the number of strokes was reduced from 30 to 6. In addition, intensive therapy was associated with a 57% lower risk of death from cardiovascular causes (HR, 0.43; 95% CI, 0.19 to 0.94; $P = 0.04$). Although 18 of 30 strokes in the conventional therapy group were fatal, all 6 strokes in the intensive therapy group were fatal.

In the Euro Heart Survey on Diabetes and the Heart, a total of 3488 patients were entered in the study: 59% without diabetes and 41% with diabetes.¹⁵⁸ Evidenced-based medicine was defined as the combined use of renin-angiotensin-

aldosterone system inhibitors, β -adrenergic receptor blockers, antiplatelet agents, and statins. In patients with diabetes, evidence-based medicine (RR, 0.37; 95% CI, 0.20 to 0.67; $P=0.001$) had an independent protective effect on 1-year mortality and cardiovascular events (RR, 0.61; 95% CI, 0.40 to 0.91; $P=0.015$). Although stroke rates were not changed, cerebrovascular revascularization procedures were reduced by half.

Glycemic Control

In the Northern Manhattan Study (NOMAS) of 3298 stroke-free community residents, 572 reported a history of diabetes and 59% ($n=338$) had elevated fasting blood glucose.¹⁵⁹ Those subjects with an elevated fasting glucose had a 2.7-fold HR (95% CI, 2.0 to 3.8) increased stroke risk, but those with a fasting blood glucose level of <126 mg/dL were not at increased risk.

The effect of previous randomization of the United Kingdom Prospective Diabetes Study (UKPDS)¹⁶⁰ to either conventional therapy (dietary restriction) or intensive therapy (either sulfonylurea or insulin or, in overweight patients, metformin) for glucose control was assessed in an open-label extension study. In posttrial monitoring, 3277 patients were asked to attend annual UKPDS clinics for 5 years; however, there were no attempts to maintain their previously assigned therapy.¹⁶¹ A reduction in MI and all-cause mortality was found; however, stroke incidence was not affected by assignment to either sulfonylurea-insulin or metformin treatment.

Three trials have evaluated the effects of reduced glycemia on cardiovascular events in patients with type 2 diabetes. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study recruited 10 251 patients (mean age, 62 years) with a mean glycohemoglobin level of 8.1%.¹⁶² Participants were then randomly assigned to receive intensive (glycohemoglobin goal of $<6.0\%$) or standard (goal, 7.0% to 7.9%) therapy. The study was stopped earlier than planned because of an increase in all-cause mortality in the intensive therapy group with no difference in the numbers of fatal and nonfatal strokes. The Action in Diabetes and Vascular Disease: PreterAx and DiamacroN MR Controlled Evaluation (ADVANCE) trial included 11 140 patients (mean age, 66.6 years) with type 2 diabetes and used a number of strategies to reduce glycemia in an intensive-treatment group.¹⁶³ Mean glycohemoglobin levels were 6.5% and 7.4% at 5 years, respectively. There was no effect of more-intensive therapy on risk of cardiovascular events or risk of nonfatal strokes between groups. In another study, 1791 US veterans with diabetes of an average duration of >10 years (mean age, 60.4 years) were randomly assigned to a regimen to decrease glycohemoglobin by 1.5% or standard of care.¹⁶⁴ After 5.6 years, the mean levels of glycohemoglobin were 6.9% and 8.4%, respectively. As in the other trials, there was no difference in the number of macrovascular events, including stroke, between the 2 groups. On the basis of currently available clinical trial results, there is no evidence that reduced glycemia decreases short-term risk of macrovascular events, including stroke, in patients with type 2 diabetes. A glycohemoglobin goal of $<7.0\%$ has been recommended by the American Diabetes Association to prevent long-term

microangiopathic complications in patients with type 2 diabetes.¹⁶⁵ Whether control to this level also reduces the long-term risk of cardiovascular events and stroke requires further study.

In patients with recent-onset type 1 diabetes mellitus, intensive diabetes therapy aimed at achieving near normoglycemia can be accomplished with good adherence but with more frequent episodes of severe hypoglycemia.¹⁶⁶ Although glycemia was similar between the groups over a mean 17 years of follow-up, intensive treatment reduced the risk of any cardiovascular event by 42% (95% CI, 9% to 63%; $P=0.02$) and reduced the combined risk of nonfatal MI, stroke, or death from cardiovascular events by 57% (95% CI, 12% to 79%, $P=0.02$).¹⁶⁷ The decrease in glycohemoglobin was associated with the positive effects of intensive treatment on the overall risk of CVD. The number of strokes, however, was too few to evaluate the impact of improved glycemia during the trial, and as with type 2 diabetes, there remains no evidence that tight glycemic control reduces stroke risk.

Diabetes and Hypertension

More aggressive lowering of BP in patients with diabetes and hypertension reduces stroke incidence.¹⁶⁸ In addition to comparing the effects of more intensive glycemic control versus standard care on the complications of type 2 diabetes, the UKPDS found tight BP control (mean BP achieved, 144/82 mm Hg) resulted in a 44% reduction (95% CI, 11% to 65%, $P=0.013$) in the risk of stroke as compared with more liberal control (mean BP achieved, 154/87 mm Hg).¹⁶⁹ There was also a nonstatistically significant 22% risk reduction (RR, 0.78; 95% CI, 0.45 to 1.34) with antihypertensive treatment in subjects with diabetes in SHEP.¹⁷⁰ No attempt was made to maintain the previously assigned therapy follow-up of 884 UKPDS patients who attended annual UKPDS clinics for 5 years.¹⁷¹ Differences in BP between the 2 groups disappeared within 2 years. There was a nonsignificant trend toward reduction in stroke with more intensive BP control (RR, 0.77; 95% CI, 0.55 to 1.07; $P=0.12$). Continued efforts to maintain BP targets might lead to maintenance of benefit.

The Heart Outcomes Prevention Evaluation (HOPE) Study compared the addition of an ACEI to the current medical regimen in high-risk patients. The substudy of 3577 patients with diabetes with a previous cardiovascular event or an additional cardiovascular risk factor (total population, 9541 participants) showed a 25% reduction (95% CI, 12 to 36; $P=0.0004$) in the primary combined outcome of MI, stroke, and cardiovascular death and a 33% reduction (95% CI, 10 to 50; $P=0.0074$) in stroke.¹⁷² Whether these benefits represent a specific effect of the ACEI or were an effect of BP lowering remains unclear. The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Study compared the effects of an ARB with a β -adrenergic receptor blocker in 9193 persons with essential hypertension (160 to 200 mm Hg/95 to 115 mm Hg) and electrocardiographically determined left ventricular hypertrophy over 4 years.¹⁷³ BP reductions were similar for each group. The 2 regimens were compared among the subgroup of 1195 persons who also had diabetes in a prespecified analysis.¹⁷⁴ There was a 24% reduction (RR 0.76; 95% CI, 0.58 to 0.98) in major vascular events and a

nonsignificant 21% reduction (RR, 0.791; 95% CI, 0.55 to 1.14) in stroke among those treated with the ARB.

The ADVANCE Trial also determined whether a fixed combination of perindopril and indapamide or matching placebo in 11 140 patients with type 2 diabetes would decrease major macrovascular and microvascular events.¹⁷⁵ After 4.3 years of follow-up, subjects assigned to the combination had a mean reduction in BP of 5.6/2.2 mm Hg. The risk of a major vascular event was reduced by 9% (HR, 0.91; 95% CI, 0.83 to 1.00; $P=0.04$), but there was no reduction in the incidence of major macrovascular events, including stroke.

Yet antihypertensive therapy can also modify the risk for type 2 diabetes. A meta-analysis examined whether β -adrenergic receptor blockers used for the treatment of hypertension were associated with increased risk for development of type 2 diabetes mellitus.¹⁷⁶ In 12 studies evaluating 94 492 patients, β -blocker therapy resulted in a 22% increased risk (RR, 1.22; 95% CI, 1.12 to 1.33) for type 2 diabetes compared with nondiuretic antihypertensive agents. A higher baseline fasting glucose level, greater systolic and diastolic BP, and a higher body mass index (BMI) were univariately associated with the development of diabetes. Multivariate meta-regression found higher baseline BMI was an independent predictor. In the elderly, risk for new-onset type 2 diabetes was greater with atenolol and with longer duration of treatment with a β -blocker. Of interest, β -blocker therapy was also associated with a 15% increased risk (RR, 1.15; 95% CI, 1.01 to 1.30; $P=0.029$) for stroke, with no reductions in all-cause mortality or MI. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), although the odds for developing diabetes with lisinopril or amlodipine therapy were lower than with chlorthalidone, there was no association of a change in fasting plasma glucose level at 2 years with subsequent coronary heart disease or stroke.¹⁷⁷

In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effects of 2 antihypertensive treatment strategies (amlodipine with the addition of perindopril as required [amlodipine based] or atenolol with the addition of thiazide as required [atenolol based]) for the prevention of major cardiovascular events were compared in 5137 patients with diabetes mellitus.¹⁷⁸ The target BP was <130/80 mm Hg. The trial was terminated early because of reductions in mortality and stroke with the amlodipine-based regimen. In patients with diabetes mellitus, the amlodipine-based therapy reduced the incidence of total cardiovascular events and procedures compared with the atenolol-based regimen (HR, 0.86; 95% CI, 0.76 to 0.98; $P=0.026$), including a 25% reduction ($P=0.017$) in fatal and nonfatal strokes.

The open-label ACCORD trial randomly assigned 4733 participants to 1 of 2 groups with different treatment goals: systolic BP <120 mm Hg as the more intensive goal and systolic BP <140 mm Hg as the less intensive goal.¹⁷⁴ Randomization to the more intensive goal did not reduce the rate of the composite outcome of fatal and nonfatal major cardiovascular events (HR, 0.88; 95% CI, 0.73 to 1.06; $P=0.20$). Stroke was a prespecified secondary end point occurring at annual rates of 0.32% (more intensive) and 0.53% (less intensive) treatment (HR, 0.59; 95% CI, 0.39 to 0.89; $P=0.01$).¹⁷⁹

In the Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension trial (ACCOMPLISH), 11 506 patients (6746 with diabetes) with hypertension were randomized to treatment with benazepril plus amlodipine or benazepril plus hydrochlorothiazide.¹⁸⁰ The primary end point was the composite of death from CVD, nonfatal MI, nonfatal stroke, hospitalization for angina, resuscitated cardiac arrest, and coronary revascularization. The trial was terminated early after a mean follow-up of 36 months when there were 552 primary outcome events in the benazepril-amlodipine group (9.6%) and 679 in the benazepril-hydrochlorothiazide group (11.8%), an absolute risk reduction of 2.2% (HR, 0.80; 95% CI, 0.72 to 0.90; $P<0.001$). There was no difference in stroke between the groups, however.

Lipid-Altering Therapy and Diabetes

Although secondary subgroup analyses of some studies did not find a benefit of statins in patients with diabetes,^{181,182} the Medical Research Council/British Heart Foundation Heart Protection Study (HPS) found that the addition of a statin to existing treatments in high-risk patients resulted in a 24% reduction in the rate of major cardiovascular events (95% CI, 19% to 28%).¹⁸³ A 22% reduction (95% CI, 13% to 30%) in major vascular events (regardless of the presence of known coronary heart disease or cholesterol levels) and a 24% reduction (95% CI, 6% to 39%; $P=0.01$) in strokes was found among 5963 diabetic individuals treated with a statin in addition to best medical care.¹⁸⁴ The Collaborative Atorvastatin Diabetes Study (CARDS) reported that in patients with type 2 diabetes with at least 1 additional risk factor (retinopathy, albuminuria, current smoking, or hypertension) and a low-density lipoprotein (LDL) cholesterol level of <160 mg/dL but without a prior history of CVD, treatment with a statin resulted in a 48% reduction in stroke (95% CI, 11% to 69%).¹⁸⁵

In a post hoc analysis of the Treating to New Targets (TNT) study, the effect of intensive lowering of LDL cholesterol with high-dose (80 mg daily) versus low-dose (10 mg daily) atorvastatin on cardiovascular events was compared for patients with coronary heart disease and diabetes.¹⁸⁶ After a median follow-up of 4.9 years, higher-dose treatment was associated with a 40% reduction in the time to a cerebrovascular event (HR, 0.69; 95% CI, 0.48 to 0.98; $P=0.037$).

Clinical trials with a statin or any other single intervention in patients with high cardiovascular risk, including the presence of diabetes, are often insufficiently powered to determine an effect on incident stroke. In 2008, data from 18 686 persons with diabetes (1466 with type 1 and 17 220 with type 2 diabetes) were assessed to determine the impact of a 1.0 mmol/L (approximately 40 mg/dL) reduction in LDL cholesterol. During a mean follow-up of 4.3 years, there were 3247 major cardiovascular events with a 9% proportional reduction in all-cause mortality per millimole per liter LDL cholesterol reduction (RR, 0.91; 95% CI, 0.82 to 1.01; $P=0.02$) and a 13% reduction in cardiovascular mortality (RR, 0.87; 95% CI, 0.76 to 1.00; $P=0.008$). There were also reductions in MI or coronary death (RR, 0.78; 95% CI, 0.69 to 0.87; $P<0.0001$) and stroke (RR, 0.79; 95% CI, 0.67 to 0.93; $P=0.0002$).

A subgroup analysis was carried out from the Department of Veterans Affairs High-Density Lipoprotein Intervention

Trial (VA-HIT), in which subjects received either gemfibrozil (1200 mg/d) or placebo for 5.1 years.¹⁸⁷ Compared with those with a normal fasting plasma glucose, risk for major cardiovascular events was higher in subjects with either known (HR, 1.87; 95% CI, 1.44 to 2.43; $P=0.001$) or newly diagnosed diabetes (HR, 1.72; 95% CI, 1.10 to 2.68; $P=0.02$). Gemfibrozil treatment did not affect the risk of stroke among subjects without diabetes, but treatment was associated with a 40% reduction in stroke in those with diabetes (HR, 0.60; 95% CI, 0.37 to 0.99; $P=0.046$).

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study assessed the effect of fenofibrate on cardiovascular events in 9795 subjects with type 2 diabetes mellitus, 50 to 75 years of age, who were not taking a statin at study entry.¹⁸⁸ The study population included 2131 persons with and 7664 persons without previous CVD. Over 5 years, 5.9% ($n=288$) of patients on placebo and 5.2% ($n=256$) on fenofibrate had a coronary event ($P=0.16$). There was a 24% reduction (RR, 0.76; 95% CI, 0.62 to 0.94; $P=0.010$) in nonfatal MI. There was no effect on stroke (4% versus 3%; $P=NS$) with fenofibrate. A higher rate of statin therapy initiation occurred in patients allocated to placebo that might have masked a treatment effect. The ACCORD trial randomized 5518 patients with type 2 diabetes who were being treated with open-label simvastatin to double-blind treatment with fenofibrate or placebo.¹⁸⁹ There was no effect of added fenofibrate on the primary outcome (first occurrence of nonfatal MI, nonfatal stroke, or death from cardiovascular causes; HR, 0.92; 95% CI, 0.79 to 1.08; $P=0.32$) and no effect on any secondary outcome, including stroke (HR, 1.05; 95% CI, 0.71 to 1.56; $P=0.80$).

Diabetes, Aspirin, and Stroke

The benefit of aspirin therapy in prevention of cardiovascular events, including stroke in patients with diabetes, remains unclear. A recent study at 163 institutions throughout Japan enrolled 2539 patients with type 2 diabetes and no history of atherosclerotic vascular disease.¹⁹⁰ Patients were assigned to receive low-dose aspirin (81 or 100 mg/d) versus no aspirin. Over 4.37 years, a total of 154 atherosclerotic vascular events occurred (68 in the aspirin group, 13.6 per 1000 person-years, and 86 in the nonaspirin group, 17.0 per 1000 person-years; HR, 0.80, 95% CI, 0.58 to 1.10; $P=0.16$). Only a single fatal stroke occurred in the aspirin group, but 5 occurred in the nonaspirin group; therefore, the study was insufficiently powered to detect an effect on stroke.

Several large primary prevention trials have included subgroup analyses of patients with diabetes. The Antithrombotic Trialists' Collaboration meta-analysis of 287 randomized trials reported effects of antiplatelet therapy (mainly aspirin) versus control in 135 000 patients.¹⁹¹ There was a nonsignificant 7% reduction in serious vascular events, including stroke, in the subgroup of 5126 patients with diabetes.

Summary and Gaps

A comprehensive program that includes tight control of hypertension with ACEI or ARB treatment reduces risk of stroke in persons with diabetes. Glycemic control reduces microvascular complications, but there is no evidence that improved glycemic control reduces the risk of incident stroke.

Adequately powered studies show that statin treatment of patients with diabetes decreases risk of a first stroke. Although a subgroup analysis of VA-HIT suggests that gemfibrozil reduces stroke in men with diabetes and dyslipidemia, a fibrate effect was not seen in the FIELD study, and ACCORD found no benefit of adding fenofibrate to a statin. General measures are given in Table 7.

Recommendations

- 1. Control of BP in patients with either type 1 or type 2 diabetes as part of a comprehensive cardiovascular risk-reduction program as reflected in the JNC 7 guidelines is recommended (Class I; Level of Evidence A).**
- 2. Treatment of hypertension in adults with diabetes with an ACEI or an ARB is useful (Class I; Level of Evidence A).**
- 3. Treatment of adults with diabetes with a statin, especially those with additional risk factors, is recommended to lower risk of a first stroke (Class I; Level of Evidence A).**
- 4. The use of monotherapy with a fibrate to lower stroke risk might be considered for patients with diabetes (Class IIb; Level of Evidence B).**
- 5. The addition of a fibrate to a statin in persons with diabetes is not useful for decreasing stroke risk (Class III; Level of Evidence B).**
- 6. The benefit of aspirin for reduction of stroke risk has not been satisfactorily demonstrated for patients with diabetes; however, administration of aspirin may be reasonable in those at high CVD risk (also see section on aspirin) (Class IIb; Level of Evidence B).**

Dyslipidemia

Total Cholesterol

Most but not all epidemiological studies find an association between higher cholesterol levels and an increased risk of ischemic stroke. In the Multiple Risk Factor Intervention Trial (MRFIT), which included >350 000 men, the relative risk of death from nonhemorrhagic stroke increased progressively for each level of cholesterol.¹⁹² In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study, which included >28 000 men who smoked, the risk of cerebral infarction was increased among those with total cholesterol levels ≥ 7 mmol/L (≥ 271 mg/dL).¹⁹³ In the Asia Pacific Cohort Studies Collaboration (APCSC), which included 352 033 persons, there was a 25% increase (95% CI, 13% to 40%) in ischemic stroke rates for every 1 mmol/L (38.7 mg/dL) increase in total cholesterol.¹⁹⁴ In the Women's Pooling Project, which included 24 343 US women <55 years of age with no previous CVD, and in the WHS, a prospective cohort study of 27 937 US women ≥ 45 years of age, higher cholesterol levels were also associated with increased risk of ischemic stroke.^{195,196} In other studies the association between cholesterol and stroke risk was not as clear. In the ARIC study, which included 14 175 middle-aged men and women free of clinical CVD, the relationships between lipid values and incident ischemic stroke were weak.¹⁹⁷ In the Eurostroke Project of 22 183 men and women, there was no relationship between cholesterol with cerebral infarction.¹⁹⁸ Interpretation of studies evaluating the relation-

ship between cholesterol levels and risk of ischemic stroke may be confounded by the types of ischemic stroke included in the analysis. Epidemiological studies consistently find an association between cholesterol levels and carotid artery atherosclerosis.^{199–203}

Most, but not all studies, also find an association between lower cholesterol levels and increased risk of hemorrhagic stroke. In MRFIT the risk of death from intracranial hemorrhage was increased 3-fold in men with total cholesterol concentrations of <4.14 mmol/L (160 mg/dL) compared with higher levels.¹⁹² In a pooled cohort analysis of the ARIC study and the CHS, low LDL cholesterol was inversely associated with incident intracranial hemorrhage.¹⁹ In the APCSC there was a 20% (95% CI, 8% to 30%) decreased risk of hemorrhagic stroke for every 1 mmol/L (38.7 mg/dL) increase in total cholesterol.¹⁹⁴ Similar findings were reported in the Ibaraki Prefectural Health Study, in which the age- and sex-adjusted risk of death from parenchymal hemorrhagic stroke in persons with LDL-cholesterol levels \geq 140 mg/dL was approximately half of that in persons with LDL-cholesterol levels <80 mg/dL (OR, 0.45; 95% CI, 0.30 to 0.69).²⁰⁴ The Kaiser Permanente Medical Care Program reported that serum cholesterol levels <178 mg/dL increased the risk of ICH among men \geq 65 years of age (RR, 2.7; 95% CI, 1.4 to 5.0).²⁰⁵ In a Japanese nested case-control study, patients with intraparenchymal hemorrhage had lower cholesterol levels than control subjects.²⁰⁶ In contrast, in the Korean Medical Insurance Corporation Study of approximately 115 000 men, low serum cholesterol was not an independent risk factor for ICH.²⁰⁷ Overall, epidemiological studies suggest competing stroke risk related to total cholesterol levels in the general population; high total cholesterol may be associated with higher risk of ischemic stroke, whereas lower levels are associated with higher risk of brain hemorrhage.

HDL Cholesterol

Most but not all epidemiological studies show an inverse relationship between high-density lipoprotein (HDL) cholesterol and stroke.²⁰⁸ HDL cholesterol was inversely related to ischemic stroke in the Copenhagen City Heart Study, the Oyabe Study of Japanese men and women, middle-aged British men, and middle-aged and elderly men in the Israeli Ischemic Heart Disease Study.^{209–212} In the Northern Manhattan Stroke Study (NOMASS) that involved a multiethnic community, higher HDL-cholesterol levels were also associated with reduced risk of ischemic stroke.²¹³ In the CHS study, high HDL cholesterol was associated with a decreased risk of ischemic stroke in men but not women.²¹⁴ The ARIC Study did not find a significant relationship between HDL cholesterol and ischemic stroke.¹⁹⁷ Five prospective cohort studies included in a systematic review found a decreased risk of stroke ranging from 11% to 15% for each 10 mg/dL increase in HDL cholesterol.²¹⁵

Triglycerides

The results of epidemiological studies that have evaluated the relationship between triglycerides and ischemic stroke are inconsistent, in part because some have used fasting levels and others nonfasting levels. Fasting triglyceride levels were not associated with ischemic stroke in the ARIC study.¹⁹⁷

Triglycerides did not predict the risk of ischemic stroke among healthy men enrolled in the Physicians' Health Study.²¹⁶ Similarly, in the Oslo study of healthy men, triglycerides were not related to the risk of stroke.²¹⁷ In contrast, a meta-analysis of prospective studies conducted in the Asia-Pacific region found a 50% increased risk of ischemic stroke among those in the highest quintile of fasting triglycerides compared with those in the lowest quintile.²¹⁸ The Copenhagen City Heart Study, a prospective, population-based cohort study composed of approximately 14 000 persons, found that elevated nonfasting triglyceride levels increased the risk of ischemic stroke in both men and women. After multivariate adjustment, there was a 15% increased risk (95% CI, 9% to 22%) of ischemic stroke for each 89 mg/dL increase in nonfasting triglycerides. The hazard ratios for ischemic stroke among men and women with the highest compared with the lowest nonfasting triglycerides were 2.5 (95% CI, 1.3 to 4.8) and 3.8 (95% CI, 1.3 to 11), respectively. The 10-year risks of ischemic stroke were 16.7% and 12.2%, respectively, in men and women aged \geq 55 years with triglyceride levels \geq 443 mg/dL.²¹⁹ Similarly, the WHS found that in models adjusted for total and HDL cholesterol and measures of insulin resistance, nonfasting triglycerides, but not fasting triglycerides, were associated with cardiovascular events, including ischemic stroke.²²⁰

Treatment of Dyslipidemia

Table 8 provides a general approach to treatment of dyslipidemia based on recommendations from the National Cholesterol Education Program (NCEP) Adult Treatment Panel III.^{221,222} Statins [3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors] lower LDL cholesterol by 30% to 50%, depending on the formulation and dose. Treatment with statins reduces the risk of stroke in patients with atherosclerosis or at high risk for atherosclerosis.^{223,224} One meta-analysis of 26 trials that included >90 000 patients found that statins reduced the risk of all strokes by approximately 21% (95% CI, 15% to 27%).²²³ Baseline mean LDL cholesterol in the studies included in this meta-analysis ranged from 124 mg/dL to 188 mg/dL and averaged 149 mg/dL. The risk of all strokes was estimated to decrease by 15.6% (95% CI, 6.7% to 23.6%) for each 10% reduction in LDL cholesterol. Another meta-analysis of randomized trials of statins in combination with other preventive strategies, including 165 792 individuals, showed that each 1 mmol/L (39 mg/dL) decrease in LDL cholesterol was associated with a 21.1% reduction (95% CI, 6.3 to 33.5; $P=0.009$) in stroke.²²⁵

The beneficial effect of statins on ischemic stroke is most likely related to their capacity to reduce progression or induce regression of atherosclerosis. A meta-analysis of statin trials found that the magnitude of LDL-cholesterol reduction correlated inversely with progression of carotid intima media thickness (IMT).²²³ Moreover, the beneficial effects on carotid IMT appear to be greater with higher-intensity statin therapy.^{226–228}

The effect of lipid-modifying therapies other than statins on the risk of ischemic stroke is not established. Niacin increases HDL cholesterol and lowers plasma levels of lipoprotein(a). Long-term follow-up of men with prior MI who were enrolled in the Coronary Drug Project found that

Table 8. Dyslipidemia: Guideline Management Recommendations*^{221,222}

Factor	Goal	Recommendations
LDL-C		
0–1 CHD risk factor*	LDL-C <160 mg/dL	Diet, weight management, and physical activity. Drug therapy recommended if LDL-C remains \geq 190 mg/dL. Drug therapy optional for LDL-C 160–189 mg/dL.
2+ CHD risk factors and 10-year CHD risk <20%	LDL-C <130 mg/dL	Diet, weight management, and physical activity. Drug therapy recommended if LDL-C remains \geq 160 mg/dL.
2+ CHD risk factors and 10-year CHD risk 10%–20%	LDL-C <130 mg/dL, or optionally LDL-C <100 mg/dL	Diet, weight management, and physical activity. Drug therapy recommended if LDL-C remains \geq 130 mg/dL (optionally \geq 100 mg/dL).
CHD or CHD risk equivalent† (10-year risk >20%)	LDL-C <100 mg/dL or optionally LDL-C <70 mg/dL	Diet, weight management, and physical activity. Drug therapy recommended if LDL-C \geq 130 mg/dL. Drug therapy optional for LDL-C 70–129 mg/dL.
Non-HDL-C in persons with triglyceride \geq 200 mg/dL	Goals are 30 mg/dL higher than LDL-C goal	Same as LDL-C with goals 30 mg/dL higher.
Low HDL-C	No consensus goal	Weight management and physical activity. Consider niacin (nicotinic acid) or fibrate in high-risk persons with HDL-C <40 mg/dL.
Lp(a)	No consensus goal	Treat other atherosclerotic risk factors in patients with high Lp(a). Consider niacin (immediate- or extended-release formulation), up to 2000 mg/d for reduction of Lp(a) levels, optimally in conjunction with glycemic control and LDL control.

CHD indicates coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and Lp(a), lipoprotein a.

*To screen for dyslipidemia, a fasting lipoprotein profile (cholesterol, triglyceride, HDL-C, and LDL-C) should be obtained every 5 y in adults. It should be obtained more often if \geq 2 CHD risk factors are present (risk factors include cigarette smoking; hypertension; HDL-C <40 mg/dL; CHD in a male first-degree relative <55 y or in a female first-degree relative <65 y; or age >45 y for men or >65 y for women) or if LDL-C levels are borderline or high. Screening for Lp(a) is not recommended for primary prevention unless (1) unexplained early cardiovascular events have occurred in first-degree relatives or (2) high Lp(a) is known to be present in first-degree relatives.

†CHD risk equivalents include diabetes or other forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, or symptomatic carotid artery disease).

treatment with niacin reduced mortality, including a trend toward fewer deaths from cerebrovascular disease.²²⁹ Fibrin acid derivatives such as gemfibrozil, fenofibrate, and bezafibrate lower triglyceride levels and increase HDL cholesterol. The Bezafibrate Infarction Prevention study, which included patients with prior MI or stable angina and HDL-cholesterol levels \leq 45 mg/dL, found bezafibrate did not significantly decrease risk of MI or sudden death (primary end point) nor stroke (secondary end point).²³⁰ The VA-HIT, which included men with coronary artery disease and low HDL cholesterol, found gemfibrozil reduced the risk of all strokes, primarily ischemic strokes.²³¹ In the FIELD study, fenofibrate did not decrease the composite primary end point of coronary heart disease death or nonfatal MI, nor did it decrease risk of stroke, which was a secondary end point. Ezetimibe lowers cholesterol levels by reducing intestinal absorption of cholesterol. In a study of patients with familial hypercholesterolemia, the addition of ezetimibe to simvastatin did not affect progression of carotid IMT more than simvastatin alone.²³² In another trial of subjects receiving a statin, the addition of ezetimibe compared with niacin found niacin led to greater reductions in mean carotid IMT over 14 months ($P=0.003$), with those receiving ezetimibe who had greater reductions in LDL cholesterol having an increase in carotid IMT ($r=-0.31$; $P<0.001$).²³³ The rate of major cardiovascular events was lower in those randomized to niacin (1% versus 5%; $P=0.04$). Stroke events were not reported. A clinical outcome trial comparing the effect of ezetimibe plus simvastatin with simvastatin monotherapy on cardiovascular outcomes is in progress.²³⁴ There are no studies showing that ezetimibe treatment decreases cardiovascular events or stroke.

Recommendations

- 1. Treatment with an HMG-CoA reductase inhibitor (statin) medication in addition to therapeutic lifestyle changes with LDL-cholesterol goals as reflected in the NCEP guidelines^{221,222} is recommended for primary prevention of ischemic stroke in patients with coronary heart disease or certain high-risk conditions such as diabetes (Class I; Level of Evidence A).**
- 2. Fibrin acid derivatives may be considered for patients with hypertriglyceridemia, but their efficacy in the prevention of ischemic stroke is not established (Class IIb; Level of Evidence C).**
- 3. Niacin may be considered for patients with low HDL cholesterol or elevated lipoprotein(a), but its efficacy in prevention of ischemic stroke in patients with these conditions is not established (Class IIb; Level of Evidence C).**
- 4. Treatment with other lipid-lowering therapies, such as fibrin acid derivatives, bile acid sequestrants, niacin, and ezetimibe, may be considered in patients who do not achieve target LDL cholesterol with statins or cannot tolerate statins, but the effectiveness of these therapies in decreasing risk of stroke is not established (Class IIb; Level of Evidence C).**

Atrial Fibrillation

Atrial fibrillation, even in the absence of cardiac valvular disease, is associated with a 4- to 5-fold increased risk of ischemic stroke due to embolism of stasis-induced thrombi forming in the left atrial appendage.²³⁵ About 2.3 million Americans are estimated to have either sustained or paroxys-

mal atrial fibrillation.²³⁵ Embolism of appendage thrombi associated with atrial fibrillation accounts for about 10% of all ischemic strokes and an even higher fraction in the very elderly in the United States.²³⁶ The absolute stroke rate averages about 3.5% per year for persons aged 70 years with atrial fibrillation, but the risk varies 20-fold among patients depending on age and other clinical features (see below).^{237,238} Atrial fibrillation is also an independent predictor of increased mortality.²³⁹ Paroxysmal atrial fibrillation is associated with an increased stroke risk that is similar to that of chronic atrial fibrillation.²⁴⁰

There is an important opportunity for primary stroke prevention in patients with atrial fibrillation because atrial fibrillation is diagnosed before stroke in many patients. However, a substantial minority of atrial fibrillation-related stroke occurs in patients without a prior diagnosis of the condition. Studies of active screening for atrial fibrillation in patients >65 years of age in primary care settings show that pulse assessment by trained personnel increases detection of undiagnosed atrial fibrillation.^{241,242} Systematic pulse assessment during routine clinic visits followed by 12-lead ECG in those with an irregular pulse resulted in a 60% increase in detection of atrial fibrillation.²⁴¹

Stroke Risk Stratification in Atrial Fibrillation Patients

Estimating stroke risk for individual patients is a critical first step when balancing the benefits and risks of long-term antithrombotic therapy for primary stroke prevention. Four clinical features (prior stroke/transient ischemic attack [TIA], advancing age, hypertension/elevated systolic BP, and diabetes) have consistently been found to be independent risk factors for stroke in atrial fibrillation patients.²³⁷ Although not relevant for primary prevention, prior stroke/TIA is the most powerful risk factor and reliably confers a high risk of stroke (>5% per year, averaging 10% per year). Female sex is inconsistently associated with stroke risk, and the evidence is inconclusive that either heart failure or coronary artery disease is independently predictive of stroke in patients with atrial fibrillation.²³⁷

More than a dozen stroke risk stratification schemes for patients with atrial fibrillation have been proposed based on various combinations of clinical and echocardiographic predictors.²³⁸ None have been convincingly shown to be “the best.” Two closely related schemes have received wide attention and are summarized in Table 9.

The CHADS₂ scheme uses a point system, with 1 point each for congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus, and 2 points for prior stroke/TIA.²⁴³ This scheme has been tested in 6 independent cohorts of patients with atrial fibrillation, with a score of 0 points indicating low risk (0.5% to 1.7%); 1 point, moderate risk (1.2% to 2.2% per year); and ≥2 points, high risk (1.9% to 7.6% per year).²³⁸ The American College of Cardiology/AHA/European Society of Cardiology (ACC/AHA/ESC) 2006 guideline recommendation for stroke risk stratification in atrial fibrillation patients is almost identical to the CHADS₂ scheme if patients with CHADS₂ scores of 2 are considered moderate risk, but the guideline also includes echocardiographically defined impaired left ventricular sys-

Table 9. Stroke Risk Stratification Schemes for Patients With Atrial Fibrillation

CHADS ₂ ²⁴³	ACC/AHA/ESC 2006 Guidelines ^{*244}
Congestive heart failure†–1 point	High risk
Hypertension‡–1 point	Prior thromboembolism
Age >75 y–1 point	>2 moderate risk features
Diabetes–1 point	Moderate risk
Stroke/TIA–2 points	Age >75 y
	Heart failure
Risk scores range from 0–6 points	Hypertension‡
Low risk=0 points	Diabetes
Moderate risk=1 point	LVEF <35% or fractional shortening <25%
High risk=>2 points	Low risk
	No moderate- or high-risk features

ACC/AHA/ESC indicates American College of Cardiology/American Heart Association/European Society of Cardiology; LVEF, left ventricular ejection fraction; and TIA, transient ischemic attack.

*This scheme is identical to the stratification recommended by the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition).²⁴⁷

†Recent heart failure exacerbation was used in original stratification, but subsequently any prior heart failure has supplanted.

‡History of hypertension; not specifically defined.

tolic function as a risk factor.²⁴⁴ In either scheme, patients with recurrent paroxysmal atrial fibrillation are stratified according to the same criteria as those with persistent atrial fibrillation,^{245,246} but those with a single brief episode or self-limited atrial fibrillation due to a reversible cause are not included.

The threshold of absolute stroke risk warranting anticoagulation is importantly influenced by estimated bleeding risk during anticoagulation, patient preferences, and access to good monitoring of anticoagulation. Most experts agree that adjusted-dose warfarin should be given to high-risk patients with atrial fibrillation, with aspirin for those deemed to be at low risk. There is more controversy for those at moderate risk, with some favoring anticoagulation for all atrial fibrillation patients except those estimated to be at low risk.²⁴⁷ The 2006 ACC/AHA/ESC guideline indicates that “antithrombotic therapy with either aspirin or vitamin K antagonists is reasonable based on an assessment of risk of bleeding complications, ability to safely sustain adjusted chronic anticoagulation, and patient preferences” for those deemed moderate risk (equivalent to a CHADS₂ score of 1).²⁴⁴ A recent large cohort study did not find a net clinical benefit of warfarin for atrial fibrillation patients with a CHADS₂ score of 1 once intracranial hemorrhage was considered.²⁴⁸ Patients >75 years of age with atrial fibrillation benefit substantially from anticoagulation,²⁴² and age is not a contraindication to use of anticoagulation.

Treatment to Reduce Stroke Risk in Atrial Fibrillation Patients

Therapeutic cardioversion and rhythm control do not reduce stroke risk,²⁴⁹ and percutaneous left atrial occlusion is of unclear overall benefit.^{250,251} On the basis of consistent results

Table 10. Efficacy of Warfarin and Aspirin for Stroke Prevention in Atrial Fibrillation: Meta-Analysis of Randomized Trials*

Comparison	No. of Trials	No. of Patients	Relative Risk Reduction, 95% CI	Estimated NNT for Primary Prevention†
Adjusted-dose warfarin vs control	6	2900	64% (49–74)	40
Aspirin vs control	7	3990	19% (–1–35)	140
Adjusted-dose warfarin vs aspirin	9	4620	39% (19–53)	90

CI indicates confidence interval, and NNT, No. needed to treat.

*Adapted from Hart et al.²⁵² Includes all strokes (ischemic and hemorrhagic).

†No. needed to treat for 1 y to prevent 1 stroke, based on a 3.5%/y stroke rate in untreated patients with atrial fibrillation and without prior stroke or TIA.

from >12 randomized trials, anticoagulation is established as highly efficacious for prevention of stroke and moderately efficacious for reducing mortality.²⁵²

Thirty-three randomized trials involving >60 000 participants have compared various antithrombotic agents with placebo/control or with one another.^{252,253–256} Treatment with adjusted-dose warfarin (target INR, range 2.0 to 3.0) provides the greatest protection against stroke [relative risk reduction (RRR) 64%; 95% CI, 49% to 74%], virtually eliminating the excess number of ischemic strokes associated with atrial fibrillation if the intensity of anticoagulation is adequate and reducing all-cause mortality by 26% (95% CI, 3% to 23%) (Table 10).²⁵² In addition, anticoagulation reduces stroke severity and poststroke mortality.^{257–259} Aspirin offers modest protection against stroke (RRR, 22%; 95% CI, 6% to 35%).²⁵² There are no convincing data that favor one dose of aspirin (50 mg to 325 mg daily) over another. Compared with aspirin, adjusted-dose warfarin reduces stroke by 39% (RRR; 95% CI, 22% to 52%) (Table 10).^{252,255}

Two randomized trials assessed the potential role of the combination of clopidogrel (75 mg daily) plus aspirin (75 mg to 100 mg daily) for preventing stroke in patients with atrial fibrillation. The Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE) investigators compared this combination antiplatelet regimen with adjusted-dose warfarin (target INR, 2.0 to 3.0) in patients with atrial fibrillation with 1 additional risk factor for stroke in ACTIVE W and found a 40% relative risk reduction (95% CI, 18% to 56%, $P=0.001$) for stroke with warfarin compared with the dual antiplatelet regimen.^{252,260} ACTIVE A compared clopidogrel combined with aspirin with aspirin alone in atrial fibrillation patients deemed unsuitable for warfarin anticoagulation and who had at least 1 additional risk factor for stroke (approximately 25% were deemed unsuitable because of concern for warfarin-associated bleeding).²⁵³ Dual antiplatelet therapy resulted in a 28% relative risk reduction (95% CI, 17% to 38%; $P=0.0002$) in all strokes (including parenchymal ICH) over treatment with aspirin alone, but major bleeding was increased by 57% (increase in RR; 95% CI, 29% to 92%, $P<0.001$); overall and in absolute terms, major vascular events (the study primary end point) were decreased 0.8% per year, but major hemorrhages increased 0.7% per year (RR for major vascular events and

major hemorrhages, 0.97; 95% CI, 0.89 to 1.06; $P=0.54$). Disabling/fatal stroke, however, was decreased by dual antiplatelet therapy (RRR, 26%; 95% CI, 11% to 38%; $P=0.001$).

On the basis of results from ACTIVE W and A, adjusted-dose warfarin is superior to clopidogrel plus aspirin, and clopidogrel plus aspirin is superior to aspirin alone for stroke prevention; however, it is important to recognize that the latter benefit is limited by a concomitant increase in major bleeding complications. Less clear is how bleeding risks and rates compare between adjusted-dose warfarin and clopidogrel plus aspirin in warfarin-naïve patients.^{260,261}

The initial 3 months of adjusted-dose warfarin are a particularly high-risk period for bleeding,²⁶² and especially close monitoring of anticoagulation is advised during this interval. ICH is the most devastating complication of anticoagulation; the absolute increase in ICH remains relatively small if the INR is ≤ 3.5 .²⁵⁸ Treatment of hypertension in atrial fibrillation patients reduces the risk of both ICH and ischemic stroke; hence, it has double benefits for atrial fibrillation patients who have received anticoagulation.^{263–265} Anticoagulation of elderly atrial fibrillation patients should come with a firm commitment both by the physician and patient to control BP (target systolic BP, <140 mm Hg). Warfarin therapy is inherently risky, and in 2008 The Joint Commission challenged hospitals to “reduce the likelihood of harm associated with the use of anticoagulation therapy” as a national patient safety goal.²⁶⁶ A consensus statement about the delivery of optimal anticoagulant care has recently been published.²⁶⁷

The benefits versus risks of the combined use of antiplatelet agents in addition to warfarin in elderly atrial fibrillation patients are inadequately defined. Combined use of warfarin with antiplatelet therapy increases the risk of intracranial and extracranial hemorrhage.²⁶⁸ Adjusted-dose anticoagulation (target INR, 2.0 to 3.0) appears to offer protection against MI that is comparable to aspirin in atrial fibrillation patients,²⁶⁹ and the addition of aspirin to warfarin is not recommended for most atrial fibrillation patients with stable coronary artery disease.^{244,247} Data are meager on the type and duration of optimal antiplatelet therapy when combined with warfarin in atrial fibrillation patients with recent coronary angioplasty and stenting.^{270,271} Clopidogrel plus aspirin combined with warfarin has been suggested for 9 to 12 months after placement of bare-metal coronary stents. Because drug-eluting stents require even more prolonged antiplatelet therapy, bare-metal stents are generally preferred for atrial fibrillation patients taking warfarin.^{272,273} A lower target INR of 2.0 to 2.5 has been recommended in patients requiring warfarin, aspirin, and clopidogrel after percutaneous coronary intervention during the period of combined antiplatelet and anticoagulant therapy.²⁷⁴

Direct thrombin inhibitors offer a potential alternative to warfarin in patients with atrial fibrillation. Ximelagatran showed promise, but the drug was associated with toxicity and was not approved for use in the United States.^{275,276} In the Randomized Evaluation of Long-term anticoagulant therapy (RE-LY), 18 113 atrial fibrillation patients with at least 1 additional risk factor for stroke were randomly assigned to dabigatran 110 mg twice daily, dabigatran 150 mg twice daily

(double-blind), or adjusted-dose warfarin (target INR, 2.0 to 3.0, open label).²⁵⁶ The primary outcome was stroke or systemic embolism during the mean follow-up of 2 years, which occurred at a rate of 1.7% per year in the warfarin group compared with 1.5% per year in the 110-mg dabigatran group (RR, 0.91; 95% CI, 0.74 to 1.1; $P < 0.001$ for noninferiority) and 1.11% per year in the 150-mg dabigatran group (RR 0.66 versus warfarin; 95% CI, 0.53 to 0.82, $P < 0.001$ for superiority). The rates of major bleeding were 3.4% per year in the warfarin group, 2.7% per year with 110 mg dabigatran ($P = 0.003$), and 3.11% per year with 150 mg dabigatran ($P = 0.31$). Therefore, dabigatran 110 mg/d was associated with rates of stroke and systemic embolism similar to warfarin but with lower rates of major hemorrhages. Dabigatran 150 mg/d was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage compared with warfarin. The comparison with warfarin was open label, a potential source of bias. The rate of major hemorrhage with warfarin was higher than in other recent international trials. Dabigatran may have important drug interactions with P-glycoprotein inhibitors, such as verapamil, amiodarone, and quinidine, and was not tested in patients with significant renal dysfunction.²⁷⁷ The drug has been recently FDA approved for use in the United States.

Summary and Gaps

Atrial fibrillation is a major, prevalent, independent risk factor for ischemic stroke, and adjusted-dose warfarin is highly efficacious for reducing stroke and death in high-risk patients with this condition. Several validated stroke risk stratification schemes are available to identify atrial fibrillation patients who benefit most and least, in absolute terms, from long-term anticoagulation. However, there can be considerable variation in anticipated risk depending on the scheme used. Guidelines vary in recommendations about stroke risk stratification, resulting in confusion among clinicians and nonuniform antithrombotic prophylaxis. Additional research to identify an optimal valid scheme that could be widely endorsed would likely lead to more uniform antithrombotic prophylaxis and better outcomes for stroke prevention.

Adjusted-dose warfarin continues to be underused, particularly among very elderly atrial fibrillation patients. Development of safer, easier-to-use oral anticoagulants might improve the benefit-risk ratio. Novel oral anticoagulants (eg, direct thrombin inhibitors, factor Xa inhibitors) have and are being tested in several ongoing large randomized trials, and additional treatment options appear to be on the horizon. Whether aggressive treatment of systemic hypertension sufficiently lowers the risk of cardioembolic stroke in atrial fibrillation below the threshold warranting anticoagulation is a clinically important, but as yet unanswered, question. Additional large scale magnetic resonance imaging (MRI) studies of cerebral microhemorrhages as predictors of cerebral macrohemorrhages may prove to be useful in the future in relation to the safety of administration of antithrombotic agents, especially in the elderly.

Recommendations

1. Active screening for atrial fibrillation in patients >65 years of age in primary care settings using pulse

taking followed by an ECG as indicated can be useful (*Class IIa; Level of Evidence B*).

- Adjusted-dose warfarin (target INR, 2.0 to 3.0) is recommended for all patients with nonvalvular atrial fibrillation deemed to be at high risk and many deemed to be at moderate risk for stroke who can receive it safely (*Class I; Level of Evidence A*).
- Antiplatelet therapy with aspirin is recommended for low-risk and some moderate-risk patients with atrial fibrillation, based on patient preference, estimated bleeding risk if anticoagulated, and access to high-quality anticoagulation monitoring (*Class I; Level of Evidence A*).
- For high-risk patients with atrial fibrillation deemed unsuitable for anticoagulation, dual antiplatelet therapy with clopidogrel and aspirin offers more protection against stroke than aspirin alone but with increased risk of major bleeding and might be reasonable (*Class IIb; Level of Evidence B*).
- Aggressive management of BP coupled with antithrombotic prophylaxis in elderly patients with atrial fibrillation can be useful (*Class IIa; Level of Evidence B*).

Other Cardiac Conditions

The elimination of possible cardiac sources of embolism is an important way to reduce stroke risk. Cardiogenic embolism is the cause of approximately 20% of ischemic strokes.²⁷⁸ Cryptogenic strokes frequently have embolic features suggesting a cardiogenic origin.²⁷⁹ Cardioembolic strokes are relatively severe, are associated with greater neurological deficits at admission, greater residual deficits at discharge, and greater neurological deficits after 6 months compared with noncardioembolic strokes.²⁸⁰ Cardioembolic strokes may constitute >40% of strokes in patients with cryptogenic stroke.^{279,281} The awareness that different forms of cardiac disease may place an individual patient at increased risk of stroke mandates a comprehensive diagnostic evaluation.^{279,282}

Cardiac conditions associated with a high risk for stroke include atrial arrhythmias (eg, atrial fibrillation/flutter, sick sinus syndrome), left atrial thrombus, primary cardiac tumors, vegetations, and prosthetic cardiac valves.²⁷⁹ Other cardiac conditions that increase the risk of stroke include dilated cardiomyopathy, coronary artery disease, valvular heart disease, and endocarditis. Stroke may occur in patients undergoing cardiac catheterization, pacemaker implantation, and coronary artery bypass surgery.^{283,284} Although the increased risk of stroke associated with these procedures is related to the nature of the procedure, risk is also related to procedural duration.²⁸⁵

The incidence of stroke is inversely proportional to left ventricular ejection fraction.^{286–288} Patients having an acute coronary syndrome are also at an increased risk for stroke,^{289–291} with the risk also inversely proportional to left ventricular ejection fraction^{286–288,289–291} and further increasing with associated atrial fibrillation.^{289–291} The documentation of a left ventricular mural thrombus in these patients further adds to stroke risk.²⁸⁶

Patients with rheumatic mitral valve disease are at increased risk for stroke.²⁹² Mitral valvuloplasty does not eliminate this risk.²⁹³ Thromboembolic events have been

reported in association with and attributed to mitral valve prolapse when no other source could be identified.²⁹⁴ Patients with mitral annular calcification are predisposed to embolic phenomena, particularly in older patients with dense calcifications.²⁹⁵ Systemic embolism from isolated aortic valve disease may also occur.²⁹⁶ It is less frequent in the absence of associated mitral valve disease or atrial fibrillation.²⁹⁶ Multiple mechanical prosthetic valves are currently available and deployed.²⁹² The intensity of anticoagulation should be proportional to the thromboembolic risk of the individual mechanical prosthetic valve.²⁹² Ischemic stroke occurs in 15% to 20% of patients with infective endocarditis.^{297,298} Mitral valve endocarditis carries the greatest stroke risk.²⁹⁷ The management of endocarditis is directed at the underlying etiology.

Cardiac tumors are uncommon and account for a very small minority of embolic events.^{299,300} Congenital cardiac anomalies, such as patent foramen ovale (PFO), atrial septal defect, and atrial septal aneurysm, can be associated with stroke, especially in younger patients (see sections on migraine and coagulopathy).^{301–303} Meta-analysis of case-control studies focused on patients who have had a stroke found an increased risk in those <55 years of age (for PFO: OR, 3.10; 95% CI, 2.29 to 4.21; for atrial septal aneurysm: OR, 6.14; 95% CI, 2.47 to 15.22; and for PFO plus atrial septal aneurysm: OR, 15.59; 95% CI, 2.83 to 85.87).³⁰⁴ In contrast, population-based studies find no increased risk of a first stroke associated with PFO.^{305,306}

For patients with cryptogenic stroke who were found to have a PFO, a subanalysis of the Warfarin Aspirin Recurrent Stroke Study (WARSS) found no difference in the rate of recurrent stroke with warfarin compared with aspirin (HR, 1.29; 95% CI, 0.63 to 2.64; $P=0.049$; 2-year event rates, 17% versus 13%).³⁰⁷ Clinical trials assessing whether closure of a PFO in a patient who has had an otherwise cryptogenic stroke are in progress. There are no trials assessing whether persons found to have a PFO not associated with cerebrovascular symptoms benefit from specific medical or interventional treatments.

Data from the Warfarin and Antiplatelet Therapy in Chronic Heart failure trial (WATCH) have shown no significant differences in morbidity and mortality outcomes in patients with ejection fractions of <35% randomly given aspirin, warfarin, or clopidogrel.³⁰⁸

Some studies have found that atherosclerotic aortic plaques ≥ 4 mm in thickness were associated with an increased risk of stroke, presumably through an embolic mechanism.³⁰⁹ A population-based study found the complexity of aortic arch atheromata, rather than size, was associated with stroke risk.³¹⁰ Another population-based study, however, found that the presence of a complex aortic plaque was not a risk factor for cryptogenic ischemic stroke or TIA but was a marker of generalized atherosclerosis.³¹¹ There are no prospective randomized trials assessing treatment interventions aimed at reducing stroke in patients with atherosclerosis of the ascending aorta.

Summary and Gaps

A variety of cardiac conditions, which may predispose persons to stroke, are addressed in the ACC/AHA practice guidelines. Evaluation of interventions for primary stroke prevention in persons with PFO has not been undertaken, because of the low

risk of ischemic cerebrovascular events. The role of atherosclerotic aortic plaques as an independent risk factor for cryptogenic stroke is unclear, and no primary prevention trials have yet been conducted in patients with this condition.

Recommendations

1. ACC/AHA practice guidelines providing strategies to reduce the risk of stroke in patients with a variety of cardiac conditions, including valvular heart disease,³¹² unstable angina,³¹³ chronic stable angina,³¹⁴ and acute MI are endorsed.³¹⁵
2. Screening for cardiac conditions such as PFO in the absence of neurological conditions or a specific cardiac cause is not recommended (Class III; Level of Evidence A).
3. It is reasonable to prescribe warfarin to post-ST-segment elevation MI patients with left ventricular mural thrombi or an akinetic left ventricular segment to prevent stroke³¹⁵ (Class IIa; Level of Evidence A).

Asymptomatic Carotid Stenosis

The presence of an atherosclerotic stenotic lesion in the extracranial internal carotid artery or carotid bulb has been associated with an increased risk of stroke. Randomized trials have shown that prophylactic carotid endarterectomy (CEA) in appropriately selected patients with carotid stenosis modestly reduces stroke risk compared with patients treated by medical management alone.^{316–318}

Assessment of Carotid Stenosis

A “hemodynamically significant” carotid stenosis produces a drop in pressure, a reduction in flow, or both. This generally corresponds to a 60% diameter-reducing stenosis as measured by catheter angiography using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method.³¹⁹ The NASCET method measures the minimal residual lumen at the level of the stenotic lesion compared with the diameter of the more distal internal carotid artery, where the walls of the artery become parallel. The following formula is used: stenosis=(1–R/D)×100%.

Catheter angiography was used in the randomized trials of CEA for symptomatic disease and the NASCET method used for asymptomatic disease, and this has become the “gold standard” against which other imaging technologies must be compared. Catheter angiography, however, carries a risk of approximately 1% of causing a stroke in patients with atherosclerotic disease.^{316,320} Duplex ultrasound is the least expensive and lowest-risk noninvasive method of screening the extracranial carotid artery for an atherosclerotic stenosis. Although there can be considerable variation in the accuracy of duplex scanning among laboratories,³²¹ certification programs are available that set standards for levels of performance and accuracy. Duplex ultrasound may be insensitive to differentiating high-grade stenosis from complete occlusion. Magnetic resonance angiography (MRA), with and without contrast, is also used as a noninvasive method for evaluating arterial anatomy and has the advantage of providing images of both the cervical and intracranial portions of the carotid artery and its proximal intracranial branches. MRA may overestimate the degree of stenosis, leading to false-positive results, and as

with duplex ultrasound, there may be errors when differentiating high-grade stenosis from complete occlusion. Magnetic resonance contrast material may cause nephrosclerosis and a dermatopathy in patients with renal dysfunction. When concordant, the combination of duplex ultrasound and MRA is more accurate than either test alone.³²²

Computed tomographic angiography is another means of identifying and measuring stenosis of the extracranial carotid artery.³²³ It also has the advantage of being able to evaluate the intracranial circulation. Its disadvantages include radiation exposure and the need for intravenous injection of contrast material. Atherosclerotic calcification may make it difficult to accurately measure the degree of stenosis.

A variety of vascular risk factors reviewed in this guideline are associated with carotid atherosclerosis.^{324,325} The presence of a carotid bruit also identifies persons who may have an underlying carotid stenosis. However, the sensitivity and specificity of a carotid bruit is low.^{326,327} Therefore, the presence of a carotid bruit is not diagnostic of an underlying critical carotid stenosis, nor does the absence of a carotid bruit indicate that no stenosis is present.

CEA for Asymptomatic Stenosis

The first prospective randomized trial comparing CEA with medical management alone was the multi-institutional VA study published in 1986.³¹⁸ In that study 211 patients underwent CEA plus aspirin therapy and 233 patients were treated with aspirin alone. The incidence of death, ipsilateral TIA, and ipsilateral stroke in the surgical group was 10% compared with 19.7% in the group treated with medical management alone ($P < 0.002$). Although not powered for comparison of components of the primary end point, the rate of ipsilateral stroke was 4.7% in the surgical group compared with 8.6% in the nonsurgical group ($P = 0.056$). The Asymptomatic Carotid Atherosclerosis Study (ACAS) was sponsored by the National Institutes of Health.³¹⁶ The initial trial design was similar to the VA trial, but the primary outcome was later modified to the composite of death occurring in the perioperative period and ipsilateral cerebral infarction thereafter. The Data Safety and Monitoring Committee called a halt to the trial because of a clear benefit in favor of CEA after 34 centers randomized 1662 patients. Those randomized to surgery had contrast angiography showing diameter-reducing lesions of $\geq 60\%$ using the NASCET method of measurement. Both those allocated to receive CEA or to no endarterectomy received what was considered best medical management at the time, including aspirin. The aggregate risk over 5 years for ipsilateral stroke, any perioperative stroke, and death was 5.1% for surgical patients and 11% for patients treated medically (RRR, 53%; 95% CI, 22% to 72%). The 30-day stroke morbidity and mortality for CEA was 2.3%, including a 1.2% stroke complication rate for catheter angiography. It was suggested that the complications of angiography should be considered as part of the risk of surgery because an angiogram would not have been performed if surgery were not contemplated. It should be noted that these 2 trials were conducted at a time when best medical management was limited to BP control, diabetes control, and aspirin

antiplatelet therapy. The value of statins and newer antiplatelet drugs had not been established.

The Asymptomatic Carotid Surgery Trial (ACST) was carried out in the United Kingdom³¹⁷ and included 3128 patients with asymptomatic carotid stenoses of $\geq 70\%$ as measured by duplex ultrasonography. Subjects were randomized to immediate CEA versus indefinite deferral of the operation. The trial used different end points than were used in ACAS (perioperative stroke, MI or death and nonperioperative stroke). The net 5-year risks were 6.4% versus 11.8% for any stroke or perioperative death (net gain, 5.4%; 95% CI, 3.0% to 7.8%; $P < 0.0001$). The authors concluded that in asymptomatic patients ≤ 75 years of age with a diameter-reducing stenosis of $\geq 70\%$ as measured by duplex ultrasound, immediate CEA reduced stroke risk by half.

It was pointed out that careful screening of surgeons participating in the clinical trials might lead to results that could not be duplicated in the community. This was particularly true when complications from angiography were removed from the surgical group. When that was done, the 30-day stroke morbidity and mortality for CEA in ACAS was actually 1.54%.³²⁰ The perioperative complication rate in ACST was 3.1%.

The results of CEA for asymptomatic patients were examined in the National Hospital Discharge Database for 2003 and 2004.³²⁸ Stroke morbidity and mortality for CEA was 1.16%. This compares favorably with stroke morbidity and mortality for carotid artery angioplasty and stenting (CAS) during the same interval, which was 2.24%. These estimates, however, are based on administrative data and limited to the procedural hospitalization. A 10-state survey of 30-day complication rates after CEA performed in asymptomatic patients a few years earlier found rates that varied from 1.4% (Georgia) to 6.0% (Oklahoma).³²⁹ Thus, it would appear that the perioperative complication rates for CEA found in the ACAS trial can be similar or better in the community; however, in at least some areas, these rates may be higher.

Endovascular Treatment for Asymptomatic Stenosis

CAS is being performed more frequently,³³⁰ but adequate studies demonstrating its superiority to either endarterectomy or medical management in patients with an asymptomatic carotid artery stenosis are lacking. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial found that CAS was not inferior (within 3%; $P = 0.004$) to endarterectomy (based on a composite outcome of stroke, MI, or death within 30 days or death from neurological cause or ipsilateral stroke between 31 and 365 days) in a group of patients considered to be at high risk for CEA.³³¹ Approximately 70% of subjects had asymptomatic stenosis, with rates of stroke, MI, or death of 5.4% with stenting and 10.2% with endarterectomy ($P = 0.20$) at 30 days. At 1 year the composite end point occurred in 9.9% of CAS patients and 21.5% of CEA patients ($P = 0.02$). Three-year outcomes from the SAPPHIRE trial found that patients receiving CAS have a significantly higher death rate (20.0%) than stroke rate (10.1%),³³² raising questions about the long-term value of the procedure in this high-risk cohort of

patients. In addition, there was no control group of asymptomatic patients treated with only medical therapy.

The Carotid Revascularization using Endarterectomy or Stenting Systems (CaRESS) study was a phase I, multicenter, nonrandomized equivalence cohort study that enrolled subjects with symptomatic carotid artery stenosis >50% or asymptomatic carotid stenosis >75% for carotid stenting with distal protection (n=143) or endarterectomy (n=254).³³³ There were no significant differences in the occurrence of the primary outcome (all-cause mortality or stroke within 30 days, 3.6% CEA versus 2.1% CAS, or 1 year, 13.6% CEA versus 10.0% CAS of the procedure). Multivariable analysis did not show a difference in outcomes based on baseline symptom status; however, outcomes in the asymptomatic subgroup were not presented separately, and 1-year stroke and death rates were higher with either procedure than would be expected for a purely asymptomatic cohort. A retrospective, nonrandomized review of asymptomatic patients undergoing CEA (n=145) or CAS (n=93) at a single site found no differences in the rates of periprocedural complications.³³⁴

Several industry-supported registries have been reported with periprocedural complication rates of 2.1% to 8.3%.³³⁵ The lack of medically treated control groups makes the results of these registries difficult to interpret.

The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) enrolled both symptomatic and asymptomatic patients with carotid stenosis who could technically undergo either procedure.³³⁶ Asymptomatic patients could be included if they had a stenosis $\geq 60\%$ on angiography, $\geq 70\%$ on ultrasonography, or $\geq 80\%$ on computed tomographic angiography or MRA if the stenosis on ultrasonography was 50% to 69%. Randomization was stratified according to symptom status. The CREST primary end point was a composite of stroke, MI, or death from any cause during the periprocedural period or any ipsilateral stroke within 4 years after randomization. There was no difference in the estimated 4-year occurrence of the primary end point between stenting (7.2%) and endarterectomy (6.8%; HR, 1.11; 95% CI, 0.81 to 1.51; $P=0.51$) with no statistical heterogeneity based on symptom status ($P=0.84$). The overall estimated 4-year rate of any periprocedural stroke or death or postprocedural ipsilateral stroke, however, was higher with stenting (HR, 1.50; 95% CI, 1.05 to 2.15; $P=0.03$). Similar to the overall trial results, the 4-year primary end point rates for asymptomatic subjects were not different for stenting (5.6%) compared with endarterectomy (4.9%; HR, 1.17; 95% CI, 0.69 to 1.98; $P=0.56$) and not different in the periprocedural period (3.5% for stenting versus 3.6% for endarterectomy; HR, 1.02; 95% CI, 0.55 to 1.86; $P=0.96$). Particularly important for asymptomatic patients, post hoc analysis found that major and minor stroke negatively affected quality of life at 1 year (SF-36 [Short Form Health Survey], physical component scale) with minor stroke affecting mental health at 1 year (SF-36, mental component scale), but the effect of periprocedural MI was less certain. In the periprocedural period the point estimates for rates of any stroke or death were low but tended to be higher for stenting (2.5% versus 1.4% for endarterectomy; HR, 1.88; 95% CI, 0.79 to 4.42; $P=0.15$); the estimated 4-year rates of any periprocedural stroke

or death or postprocedural ipsilateral stroke were 4.5% for stenting compared with 2.7% for endarterectomy (HR, 1.86; 95% CI, 0.95 to 3.66; $P=0.07$). It should be noted that CREST was not powered for subgroup analyses based on symptom status. The advantage of revascularization over medical therapy alone was not addressed by CREST, which did not randomize a group of asymptomatic subjects to medical therapy without stenting or endarterectomy. An industry-sponsored study, the Asymptomatic Carotid stenosis, stenting versus endarterectomy Trial (ACT-1), is in progress.

Although carotid artery stenosis is a risk factor for stroke, it is not possible to identify a subgroup of persons in the general population for whom screening would be of benefit, and there are no studies showing that general screening would reduce stroke risk on a population basis.³³⁷ Population screening for asymptomatic carotid artery stenosis is not recommended by the US Preventive Services Task Force, which found “no direct evidence that screening adults with duplex ultrasonography for asymptomatic stenosis reduces stroke.”³³⁷ Screening for other risk factors are addressed in relevant sections of this guideline.

Summary and Gaps

Medical therapy has advanced since clinical trials comparing endarterectomy plus “best” medical therapy compared with “best” medical therapy alone in patients with an asymptomatic carotid artery stenosis.³³⁸ Recent studies suggest that the annual rate of stroke in medically treated patients with an asymptomatic carotid artery stenosis has fallen to approximately $\leq 1\%$.^{338–340} Interventional therapy has also advanced, particularly with regard to perioperative management and device design. Because the absolute reduction in stroke risk with endarterectomy in patients with symptomatic stenosis is small, however, the benefit of revascularization may be reduced or eliminated with current medical therapy.³³⁸ The benefit of endarterectomy for carotid stenosis in asymptomatic women remains controversial.³⁴¹ Given the reported 30-day, 1-year, and 3-year results in the high surgical risk population, it remains uncertain whether this group of asymptomatic patients should have any revascularization procedure. More data are needed to compare long-term outcomes following CEA and CAS. The US Food and Drug Administration has not approved the use of CAS for asymptomatic stenosis.

Recommendations

1. **Patients with asymptomatic carotid artery stenosis should be screened for other treatable risk factors for stroke with institution of appropriate lifestyle changes and medical therapy (Class I; Level of Evidence C).**
2. **Selection of asymptomatic patients for carotid revascularization should be guided by an assessment of comorbid conditions and life expectancy, as well as other individual factors, and should include a thorough discussion of the risks and benefits of the procedure with an understanding of patient preferences (Class I; Level of Evidence C).**
3. **The use of aspirin in conjunction with CEA is recommended unless contraindicated because aspirin was used in all of the cited trials of CEA as an antiplatelet drug (Class I; Level of Evidence C).**

4. Prophylactic CEA performed with <3% morbidity and mortality can be useful in highly selected patients with an asymptomatic carotid stenosis (minimum 60% by angiography, 70% by validated Doppler ultrasound) (*Class IIa; Level of Evidence A*). It should be noted that the benefit of surgery may now be lower than anticipated based on randomized trial results, and the cited 3% threshold for complication rates may be high because of interim advances in medical therapy.
5. Prophylactic carotid artery stenting might be considered in highly selected patients with an asymptomatic carotid stenosis ($\geq 60\%$ on angiography, $\geq 70\%$ on validated Doppler ultrasonography, or $\geq 80\%$ on computed tomographic angiography or MRA if the stenosis on ultrasonography was 50% to 69%). The advantage of revascularization over current medical therapy alone is not well established (*Class IIb; Level of Evidence B*).
6. The usefulness of CAS as an alternative to CEA in asymptomatic patients at high risk for the surgical procedure is uncertain (*Class IIb; Level of Evidence C*).
7. Population screening for asymptomatic carotid artery stenosis is not recommended (*Class III; Level of Evidence B*).

Sickle Cell Disease

Sickle cell disease (SCD) is an autosomal recessive inherited disorder in which the abnormal gene product is an altered hemoglobin β -chain. Although the clinical manifestations are highly variable, SCD typically manifests early in life as a severe hemolytic anemia with painful episodes involving the extremities and bones ("vaso-occlusive crises"), bacterial infections, and organ infarctions, including stroke. Other effects include cognitive deficits related to MRI-demonstrated strokes and otherwise asymptomatic white matter hyperintensities.^{342,343}

Prevention of stroke is most important for patients with homozygous SCD disease because the majority of strokes associated with SCD occur in these patients. The prevalence of stroke by 20 years of age is at least 11%,³⁴⁴ with a substantial number having "silent" strokes on brain MRI.³⁴³ The highest stroke rates occur in early childhood. Transcranial Doppler ultrasound (TCD) has made identification of those at highest stroke risk possible, allowing rational decisions about treatment for primary stroke prevention.^{345,346} The risk of stroke during childhood in those with SCD is 1% per year, but patients with TCD evidence of high cerebral blood flow velocities (time-averaged mean velocity >200 cm/s) have a stroke rate of $>10\%$ per year.^{346,347} Retrospective analysis of the Stroke Prevention Trial in Sickle Cell Anemia (STOP) study data suggested that elevations >170 cm/s in the anterior cerebral artery increased stroke risk after controlling for the middle cerebral artery/internal carotid artery velocities.³⁴⁸

The frequency of screening needed to detect most cases at risk has not been systematically determined. The STOP study, which compared periodic blood transfusion with standard care in 130 children with SCD, used time-averaged means of the maximum velocity. Peak systolic velocity may also be used with a threshold for prophylactic transfusion placed at 250 cm/s.³⁴⁹ In general, younger children and those

with relatively high cerebral blood flow velocities should be monitored more frequently because of a higher risk of conversion to abnormal in younger patients and in those with TCD velocities closer to the 200 cm/s cutoff.³⁵⁰ Despite strong evidence for its value, TCD screening rates are often suboptimal due to patient and provider factors.³⁵¹

Although TCD remains the most extensively validated stroke prediction tool, other methods are being tested. One study found that nocturnal desaturation predicted neurological events in 95 patients with SCD (age, 7.7 years median; range, 1 to 23 years) followed for a median of 6 years.³⁵² There were 7 strokes among 19 patients with events. Mean overnight oxygen saturation and TCD independently predicted events.³⁵² A trial of management of nocturnal hypoxemia is under way.

Explaining why TCD velocities increase in only some children with SCD might lead to better prediction and more targeted intervention. Multivariate logistic regression analysis in 1 study found that G6PD deficiency (OR, 3.36; 95% CI, 1.10 to 10.33; $P=0.034$), absence of α -thalassemia (OR, 6.45; 95% CI, 2.21 to 18.87; $P=0.001$), hemoglobin (OR per gram per deciliter, 0.63; 95% CI, 0.41 to 0.97; $P=0.038$), and lactate dehydrogenase levels (OR per international unit per liter, 1.001; 95% CI, 1.000 to 1.002; $P=0.047$) were independent risk factors for abnormally high velocities.³⁵³ This confirmed a previously reported protective effect of α -thalassemia³⁵⁴ and found for the first time that G6PD deficiency and hemolysis independently increased the risk of an abnormal TCD study result.³⁵⁵ Another study found independent effects of hemoglobin and aspartate transaminase levels, whereas age had borderline significance.³⁵⁶

Genetic factors may also affect stroke risk in patients with SCD. A study evaluated 108 single-nucleotide polymorphisms (SNPs) in 39 candidate genes in 1398 individuals with SCD using Bayesian networks. The study found that 31 SNPs in 12 genes interact with fetal hemoglobin to modulate the risk of stroke.³⁵⁷ This network of interactions includes 3 genes in the transforming growth factor- β pathway and selectin P, which is associated with stroke in the general population. The model was validated in a different population, predicting the occurrence of stroke in 114 individuals with 98.2% accuracy.³⁵⁷ STOP data were used to confirm previous findings of associations between the tumor necrosis factor (TNF)(-308) G/A, IL4R 503 S/P, and ADRB2 27 Q/E polymorphisms and large-vessel stroke risk in SCD.³⁵⁸ Consistent with prior findings, the TNF(-308) GG genotype was associated with a >3 -fold increased risk of large-vessel disease (OR, 3.27; 95% CI, 1.6 to 6.9; $P=0.006$). Unadjusted analyses also showed a previously unidentified association between the leukotriene C4-synthase (-444) A/C variant and large-vessel stroke risk.³⁵⁸

Few studies have been done in adults to determine if TCD also predicts stroke in older persons with SCD. One study compared TCD velocities in SCD adults ($n=56$) with those of healthy controls ($n=56$). Velocities in SCD adults were lower than those found in children, higher than in controls, and negatively correlated with the hematocrit in both groups.³⁵⁹ Another study found no examples of high TCD (>200 cm/s) among 112 adults with SCD. Mean velocity was 110 cm/s,

which is higher than in normal adults but lower than in children with SCD.³⁶⁰ At present no TCD or other predictive criteria for adults have been evaluated.

Regular red blood cell transfusion is the only preventive intervention proven in randomized trials to prevent stroke in patients with SCD. STOP randomized children with SCD who had an abnormal (high risk) result on TCD to either standard care (eg, episodic transfusion as needed for pain) or regular red blood cell transfusion an average of 14 times per year for >2 years with a target reduction of hemoglobin S from a baseline of >90% to <30%. The risk of stroke was reduced from 10% per year to <1%.³⁴⁷ Unless exchange methods in which blood is removed from the patient with each transfusion are used, long-term transfusion is associated with iron toxicity that must be treated with chelation.³⁶¹ In the STOP study, there was no evidence of transfusion-related infection, but iron overload and alloimmunization remain important transfusion risks.³⁶² To address these risks, STOP II tested whether long-term transfusions for primary stroke prevention could be safely discontinued after at least 30 months (range, 30 to 91 months) in children who had not had an overt stroke and who had reversion to low-risk TCD velocities (defined as <170 cm/s time-averaged mean) with long-term transfusion therapy. The study end points were the first occurrence of reversion of TCD to abnormal, confirmed by ≥ 2 TCD studies with mean velocities of ≥ 200 cm/s or stroke. The study was stopped early when an interim analysis showed poorer outcomes in those who had transfusion therapy discontinued. Eight children (approximately 20%) tolerated removal from long-term transfusion therapy, but there was a high TCD reversion rate and a small risk of stroke despite frequent TCD surveillance.^{363,364}

MRI has also been used to identify children with SCD who are at higher risk of clinical events. Observational data from the Cooperative Study of Sickle Cell Disease, which preceded the use of TCD-based monitoring, found that 8.1% of children with an asymptomatic MRI lesion versus 0.5% of those with a normal MRI had a stroke during the ensuing 5 years.³⁶⁵ A randomized controlled trial of MRI-guided prophylactic transfusion is in progress (the Silent Infarct Transfusion [SIT] Study).³⁶⁶ The role of therapies other than transfusion, 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. Bone marrow transplantation is usually entertained after stroke, but TCD and other indices of cerebral vasculopathy have also been used as an indication for myeloablative stem-cell transplantation. One study of 55 patients with a median follow-up of 6 years found overall and event-free survival rates of 93% and 85%, respectively. No new ischemic lesions were reported, and TCD velocities decreased.³⁶⁷

Hydroxyurea was evaluated in a study of 127 children with SCD. In 72 patients evaluated by TCD studies, 34 were at risk of stroke, and only 1 patient had a cerebrovascular event after a follow-up of 96 patient-years.³⁶⁸ A study of 291 screened children with SCD included clinical and imaging follow-up of 35 children with abnormal TCD studies who were placed on transfusion therapy. Median follow-up was 4.4 years. Of 13 patients with normalized velocities on transfusion, 10 had

normal MRAs, and transfusion therapy was stopped and hydroxyurea begun. Four of these 10 patients redeveloped high velocities, so only 6 patients remained transfusion-free.³⁵³ In another study, the adjusted mean change in TCD velocities was -13.0 cm/s (95% CI, -20.19 to -5.92) in an hydroxyurea-treated group and +4.72 cm/s (95% CI, -3.24 to 12.69) in controls ($P < 0.001$).³⁶⁹ Children ($n = 59$) for whom hydroxyurea therapy was initiated for clinical severity who had pretreatment baseline TCD measurements, 37 of whom had increased flow velocities (≥ 140 cm/s), were enrolled in a prospective phase 2 trial with TCD velocities measured at maximum tolerated dose and 1 year later.³⁷⁰ At hydroxyurea maximum tolerated dose [mean ± 1 standard deviation (SD) = 27.9 ± 2.7 mg/kg per day], decreases were observed in bilateral middle carotid artery velocities. The magnitude of TCD velocity decline correlated with the maximal baseline TCD value.³⁷⁰ These studies suggest a possible role in primary stroke prevention that needs to be confirmed.

No systematic data are available on prevention of stroke in adults with SCD. Improvements in care have increased life expectancy in persons with SCD, and it is anticipated that stroke prophylaxis in older SCD patients will pose an increasing challenge in the future.

Summary and Gaps

TCD can be used to identify children with SCD who are at high risk of stroke and who may benefit from transfusion therapy. Although the optimal screening interval has not been established, it remains the most extensively validated method for risk assessment. Improvements in prediction may be possible by evaluating the anterior cerebral artery velocity, modeling laboratory or genetic variables, and measuring oxygen desaturation. On the basis of STOP II, even those whose risk of stroke decreases with transfusion therapy based on TCD criteria have an approximately 50% probability of reverting to high risk or having a stroke if transfusion therapy is discontinued. Alternative methods of maintenance therapy that are safer than transfusion need to be developed in view of the data indicating the need for ongoing active treatment despite TCD normalization and the risk of iron toxicity with repeated transfusions. Predictive methods other than TCD (eg, MR-based techniques) need to be systematically compared with and combined with TCD to further refine the estimation of stroke risk in individuals. Considerable phase II evidence suggests that hydroxyurea may be beneficial for primary stroke prevention, and it needs to be compared with transfusion for primary prevention in a phase III trial. Data on risk of stroke and prevention options in adults with SCD are needed, and a stroke prevention strategy for adults needs to be developed. General measures are given in Table 7.

Recommendations

1. **Children with SCD should be screened with TCD starting at age 2 years (Class I; Level of Evidence B).**
2. **Although the optimal screening interval has not been established, it is reasonable for younger children and those with borderline abnormal TCD velocities to be screened more frequently to detect development of high-risk TCD indications for intervention (Class IIa; Level of Evidence B).**

3. **Transfusion therapy (target reduction of hemoglobin S from a baseline of >90% to <30%) is effective for reducing stroke risk in those children at elevated stroke risk (Class I; Level of Evidence B).**
4. **Pending further studies, continued transfusion, even in those with TCD velocities that revert to normal, is probably indicated (Class IIa; Level of Evidence B).**
5. **In children at high risk for stroke who are unable or unwilling to be treated with regular red blood cell transfusion, it might be reasonable to consider hydroxyurea or bone marrow transplantation (Class IIb; Level of Evidence C).**
6. **MRI and MRA criteria for selection of children for primary stroke prevention using transfusion have not been established, and these tests are not recommended in place of TCD for this purpose (Class III; Level of Evidence B).**
7. **Adults with SCD should be evaluated for known stroke risk factors and managed according to the general guidelines in this statement (Class I; Level of Evidence A).**

Postmenopausal Hormone Therapy

The Women's Health Initiative (WHI), a randomized trial of conjugated equine estrogens (CEE) combined with medroxyprogesterone acetate (MPA) versus placebo in women 55 to 79 years of age,³⁷¹ has had a profound impact on the practice of prescribing these therapies to postmenopausal women.³⁷² Although earlier secondary prevention trials, such as the Heart Estrogen Replacement Study³⁷³ and the Women Estrogen Stroke Trial,³⁷⁴ showed no protection from stroke, the WHI reported an increased risk with any therapy containing CEE.^{371,375} Therefore, the AHA guidelines on cardiovascular prevention in women recommended against prescribing these hormone therapies for prevention of CVD.³⁷⁶

Additional analyses of the WHI focused on specific subgroups of women to determine those at particularly high risk.³⁷⁷ The risk of stroke with CEE was limited to ischemic (HR, 1.55; 95% CI, 1.19 to 2.01) and not hemorrhagic stroke (HR, 0.64; 95% CI, 0.35 to 1.18). There was no difference based on stroke etiologic subtype, severity, or mortality.³⁷⁷ Women with no prior history of CVD were at higher risk (HR, 1.73; 95% CI, 1.28 to 2.33) compared with women with a prior history (HR, 1.01; 95% CI, 0.58 to 1.75). Women 50 to 59 years of age had a lower risk (HR, 1.09; 95% CI, 0.54 to 2.21) than those 60 to 69 years of age (HR, 1.72; 95% CI, 1.17 to 2.54), or those 70 to 79 years of age (HR, 1.52; 95% CI, 1.02 to 2.29).³⁷⁷ Although the cohort was primarily white, when the estimates were adjusted for adherence to the study drugs, the risk for blacks was higher (HR, 3.48; 95% CI, 1.12 to 10.8) and remained essentially unchanged for whites (HR, 1.67; 95% CI, 1.12 to 2.50).³⁷⁷ No other baseline factors, such as use of aspirin or statins, or BP changes (as a time-dependent variable) were associated with lower or higher risk of stroke.³⁷⁷

One of the major limitations of the WHI was that the mean age of participants was about 63 years and therefore >5 years postmenopause. There is emerging interest in the "timing hypothesis," which holds that estrogens promote beneficial effects on the vasculature in young women and those with healthy blood vessels. Beyond 5 years postmenopause or

when atherosclerosis is advanced, however, estrogen is harmful and further promotes the acceleration of atherosclerosis.³⁷⁸ An analysis of the WHI subjects was performed to test this hypothesis, and interestingly, women <10 years from menopause had no increased risk of coronary heart disease events with any CEE (alone or CEE/MPA; HR, 0.76; 95% CI, 0.50 to 1.16), whereas women \geq 20 years postmenopause had an elevated risk (HR, 1.28; 95% CI, 1.03 to 1.58; *P* for trend=0.02). There was, however, no trend for increased stroke based on years since menopause (*P* for trend=0.36).³⁷⁹ An analysis of the Nurses' Health Study reported similar findings: women using hormone therapy had an increased risk of stroke regardless of age at initiation or years since menopause.³⁸⁰ The Estonian trial of hormone therapy, a study of women 50 to 64 years of age, also confirmed the findings of the WHI. There was a trend toward an increase in cerebrovascular events in women taking the same dose and formulation of hormone therapy as in the WHI (HR, 1.24; 95% CI, 0.85 to 1.82).³⁸¹ The Kronos Early Estrogen Prevention Study (KEEPS) is an ongoing trial of women 42 to 58 years of age who are within 36 months of their final menstrual period and randomized to estrogen replacement in low doses (0.45 mg CEE), transdermal formulation (50 μ g/wk), and combined with cyclic oral, micronized progesterone 200 mg for 12 days each month.³⁸² The primary outcomes are progression of subclinical atherosclerosis as measured by carotid IMT and coronary calcium scores.³⁸² This trial will provide information specifically related to the timing hypothesis, although a weakness will be that it will provide information regarding only intermediate outcomes and not those of interest, such as coronary disease and stroke events.

Raloxifene, a selective estrogen receptor modulator (SERM), has been studied extensively for its effects in preventing breast cancer and bone density loss, which can increase risk of hip fractures. Two large clinical trials of raloxifene and tamoxifen have been published. The Raloxifene Use for The Heart (RUTH) trial was designed to determine whether women randomly assigned to raloxifene 60 mg versus placebo would have a lower risk of coronary disease, breast cancer, and stroke as a secondary outcome.³⁸³ After a median follow-up of 5.6 years, the trial showed no benefit for nonfatal or fatal MI/acute coronary syndromes (HR, 0.95; 95% CI, 0.84 to 1.07) or nonfatal stroke (HR, 1.10; 95% CI, 0.92 to 1.32). There was an increased risk of fatal strokes (HR, 1.49; 95% CI, 1.00 to 1.24; *P*=0.05) in the women randomized to raloxifene. A detailed secondary analysis of these stroke events revealed an absolute risk of 0.07 per 100 women treated for 1 year.³⁸⁴ This risk was evident only after 3 years of follow-up, and no specific characteristics were associated with risk of fatal stroke.³⁸⁴ The Study of Tamoxifen and Raloxifene (STAR) trial was designed to compare both SERMs for prevention of invasive breast cancer and other cardiovascular events. This study found no difference in stroke rates between these 2 treatments.³⁸⁵

Tibolone, a drug with metabolites that have estrogenic, progestogenic, and androgenic activities, is used for treatment of menopausal symptoms as well as osteoporosis in >90 countries. The Long-Term Intervention on Fractures with

Tibolone (LIFT) trial was a randomized, double-blind, placebo-controlled clinical trial of tibolone 1.25 mg daily versus placebo.³⁸⁶ The trial showed that the drug significantly reduced the risk of vertebral (relative hazard, 0.55; 95% CI, 0.41 to 0.74) and nonvertebral fractures (relative hazard, 0.74; 95% CI, 0.58 to 0.93; $P=0.01$). The trial was stopped earlier than planned because the tibolone group had an increased risk of stroke (relative hazard, 2.19; 95% CI, 1.14 to 4.23; $P=0.02$), although there was no increased risk of coronary heart disease or venous thromboembolism.³⁸⁶

Summary and Gaps

An increased risk of stroke is associated with the tested forms of hormone replacement therapy, which include CEE/MPA in standard formulations. There is no benefit in stroke protection with raloxifene or tamoxifen, and raloxifene may increase the risk of fatal stroke. Tibolone is also associated with an increased risk of stroke. Prospective randomized trials of alternative forms of hormone therapy are ongoing, although the primary outcomes are an intermediate measurement of subclinical atherosclerosis and not stroke. The use of hormone therapy for other indications needs to be informed by the risk estimate for vascular outcomes provided by the clinical trials that have been reviewed.

Recommendations

1. **Hormone therapy (CEE with or without MPA) should not be used for primary prevention of stroke in postmenopausal women (Class III; Level of Evidence A).**
2. **SERMs, such as raloxifene, tamoxifen, or tibolone, should not be used for primary prevention of stroke (Class III; Level of Evidence A).**

Oral Contraceptives

The risk of stroke, particularly ischemic stroke, with use of OCs continues to be controversial. This is primarily due to inconsistent study results, geographic variability among the cohorts studied, and lack of any randomized controlled trials. Much of the perceived risk of stroke with OCs is based on early studies with high-dose preparations (ie, first-generation OCs containing $\geq 50 \mu\text{g}$ estradiol).^{387,388} A meta-analysis of 16 case-control and cohort studies between 1960 and 1999 calculated that OC use was associated with a 2.75 increased odds (95% CI, 2.24 to 3.38) of stroke.³⁸⁹ A later meta-analysis of 20 studies published between 1970 and 2000 that separated the studies by design (case-control versus cohort) found no increased risk of stroke in the cohort studies but an increased risk with use of OCs in case-control studies (OR, 2.13; 95% CI, 1.59 to 2.86).³⁹⁰ Importantly, only 2 of the 4 cohort studies reported strokes by type, with the risk increased for thrombotic but not hemorrhagic strokes.³⁹⁰ An additional meta-analysis of studies from 1980 to 2002 limited only to low-dose combined OCs (second and third generation only) also showed a comparable increased risk with OC use (OR, 2.12; 95% CI, 1.56 to 2.86).²⁵

Data have been less consistent for hemorrhagic stroke than for ischemic stroke. The World Health Organization (WHO) reported an overall slightly increased risk of hemorrhagic stroke (both intracerebral and subarachnoid) with use of OCs; however,

this risk was present in developing countries but not in Europe.¹²⁸ Also, European women >35 years of age were at increased risk of SAH, whereas women in developing nations were at increased risk of both ICH and SAH. Women with hypertension and who smoked cigarettes were also at increased risk.¹²⁹

More recent studies have provided additional data that can help identify women at risk of stroke with use of OCs. Besides the well-established risk associated with older age, cigarette smoking, hypertension, and migraine headaches,³⁹¹ the Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO) study from the Netherlands showed that women who were obese (OR, 4.6; 95% CI, 2.4 to 8.9) and had a history of hypercholesterolemia (OR, 10.8; 95% CI, 2.3 to 49.9) were also at increased risk compared with women with these risk factors who did not use OCs.³⁹² A separate analysis of this same cohort showed that women using OCs who were also found to have prothrombotic mutations such as factor V Leiden (OR, 11.2; 95% CI, 4.2 to 29.0) and methyl tetrahydrofolate reductase or MTHFR 677TT mutation (OR, 5.4; 95% CI, 2.4 to 12.0) were at increased risk of ischemic stroke. There may have been some synergism between OCs and these mutations, because the increased risk was not evident in nonusers with these mutations.³⁹³

The mechanism by which OCs increase risk of stroke is not well established. Because of the increased risk of venous thrombosis, the hemostatic effects of OCs on the coagulation system have been extensively studied, but the exact mechanism has not been clearly established. There are increased procoagulant effects with higher doses of estrogens in OC formulations in addition to beneficial effects on fibrinolysis, so overall there is a slight net tendency for OCs to induce coagulation.³⁹⁴ OCs have also been shown to induce hypertension, but this appears to be associated with higher rather than lower estrogen doses.³⁹⁵ Understanding the mechanisms could help identify women who may be at increased risk for stroke related to use of OCs.

The absolute increase in stroke risk with low-dose OCs, if one exists, is small.^{25,389,390} Estimates of the incidence of ischemic stroke in young women range from 0.9 to about 10 per 100 000.^{396–399} Even if the highest relative risk of stroke is doubled (as reported in meta-analyses^{25,389,390}), an absolute risk of stroke of 20 per 100 000 is still less than recent estimates of the rate of stroke with pregnancy (34 per 100 000 deliveries).²⁶

Summary and Gaps

The risk of stroke associated with use of OCs is low (Table 4). Certain women, particularly those who are older; who smoke cigarettes; and who have hypertension, diabetes, obesity, hypercholesterolemia, and prothrombotic mutations may be at higher risk. Estimates are based primarily on case-control studies and a smaller number of cohort studies, both of which are limited by small numbers of women with stroke events. The incremental risk of stroke associated with use of low-dose OCs in women without additional risk factors, if one exists, appears to be low.^{25,389,390,401}

Recommendations

1. **OCs may be harmful in women with additional risk factors (eg, cigarette smoking, prior thromboembolic events) (Class III; Level of Evidence C).**^{390,402}

2. For those who choose to use OCs despite the increased risk associated with their use, aggressive therapy for stroke risk factors may be reasonable (Class IIb; Level of Evidence C).^{390,392,402}

Diet and Nutrition

A large and diverse body of evidence has implicated several aspects of diet in the pathogenesis of high BP, the major modifiable risk factor for ischemic stroke. A recent AHA scientific statement concluded that several aspects of diet lead to elevated BP,⁴⁰³ specifically, excess salt intake, low potassium intake, excess weight, high alcohol consumption, and suboptimal dietary pattern. Blacks are especially sensitive to the BP-raising effects of high salt intake, low potassium intake, and suboptimal diet.⁴⁰³ In this setting, dietary changes have the potential to substantially reduce racial disparities in BP and stroke.⁴⁰³

In observational studies, several aspects of diet are associated with risk of stroke. A meta-analysis found a strong, inverse relationship between servings of fruits and vegetables and subsequent stroke.⁴⁰⁴ Compared with persons who consumed <3 servings of fruits and vegetables per day, the relative risk of ischemic stroke was less in those who consumed 3 to 5 servings per day (RR, 0.88; 95% CI, 0.79 to 0.98) and those who consumed >5 servings per day (RR, 0.72; 95% CI, 0.66 to 0.79). The dose-response relationship extends into the higher ranges of intake.⁴⁰⁵ Specifically, in analyses of the Nurses' Health Study and the Health Professionals' Follow-Up Study,⁴⁰⁵ the relative risk of incident stroke was 0.69 (95% CI, 0.52 to 0.92) for persons in the highest versus lowest quintile of fruit and vegetable intake. Median intake in the highest quintile was 10.2 servings of fruits and vegetables in men and 9.2 servings in women. Risk of stroke was reduced by 6% (95% CI, 1% to 10%) for each 1 serving per day increment in intake of fruits and vegetables. As highlighted in the 2005 report *Dietary Guidelines for Americans*, daily intake of fruits and vegetables remains low at an average intake of <5 servings per day.⁴⁰⁶

In ecological⁴⁰⁷ and some prospective studies,^{408,409} a higher level of sodium intake is associated with an increased risk of stroke. A higher level of potassium intake is also associated with a reduced risk of stroke in prospective studies.^{410,411} It should be emphasized that a plethora of methodological limitations, particularly difficulties in estimating dietary electrolyte intake, hinder risk assessment and may lead to false-negative or even paradoxical results in observational studies.

One trial tested the effects of replacing regular salt (sodium chloride) with a potassium-enriched salt in elderly Taiwanese men.⁴¹² In addition to increased overall survivorship and reduced costs, the potassium-enriched salt reduced the risk of death from cerebrovascular disease (RR, 0.50). This trial did not present follow-up BP measurements; hence, it is unclear whether BP reduction accounted for the beneficial effects of the intervention. In contrast, in WHI, a low-fat diet that emphasized consumption of whole grains, fruits, and vegetables did not reduce stroke incidence; however, the intervention did not achieve a substantial difference in fruit and vegetable consumption (mean difference of only 1.1 servings

per day) and did not reduce BP substantially (mean difference of <0.5 mm Hg for both systolic and diastolic BP).⁴¹³

The effects of sodium and potassium on stroke risk are likely mediated through direct effects on BP, as well as mechanisms that are independent of BP.⁴¹⁴ In clinical trials, particularly dose-response studies, the relationship between sodium intake and BP is direct and progressive without an apparent threshold.^{415–417} Blacks, people with hypertension, and middle- and older-aged adults are especially sensitive to the BP-lowering effects of reduced sodium intake.⁴¹⁸ In other trials an increased intake of potassium was shown to lower BP⁴¹⁹ and blunt the pressor effects of sodium.⁴²⁰ Diets rich in fruits and vegetables, including those based on the Dietary Approaches to Stop Hypertension (DASH) diet (rich in fruits, vegetables, and low-fat dairy products and reduced in saturated and total fat), lower BP.^{421–423} As documented in a study by the Institute of Medicine,⁴²⁴ in the United States, sodium intake remains high and potassium intake quite low.

Other dietary factors may affect the risk of stroke, but the evidence is insufficient to make specific recommendations.⁴⁰³ In Asian countries, a low intake of animal protein, saturated fat, and cholesterol has been associated with a decreased risk of stroke,⁴²⁵ but such relationships have been less apparent in Western countries.⁴²⁶

Summary and Gaps

On the basis of evidence from epidemiological studies and randomized trials, it is likely that consumption of a diet with reduced sodium that is rich in fruits and vegetables, such as a DASH-style diet, will reduce stroke risk. Few randomized trials with clinical outcomes have been conducted. The *Dietary Guidelines for Americans* report recommends a sodium intake of <2.3 g/d (100 mmol/d) for the general population. In blacks, persons with hypertension, and middle- and older-aged persons, a lower level of intake is recommended because these groups are especially sensitive to the BP-lowering effects of a reduced-sodium diet. The *Dietary Guidelines for Americans* recommend a potassium intake of at least 4.7 g/d (120 mmol/d). General measures are given in Table 7.

Recommendations

- 1. Reduced intake of sodium and increased intake of potassium as indicated in the report *Dietary Guidelines for Americans* are recommended to lower BP (Class I; Level of Evidence A).**
- 2. A DASH-style diet, which emphasizes consumption of fruits, vegetables, and low-fat dairy products and is reduced in saturated fat, also lowers BP and is recommended (Class I; Level of Evidence A).**
- 3. A diet that is rich in fruits and vegetables and thereby high in potassium is beneficial and may lower risk of stroke (Class I; Level of Evidence B).**

Physical Inactivity

Physical inactivity is associated with numerous adverse health effects, including an increased risk of total mortality, cardiovascular mortality, cardiovascular morbidity, and stroke. The 2008 Physical Activity Guidelines for Americans provides an extensive review and concludes that physically active men and women generally have a 25% to 30% lower

risk of stroke or death than the least active people.⁴²⁷ Two other meta-analyses reached the same conclusion.^{428,429} The benefits appear to occur from a variety of types of activity, including leisure time physical activity, occupational activity, and walking. Overall, the relationship between activity and stroke is not influenced by sex or age, but the data are very sparse for race and ethnicity other than for non-Hispanic whites.^{430,431}

The dose-response relationship between amount or intensity of physical activity and stroke risk is unclear, with the possibility of a gender interaction. Specifically there appears to be increasing benefit with greater intensity in women (median RR, 0.82 for all strokes for moderate-intensity activity versus no or light activity; RR, 0.72 for high-intensity or amount versus no or light activity). In men there was no apparent benefit of greater intensity (median RR, 0.65 for moderate-intensity versus no or light activity; RR, 0.72 for high-intensity or amount versus no or light activity).⁴²⁷

The protective effect of physical activity may be partly mediated through its role in reducing BP⁴³² and controlling other risk factors for CVD,^{433,434} including diabetes,⁴³² and excess body weight. Other biological mechanisms have also been associated with physical activity, including reductions in plasma fibrinogen and platelet activity and elevations in plasma tissue plasminogen activator activity and HDL-cholesterol concentrations.^{435–437}

A large and generally consistent body of evidence from prospective observational studies indicates that routine physical activity can prevent stroke (Table 4). The 2008 Physical Activity Guidelines for Americans recommend that adults should engage in at least 150 minutes (2 hours and 30 minutes) per week of moderate intensity or 75 minutes (1 hour and 15 minutes) per week of vigorous intensity aerobic physical activity, or an equivalent combination of moderate and vigorous intensity aerobic activity. These guidelines also note that some physical activity is better than none, and that adults who participate in any amount of physical activity gain some health benefits.⁴²⁷

Summary and Gaps

A sedentary lifestyle is associated with several adverse health effects, including increased risk of stroke. Clinical trials documenting a reduction in the risk of a first stroke with regular physical activity have not been conducted. Evidence from observational studies is sufficiently strong to make recommendations for routine physical activity as a means to prevent stroke. General measures are given in Table 7.

Recommendations

- 1. Increased physical activity is recommended because it is associated with a reduction in risk of stroke (Class I; Level of Evidence B).**
- 2. The 2008 Physical Activity Guidelines for Americans are endorsed and recommend that adults should engage in at least 150 minutes (2 hours and 30 minutes) per week of moderate intensity or 75 minutes (1 hour and 15 minutes) per week of vigorous intensity aerobic physical activity (Class I; Level of Evidence B).**

Obesity and Body Fat Distribution

The traditional classification of weight status is defined by BMI (weight in kilograms divided by the square of height in meters). Persons with a BMI of 25 to 29.9 kg/m² are classified as overweight, and those with a BMI \geq 30 kg/m² are classified as obese.⁴³⁸ Abdominal obesity is commonly measured by either the waist-to-hip ratio or waist circumference. Clinically, abdominal obesity is defined by a waist circumference $>$ 102 cm (40 in) in men and 88 cm (35 in) in women.

The prevalence rates of obesity and overweight have been increasing in the United States and elsewhere, with the epidemic affecting children as well as adults (Table 4).^{439–441} Overweight is particularly common among black and Hispanic/Latino children. According to national survey data collected from 2003 to 2004, the prevalence of overweight and obesity in the United States remains extraordinarily high; 66.3% of adults are either overweight or obese, and 32.2% are obese.⁴³⁹ Among the 3 race/ethnic groups surveyed in the United States, obesity is most common in blacks (45%) and least common in whites (30%), with intermediate prevalence in Mexican Americans (36%).

A large number of prospective studies have examined the relationship between weight (or measures of adiposity) and incident stroke. A meta-analysis found a nonlinear association between BMI and mortality.⁴⁴² In the BMI range of 25 to 50 kg/m², each 5 kg/m² increase in BMI was associated with a 40% increased risk of stroke mortality; in the lower BMI range (15 to 25 kg/m²), there was no relationship between BMI and stroke mortality, even after excluding smokers.

BMI is highly correlated with waist circumference and other measures of adiposity.⁴⁴³ Still, in those studies that examined the effects of BMI and abdominal body fat, abdominal body fat tended to be a stronger predictor of stroke risk.^{444–447} The direct relationship of BMI with stroke often persists in multivariable analyses that control for other cardiovascular risk factors (BP, blood lipids, and diabetes/insulin resistance), but the strength of the relationship is generally attenuated. This apparent reduction in the strength of the association suggests that the effect of BMI on stroke risk is in part mediated by the effect of adiposity on other stroke risk factors.

To date, no clinical trial has tested the effects of weight reduction on stroke risk. Numerous trials, however, have examined the effects of weight reduction on BP in both nonhypertensive and hypertensive individuals. In a meta-analysis that aggregated results across 25 trials, mean systolic and diastolic BP reductions from an average weight loss of 5.1 kg were 4.4 mm Hg and 3.6 mm Hg, respectively.⁴⁴⁸

Summary and Gaps

A substantial body of evidence has documented that increased adiposity is associated with increased risk of stroke. For stroke mortality there is a progressive, direct, dose-response relationship above 25 kg/m² with no clear relationship below 25 kg/m². Although no clinical trial has tested the effects of weight reduction on stroke outcomes, weight reduction is associated with a lowering in BP (see section on hypertension) and may thereby reduce stroke risk.

Recommendations

1. **Among overweight and obese persons, weight reduction is recommended as a means to lower BP (Class I; Level of Evidence A).**
2. **Among overweight and obese persons, weight reduction is reasonable as a means of reducing risk of stroke (Class IIa; Level of Evidence B).**

Less Well-Documented or Potentially Modifiable Risk Factors

Migraine

Migraine headache has been most consistently associated with stroke in young women, especially those with migraine with aura.⁴⁴⁹ A meta-analysis of 14 studies (11 case-control and 3 cohort) reported a pooled relative risk of 2.16 (95% CI, 1.89 to 2.48).⁴⁵⁰ Similar to the individual studies included in this analysis, risk was greatest in those who used OCs (RR, 8.72; 95% CI, 5.05 to 15.05), in women <45 years of age (RR, 2.76; 95% CI, 2.17 to 3.52), and in those with migraine with aura (RR, 2.27; 95% CI, 1.61 to 3.19). An analysis of 6 studies also showed that migraine without aura was associated with an increased risk but with a lower magnitude (RR, 1.83; 95% CI, 1.06 to 3.15).⁴⁵⁰

Additional important information about the association between migraine and vascular disease has come from the WHS, a primary prevention trial of women ≥ 45 years of age and free of CVD at enrollment. The analysis of women with stroke showed no overall association between migraine and stroke of any type.⁴⁵¹ The women with migraine with aura, however, were at increased risk of stroke (HR, 1.53; 95% CI, 1.02 to 2.31), particularly ischemic stroke (HR, 1.71; 95% CI, 1.11 to 2.66). Women >55 years of age with migraine with aura had more than twice the risk of ischemic stroke (HR, 2.25; 95% CI, 1.30 to 3.91) than those without migraines.⁴⁵¹ At baseline, 13% of women in the WHS reported migraine, about 40% of whom had symptoms of aura, giving a prevalence of about 5.2% of women with migraine with aura. On the basis of an odds ratio of ischemic stroke of about 1.7 for migraine with aura,⁴⁵¹ the population attributable risk for ischemic stroke is estimated to be about 3.5% for women over the age of 45 (Table 5).

The WHS also reported an increased risk of coronary disease events with migraine with aura (MI, HR, 2.08; 95% CI, 1.30 to 3.31; coronary revascularization, HR, 1.74; 95% CI, 1.23 to 2.46; and major cardiovascular events, HR, 1.91; 95% CI, 1.17 to 3.10). With adjustment for age, there were 18 additional major cardiovascular events attributable to migraine with aura per 10 000 women per year. Additional WHS analyses were performed with focus on risk factors and Framingham risk scores to identify mechanisms for the relationship between migraine with aura and vascular disease.⁴⁵² Interestingly, women with migraine with aura who also had ischemic stroke events had a low Framingham risk score (0% to 1%, 10-year risk), whereas women with migraine with aura and MI had a risk score of $\geq 10\%$ over 10 years.⁴⁵²

The Stroke Prevention in Young Women Study (SPYW), a case-control study of women 15 to 40 years of age, reported a 50% increased risk of ischemic stroke in those with

probable migraine and visual aura (OR, 1.5; 95% CI, 1.1 to 2.0).⁴⁵³ This was also one of the first studies to document headache characteristics such as frequency, severity, and duration of migraines in relation to stroke risk. The analysis showed that headache frequency of >12 times per year (adjusted OR, 1.7; 95% CI, 1.1 to 2.8) and lifetime duration <1 year (adjusted OR, 8.3; 95% CI, 2.6 to 25.7) were associated with ischemic stroke risk, although there was no association with headache severity.⁴⁵³

The mechanisms for increased risk of stroke with migraine have not yet been uncovered, although additional associations continue to be identified. Persons with migraine without additional risk factors have a higher likelihood of having white-matter hyperintensities on brain MRI scans than similar persons without migraine (OR, 4.14; 95% CI, 2.05 to 8.37); however, whether this confers a higher risk of stroke is not certain.⁴⁵⁴ A study in the Netherlands identified an increased lifetime risk of venous thromboembolism in subjects with migraine without aura (17%), and those with migraine with aura had an even higher risk (20%; $P=0.03$ versus migraine without aura) compared with those without migraines (7.6%; $P<0.001$ for migraine versus no migraine).⁴⁵⁵ This same study found no relationship with atherosclerosis, which would have helped explain the possible increased risk of CVD. Another mechanism that links migraine and stroke in young adults is paradoxical embolism via a PFO. PFOs are more common in young patients with cryptogenic stroke and those with migraine,^{304,456,457} particularly migraine with aura.⁴⁵⁹ It is speculated that the relationship between PFO and migraine involves microemboli that flow through the PFO, causing brain ischemia and thereby triggering migraine.⁴⁶⁰ Migraine patients also have increased platelet activation and platelet-leukocyte aggregation,⁴⁶¹ a mechanism that may increase the risk for emboli formation, as well as provide a link between migraine and stroke risk at a cellular level. The increased risk of venous thromboembolism,⁴⁵⁵ if occurring in the setting of a PFO, supports the link between migraine and paradoxical embolism. Although there had been enthusiasm regarding treatment of migraines by PFO closure devices, the Migraine Intervention with STAR-Flex Technology (MIST) trial, a randomized, double-blind, sham-controlled trial, showed no benefit of PFO closure on the cessation of migraine headaches (primary outcome; 3 of 74 versus 3 of 73; $P=0.51$) or any secondary outcome.⁴⁶² There is much controversy regarding the results of this trial,⁴⁶³ which was not designed to evaluate primary prevention of stroke in patients with migraines with aura.

Summary and Gaps

Migraine headache, and perhaps exclusively migraine with aura, appears to be associated with stroke in women <55 years of age. Specific data showing that migraine prophylaxis decreases stroke risk are lacking, although there may be an association between migraine with aura and frequency of attacks. No proven primary prevention strategies exist for patients with migraine or PFO or both.

Recommendation

1. **Because there is an association between higher migraine frequency and stroke risk, treatments to**

reduce migraine frequency might be reasonable, although there are no data showing that this treatment approach would reduce the risk of first stroke (Class IIb; Level of Evidence C).

Metabolic Syndrome

The NCEP Adult Treatment Panel III (ATP III) defined metabolic syndrome as the presence of ≥ 3 of the following: (1) abdominal obesity as determined by waist circumference >102 cm or >40 inches for men and >88 cm or >35 inches for women; (2) triglycerides ≥ 150 mg/dL; (3) HDL cholesterol <40 mg/dL for men and <50 mg/dL for women; (4) BP $\geq 130/\geq 85$ mm Hg; and (5) fasting glucose ≥ 110 mg/dL.²²² The International Diabetes Foundation (IDF) modified the definition by the necessary inclusion of a waist circumference >88 cm for men and >80 cm in women plus 2 of the other NCEP-ATP III criteria.⁴⁶⁴ Because the waist circumference and risk for CVD and diabetes varies around the world, both the NCEP-ATP III and IDF definitions make a provision for an ethnic/racial/geographic modification of waist circumference.⁴⁶⁵ Obesity and sedentary lifestyle in addition to other genetic and acquired factors seem to interact to produce the metabolic syndrome.⁴⁶⁶

Obesity, discussed separately, is an important component of the metabolic syndrome and is associated with major health risk factors (eg, diabetes, hypertension, dyslipidemia), poor health status, and lower life expectancy.^{467,468} The visceral adiposity characteristic of the metabolic syndrome is associated with insulin resistance, inflammation, diabetes, and other metabolic and cardiovascular derangements.⁴⁶⁹ Visceral adipocytes provoke insulin resistance by promoting extensive lipolysis and release of fatty acids. Leptin, plasminogen activator inhibitor-1, TNF- α , and other proinflammatory cytokines, in addition to reduced production and release of adiponectin by adipocytes have all been implicated in the pathophysiological process.⁴⁶⁹

Hyperinsulinemia/insulin resistance is an important marker of the metabolic syndrome. A variety of studies support or refute a relationship between glucose intolerance and stroke risk.^{470–481} The relationship between other individual components of the metabolic syndrome and stroke risk, including BP, is reviewed in other sections of this guideline.

Metabolic syndrome has been associated with an increased risk of prevalent stroke. In the National Health and Nutrition Examination Survey, among 10 357 subjects,⁴⁸² the prevalence of metabolic syndrome was higher in persons with a self-reported history of stroke (43.5%) than in subjects with no history of CVD (22.8%; $P \leq 0.001$). The metabolic syndrome was independently associated with stroke history in all ethnic groups and both sexes (OR, 2.16; 95% CI, 0.48 to 3.16). The association between metabolic syndrome and stroke has been confirmed in other populations, including those with many elderly subjects, and the frequency of metabolic syndrome was higher in patients with a history of nonhemorrhagic stroke.^{446,482,483} The adjusted risk ratios for ischemic stroke associated with the metabolic syndrome in prospective studies have ranged between 2.10 and 2.47, and a HR as high as 5.15 has been reported.^{484–487} This predictive capacity appears not to be influenced by the definition used

for the metabolic syndrome and showed no significant variation across sex, age, or ethnic groups. Whether there is a relationship between metabolic syndrome and stroke risk that is independent of the sum of the risks associated with individual components remains controversial.

The metabolic syndrome is highly prevalent in the United States.⁴⁶⁹ Based on the NCEP-ATP III definition, the overall unadjusted prevalence of the syndrome was 34.5%, 33.7% among men, and 35.4% among women in a total of 3601 persons ≥ 20 years of age who participated in the National Health and Nutrition Examination Survey, 1999 to 2002.⁴⁸⁸ When the IDF definition was used, the unadjusted prevalence of the metabolic syndrome was 39.0% among all participants, 39.9% among men, and 38.1% among women. Mostly attributable to the obligatory use of a lower waist circumference for the IDF, the IDF definition led to higher estimates of prevalence in all demographic groups, especially among Mexican-American men. Of note, the 2 definitions classified approximately 93% of the participants as either having or not having the syndrome.

The metabolic syndrome is a substantial predictor of CVD (which includes coronary heart disease and stroke) and all-cause mortality.⁴⁶⁹ There is a paucity of information about the specific risk of stroke. Most stroke risk estimates are combined with other outcomes (eg, “CVD”), making it difficult to determine the specific stroke risk component. For example, in the 1351 subjects enrolled in the “Ventimiglia di Sicilia” epidemiological project, the metabolic syndrome was associated with a nearly 2-fold increased risk of cardiovascular events but not stroke.⁴⁸⁹ As in many studies, this lack of relationship may be attributable to sample size and a small number of stroke events.

Few trials have investigated the effects of treatment on cardiovascular morbidity and mortality in patients with the metabolic syndrome. The TNT study included 10 001 patients with clinically evident coronary heart disease.⁴⁹⁰ Treating to an LDL-cholesterol level substantially lower than 100 mg/dL with a high dose of a high-potency statin reduced both stroke and cerebrovascular events by an additional 20% to 25% compared with a lower dose. Of these subjects, 5584 patients with the metabolic syndrome were randomly assigned to high- or low-dose statin.⁴⁹¹ As expected, the higher dose led to greater reductions in LDL cholesterol (73 versus 99 mg/dL at 3 months). Irrespective of treatment assignment, more patients with the metabolic syndrome (11.3%) had a major cardiovascular event than those without the metabolic syndrome (8.0%; HR, 1.44; 95% CI, 1.26 to 1.64; $P < 0.0001$). At a median follow-up of 4.9 years, major cardiovascular events occurred in 13% of patients receiving the low-dose statin compared with 9.5% receiving the higher dose (HR, 0.71; 95% CI, 0.61 to 0.84; $P < 0.0001$), and cerebrovascular events were reduced by 26% (HR, 0.74; 95% CI, 0.59 to 0.93; $P = 0.011$).

Summary and Gaps

Individual components of the metabolic syndrome are associated with an increased risk of ischemic stroke and should be treated appropriately. The specific risk of stroke in persons with the

metabolic syndrome appears to be higher but remains uncertain, as does the impact of treatment of the syndrome.

Recommendations

1. **Management of individual components of the metabolic syndrome is recommended, including lifestyle measures (ie, exercise, appropriate weight loss, proper diet) and pharmacotherapy (ie, medications for lowering BP, lowering lipids, glycemic control, and antiplatelet therapy) as reflected in the NCEP-ATP III²²² and the JNC 7,⁹⁰ and as endorsed or indicated in other sections of this guideline.** (Refer to relevant sections for Classes and Levels of Evidence for each recommendation.)
2. **The effectiveness of agents that ameliorate aspects of the insulin resistance syndrome for reducing stroke risk is unknown (Class IIb; Level of Evidence C).**

Alcohol Consumption

Excessive consumption of alcohol can lead to multiple medical complications, including stroke. Strong evidence exists that heavy alcohol consumption is a risk factor for all stroke subtypes (Table 5).^{492–496} Most studies suggest a J-shaped association between alcohol consumption and the risk of total and ischemic stroke, with a protective effect in light or moderate drinkers and an elevated risk with heavy alcohol consumption.^{8,492,493,497–504} In contrast, a linear association exists between alcohol consumption and risk of hemorrhagic stroke.^{16,116,505,506}

Light to moderate alcohol consumption is associated with greater levels of HDL cholesterol,^{507–509} reduced platelet aggregation,^{510,511} lower fibrinogen concentrations,^{512,513} and increased insulin sensitivity and glucose metabolism.⁵¹⁴ Heavy alcohol consumption can result in hypertension, hypercoagulability, reduced cerebral blood flow, and increased risk of atrial fibrillation.^{493,498,500,513,515}

A recent prospective cohort study among 43 685 men from the Health Professionals Follow-up Study and 71 243 women from the Nurses' Health Study⁸ showed that alcohol intake had a J-shaped association for risk of stroke. A lower risk of stroke was found in women who were light drinkers, but women who drank ≥ 30 g of alcohol per day had a 40% increased risk of stroke (RR, 1.41; 95% CI, 1.07 to 1.88 for ischemic stroke; RR, 1.40; 95% CI, 0.86 to 2.28 for hemorrhagic stroke). There was a similar but nonsignificant pattern for men. In the WHS,⁵¹⁶ alcohol consumption was not associated with stroke risk, even with ≥ 10.5 drinks per week. A large prospective study in Chinese men,⁵¹⁷ however, supports the association between heavy alcohol and stroke risk. A 22% increase in stroke occurred in those consuming at least 21 drinks per week, whereas consumption of 1 to 6 drinks per week was associated with the lowest stroke risk. In a meta-analysis of 35 observational studies,⁵⁰⁶ consumption of 60 g of alcohol per day was associated with a 64% increased risk of stroke (RR, 1.64; 95% CI, 1.39 to 1.93), a 69% increase in ischemic stroke (RR, 1.69; 95% CI, 1.34 to 2.15), and more than double the risk of hemorrhagic stroke (RR, 2.18; 95% CI, 1.48 to 3.20). Consumption of < 12 g of alcohol per day was associated with a reduced risk of total stroke (RR, 0.83; 95% CI, 0.75 to 0.91) and ischemic stroke

(RR, 0.80; 95% CI, 0.67 to 0.96), with consumption of 12 to 24 g/d associated with a lower risk of ischemic stroke (RR, 0.72; 95% CI, 0.57 to 0.91).

Summary and Gaps

In observational studies, light to moderate consumption of alcohol, particularly in the form of wine, is associated with reduced risk of total and ischemic stroke, whereas heavier consumption of alcohol increases risk of stroke. Prospective, randomized clinical trials showing that reduction of heavy alcohol consumption reduces risk or that light alcohol consumption is beneficial are lacking and cannot be performed, because it is well established that alcohol dependence is a major health problem. General measures are given in Table 7.

Recommendations

1. **For numerous health considerations, reduction or elimination of alcohol consumption by heavy drinkers through established screening and counseling strategies as described in the US Preventive Services Task Force Recommendation Statement of 2004 are recommended⁵¹⁸ (Class I; Level of Evidence A).**
2. **For persons who choose to consume alcohol, consumption of ≤ 2 drinks per day for men and ≤ 1 drink per day for nonpregnant women might be reasonable^{519,520} (Class IIb; Level of Evidence B).**

Drug Abuse

Drug addiction is often a chronic, relapsing condition associated with societal and health-related problems.⁵²¹ Drugs of abuse, including cocaine, amphetamines, and heroin, are associated with increased risk of stroke.⁵²² These drugs can produce acute and severe BP elevation, cerebral vasospasm, vasculitis, embolization due to infective endocarditis, hemostatic and hematologic abnormalities resulting in increased blood viscosity and platelet aggregation, and ICH.^{523–528} Information about stroke-related drug abuse is mainly limited to epidemiological studies focused on urban populations. There is an increase in the risk of both ischemic and hemorrhagic stroke.^{529–534} In a cross-sectional study of hospitalized patients,⁵³⁴ amphetamine abuse was associated with hemorrhagic stroke (adjusted OR, 4.95; 95% CI, 3.24 to 7.55) but not with ischemic stroke; cocaine abuse was associated with hemorrhagic stroke (OR, 2.33; 95% CI, 1.74 to 3.11) and ischemic stroke (OR, 2.03; 95% CI, 1.48 to 2.79). Only amphetamine abuse was associated with a higher risk of death after hemorrhagic stroke (OR, 2.63; 95% CI, 1.07 to 6.50). Long-term treatment strategies, including medication, psychological counseling, and community-based programs, are important in the management of drug dependency.^{521,535} There is insufficient evidence to evaluate the clinical utility of screening tests for drug abuse in primary care settings, including toxicology tests of blood or urine, or the use of standardized questionnaires to screen for drug use or misuse.⁵³⁶

Summary and Gaps

Several drugs of abuse are associated with ischemic and hemorrhagic stroke. Data are lacking on the independent risk of stroke associated with specific drugs of abuse. There are no controlled trials demonstrating a reduction in stroke risk with abstinence.

Recommendation

- 1. Referral to an appropriate therapeutic program is reasonable for patients with drug abuse (Class IIa; Level of Evidence C).**

Sleep-Disordered Breathing

Epidemiological studies suggest that habitual snoring is a risk factor for ischemic stroke, independent of confounding factors such as hypertension, ischemic heart disease, obesity, and age.^{537,538} Loud snoring is associated with an increased risk of carotid compared with femoral atherosclerosis (OR, 10.5; 95% CI, 2.1 to 51.8; $P=0.004$) independent of other risk factors, including measures of nocturnal hypoxia and severity of obstructive sleep apnea.⁵³⁹ Consistent with these observations, a 10-year observational study of 1651 men found that severe obstructive sleep apnea-hypopnea (according to the apnea-hypopnea index, >30 occurrences per hour of sleep) increased the risk of fatal (OR, 2.87; 95% CI, 1.17 to 7.51) and nonfatal (OR, 3.17; 95% CI, 1.12 to 7.52) cardiovascular events (MI, acute coronary insufficiency requiring coronary artery bypass surgery and/or percutaneous transluminal angioplasty, and stroke) as compared with healthy participants.⁵⁴⁰ Those with obstructive sleep apnea who were treated with continuous positive airway pressure (CPAP) did not differ with regard to fatal (OR, 1.05; 95% CI, 0.39 to 2.21) or nonfatal (OR, 1.42; 95% CI, 0.52 to 3.40) cardiovascular events compared with healthy participants. The outcomes of those who were or were not treated with CPAP did not differ. Data on stroke were not reported separately. In another observational study of 1022 patients,⁵⁴¹ 68% had obstructive sleep apnea syndrome. At baseline the mean apnea-hypopnea index in patients with the syndrome was 35 compared with 2 in the comparison group. In an unadjusted analysis, obstructive sleep apnea syndrome was associated with stroke or death from any cause (HR, 2.24; 95% CI, 1.30 to 3.86; $P=0.004$). The obstructive sleep apnea syndrome retained an independent association with stroke or death (HR, 1.97; 95% CI, 1.12 to 3.4; $P=0.01$) after adjustment for age, sex, race, smoking status, alcohol consumption status, BMI, and the presence or absence of diabetes mellitus, hyperlipidemia, atrial fibrillation, and hypertension (Table 5). In a trend analysis, increased severity of sleep apnea at baseline was associated with an increased risk of the composite end point ($P=0.005$).

A 6-year longitudinal prospective study of 394 noninstitutionalized, initially event-free subjects (70 to 100 years of age, median 77.28 years, 57.1% male) found that severe obstructive sleep apnea-hypopnea (defined as apnea-hypopnea index ≥ 30) increased the risk of ischemic stroke independent of known confounding factors.⁵⁴² Demographic and polysomnographic data and known confounding factors (age, sex, smoking status, alcohol consumption status, BMI, systolic and diastolic BP, total serum cholesterol levels, and the presence or absence of diabetes mellitus, atrial fibrillation, and hypertension) were assessed at baseline. The risk for developing an ischemic stroke in relation to the apnea-hypopnea index at baseline was increased 2- to 5-fold (HR, 2.52; 95% CI, 1.04 to 6.01; $P=0.04$).

Cross-sectional and longitudinal analyses of 1475 and 1189 subjects, respectively,⁵⁴³ found that sleep-disordered breathing (SDB) with an apnea-hypopnea index ≥ 20 measured with attended polysomnography was associated with an increased risk of a first-ever stroke over the ensuing 4 years (unadjusted OR, 4.31; 95% CI, 1.31 to 14.15; $P=0.02$). The effect was no longer significant after adjustment for age, sex, and BMI (OR, 3.08; 95% CI, 0.74 to 12.81; $P=0.12$).

Sleep apnea (assessed by use of overnight sleep apnea recordings) was associated with stroke risk in a prospective study of 392 patients with coronary artery disease who were being evaluated for coronary intervention.⁵⁴⁴ Over 10 years of follow-up, those with an apnea-hypopnea index ≥ 5 (54%) had an increased risk of stroke (adjusted HR, 2.89; 95% CI, 1.37 to 6.09; $P=0.005$) independent of age, BMI, left ventricular function, diabetes mellitus, sex, intervention, hypertension, atrial fibrillation, previous stroke or TIA, and smoking. Patients with an apnea-hypopnea index of 5 to 15 and patients with an apnea-hypopnea index ≥ 15 had a 2.44 (95% CI, 1.08 to 5.52) and 3.56 (95% CI, 1.56 to 8.16) increased risk of stroke, respectively, compared with patients without sleep apnea, independent of confounders (P for trend=0.011). Death and MI were not associated with sleep apnea.

SDB can increase stroke risk by leading to or worsening hypertension and heart disease and possibly by causing reductions in cerebral blood flow, altered cerebral autoregulation, impaired endothelial function, accelerated atherogenesis, hypercoagulability, inflammation, and paradoxical embolism in patients with PFO.⁵⁴⁵⁻⁵⁴⁷ For example, the community-based Sleep Heart Health Study found a dose-response relationship between SDB and hypertension.⁵⁴⁸ Another study found a similar association.⁵⁴⁹ Each additional apneic event per hour of sleep increases the odds of hypertension by 1%, and each 10% decrease in nocturnal oxygen saturation increases the odds by 13%.⁵⁵⁰ The association of SDB with drug-resistant hypertension is particularly high.⁵⁵¹ In patients with advanced SDB, cardiac arrhythmias, atrioventricular block, and atrial fibrillation appear when the oxyhemoglobin saturation falls to $<65\%$.⁵⁵²⁻⁵⁵⁵ In 1 study of 35 patients with severe ventricular arrhythmias and normal left ventricular function,⁵⁵⁶ 60% of the patients had SDB with an apnea-hypopnea index ≥ 5 per hour (mean apnea-hypopnea index 22.7 ± 17.9 per hour). A high prevalence of SDB was found in relatively young patients with both paroxysmal and persistent atrial fibrillation with normal left ventricular function.⁵⁵⁷ SDB seems to be common in lone atrial fibrillation, as noted in another study; however, SDB was not more common in patients with atrial fibrillation than in sex-, age-, and cardiovascular morbidity-matched community controls.⁵⁵⁸ SDB is more frequent in patients with chronic persistent and permanent atrial fibrillation than in age-matched community-dwelling subjects (81.6% with SDB in the atrial fibrillation group versus 60% in the control group; $P=0.03$)⁵⁵⁹ or when compared with general cardiology patients (49% versus 32%; $P=0.0004$).⁵⁶⁰

Rapid eye movement sleep-related apneic events with oxygen desaturation can be profound in the setting of abdominal obesity,⁵⁶¹ which may contribute to the epidemiological link

between abdominal obesity, hypertension,⁵⁶² and vascular risk. Obesity and the magnitude of nocturnal oxygen desaturation, which is an important pathophysiological consequence of obstructive sleep apnea, are independent risk factors for incident atrial fibrillation in persons <65 years of age.⁵⁶³

In a study of 50 men with SDB and 15 obese male control subjects, silent brain infarctions on MRI were higher in patients with moderate to severe SDB (25.0%) than in obese control subjects (6.7%; $P < 0.05$) or patients with mild SDB.⁵⁶⁴

Treatment of SDB must be individualized and can include CPAP ventilation, bilevel positive airway pressure, and automatic control of airway pressure delivery with CPAP devices. A variety of surgical interventions and prosthetic oral devices are available. Successful treatment of SDB can lead to a reduction in BP.^{565–567} Few data support the efficacy of therapy with CPAP as an adjunct for prevention or management of arrhythmia.⁵⁶⁸ In 1 study SDB treatment with CPAP was associated with a reduction in cardiovascular risk independent of age and preexisting cardiovascular comorbidities. End points were nonfatal (MI, stroke, and acute coronary syndrome requiring revascularization procedures) and fatal (death from MI or stroke) cardiovascular events. The estimated event-free survival after 10 years was 51.8% in untreated patients and 83.1% (log-rank test; $P < 0.001$) in treated patients who were compliant with CPAP.⁵⁶⁹ The authors concluded that treatment of SDB should be considered for primary and secondary cardiovascular prevention, even in those with mild SDB. There are no prospective studies showing that treatment of SDB specifically reduces stroke risk.

Summary and Gaps

SDB (sleep apnea) is associated with a variety of other stroke risk factors and adverse cardiovascular events. SDB may independently contribute to stroke risk. Successful treatment of sleep apnea can reduce BP. There are no prospective randomized studies showing that treatment of sleep apnea reduces stroke risk. General measures are given in Table 7.

Recommendations

1. **Because of its association with other vascular risk factors and cardiovascular morbidity, evaluation for SDB through a detailed history and, if indicated, specific testing is recommended, particularly in those with abdominal obesity, hypertension, heart disease, or drug-resistant hypertension (Class I; Level of Evidence A).**
2. **Treatment of sleep apnea to reduce risk of stroke might be reasonable, although its effectiveness is unknown (Class IIb; Level of Evidence C).**

Hyperhomocysteinemia

Homocysteine is an amino acid that is derived from the metabolism of the essential amino acid methionine. Increased plasma levels of homocysteine are often a consequence of reduced enzymatic activity in its metabolic pathways. This may be caused by genetic defects in the enzymes involved in homocysteine metabolism, such as deficiencies of cystathionine β -synthase and methylenetetrahydrofolate reductase (MTHFR), involved in the transsulfuration and remethylation

pathways, respectively, or by a thermolabile variant of MTHFR that results from a point mutation in which cytosine is replaced by thymidine at position 677 (MTHFR C677T).⁵⁷⁰ Hyperhomocysteinemia is also caused by nutritional deficiencies of pyridoxine (vitamin B₆), a cofactor of cystathionine β -synthase, and of folic acid and cobalamin (vitamin B₁₂), cofactors of MTHFR.⁵⁷¹ Decreased renal clearance of homocysteine in patients with chronic renal failure may contribute to hyperhomocysteinemia.

Elevated levels of plasma homocysteine are associated with a 2- to 3-fold increased risk for atherosclerotic vascular disease, including stroke.^{572–578} Carotid IMT and carotid artery stenosis are increased in persons with elevated homocysteine levels.^{579–581} In the Study of Health Assessment and Risk in Ethnic groups (SHARE), a cross-sectional study of south Asian Chinese and white Canadians, plasma homocysteine $>11.7 \mu\text{mol/L}$, but not MTHFR C677T, was associated with increased carotid IMT.⁵⁸² Several recent investigations found that the relationship between homocysteine levels and carotid IMT was eliminated after adjustment for other cardiovascular risk factors or renal function.^{583,584} One meta-analysis of epidemiological studies found a 19% (95% CI, 5% to 31%) reduction in stroke risk per 25% lower homocysteine concentration after adjustment for smoking, systolic BP, and cholesterol.⁵⁸⁵ Another meta-analysis found that for each 5 $\mu\text{mol/L}$ increase in homocysteine, risk of stroke increased by 59% (95% CI, 29% to 96%) and for each 3 $\mu\text{mol/L}$ decrease in homocysteine, risk of stroke decreased by 24% (95% CI, 15% to 33%).⁵⁸⁶

The B-complex vitamins pyridoxine (B₆), cobalamin (B₁₂), and folic acid lower homocysteine levels. Folic acid intake is associated with reduced risk of ischemic stroke in some epidemiological studies but not in others.^{587–590} In a clinical trial of healthy adults without diabetes and CVD, B-complex vitamin supplementation compared with placebo decreased carotid IMT in the group of participants whose baseline plasma homocysteine was $\geq 9.1 \mu\text{mol/L}$, but not in those whose homocysteine levels were lower.⁵⁹¹ The Vitamins to Prevent Stroke (VITATOPS) trial, a placebo-controlled intervention trial designed to test the efficacy of long term B-vitamin supplementation in the prevention of vascular events in patients with a history of stroke, is in progress. A substudy of VITATOPS reported that B-complex vitamins did not reduce the change in carotid IMT.⁵⁹² Similarly, folic acid did not significantly affect carotid IMT in the Atherosclerosis and Folic Acid Supplementation Trial (ASFAST).⁵⁹³

Most studies of patients with established atherosclerotic vascular disease have found no benefit of homocysteine lowering by B-complex vitamin therapy on clinical cardiovascular end points. In the Vitamin Intervention for Stroke Prevention (VISP) trial, therapy with high doses of vitamins B₆ and B₁₂ and folic acid did not affect the risk of recurrent ischemic stroke compared with a low-dose formulation of these B-complex vitamins. In 2 Norwegian trials, one studying patients with MI and the other studying patients with coronary artery disease or aortic stenosis, B-complex vitamins did not reduce mortality or cardiovascular events, including stroke.^{594,595} Similarly, in the Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS), these

B-complex vitamins did not alter risk of stroke in women with established CVD or ≥ 3 risk factors.⁵⁹⁶ The effect of folic acid therapy has also been studied in patients with chronic renal disease and hyperhomocysteinemia, but the results of these studies are inconsistent.^{593,597,598} In ASFAST, a placebo-controlled study of 315 patients with chronic renal failure, folic acid supplementation did not reduce the composite risk of cardiovascular events, with fewer treated patients having strokes (RRR, 0.55; 95% CI, -0.01 to 0.80).^{593,599} Similarly, in the HOPE 2 study of persons with established vascular disease or diabetes, combination therapy with vitamins B₆ and B₁₂ and folic acid lowered plasma homocysteine levels but did not affect the composite end point of cardiovascular death, MI, or stroke. However, it did reduce risk of stroke by 25% (95% CI, 0.59 to 0.97).⁶⁰⁰ A subsequent exploratory analysis found no heterogeneity in the effect on stroke based on whether or not subjects had a prior history of stroke or TIA (interaction, $P=0.88$).⁶⁰¹ One meta-analysis of 12 randomized controlled trials composed of 16,958 patients with preexisting cardiovascular or renal disease found that folic acid supplementation did not reduce risk of CVD or all-cause mortality, although a reduction in stroke approached significance (RR, 0.86; 95% CI, 0.71 to 1.04).⁶⁰² A subsequent meta-analysis of 8 randomized trials consisting of 16 841 persons found that folic acid supplementation reduced risk of stroke by 18% (95% CI, 0% to 32%; $P=0.045$).⁶⁰³

Summary and Gaps

Hyperhomocysteinemia is associated with an increased risk of stroke. The results of trials that have examined the effect of homocysteine-lowering therapy with B-complex vitamins on risk of stroke are inconsistent. Stroke reduction generally was found in trials in which the duration of treatment exceeded 3 years, the decrease in plasma homocysteine concentration was $>20\%$, the region did not fortify diet with folate, and participants had no prior history of stroke. Better understanding of the mechanisms through which homocysteine causes atherosclerosis may enable identification of more targeted and effective therapies to reduce risk of stroke in patients with elevated homocysteine levels.

Recommendation

1. **The use of the B-complex vitamins, pyridoxine (B₆), cobalamin (B₁₂), and folic acid, might be considered for prevention of ischemic stroke in patients with hyperhomocysteinemia, but its effectiveness is not well established (Class IIb; Level of Evidence B).**

Elevated Lipoprotein(a)

Lipoprotein(a) [Lp(a)] is a low-density lipoprotein particle in which apolipoprotein B-100 is covalently linked to the glycoprotein, apoprotein(a). The structure and chemical properties of this lipoprotein particle are similar to LDL. Lp(a) contributes to atherogenesis in experimental models⁶⁰⁴ and is associated with an increased risk for coronary artery disease.^{605,606} Apoprotein(a) also has structural homology to plasminogen but does not possess its enzymatic activity. Thus, it may inhibit fibrinolysis binding to the catalytic

Table 11. Strength of the Association Between Lupus Anticoagulants, Anticardiolipin Antibodies, and Thrombosis⁶²⁵

Type of Thrombosis	LA*	OR Range	aCL†	OR Range
Arterial	2/2	8.65–10.84	13/19	NS – 18
Venous	5/5	4.09–16.2	2/12	NS – 2.51
Any‡	2/2	5.71–7.3	1/2	NS – 3.66

aCL indicates anticardiolipin antibodies; LA, lupus anticoagulant; NS, not significant; and OR, odds ratio.

*No. of statistically significant associations/total No. of available associations.

†No distinction was made between aCL isotypes.

‡No distinction was possible between arterial and venous thrombosis.

complex of plasminogen, tissue plasminogen activator, and fibrin, thereby contributing to thrombosis.^{604,607}

Some, but not all, population-based epidemiological studies have found that Lp(a) is associated with an increased risk of stroke.^{608–610} In the Physicians' Health Study, which was composed primarily of white, healthy, middle-aged men, there was no association between baseline plasma concentration of Lp(a) and future risk of stroke.⁶¹¹ In the Cardiovascular Health Study, risk of stroke was increased 3-fold (RR, 3.00; 95% CI, 1.59 to 5.65) in older men whose Lp(a) levels were in the highest quintile compared with men in the lowest quintile, but not older women.⁶⁰⁸ In the ARIC study the incidence of ischemic stroke was increased by approximately 80% (RR, 1.79; 95% CI, 1.32 to 2.42) in those with elevated Lp(a) levels after adjustment for age, sex, and race.⁶¹⁰ When analyzed by sex and race, elevated levels of Lp(a) were associated with an increased risk of stroke in black women, black men, and white women, but not white men. Several studies have found that Lp(a) level is associated with the severity of carotid artery stenosis and occlusion.^{612,613} One found that Lp(a) levels were higher in patients with stroke related to large-vessel atherothrombotic disease than in patients with lacunar stroke.⁶¹⁴ A meta-analysis of 31 studies comprising 56 010 subjects found that Lp(a) was higher in stroke patients and that incident stroke was 22% (RR, 1.22; 95% CI, 1.04 to 1.43) more frequent in patients in the highest compared with the lowest tertile of Lp(a).⁶¹⁵

Recommendation

1. **The use of niacin might be reasonable for prevention of ischemic stroke in patients with high Lp(a), but its effectiveness is not well established (Class IIb; Level of Evidence B).**

Hypercoagulability

The acquired and hereditary hypercoagulable states (thrombophilias) are associated with venous thrombosis, but a relationship with arterial cerebral infarction is either anecdotal or based on case series reports or case-control studies (Table 11). Of these, the presence of antiphospholipid antibodies (aPLs), generally an acquired condition, is most strongly associated with arterial thrombosis. Anticardiolipin antibody (aCL) (more prevalent but less specific) and lupus anticoagulant (less prevalent but more specific) are most frequently used to detect aPLs. Retrospective and prospective studies suggested an association between aCL and first

Table 12. Summary of Prospective Studies of aPL-Associated Risk for First Event

Study	Year	aPL Assay*	Outcome	OR/HR	95% CI	Follow-up, y	Sex
PHS ⁶¹⁹	1992	aCL	DVT, PE	OR 5.3	1.6, 18.3	5	Male
HHS ⁶²⁰	2001	β_2 -GPI-aCL	Stroke	OR 2.2	1.5, 3.4	15	Male
HHS ⁶²⁰	2001	β_2 -GPI-aCL	Stroke	OR 1.5	1.0, 2.3	20	Male
HHS ⁶²⁰	2001	β_2 -GPI-aCL	MI	OR 1.8	1.2, 2.6	15	Male
HHS ⁶²⁰	2001	β_2 -GPI-aCL	MI	OR 1.5	1.1, 2.1	20	Male
FCOS ⁶²¹	2004	aCL	Stroke, TIA	HR 2.6	1.3, 5.4	11	Female
FCOS ⁶²¹	2004	aCL	Stroke, TIA	HR 1.3	0.7, 2.4	11	Male

aCL indicates anticardiolipin; aPL, antiphospholipid; CI, confidence interval; DVT, deep vein thrombosis; FCOS, Framingham Cohort and Offspring Study; GPI, glycoprotein-I; HHS, Honolulu Heart Study; HR, hazard ratio; MI, myocardial infarction; OR, odds ratio; PE, pulmonary embolism; PHS, Physicians' Health Study; and TIA, transient ischemic attack.

These studies only investigated baseline aCL levels. Gaps include assaying plasma for lupus anticoagulant, studies using newer aPL assays, assaying aPL over time to determine persistence and significance of aPL+, and studying women (except for FCOS).

ischemic stroke.⁶¹⁶ From limited, often uncontrolled data that predominantly include patients with systemic lupus erythematosus (SLE) and potentially other vascular risk factors that are poorly detailed, asymptomatic patients with aPLs are estimated to have an annual risk of thrombosis of 0% to 3.8%.⁶¹⁷ Sneddon's syndrome may be present in patients with and without aPLs.⁶¹⁸

Case-control studies of aPL-associated stroke in young people have been uniformly positive, as have most studies of unselected stroke populations. Some but not all case-control studies among older adults have generally found aPL to be associated with ischemic stroke.

Several prospective cohort studies have assessed the relationship between aPL and ischemic stroke (Table 12). Stored frozen plasma from the Physicians' Health Study was used to determine whether aCL was a risk factor for ischemic stroke and venous thrombosis in healthy men.⁶¹⁹ This was a nested, case-control study in a prospective cohort with 60.2 months of follow-up. At entry, 68% of 22 071 participants submitted plasma samples. A control was matched by age, smoking history, and length of follow-up to each of the 100 patients with ischemic stroke and the 90 patients with deep vein thrombosis (DVT) or pulmonary embolus (PE). aCL titers were higher in case patients with DVT or PE than in their matched controls ($P=0.01$). Persons with aCL titers above the 95th percentile had a relative risk of 5.3 (95% CI, 1.55 to 18.3; $P=0.01$) for developing DVT or PE. Although an aCL level above the 95th percentile was an important risk factor for DVT or PE, there was no effect on stroke (a relative risk of 2 for ischemic stroke could not be excluded due to low power, however).

The Honolulu Heart Study was a nested case-control study examining aCL as a risk factor for ischemic stroke and MI.⁶²⁰ The study used stored frozen sera obtained from subjects in the Honolulu Heart Program who were monitored for up to 20 years. aCL (β_2 glycoprotein-I [GPI] dependent) was tested in 259 men who developed ischemic stroke, 374 men who developed MI, and a control group of 1360 men who remained free of either condition. aCL was significantly associated with both incident ischemic stroke and MI. For stroke, the adjusted relative odds for men with a positive versus a negative aCL were 2.2 (95% CI, 1.5 to 3.4) at 15 years and 1.5 (95% CI, 1.0 to 2.3) at 20 years. These data

suggest that aCL is an important predictor of future stroke and MI in men.

aCL was also assessed in the Framingham Cohort and Offspring Study.⁶²¹ The study included 2712 women (mean age, 59.3 years) and 2262 men (mean age, 58.3 years) who were free of stroke or TIA at the time of their baseline examination. An enzyme-linked immunosorbent assay (ELISA) was used to measure aCL from stored frozen sera. During the 11-year follow-up, 222 ischemic strokes or TIAs occurred. After adjustment for age, prior CVD, systolic BP, diabetes, smoking, C-reactive protein, and total and HDL cholesterol levels, an aCL standardized ratio of >0.4 was associated with an increased risk of ischemic stroke or TIA in women (HR, 2.6; 95% CI, 1.3 to 5.4; absolute risk, 3.2%; 95% CI, 2.2 to 4.3) but not in men (HR, 1.3; 95% CI, 0.7 to 2.4; absolute risk, 4.5%; 95% CI, 3.0 to 6.0). Similar results were obtained when the highest 3 aCL quartiles were compared with the lowest, suggesting that elevated aCL was independently associated with risk of future ischemic stroke and TIA in women but not men.

The Antiphospholipid Antibody and Stroke Study (APASS), using a cutoff of aCL immunoglobulin G titer of $>21 \mu\text{g/dL}$ ($>21 \text{ GPL}$ [1 GPL unit = $1 \mu\text{g}$ of affinity-purified IgG from an original index serum sample]), did not find an association between aPL and recurrent ischemic stroke (or any subsequent vascular occlusive event).⁶²² Two other well-designed longitudinal studies in the elderly found no association between stroke recurrence and elevated aCL titers.^{623,624} The Framingham Cohort and Offspring Study did find an association between aCL titers and ischemic stroke or TIA, but only in women.⁶²¹ Overall, although elevated aCL titers may be commonly found in ischemic stroke patients, the strength of the association between elevated aCL titers and stroke etiology or risk is uncertain.

The shortcoming of many studies of aCL in stroke patients has been the use of the aCL ELISA, a test with low sensitivity. The assay for anti- β_2 GPI antibodies, a cofactor for aPL binding, may be more specific for thrombosis, including stroke and MI.^{620,625} Only a few studies have investigated β_2 GPI in the absence of SLE.^{620,623,625} Because most studies involved patients with SLE, lupus anticoagulant, or aCL, it is difficult to establish the value of anti- β_2 GPI as an independent risk factor. Therefore, the

clinical significance of these antibodies requires further investigation.⁶²⁵

Adequately powered controlled studies evaluating treatment of elevated aCL to prevent a first stroke are not available. Some data suggest that young women with ischemic stroke have a higher prevalence of aPL.⁶²⁶ In a subgroup analysis of the Physicians' Health Study,⁶¹⁹ aspirin 325 mg taken every other day did not protect against venous thromboembolism in men 40 to 84 years of age with moderate to high aCL titers. Therefore, those stroke patients (primarily young women) who have a history of thrombotic events and meet the laboratory criteria for aPL syndrome⁶²⁷ might benefit from primary prevention strategies such as moderate-intensity warfarin (INR, 2.0 to 3.0). This is currently being tested in a primary prevention trial of warfarin therapy (INR, 2.0 to 2.5) to decrease thromboembolic events in patients with lupus and aPL.⁶²⁸

The Antiphospholipid Antibody Acetylsalicylic Acid (APLASA) study was a small, multicenter, double-blind, placebo-controlled trial for primary prevention of thrombosis in asymptomatic patients who were persistently aPL positive. The study compared low-dose aspirin (81 mg/d; n=48) with placebo (n=50)⁶¹⁷ over an average follow-up period of 2.30±0.95 years. The rates of acute thrombosis were 2.75/100 patient-years for aspirin-treated subjects and 0/100 patient-years for placebo-treated subjects (HR, 1.04; 95% CI, 0.69 to 1.56; *P*=0.83). The sample size was relatively small and the study insufficiently powered. A parallel and separate observational study published within the APLASA study⁵⁷⁹ found no reduction in the rate of first thrombotic events with low-dose (81 mg/d) aspirin over placebo in persistently aPL-positive asymptomatic persons. These persons also appeared to have a low overall annual incidence rate of acute thrombosis and often developed vascular events in the setting of additional thrombotic risk factors.

Even if an elevated aCL titer was found in a stroke patient, APASS found no differential response to aspirin (325 mg/d) versus warfarin (adjusted dose; target INR, 1.4 to 2.8) in the prevention of recurrent thrombo-occlusive events.⁶²²

Inherited hypercoagulable states associated with stroke include fibrinogen level, the β -chain-455 G/A fibrinogen, factor VIII levels, factor XIII Val34 Leu, von Willebrand factor (vWF) small polymorphism in intron 2, tissue-type plasminogen activator (tPA) – 7351 C/T, thrombotic thrombocytopenic purpura, and heparin-induced thrombocytopenia.⁶²⁹ The majority of case-control studies have not found an association between other hereditary hypercoagulable states, such as factor V Leiden or prothrombin 20210 mutations, or deficiencies of protein C, protein S, or antithrombin III and arterial stroke (Table 5).^{54,55} One study suggests that hypercoagulable states may be more frequent in stroke patients with PFO compared with those without PFO. That study found no difference in the prevalence of either the factor V Leiden or prothrombin 20210 mutation in patients with cryptogenic strokes compared with controls. The prevalence of prothrombin 20210 mutation alone (OR, 10.09; 95% CI, 1.09 to 109) was higher in those with cryptogenic stroke and PFO versus those without PFO,⁶³⁰ suggesting a greater thrombotic risk in the setting of PFO versus either

condition alone. The presumed stroke mechanism is paradoxical embolism related to venous rather than arterial thrombosis.

The 2 most common genetic causes of thrombophilia are the Leiden mutation of factor V and the G20210A mutation of prothrombin.⁶³¹ The most common acquired cause is the antiphospholipid syndrome (APS). These factors increase the relative risk of a first venous thromboembolism 2 to 10 times, but the actual (absolute) risk is relatively modest.⁶³¹ Therefore, thrombophilia screening for primary prevention of venous thromboembolism is not indicated, except possibly in women with a family history of idiopathic venous thromboembolism who are considering using OCs. Coagulation inhibitor deficiencies are present in approximately 2.5% to 5% of all episodes of venous thromboembolism,^{632,633} but their rarity has prevented quantitation of their effects on the relative risk of an initial thromboembolic event. One retrospective study of antithrombin III-, protein C-, or protein S-deficient relatives of patients with venous thromboembolism found an increased risk of thromboembolism (RR, 16.2; 95% CI, 6.1 to 43.4) for protein S-deficient families; relative risk was 16.2 (95% CI, 6.4 to 41.2) for protein C-deficient families and 18.4 (95% CI, 6.7 to 50.1) for antithrombin III-deficient families.⁶³⁴ But another study found that risk of thromboembolism was not increased unless the relatives took OCs.⁶³⁵ A combined retrospective and prospective multicenter study of cerebral venous thrombosis found that a hypercoagulable state was the most common predisposing factor, followed by pregnancy, malignancy, and homocystinemia.⁶³⁶ These coagulopathies may therefore predispose to venous thromboembolism, including cerebral venous sinus thrombosis but may only rarely be associated with ischemic stroke.

A systematic review assessed the risk of thrombosis associated with thrombophilia in 3 high-risk groups: (1) women using oral estrogen preparations, (2) women who are pregnant, and (3) patients undergoing major orthopedic surgery.⁶³⁷ This is relevant for primary stroke prevention due to cerebral venous thrombosis and paradoxical cerebral embolism in the setting of a PFO. The effectiveness of prophylactic treatments in preventing venous thromboembolism in these groups and the relative cost-effectiveness of universal and selective venous thromboembolism history-based screening for thrombophilia compared with no screening were evaluated. Selective screening based on prior history of venous thromboembolism was more cost-effective than universal screening.

Prothrombotic abnormalities have been identified in 20% to 50% of children with acute ischemic stroke and 33% to 99% of children with cerebral sinus venous thrombosis.⁶³⁸ In children with arterial ischemic stroke, emerging associations include an increased frequency of factor V Leiden mutation, elevated Lp(a), protein C deficiency, and aPL.

Summary and Gaps

Young women with ischemic stroke have a higher prevalence of aPL. aPL also increases with age in both sexes. The majority of case-control studies have not found an association between other hereditary hypercoagulable states and stroke. The relationship between the presence of PFO and thrombophilia deserves further study, because it may affect primary

and secondary stroke prevention strategies. Large prospective studies should be undertaken to refine the risks and establish the associations of thrombophilias with venous thromboembolism and ischemic stroke. Although the pathogenic role of prothrombotic abnormalities as a risk factor for initial and recurrent childhood ischemic stroke is increasingly becoming evident, the lack of any clinical trial data precludes definitive recommendations for screening or treatment.

Recommendations

1. **The usefulness of genetic screening to detect inherited hypercoagulable states for prevention of first stroke is not well established (Class IIb; Level of Evidence C).**
2. **The usefulness of specific treatments for primary stroke prevention in asymptomatic patients with hereditary or acquired thrombophilia is not well established (Class IIb; Level of Evidence C).**
3. **Low-dose aspirin (81 mg/d) is not indicated for primary stroke prevention in persons who are persistently aPL positive (Class III; Level of Evidence B).**

Inflammation and Infection

Table 5 lists stroke risks associated with several inflammatory conditions and markers. Inflammation affects the initiation, growth, and destabilization of atherosclerotic lesions,⁶³⁹ but the application of this knowledge to risk assessment or treatment in the primary prevention of stroke is controversial. A number of serum markers of inflammation, including fibrinogen, serum amyloid A, Lp-PLA2, and interleukin 6 have been proposed as risk markers. Several studies suggest a relationship between Lp-PLA2 and stroke risk (approved by the US Food and Drug Administration as a predictor of ischemic stroke and coronary artery disease),^{640–642} with high-sensitivity C-reactive protein (hs-CRP) being the most commonly used.⁶⁴³ In addition to numerous epidemiological studies and randomized clinical trials with coronary disease end points, several epidemiological studies have identified associations between hs-CRP and stroke, including the Physician's Health Study,⁶⁴⁴ the WHS,⁶⁴⁵ and the Framingham Heart Study.⁶⁴⁶ The relative risks between the highest tertiles/quartiles and the lowest tertile/quartiles range from 1.5 to 2.0. The association persists after adjustment for multiple risk factors. On the basis of multiple prospective studies, hs-CRP was recommended for measurement limited to persons with moderate risk for coronary disease (10% to 20% 10-year risk using the Framingham Risk Score) as an adjunct to global risk assessment to help guide the aggressiveness of risk factor interventions.⁶³⁹ The Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) Study, a randomized trial of a statin versus placebo, was performed in persons free of CVD with otherwise normal LDL-cholesterol levels (≤ 130 mg/dL) but with hs-CRP levels >2 mg/dL.^{646a} The trial found a reduction in cardiovascular end points, including stroke (RR, 0.52; 95% CI, 0.34 to 0.79), in the patients treated with statin. The study design did not include similarly treated subjects with lower levels of hs-CRP. There are no data available to determine the potential effects of other treatments such as aspirin in this population. Monitoring of hs-CRP has not

been evaluated in randomized trials to determine if it is useful in adjusting statin dose in patients who might be considered for treatment, nor has its cost-effectiveness for population screening been assessed. This is also true of the other markers of inflammation.

Another way to evaluate the role of inflammation as a risk factor for stroke is to examine the incidence of vascular disease in persons with systemic chronic inflammatory diseases, such as rheumatoid arthritis (RA) and SLE. A large number of prospective cohort studies have identified increased risks for CVD (including stroke) in persons with RA, with odds ratios consistently in the 1.4 to 2.0 range compared with persons without RA.^{647–651} Excess risk was especially apparent in women with RA who were 35 to 55 years of age.⁶⁴⁷ This association remained after adjustment for other cardiovascular risk factors. Similarly, patients with SLE had very elevated relative risks for CVD in the 2- to 52-fold range.⁶⁵² Although stroke rates were not assessed, several studies have identified a higher prevalence of atherosclerotic plaque in the carotid arteries of patients with RA or SLE compared with control subjects.^{653–655} Patients with RA or SLE might be considered a subgroup at high risk for CVD worthy of enhanced risk factor measurement and control.⁶⁵⁶

A related issue concerning inflammation is the possibility that a chronic infection with one of several viruses or bacteria such as *Helicobacter pylori* might promote atherosclerosis.⁶⁵⁷ Several randomized trials of antibiotic therapy failed to find any benefit in prevention of cardiovascular end points, including stroke.^{658,659}

A final issue in the role of infection and inflammation in stroke deals with the role of acute infectious diseases (eg, influenza) inducing a cerebrovascular event (TIA or stroke). Possible mechanisms include the induction of procoagulant acute phase reactants (eg, fibrinogen) or the destabilization of atherosclerotic plaques. An increase in cardiovascular deaths has long been observed in association with influenza.^{660,661} A retrospective study found that treatment with an antiviral agent within 2 days of an influenza diagnosis was associated with a 28% reduction (HR, 0.72; 95% CI, 0.62 to 0.82) in risk of stroke or TIA over the ensuing 6 months.⁶⁶² One case-control study⁶⁶³ and 1 cohort study⁶⁶⁴ of influenza vaccination demonstrate a reduced risk for stroke associated with vaccination. A prospective study in Taiwan found that influenza vaccination of persons >65 years of age was associated with lower all-cause mortality, including a 65% reduction in stroke (HR, 0.35; 95% CI, 0.27 to 0.45).⁶⁶⁵ All persons at increased risk of complications from influenza should receive influenza vaccinations on the basis of evidence, including randomized trials, and influenza vaccination is recommended by the AHA/ACC for the secondary prevention of cerebrovascular disease. There have been no recommendations about influenza vaccination in primary prevention of stroke. No studies have identified any increase in risk of stroke after influenza vaccinations.⁶⁶⁶

Recommendations

1. **Measurement of inflammatory markers such as hs-CRP or Lp-PLA2 in patients without CVD may be**

considered to identify patients who may be at increased risk of stroke, although their effectiveness (ie, usefulness in routine clinical practice) is not well established (*Class IIb; Level of Evidence B*).

2. Patients with chronic inflammatory disease such as RA or SLE should be considered at increased risk for stroke (*Class I; Level of Evidence B*).
3. Treatment with antibiotics for chronic infections as a means to prevent stroke is not recommended (*Class III; Level of Evidence A*).
4. Treatment of patients with elevated hs-CRP with a statin to decrease stroke risk might be considered (*Class IIb; Level of Evidence B*).
5. Annual influenza vaccination can be useful for patients at risk for stroke (*Class IIa; Level of Evidence B*).

Aspirin for Primary Stroke Prevention

The US Preventive Services Task Force recommends aspirin at a dosage of 75 mg/d for cardiac prophylaxis for persons whose 5-year risk for coronary heart disease is $\geq 3\%$.⁶⁶⁷ The most recent AHA guideline for the primary prevention of cardiovascular disease and stroke agrees with the US Preventive Services Task Force report on the use of aspirin in persons at high risk but uses a $\geq 10\%$ risk per 10 years rather than $>3\%$ risk over 5 years to improve the likelihood of a positive balance of coronary risk reduction over bleeding and hemorrhagic stroke caused by aspirin.⁶⁶⁸ There is no evidence that this class of drugs reduces the risk of stroke in the general population of persons at low risk.^{667,669,670} Several additional relevant trials have been completed since publication of the US Preventive Services Task Force and AHA guidelines.

The Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial randomized 2539 patients with type 2 diabetes without a history of atherosclerotic disease (including stroke) to low-dose aspirin (81 or 100 mg/d) or no aspirin.¹⁹⁰ The study used a PROBE (prospective, randomized, open-label, blinded, end-point assessment) design. The primary outcome was the occurrence of atherosclerotic events (fatal or nonfatal ischemic heart disease, fatal or nonfatal stroke, and peripheral arterial disease). There was no effect of aspirin on the trial's primary end point (HR, 0.80; 95% CI, 0.58 to 1.10; $P=0.16$) and no effect on cerebrovascular events (2.2% with aspirin versus 2.5% with no aspirin; HR, 0.84; 95% CI, 0.53 to 1.32; $P=0.44$). There was no difference in the combined rates of hemorrhagic stroke and severe gastrointestinal bleeding.

The Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial was a randomized, double-blind, placebo-controlled trial including 1276 adults with type 1 or type 2 diabetes, an ankle brachial pressure index ≤ 0.99 , but no symptomatic CVD, randomized in a 2×2 factorial design to 100 mg aspirin or placebo plus antioxidants or placebo daily.⁶⁷¹ The study had 2 primary end points: (1) death from coronary heart disease or stroke, nonfatal MI or stroke, or amputation above the ankle for critical limb ischemia; and (2) death from coronary heart disease or stroke. There was no interaction between aspirin and antioxidant. There was no effect of aspirin treatment on the overall primary end point (HR, 0.98; 95% CI, 0.76 to 1.26; $P=0.86$) or on death from coronary heart disease or stroke (HR, 1.23; 95% CI, 0.79 to

1.93; $P=0.36$). There was no effect of aspirin on fatal stroke (HR, 0.89; 95% CI, 0.34 to 2.30; $P=0.80$) or nonfatal stroke (HR, 0.71; 95% CI, 0.44 to 1.14; $P=0.15$). There was no difference in the risk of gastrointestinal hemorrhage (HR, 0.90; 95% CI, 0.53 to 1.52; $P=0.69$).

There were relatively few women enrolled in the primary prevention trials, which showed a benefit of aspirin in the prevention of coronary heart events but no reduction in stroke. The WHS randomly assigned 39 876 initially asymptomatic women ≥ 45 years of age to 100 mg of aspirin on alternate days or placebo and monitored them for 10 years for a first major vascular event (nonfatal MI, nonfatal stroke, or cardiovascular death).⁶⁷² Unlike data from earlier studies that included mainly men, this study found a nonsignificant 9% reduction (RR, 0.91; 95% CI, 0.80 to 1.03; $P=0.13$) for the combined primary end point among women but a 17% reduction in risk of stroke (ARR, 0.83; 95% CI, 0.69 to 0.99; $P=0.04$). This was based on a 24% reduction in the risk of ischemic stroke (RR, 0.76; 95% CI, 0.63 to 0.93; $P=0.009$) and a nonsignificant increase in the risk of hemorrhagic stroke (RR, 1.24; 95% CI, 0.82 to 1.87; $P=0.31$). The overall average stroke rates were 0.11% per year in women treated with aspirin and 0.13% per year in women treated with placebo [ARR, 0.02% per year; number needed to treat (NNT)=5000]. Gastrointestinal hemorrhage requiring transfusion was more frequent in the aspirin group (RR, 1.40; 95% CI, 1.07 to 1.83; $P=0.02$). The average gastrointestinal hemorrhage rates were 0.06% per year for aspirin and 0.05% per year for placebo [absolute risk increase, 0.01% per year; number needed to harm=10 000]. The most consistent benefit for aspirin was in women ≥ 65 years of age at study entry, among whom the risk of major cardiovascular events was reduced by 26% (RR, 0.74; 95% CI, 0.59 to 0.92; $P=0.008$), including a 30% reduction in the risk of ischemic stroke (RR, 0.70; 95% CI, 0.49 to 1.00; $P=0.05$); however, there was only a trend in the reduction of the overall (ischemic plus hemorrhagic) risk of stroke (RR, 0.78; 95% CI, 0.57 to 1.08; $P=0.13$) likely related to an increase in the risk of brain hemorrhages. Subgroup analyses showed a reduction in stroke for those women with a history of hypertension (RR, 0.76; 95% CI, 0.59 to 0.98; $P=0.04$), hyperlipidemia (RR, 0.62; 95% CI, 0.47 to 0.83; $P=0.001$), diabetes (RR, 0.46; 95% CI, 0.25 to 0.85; $P=0.01$), or having a 10-year cardiovascular risk $\geq 10\%$ (RR, 0.54; 95% CI, 0.30 to 0.98; $P=0.04$). In consideration of these data, the AHA 2007 Update of the AHA Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women recommended that aspirin therapy be considered for all women for prevention of stroke, depending on the balance of risks and benefits.³⁷⁶ These guidelines further note that aspirin (81 mg daily or 100 mg every other day) should be considered in women >65 years of age if their BP is controlled and the benefit for prevention of ischemic stroke and MI is likely to outweigh the risk of gastrointestinal bleeding and hemorrhagic stroke. Aspirin should also be considered in women >65 years of age when the benefit for prevention of ischemic stroke prevention is likely to outweigh the adverse effects of therapy.

Summary and Gaps

Previous guidelines endorse the use of aspirin (dose as low as 75 mg/d as reflected in the US Preventive Services Task Force recommendation) for cardiovascular prophylaxis among men whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment (a 10-year risk of 6% to 10%).^{667,668} These recommendations are based on a reduction of cardiovascular events, not stroke. Since these recommendations, JPAD found no primary prevention benefit of aspirin among persons with diabetes,¹⁹⁰ and POPADAD found no benefit among persons with diabetes and peripheral arterial disease.⁶⁷¹ The WHS found a reduction in the risk of a first stroke in women (including those with diabetes), but not cardiac events or death from cardiovascular causes with aspirin.⁶⁷² The overall stroke prevention benefit of aspirin is most consistent among women >65 years of age; however, there was not an overall reduction of stroke in this group. The reasons for the differences between men and women remain uncertain.

Recommendations

1. **The use of aspirin for cardiovascular (including but not specific to stroke) prophylaxis is recommended for persons whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment (a 10-year risk of cardiovascular events of 6% to 10%) (Class I; Level of Evidence A).**
2. **Aspirin (81 mg daily or 100 mg every other day) can be useful for prevention of a first stroke among women whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment (Class IIa; Level of Evidence B).**
3. **Aspirin is not useful for preventing a first stroke in persons at low risk (Class III; Level of Evidence A).**
4. **Aspirin is not useful for preventing a first stroke in persons with diabetes or diabetes plus asymptomatic peripheral artery disease (defined as an ankle brachial pressure index ≤ 0.99) in the absence of other established CVD (Class III; Level of Evidence B).**
5. **The use of aspirin for other specific situations (eg, atrial fibrillation, carotid artery stenosis) is discussed in the relevant sections of this statement.**

Assessing the Risk of First Stroke

It is helpful for healthcare providers and the public to be able to estimate a person's risk for a first stroke. As detailed in the previous sections, numerous factors can contribute to stroke risk, and many persons have >1 risk factor. Some of these risk factors are less well documented, and specific or proven treatments may be lacking. Although most risk factors have an independent effect, there may be important interactions between individual factors that need to be considered in predicting overall risk or choosing an appropriate risk-modification program. Risk-assessment tools have been used in community stroke-screening programs and in some guidelines to select certain treatments for primary stroke prevention.^{673,674} Some goals of such risk-assessment tools are to (1) identify persons at elevated risk who might be unaware of their risk; (2) assess risk in the presence of >1 condition; (3) measure risk that can be tracked and lowered by appropriate modifications; (4) estimate a quantitative risk for selecting

treatments or stratification in clinical trials; and (5) guide appropriate use of further diagnostic testing.

Although stroke risk-assessment tools exist, the complexities of the interactions of risk factors and the effects of certain risk factors stratified by age, sex, race/ethnicity, and geography are incompletely captured by any available global risk-assessment tool. In addition, these tools tend to be focused and generally do not include the full range of possible contributing factors. Some risk-assessment tools are sex specific and give 1-, 5-, or 10-year stroke risk estimates. The Framingham Stroke Profile (FSP) uses a Cox proportional hazards model with risk factors as covariates and points calculated according to the weight of the model coefficients.¹¹² Independent stroke predictors include age, systolic BP, hypertension, diabetes mellitus, current smoking, established CVD (any one of several, including MI, angina or coronary insufficiency, congestive heart failure, or intermittent claudication), atrial fibrillation, and left ventricular hypertrophy on ECG. Point values can be calculated that correspond to a sex-specific 10-year cumulative stroke risk. The FSP has been updated to account for the use of antihypertensive therapy and the risk of stroke and stroke or death among persons with new-onset atrial fibrillation (Table 13).^{675,676} Despite its widespread use, the validity of the FSP among persons of a different age range or belonging to different race/ethnic groups has not been adequately studied. The FSP has been applied to ethnic minorities in the United Kingdom and found to vary across groups, but the suitability of the scale to predict outcomes has not been well tested.⁶⁷⁷

Alternative prediction models have been developed using other cohorts and utilizing different sets of stroke risk factors. Retaining most of the Framingham covariates, 1 alternative stroke risk scoring system omits cigarette smoking and antihypertensive medication and adds "time to walk 15 feet" and serum creatinine.⁶⁷⁸ Another score is derived from a mixed cohort of stroke and stroke-free patients and includes a prior history of stroke, marital status, BP as a categorical variable, HDL cholesterol, impaired expiratory flow, physical disability, and a depression score.⁶⁷⁹ Several studies have generated risk-assessment tools for use in subjects with atrial fibrillation (see above).

Summary and Gaps

It is clear that an ideal stroke risk-assessment tool that is generally applicable, simple, and widely accepted does not exist. Each available tool has limitations. The impact of newer risk factors for stroke that were not collected in older studies needs to be considered.⁶⁸⁰ Risk-assessment tools should be used with care, because they do not include all the factors that contribute to future disease risk.⁶⁸¹ The utility of the FSP (Table 13) or other stroke risk-assessment scales as a way of improving the effectiveness of primary stroke prevention interventions is not well studied. Research is needed to validate risk-assessment tools across age, sex, and race/ethnic groups; evaluate whether any more recently identified risk factors add to the predictive accuracy of existing scales; and determine whether the use of these scales improves primary stroke prevention.

Table 13. Modified Framingham Stroke Risk Profile*^{675,676}

	Points										
	0	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10
Men											
Age, y	54–56	57–59	60–62	63–65	66–68	69–72	73–75	76–78	79–81	82–84	85
Untreated SBP, mm Hg	97–105	106–115	116–125	126–135	136–145	146–155	156–165	166–175	176–185	186–195	196–205
Treated SBP, mm Hg	97–105	106–112	113–117	118–123	124–129	130–135	136–142	143–150	151–161	162–176	177–205
Diabetes	No	Yes									
Cigarette smoking	No	Yes									
CVD	No	Yes									
AF	No	Yes									
LVH	No	Yes									

Points	10-Year Probability, %	Points	10-Year Probability, %	Points	10-Year Probability, %
1	3	11	11	21	42
2	3	12	13	22	47
3	4	13	15	23	52
4	4	14	17	24	57
5	5	15	20	25	63
6	5	16	22	26	68
7	6	17	26	27	74
8	7	18	29	28	79
9	8	19	33	29	84
10	10	20	37	30	88

	Points										
	0	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10
Women											
Age, y	54–56	57–59	60–62	63–64	65–67	68–70	71–73	74–76	77–78	79–81	82–84
Untreated SBP, mm Hg		95–106	107–118	119–130	131–143	144–155	156–167	168–180	181–192	193–204	205–216
Treated SBP, mm Hg		95–106	107–113	114–119	120–125	126–131	132–139	140–148	149–160	161–204	205–216
Diabetes	No	Yes									
Cigarette smoking	No	Yes									
CVD	No	Yes									
AF	No	Yes									
LVH	No	Yes									

Points	10-Year Probability, %	Points	10-Year Probability, %	Points	10-Year Probability, %
1	1	11	8	21	43
2	1	12	9	22	50
3	2	13	11	23	57
4	2	14	13	24	64
5	2	15	16	25	71
6	3	16	19	26	78
7	4	17	23	27	84
8	4	18	27		
9	5	19	32		
10	6	20	37		

SBP indicates systolic blood pressure; CVD, cardiovascular disease, history of MI, angina pectoris, coronary insufficiency, intermittent claudication, or congestive heart failure; AF, atrial fibrillation; and LVH, left ventricular hypertrophy on ECG.

*The table gives the probability of stroke within 10 years for men and women 55–85 years of age and free of previous stroke in the Framingham Heart Study. To use these tables, identify each of the patient's characteristics and obtain the corresponding point value from the top row of the table. Sum points for each individual and then obtain corresponding 10-year probability of stroke. For example, a 64-year-old man (3 points) has a treated SBP of 138 mm Hg (6 points), no diabetes (0 points), does not smoke (0 points), or have CVD (0 points) or AF (0 points) but has LVH (5 points). His total point score (11 points) corresponds to an 11% 10-year probability of stroke.

Table 14. Summary of Recommendations

Risk Factor	Recommendations
Generally Nonmodifiable Risk Factors	
<i>Age</i>	N/A
<i>Sex</i>	N/A
<i>Low birth weight</i>	N/A
<i>Race/ethnicity</i>	N/A
<i>Genetic factors</i>	<ul style="list-style-type: none"> ● Obtaining a family history can be useful to help identify persons who may be at increased risk of stroke (<i>Class III; Level of Evidence A</i>). ● Genetic screening of the general population for prevention of a first stroke is not recommended (<i>Class III; Level of Evidence C</i>). ● Referral for genetic counseling may be considered for patients with rare genetic causes of stroke (<i>Class IIb; Level of Evidence C</i>). ● Treatment for certain genetic conditions that predispose to stroke (eg, Fabry disease and enzyme replacement therapy) might be reasonable but has not been shown to reduce risk of stroke, and its effectiveness is unknown (<i>Class IIb; Level of Evidence C</i>). ● Screening of patients at risk for myopathy in the setting of statin use is not recommended when considering initiation of statin therapy at this time (<i>Class III; Level of Evidence C</i>). ● Noninvasive screening for unruptured intracranial aneurysms in patients with 1 relative with SAH or intracranial aneurysms is not recommended (<i>Class III; Level of Evidence C</i>). ● Noninvasive screening for unruptured intracranial aneurysms in patients with ≥ 2 first-degree relatives with SAH or intracranial aneurysms might be reasonable (<i>Class IIb; Level of Evidence C</i>).⁸⁹ ● Universal screening for intracranial aneurysms in carriers of mutations for Mendelian disorders associated with aneurysms is not recommended (<i>Class III; Level of Evidence C</i>). ● Noninvasive screening for unruptured intracranial aneurysms in patients with ADPKD and 1 or more relatives with ADPKD and SAH or intracranial aneurysm may be considered (<i>Class IIb; Level of Evidence C</i>). ● Noninvasive screening for unruptured intracranial aneurysms in patients with cervical fibromuscular dysplasia may be considered (<i>Class IIb; Level of Evidence C</i>). ● Dosing with vitamin K antagonists on the basis of pharmacogenetics is not recommended at this time (<i>Class III; Level of Evidence C</i>).
Well Documented and Modifiable Risk Factors	
<i>Hypertension</i>	<ul style="list-style-type: none"> ● In agreement with the JNC 7 report, regular BP screening and appropriate treatment, including both lifestyle modification and pharmacological therapy, are recommended (<i>Class I; Level of Evidence A</i>). ● Systolic BP should be treated to a goal of <140 mm Hg and diastolic BP to <90 mm Hg because these levels are associated with a lower risk of stroke and cardiovascular events (<i>Class I; Level of Evidence A</i>). In patients with hypertension with diabetes or renal disease, the BP goal is <130/80 mm Hg (also see section on diabetes) (<i>Class I; Level of Evidence A</i>).
<i>Cigarette smoking</i>	<ul style="list-style-type: none"> ● Abstention from cigarette smoking by nonsmokers and smoking cessation by current smokers are recommended based on epidemiological studies showing a consistent and overwhelming relationship between smoking and both ischemic stroke and SAH (<i>Class I; Level of Evidence B</i>). ● Although data are lacking that avoidance of environmental tobacco smoke reduces incident stroke, on the basis of epidemiological data showing increased stroke risk and the effects of avoidance on risk of other cardiovascular events, avoidance of exposure to environmental tobacco smoke is reasonable (<i>Class IIa; Level of Evidence C</i>). ● Status of tobacco use should be discussed at every patient encounter. The use of multimodal techniques, including counseling, nicotine replacement, and oral smoking-cessation medications, can be useful as part of an overall smoking-cessation strategy. Tobacco use status should be addressed at every patient encounter (<i>Class I; Level of Evidence B</i>).
<i>Diabetes</i>	<ul style="list-style-type: none"> ● Control of BP in patients with either type 1 or type 2 diabetes as part of a comprehensive cardiovascular risk-reduction program as reflected in the JNC 7 guidelines is recommended (<i>Class I; Level of Evidence A</i>). ● Treatment of hypertension in adults with diabetes with an ACEI or an ARB is useful (<i>Class I; Level of Evidence A</i>). ● Treatment of adults with diabetes with a statin, especially those with additional risk factors, is recommended to lower risk of a first stroke (<i>Class I; Level of Evidence A</i>). ● The use of monotherapy with a fibrate to lower stroke risk might be considered for patients with diabetes (<i>Class IIb; Level of Evidence B</i>). ● The addition of a fibrate to a statin in persons with diabetes is not useful for decreasing stroke risk (<i>Class III; Level of Evidence B</i>). ● The benefit of aspirin for reduction of stroke risk has not been satisfactorily demonstrated for patients with diabetes; however, administration of aspirin may be reasonable in those at high CVD risk (<i>Class IIb; Level of Evidence B</i>). (Also see aspirin recommendations.)
<i>Dyslipidemia</i>	<ul style="list-style-type: none"> ● Treatment with an HMG-CoA reductase inhibitor (statin) medication in addition to therapeutic lifestyle changes with LDL-cholesterol goals as reflected in the NCEP Guidelines^{221,222} is recommended for primary prevention of ischemic stroke in patients with coronary heart disease or certain high-risk conditions such as diabetes (<i>Class I; Level of Evidence A</i>).

(Continued)

Table 14. Continued

Risk Factor	Recommendations
<i>Atrial Fibrillation</i>	<ul style="list-style-type: none"> ● Fibrin acid derivatives may be considered for patients with hypertriglyceridemia, but their efficacy in the prevention of ischemic stroke is not established (<i>Class IIb; Level of Evidence C</i>). ● Niacin may be considered for patients with low HDL cholesterol or elevated lipoprotein(a), but its efficacy in prevention of ischemic stroke in patients with these conditions is not established (<i>Class IIb; Level of Evidence C</i>). ● Treatment with other lipid-lowering therapies, such as fibrin acid derivatives, bile acid sequestrants, niacin, and ezetimibe, may be considered in patients who do not achieve target LDL cholesterol with statins or cannot tolerate statins, but the effectiveness of these therapies in decreasing risk of stroke is not established (<i>Class IIb; Level of Evidence C</i>). ● Active screening for atrial fibrillation in patients >65 years of age in primary care settings using pulse taking followed by electrocardiography as indicated can be useful (<i>Class IIa; Level of Evidence B</i>). ● Adjusted-dose warfarin (target INR, 2.0 to 3.0) is recommended for all patients with nonvalvular atrial fibrillation deemed to be at high risk and many deemed to be at moderate risk for stroke who can receive it safely (<i>Class I; Level of Evidence A</i>). ● Antiplatelet therapy with aspirin is recommended for low-risk and some moderate-risk patients with atrial fibrillation, based on patient preference, estimated bleeding risk if anticoagulated, and access to high-quality anticoagulation monitoring (<i>Class I; Level of Evidence A</i>). ● For high-risk patients with atrial fibrillation deemed unsuitable for anticoagulation, dual antiplatelet therapy with clopidogrel and aspirin offers more protection against stroke than aspirin alone but with increased risk of major bleeding and might be reasonable (<i>Class IIb; Level of Evidence B</i>). ● Aggressive management of BP coupled with antithrombotic prophylaxis in elderly patients with atrial fibrillation can be useful (<i>Class IIa; Level of Evidence B</i>).
<i>Other cardiac conditions</i>	<ul style="list-style-type: none"> ● ACC/AHA practice guidelines providing strategies to reduce the risk of stroke in patients with a variety of cardiac conditions, including valvular heart disease,³¹² unstable angina,³¹³ chronic stable angina,³¹⁴ and acute MI are endorsed.³¹⁵ ● Screening for cardiac conditions such as PFO in the absence of neurologic conditions or a specific cardiac cause is not recommended (<i>Class III; Level of Evidence A</i>). ● It is reasonable to prescribe warfarin to post–ST-segment elevation MI patients with left ventricular mural thrombi or an akinetic left ventricular segment to prevent stroke³¹⁵ (<i>Class IIa; Level of Evidence A</i>).
<i>Asymptomatic carotid stenosis</i>	<ul style="list-style-type: none"> ● Patients with asymptomatic carotid artery stenosis should be screened for other treatable risk factors for stroke with institution of appropriate lifestyle changes and medical therapy (<i>Class I; Level of Evidence C</i>). ● Selection of asymptomatic patients for carotid revascularization should be guided by an assessment of comorbid conditions and life expectancy, as well as other individual factors, and should include a thorough discussion of the risks and benefits of the procedure with an understanding of patient preferences (<i>Class I; Level of Evidence C</i>). ● The use of aspirin in conjunction with CEA is recommended unless contraindicated because aspirin was used in all of the cited trials of CEA as an antiplatelet drug (<i>Class I; Level of Evidence C</i>). ● Prophylactic CEA performed with <3% morbidity and mortality can be useful in highly selected patients with an asymptomatic carotid stenosis (minimum 60% by angiography, 70% by validated Doppler ultrasound) (<i>Class IIa; Level of Evidence A</i>). It should be noted that the benefit of surgery may now be lower than anticipated based on randomized trial results, and the cited 3% threshold for complication rates may be high because of interim advances in medical therapy. ● Prophylactic carotid artery stenting might be considered in highly selected patients with an asymptomatic carotid stenosis (≥60% on angiography, ≥70% on validated Doppler ultrasonography, or ≥80% on computed tomographic angiography or MRA if the stenosis on ultrasonography was 50% to 69%). The advantage of revascularization over current medical therapy alone is not well established (<i>Class IIb; Level of Evidence B</i>). ● The usefulness of CAS as an alternative to CEA in asymptomatic patients at high risk for the surgical procedure is uncertain (<i>Class IIb; Level of Evidence C</i>).
<i>Sickle cell disease</i>	<ul style="list-style-type: none"> ● Population screening for asymptomatic carotid artery stenosis is not recommended (<i>Class III; Level of Evidence B</i>). ● Children with SCD should be screened with TCD starting at age 2 years (<i>Class I; Level of Evidence B</i>). ● Although the optimal screening interval has not been established, it is reasonable for younger children and those with borderline abnormal TCD velocities to be screened more frequently to detect development of high-risk TCD indications for intervention (<i>Class IIa; Level of Evidence B</i>). ● Transfusion therapy (target reduction of hemoglobin S from a baseline of >90% to <30%) is effective for reducing stroke risk in those children at elevated stroke risk (<i>Class I; Level of Evidence B</i>). ● Pending further studies, continued transfusion, even in those with TCD velocities that revert to normal, is probably indicated (<i>Class IIa; Level of Evidence B</i>). ● In children at high risk for stroke who are unable or unwilling to be treated with regular red blood cell transfusion, it might be reasonable to consider hydroxyurea or bone marrow transplantation (<i>Class IIb; Level of Evidence C</i>). ● MRI and MRA criteria for selection of children for primary stroke prevention using transfusion have not been established, and these tests are not recommended in place of TCD for this purpose (<i>Class III; Level of Evidence B</i>). ● Adults with SCD should be evaluated for known stroke risk factors and managed according to the general guidelines in this statement (<i>Class I; Level of Evidence A</i>).

(Continued)

Table 14. Continued

Risk Factor	Recommendations
<i>Postmenopausal hormone therapy</i>	<ul style="list-style-type: none"> ● Hormone therapy (CEE with or without MPA) should not be used for primary prevention of stroke in postmenopausal women (<i>Class III; Level of Evidence A</i>). ● SERMs, such as raloxifene, tamoxifen, or tibolone, should not be used for primary prevention of stroke (<i>Class III; Level of Evidence A</i>).
<i>Oral contraceptives</i>	<ul style="list-style-type: none"> ● OCs may be harmful in women with additional risk factors (eg cigarette smoking, prior thromboembolic events) (<i>Class III; Level of Evidence C</i>).^{390,402} ● For those who choose to use OCs despite the increased risk associated with their use, aggressive therapy for stroke risk factors may be reasonable (<i>Class IIb; Level of Evidence C</i>).^{390, 392, 402}
<i>Diet and nutrition</i>	<ul style="list-style-type: none"> ● Reduced intake of sodium and increased intake of potassium as indicated in the report <i>Dietary Guidelines for Americans</i> are recommended to lower BP (<i>Class I; Level of Evidence A</i>). ● A DASH-style diet, which emphasizes consumption of fruits, vegetables, and low-fat dairy products and is reduced in saturated fat, also lowers BP and is recommended (<i>Class I; Level of Evidence A</i>). ● A diet that is rich in fruits and vegetables and thereby high in potassium is beneficial and may lower risk of stroke (<i>Class I; Level of Evidence B</i>).
<i>Physical inactivity</i>	<ul style="list-style-type: none"> ● Increased physical activity is recommended because it is associated with a reduction in risk of stroke (<i>Class I; Level of Evidence B</i>). ● The 2008 Physical Activity Guidelines for Americans are endorsed and recommend that adults should engage in at least 150 minutes (2 hours and 30 minutes) per week of moderate intensity or 75 minutes (1 hour and 15 minutes) per week of vigorous intensity aerobic physical activity (<i>Class I; Level of Evidence B</i>).
<i>Obesity and body fat distribution</i>	<ul style="list-style-type: none"> ● Among overweight and obese persons, weight reduction is recommended as a means to lower BP (<i>Class I; Level of Evidence A</i>). ● Among overweight and obese persons, weight reduction is reasonable as a means of reducing risk of stroke (<i>Class IIa; Level of Evidence B</i>).
Less Well-Documented or Potentially Modifiable Risk Factors	
<i>Migraine</i>	<ul style="list-style-type: none"> ● Because there is an association between higher migraine frequency and stroke risk, treatments to reduce migraine frequency might be reasonable, although there are no data showing that this treatment approach would reduce the risk of first stroke (<i>Class IIb; Level of Evidence C</i>).
<i>Metabolic syndrome</i>	<ul style="list-style-type: none"> ● Management of individual components of the metabolic syndrome is recommended, including lifestyle measures (ie, exercise, appropriate weight loss, proper diet) and pharmacotherapy (ie, medications for lowering BP, lowering lipids, glycemic control, and antiplatelet therapy) as reflected in the NCEP ATP III²²² and the JNC 7,⁹⁰ and as endorsed or indicated in other sections of this guideline. (Refer to relevant sections for Class and Levels of Evidence for each recommendation.) ● The effectiveness of agents that ameliorate aspects of the insulin resistance syndrome for reducing stroke risk is unknown (<i>Class IIb; Level of Evidence C</i>).
<i>Alcohol consumption</i>	<ul style="list-style-type: none"> ● For numerous health considerations, reduction or elimination of alcohol consumption by heavy drinkers through established screening and counseling strategies as described in the US Preventive Services Task Force Recommendation Statement of 2004 are recommended⁵¹⁸ (<i>Class I; Level of Evidence A</i>). ● For persons who choose to consume alcohol, consumption of ≤ 2 drinks per day for men and ≤ 1 drink per day for nonpregnant women might be reasonable^{519, 520} (<i>Class IIb; Level of Evidence B</i>).
<i>Drug abuse</i>	<ul style="list-style-type: none"> ● Referral to an appropriate therapeutic program is reasonable for patients with drug abuse (<i>Class IIa; Level of Evidence C</i>).
<i>Sleep-disordered breathing</i>	<ul style="list-style-type: none"> ● Because of its association with other vascular risk factors and cardiovascular morbidity, evaluation for SDB through a detailed history and, if indicated, specific testing is recommended, particularly in those with abdominal obesity, hypertension, heart disease, or drug-resistant hypertension (<i>Class I; Level of Evidence A</i>). ● Treatment of sleep apnea to reduce the risk of stroke might be reasonable, although its effectiveness is unknown (<i>Class IIb; Level of Evidence C</i>).
<i>Hyperhomocysteinemia</i>	<ul style="list-style-type: none"> ● The use of the B-complex vitamins, pyridoxine (B₆), cobalamin (B₁₂), and folic acid, might be considered for prevention of ischemic stroke in patients with hyperhomocysteinemia, but its effectiveness is not well established (<i>Class IIb; Level of Evidence B</i>).
<i>Elevated Lp(a)</i>	<ul style="list-style-type: none"> ● The use of niacin might be reasonable for prevention of ischemic stroke in patients with high Lp(a), but its effectiveness is not well established (<i>Class IIb; Level of Evidence B</i>).
<i>Hypercoagulability</i>	<ul style="list-style-type: none"> ● The usefulness of genetic screening to detect inherited hypercoagulable states for prevention of first stroke is not well established (<i>Class IIb; Level of Evidence C</i>). ● The usefulness of specific treatments for primary stroke prevention in asymptomatic patients with hereditary or acquired thrombophilia is not well established (<i>Class IIb; Level of Evidence C</i>). ● Low-dose aspirin (81 mg/d) is not indicated for primary stroke prevention in persons who are persistently aPL positive (<i>Class III; Level of Evidence B</i>).

(Continued)

Table 14. Continued

Risk Factor	Recommendations
Inflammation and infection	<ul style="list-style-type: none"> • Measurement of inflammatory markers such as hs-CRP or Lp-PLA2 in patients without CVD may be considered to identify patients who may be at increased risk of stroke, although their effectiveness (ie, usefulness in routine clinical practice) is not well established (<i>Class IIb; Level of Evidence B</i>). • Patients with chronic inflammatory disease such as RA or SLE should be considered at increased risk for stroke (<i>Class I; Level of Evidence B</i>). • Treatment with antibiotics for chronic infections as a means to prevent stroke is not recommended (<i>Class III; Level of Evidence A</i>). • Treatment of patients with elevated hs-CRP with a statin to decrease stroke risk might be considered (<i>Class IIb; Level of Evidence B</i>). • Annual influenza vaccination can be useful for patients at risk for stroke (<i>Class IIa; Level of Evidence B</i>).
Aspirin for primary stroke prevention	<ul style="list-style-type: none"> • The use of aspirin for cardiovascular (including but not specific to stroke) prophylaxis is recommended for persons whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment (a 10-year risk of cardiovascular events of 6% to 10%) (<i>Class I; Level of Evidence A</i>). • Aspirin (81 mg daily or 100 mg every other day) can be useful for prevention of a first stroke among women whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment (<i>Class IIa; Level of Evidence B</i>). • Aspirin is not useful for preventing a first stroke in persons at low risk (<i>Class III; Level of Evidence A</i>). • Aspirin is not useful for preventing a first stroke in persons with diabetes or diabetes plus asymptomatic peripheral artery disease (defined as an ankle brachial pressure index ≤ 0.99) in the absence of other established CVD (<i>Class III; Level of Evidence B</i>). • The use of aspirin for other specific situations (eg, atrial fibrillation, carotid artery stenosis) is discussed in the relevant sections of this statement.
Assessing the risk of first stroke	<ul style="list-style-type: none"> • Each patient should undergo an assessment of stroke risk (<i>Class I; Level of Evidence A</i>). • The use of a risk-assessment tool such as the FSP is reasonable because these tools can help identify persons who could benefit from therapeutic interventions and who may not be treated based on any single risk factor (<i>Class IIa; Level of Evidence B</i>).
Primary prevention in the ED	<ul style="list-style-type: none"> • ED-based smoking cessation programs and interventions are recommended (<i>Class I; Level of Evidence B</i>). • Identification of atrial fibrillation and evaluation for anticoagulation in the ED is recommended (<i>Class I; Level of Evidence B</i>). • ED population screening for hypertension is reasonable (<i>Class IIa; Level of Evidence C</i>). • When a patient is identified as having a drug or alcohol abuse problem, ED referral to an appropriate therapeutic program is reasonable (<i>Class IIa; Level of Evidence C</i>). • The effectiveness of screening, brief intervention, and referral for treatment of diabetes and lifestyle stroke risk factors (obesity, alcohol/substance abuse, sedentary life style) in the ED setting is not established (<i>Class IIb; Level of Evidence C</i>).
Preventive health services/strategies to improve adherence	<ul style="list-style-type: none"> • Implementation of a method to systematically identify and treat risk factors in all patients at risk for stroke can be useful (<i>Class IIa; Level of Evidence C</i>).

Recommendations

1. Each patient should undergo an assessment of stroke risk (*Class I; Level of Evidence A*).
2. The use of a risk-assessment tool such as the FSP is reasonable because these tools can help identify persons who could benefit from therapeutic interventions and who may not be treated based on any single risk factor (*Class IIa; Level of Evidence B*).

Primary Prevention in the Emergency Department

The Institute of Medicine report on hospital-based emergency care in the United States describes the current emergency care system as being “at the breaking point.”⁶⁸² In 2006, >119 million Americans used an emergency department (ED) for access to healthcare.⁶⁸³ Ideally EDs provide immediate access to healthcare providers trained in emergency care and allow access to advanced technologies and medical specialists. Today many challenges affect the capacity of healthcare providers to deliver timely emergency care. The increasing numbers of uninsured Americans, lack of access to primary care in the community, decreasing availability of medical specialists, and inadequate preventive and chronic-care management all contribute to the

overcrowding in the country’s EDs. Despite these issues, the ED may serve as an important location for providing health promotion and disease prevention services.

An ED visit can be used to reinforce healthy living options, perform primary disease identification and prevention, provide early disease detection (secondary prevention), encourage and facilitate compliance with disease management, and provide referral of patients to primary care providers for continued management of existing disease (tertiary prevention).^{684,685} With growing numbers of Americans using the ED for primary care, especially those in socioeconomically at-risk populations, the ED may present a unique opportunity to have an impact on the increasing burden of cerebrovascular and cardiovascular disease.⁶⁸⁶

Enthusiasm to use the ED as a site for initiating primary and secondary preventive services, however, must be balanced by the higher cost of obtaining care in this setting and suboptimal use of resources.^{684,687} Although the list of modifiable and potentially modifiable risk factors for stroke as reviewed in this guideline is extensive, not all are amenable to assessment and initiation of prevention in the ED.⁶⁸⁴ Aside from resource availability, to effectively initiate primary preventive strategies, healthcare providers in the ED must be knowledgeable about

risk factors for various diseases, in this case stroke; understand the appropriate diagnostic evaluations for risk factors; be knowledgeable about the most appropriate interventions; and be able to arrange primary care follow-up to assess the impact of initiated preventive interventions. Additionally, adding the delivery of primary care and primary prevention to the growing responsibilities of healthcare providers in the ED setting will require a paradigm change in the minds of these professionals.

ED visits serve as a critical opportunity to screen and potentially treat patients with asymptomatic hypertension. The prevalence of asymptomatic hypertension in patients presenting to the ED may be as high as 1 in 20.⁶⁸⁸ Although these patients are asymptomatic, many have target organ injury. Performing screening tests in the ED for target organ damage and tests for identifiable causes of hypertension in selected patients is appropriate. Most will not require acute BP intervention or initiation of long-term use of antihypertensive medication in the ED. Screening for hypertension in the ED is cost-effective.⁶⁸⁴ For the majority of hypertensive patients, the ED encounter can serve as a means of arranging for appropriate referral to outpatient primary care coupled with counseling on lifestyle modifications.⁹⁰

The incidence of diabetes has more than doubled over the past 2 decades. On the basis of screening hemoglobin A_{1c} (HbA_{1c}) and fasting plasma glucose, the National Health and Nutrition Examination Survey estimated the prevalence of undiagnosed diabetes in the US population to be 2.8%.⁶⁸⁹ As is the case with hypertension, the prevalence of undiagnosed diabetes is even higher in the ED patient population.⁶⁸⁹ Although point-of-care glucose and HbA_{1c} testing of ED patients is feasible, it remains to be determined if such screening is cost-effective. Unselected screening by capillary blood glucose or HbA_{1c} measurement is not currently recommended by emergency medicine societies or other healthcare agencies.^{684,689,690} Patients with known diabetes commonly use EDs for acute care of complications related to their diabetes, and many present with poor glycemic control. Encouraging medication compliance, dietary management, and lifestyle modification is appropriate, as is timely referral to primary care.

Warfarin anticoagulation for prevention of stroke in patients with nonvalvular atrial fibrillation has been a long-standing recommendation from several organizations.⁶⁹¹ The US National Hospital Ambulatory Medical Care Survey reported an 88% increase in ED visits for atrial fibrillation, and visits for atrial fibrillation are likely to increase.⁶⁹² Despite the large body of evidence supporting anticoagulation in selected patients with atrial fibrillation, and as reviewed in this guideline, several studies have identified significant percentages (12% to 34%) of patients with atrial fibrillation presenting in the ED who were eligible for warfarin but were undertreated or untreated.^{693,694} The ED represents an important location for not only identifying patients with new-onset atrial fibrillation and initiating anticoagulation therapy (provided adequate follow-up is assured), but it also serves to promote patient behaviors to increase compliance and ensure access to follow-up care.

Despite decades of preventive efforts, cigarette smoking remains a leading cause of preventable deaths in the United States, "accounting for 1 of every 5 deaths each year."⁶⁹⁵ Recognizing this continuing problem, the American College of

Emergency Physicians (ACEP) recommends ED interventions aimed at smoking cessation.⁶⁹⁶ The ED represents a promising site for smoking cessation interventions through self-service kiosk and culturally appropriate literature, triage screening, brief interventions, and referral to outpatient treatment. With the high prevalence of smoking-related illnesses leading to ED visits, these episodes provide outstanding "teachable moments."

Excessive consumption of alcohol is a major contributor to many ED visits. In response to the epidemic of alcohol-related injury and illness, numerous ED-based interventions have been investigated.⁶⁹⁷ The ACEP developed a brief alcohol-use intervention brochure that does not require significant resources to produce or distribute but when used alone was found to be only marginally effective in the absence of referral for cessation counseling.⁶⁹⁸ More interactive ED interventions require more resources but are more likely to produce enduring benefits.⁶⁹⁹ Integrating health promotion into the curriculum of emergency medicine training programs will help overcome existing nihilism of many practicing emergency physicians.⁷⁰⁰

Several other lifestyle issues, such as nutrition, physical activity, and drug abuse, are targets for behavioral interventions aimed at primary stroke prevention. Of these issues, only substance abuse screening and intervention has been studied in the ED setting. Obesity and physical inactivity contribute to medical conditions frequently seen in the ED. Many physicians are reluctant to discuss these issues, and patients are not always receptive to the discussion.⁷⁰¹ No studies have investigated the use of the ED as a site for nutritional and dietary counseling. Overall, although emergency physicians recognize the need for health promotion, few actually practice routine screening and counseling of emergency patients, and many are skeptical of the impact of ED health promotion.⁷⁰¹

Health care, and in particular emergency care, is undergoing dramatic changes for the worse. The increasing demands for emergent and primary care will strain the capacity of many EDs to provide even basic care for acutely ill patients. To effectively incorporate preventive services into ED practice, a careful review of cost-effectiveness is required of each intervention, again assuming sufficient resources are available.⁶⁸⁴ Effective primary, secondary, and tertiary stroke preventions can occur in EDs, but significant healthcare organizational changes are required.⁷⁰² These changes must address limitations of healthcare provider health promotion training, program funding, resource availability, and lack of referral resources.

Summary and Gaps

The ED may serve as an important location to provide health promotion and disease prevention services, especially during these unique teachable moments, through screening, brief intervention, and referral for treatment. This opportunity to identify risk factors for stroke and begin primary prevention requires further study into use of resources, efficacy, effectiveness, and cost.

Recommendations

- 1. ED-based smoking cessation programs and interventions are recommended (Class I; Level of Evidence B).**

2. **Identification of atrial fibrillation and evaluation for anticoagulation in the ED is recommended (Class I; Level of Evidence B).**
3. **ED population screening for hypertension is reasonable (Class IIa; Level of Evidence C).**
4. **When a patient is identified as having a drug or alcohol abuse problem, ED referral to an appropriate therapeutic program is reasonable (Class IIa; Level of Evidence C).**
5. **The effectiveness of screening, brief intervention, and referral for treatment of diabetes and lifestyle stroke risk factors (obesity, alcohol/substance abuse, sedentary lifestyle) in the ED setting is not established (Class IIb; Level of Evidence C).**

Preventive Health Services/Strategies to Improve Adherence

Evidence-based guidelines are useful only if the knowledge contained in them is translated into clinical practice. There is ample evidence that primary prevention measures are underused in general practice.^{703–705} Although adherence rates to national recommendations for the treatment and control of cardiovascular risk factors are improving, there is still a large treatment gap.^{95,706,707} Across the United States, the adherence rate for the treatment of hypertension is 61%; only 35% of those treated have their hypertension under control.⁹⁵ Adherence to the treatment of elevated LDL, although improved from 11.7% between 1988 and 1994, still remains suboptimal at 40.8%, with only 25% of those treated at recommended goals.⁷⁰⁶ Treatment rates for diabetes remain suboptimal, even in patients who already have ≥ 1 identified risk factors for stroke.^{708–710}

Although often thought of as being in the purview of the generalist, specialist physicians also have the opportunity to identify stroke risk factors and should ensure their treatment.⁷⁰⁴ Strategies to help clinicians implement guideline recommendations are usually aimed at changing the physician's behavior toward risk factor prevention, including the environment in which the physician practices.^{711,712} A combination of techniques is usually necessary to improve adherence, including physician education, addressing physician inertia, audit and feedback of practice patterns, physician profiling, patient prompts, and outreach visits.^{703,708,711–713} Some general strategies to improve adherence in the outpatient setting, although relatively costly, are more consistently effective. These include computer-based clinical reminder systems, electronic medical records,^{714,715} and tailored, multifaceted programs.^{716,717} A meta-analysis of 16 randomized controlled trials to evaluate computer-based clinical reminder systems for preventive care found that such systems were associated with increased adherence to cardiovascular risk reduction measures (OR, 2.01; 95% CI, 1.55 to 2.61) compared with controls. Manual reminder systems also improved adherence to cardiovascular risk-reduction assessments.⁷¹⁴ Other methods to improve preventive services focus on slight organization changes. These include delegation of preventive services, such as having support personnel implement preventive healthcare protocols, or establishment of separate clinics devoted to screening and preventive services.^{717,718} One study investigated the elements of an organization and its

relationship to primary stroke prevention and found that practitioners who systematically noted a history of diabetes and recorded BP measurements, delegated follow-up visits of hypertensive patients to support staff, and formalized co-operations with a dietitian were more likely to deliver optimal care.⁷¹⁸ Audit and feedback of provider performance improves some cancer screening rates, but more diverse studies of other disease states need to be evaluated before the results can be generalized to all prevention of all diseases.⁷¹⁹ The American Heart Association/American Stroke Association Get With The Guidelines (GWTG)–Stroke program has shown that in the inpatient setting, audit and feedback of performance on secondary stroke preventive measures is associated with improved adherence.⁷²⁰ Just as the use of standing stroke order sets improves adherence for in-hospital care of stroke patients,^{721,722} the use of standardized tools in outpatient clinics increases the proportion of patients receiving appropriate screening and preventive care.⁷²³ These tools function as reminder systems that are easily implemented and less costly than electronic reminder systems. A comprehensive annotated reminder tool (CART) composed of forms to document history and physical examination by age-appropriate screening questions, age-specific reminders, and test-frequency recommendations, increased the proportion of patients receiving appropriate screening and preventive services, including cholesterol measurement, smoking, diet, and exercise counseling.⁷²³ Screening adherence rates returned to baseline levels after removal of the CART, suggesting that an educational intervention is not enough for sustained improvement.⁷²³ Finally, a less costly intervention, the scheduling of periodic visits (ie, yearly) aimed at a patient's overall health and preventive care increases the delivery of some appropriate preventive measures, such as cholesterol screening.⁷²⁴ Specialist physicians, as well as other healthcare professionals, can take steps to improve their own stroke prevention practices and should be prepared to identify stroke risk factors in all patients evaluated, regardless of the presenting complaint. The use of simple office tools, a preventive care chart reminder (ie, flowsheet), postcard reminders, in-office visual prompts, and patient-mediated material can provide the cues, resources, and support in the outpatient setting to promote adherence to primary stroke prevention practices.⁷⁰⁴

Summary and Gaps

More research is needed to identify practical approaches to improve the use of strategies proved to reduce risk for stroke. This includes not only processes to improve the identification of at-risk patients but tools for implementation and assessment of improved adherence.

Recommendation

1. **Implementation of a method to systematically identify and treat risk factors in all patients at risk for stroke can be useful (Class IIa; Level of Evidence C).**

Summary

The available evidence provides numerous strategies to prevent the risk of a first stroke. Table 14 summarizes evidenced-based recommendations.

Disclosures

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Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
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Lawrence J. Appel	Johns Hopkins Medical Institutions	Grant from King Pharmaceuticals†	None	None	None	None	None	None
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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be “Significant” if (a) the person receives \$10,000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10,000 or more of the fair market value of the entity. A relationship is considered to be “Modest” if it is less than “Significant” under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
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Lawrence Wechsler	University of Pittsburgh School of Medicine	None	None	Ferrer*, The Stroke Group*	None	Neuro Interventional Therapeutic*	Abbott Vascular*	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "Significant" if (a) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "Modest" if it is less than "Significant" under the preceding definition.

*Modest.

†Significant.

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