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

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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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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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The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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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

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT →			
	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	**CLASS IIa** *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	**CLASS IIb** *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	**CLASS III** *Risk ≥ Benefit* Procedure/Treatment should **NOT** be performed/administered **SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL**
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ 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	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ 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	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ 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.
Therapeutic recommendations	
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
Diagnostic recommendations	
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)	
Women	5.6	3.9¶¶	1.55 (1.17–2.07)	
Other CVD, heart failure				
Men	2.6	1.4		
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=100[727] ((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; P=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; P=0.04)[542] 3.08; 95% CI, 0.74–12.81; P=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
Chlamydia pneumoniae		72–78	IgA 1:16 4.51 (1.44–14.06)	Trials of antibiotics for general cardiovascular event reduction negative; insufficient power for stroke end points.
		85–88	IgG 1:512 and/or IgA 1:64; 8:58 (1.1–68.8) Adult men[735]	
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	
Helicobacter pylori CagA seropositivity				
Adults with vascular disease: IgG Ab >40 AU	65.7		Atherothrombotic stroke:	
		39	OR, 1.97; CI, 1.33–2.91 Carotid plaque irregularities	
		83	OR, 8.42; CI, 1.58–44.84	
Acute infection: Systemic respiratory infection			IR, 3.19; CI, 2.81–3.62 Days 1–3	
			IR, 1.27; CI, 1.15–1.41 Days 29–91	
Acute infection: Urinary tract infection			IR, 1.65 (CI, 1.19–2.28) 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; $P<0.001$, 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 antioagulant; 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 children[97] 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 ≥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 (≥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 ≥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 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 ≥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 Study[113]) 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 Study[118] 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 $\varepsilon 4$ 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 report[149] 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 End point 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, 0.79l; 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 ≥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 ≥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 ≥55 years with triglyceride levels ≥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 ≥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 ≥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 ≥130 mg/dL (optionally ≥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 ≥130 mg/dL. Drug therapy optional for LDL-C 70–129 mg/dL.
Non–HDL-C in persons with triglyceride ≥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 ≥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] Fibric 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 ≤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 simvasatin 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. **Fibric 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 fibric 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 $CHADS_2$ 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 $CHADS_2$ scheme if patients with $CHADS_2$ scores of 2 are considered moderate risk, but the guideline also includes echocardiographically defined impaired left ventricular systolic 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.

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 ejuction 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.

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 $CHADS_2$ score of 1).[244] A recent large cohort study did not find a net clinical benefit of warfarin for atrial fibrillation patients with a $CHADS_2$ 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*).**
2. **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*).**
3. **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*).**
4. **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*).**
5. **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 emdorsed.[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 stroke[315] (*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: $\text{stenosis}=(1-R/D)\times 100\%$.

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 ≥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 Kingdom[317] and included 3128 patients with asymptomatic carotid stenoses of ≥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 ≥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 ≥60% on angiography, ≥70% on ultrasonography, or ≥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 ≤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 (≥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 (*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-thalassemia[354] 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 Study[373] 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 ≥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 μg/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 ≥50 μg 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 ecological[407] 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 BP[419] 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 BP[432] 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/m^2 are classified as overweight, and those with a BMI $\geq$30 kg/m^2 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/m^2, each 5 kg/m^2 increase in BMI was associated with a 40% increased risk of stroke mortality; in the lower BMI range (15 to 25 kg/m^2), 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/m^2 with no clear relationship below 25 kg/m^2. 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 ≥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 STARFlex 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 ≥130/≥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 III[222] 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 Study[8] 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 recommended[518] (*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 trassulferation 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 B_6), a cofactor of cystathionine β-synthase, and of folic acid and cobalamin (vitamin B_{12}), 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 μmol/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 μmol/L increase in homocysteine, risk of stroke increased by 59% (95% CI, 29% to 96%) and for each 3 μmol/L decrease in homocysteine, risk of stroke decreased by 24% (95% CI, 15% to 33%).[586]

The B-complex vitamins pyridoxine (B_6), cobalamin (B_{12}), 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 ≥9.1 μmol/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 B_6 and B_{12} 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 B_6 and B_{12} 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 (B_6), cobalamin (B_{12}), 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 models[604] 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 complex of plasminogen, tissue plasminogen activator, and fibrin, thereby contributing to thrombosis.[604,607]

Table 11. Strength of the Association Between Lupus Anticoagulants, Anticardiolipin Antibodies, and Thrombosis[625]

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.

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 μg/dL (>21 GPL [1 GPL unit=1μg 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_2GPI 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_2GPI 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_2GPI 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 syndrome[627] 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 study[579] 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) amall 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 ($\leq$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 study[663] and 1 cohort study[664] 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 ≥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 ≥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 ≥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	
Age	N/A
Sex	N/A
Low birth weight	N/A
Race/ethnicity	N/A
Genetic factors	• 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).*
	• Genetic screening of the general population for prevention of a first stroke is not recommended *(Class III; Level of Evidence C).*
	• Referral for genetic counseling may be considered for patients with rare genetic causes of stroke *(Class IIb; Level of Evidence C).*
	• 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).*
	• 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).*
	• 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).*
	• 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]
	• Universal screening for intracranial aneurysms in carriers of mutations for Mendelian disorders associated with aneurysms is not recommended *(Class III; Level of Evidence C).*
	• 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 *(Class IIb; Level of Evidence C).*
	• Noninvasive screening for unruptured intracranial aneurysms in patients with cervical fibromuscular dysplasia may be considered *(Class IIb; Level of Evidence C).*
	• 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	• 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).*
	• 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	• 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).*
	• 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 *(Class IIa; Level of Evidence C).*
	• 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 *(Class I; Level of Evidence B).*
Diabetes	• 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).*
	• Treatment of hypertension in adults with diabetes with an ACEI or an ARB is useful *(Class I; Level of Evidence A).*
	• 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).*
	• The use of monotherapy with a fibrate to lower stroke risk might be considered for patients with diabetes *(Class IIb; Level of Evidence B).*
	• 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).*
	• 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 *(Class IIb; Level of Evidence B).* (Also see aspirin recommendations.)
Dyslipidemia	• 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).*

(Continued)

Table 14. Continued

Risk Factor	Recommendations
	• Fibric 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).*
	• 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).*
	• Treatment with other lipid-lowering therapies, such as fibric 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	• 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 *(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	• 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 *(Class III; Level of Evidence A).*
	• 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 stroke[315] *(Class IIa; Level of Evidence A).*
Asymptomatic carotid stenosis	• 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).*
	• 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).*
	• 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).*
	• 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.
	• 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 *(Class IIb; Level of Evidence B).*
	• 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).*
	• Population screening for asymptomatic carotid artery stenosis is not recommended *(Class III; Level of Evidence B).*
Sickle cell disease	• Children with SCD should be screened with TCD starting at age 2 years *(Class I; Level of Evidence B).*
	• 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).*
	• 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).*
	• Pending further studies, continued transfusion, even in those with TCD velocities that revert to normal, is probably indicated *(Class IIa; Level of Evidence B).*
	• 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).*
	• 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).*
	• 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).*

(Continued)

Table 14. Continued

Risk Factor	Recommendations
Postmenopausal hormone therapy	• 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).*
	• SERMs, such as raloxifene, tamoxifen, or tibolone, should not be used for primary prevention of stroke *(Class III; Level of Evidence A).*
Oral contraceptives	• OCs may be harmful in women with additional risk factors (eg cigarette smoking, prior thromboembolic events) *(Class III; Level of Evidence C).*[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 *(Class IIb; Level of Evidence C).* [390, 392, 402]
Diet and nutrition	• 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).*
	• A DASH-style diet, which emphasizes consumpton 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).*
	• 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	• Increased physical activity is recommended because it is associated with a reduction in risk of stroke *(Class I; Level of Evidence B).*
	• 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	• Among overweight and obese persons, weight reduction is recommended as a means to lower BP *(Class I; Level of Evidence A).*
	• 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	• 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	• 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 III[222] 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 *(Class IIb; Level of Evidence C).*
Alcohol consumption	• 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 recommended[518] *(Class I; Level of Evidence A).*
	• 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	• Referral to an appropriate therapeutic program is reasonable for patients with drug abuse *(Class IIa; Level of Evidence C).*
Sleep-disordered breathing	• 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).*
	• Treatment of sleep apnea to reduce the risk of stroke might be reasonable, although its effectiveness is unknown *(Class IIb; Level of Evidence C).*
Hyperhomocysteinemia	• The use of the B-complex vitamins, pyridoxine (B_6), cobalamin (B_{12}), 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 Lp(a)	• 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 usefulness of genetic screening to detect inherited hypercoagulable states for prevention of first stroke is not well established *(Class IIb; Level of Evidence C).*
	• 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).*
	• 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).*

(*Continued*)

Table 14. Continued

Risk Factor	Recommendations
Inflammation and infection	• 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).*
	• Patients with chronic inflammatory disease such as RA or SLE should be considered at increased risk for stroke *(Class I; Level of Evidence B).*
	• Treatment with antibiotics for chronic infections as a means to prevent stroke is not recommended *(Class III; Level of Evidence A).*
	• Treatment of patients with elevated hs-CRP with a statin to decrease stroke risk might be considered *(Class IIb; Level of Evidence B).*
	• Annual influenza vaccination can be useful for patients at risk for stroke *(Class IIa; Level of Evidence B).*
Aspirin for primary stroke prevention	• 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).*
	• 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).*
	• Aspirin is not useful for preventing a first stroke in persons at low risk *(Class III; Level of Evidence A).*
	• 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 $\leq$0.99) in the absence of other established CVD *(Class III; Level of Evidence B).*
	• 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	• Each patient should undergo an assessment of stroke risk *(Class I; Level of Evidence A).*
	• 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 ED	• ED-based smoking cessation programs and interventions are recommended *(Class I; Level of Evidence B).*
	• Identification of atrial fibrillation and evaluation for anticoagulation in the ED is recommended *(Class I; Level of Evidence B).*
	• ED population screening for hypertension is reasonable *(Class IIa; Level of Evidence C).*
	• 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).*
	• 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 *(Class IIb; Level of Evidence C).*
Preventive health services/strategies to improve adherence	• 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).*

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} (HbA1C) 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 HbA1C testing of ED patients is feasible, it remains to be determined if such screening is cost-effective. Unselected screening by capillary blood glucose or HbA1C 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 cooperations 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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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.

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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

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*Modest.

†Significant.

References

1. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger VL, Rosamond W, Sacco R, Sorlie P, Stafford R, Thom T, Wasserthiel-Smoller S, Wong ND, Wylie-Rosett J. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation.* 2010;121:e46–e215. Epub December 17, 2009.
2. Brown RD, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Stroke incidence, prevalence, and survival: secular trends in Rochester, Minnesota, through 1989. *Stroke*. 1996;27:373–380.
3. Fang J, Alderman MH. Trend of stroke hospitalization, United States, 1988–1997. *Stroke*. 2001;32:2221–2226.
4. Samsa GP, Matchar DB, Goldstein L, Bonito A, Duncan PW, Lipscomb J, Enarson C, Witter D, Venus P, Paul JE, Weinberger M. Utilities for major stroke: results from a survey of preferences among persons at increased risk for stroke. *Am Heart J*. 1998;136:703–713.
5. Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, Grubb RL, Higashida RT, Jauch EC, Kidwell C, Lyden PD, Morgenstern LB, Qureshi AI, Rosenwasser RH, Scott PA, Wijdicks EF. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups. *Stroke*. 2007;38:1655–1711.
6. Gorelick PB. Stroke prevention. *Arch Neurol*. 1995;52:347–355.
7. Sacco RL, Benjamin EJ, Broderick JP, Dyken M, Easton JD, Feinberg WM, Goldstein LB, Gorelick PB, Howard G, Kittner SJ, Manolio TA, Whisnant JP, Wolf PA. American Heart Association Prevention Conference, IV: prevention and rehabilitation of stroke. Risk factors. *Stroke*. 1997;28:1507–1517.
8. Chiuve SE, Rexrode KM, Spiegelman D, Logroscino G, Manson JE, Rimm EB. Primary prevention of stroke by healthy lifestyle. *Circulation*. 2008; 118:947–954.
9. Goldstein LB, Adams R, Alberts MJ, Appel LJ, Brass LM, Bushnell CD, Culebras A, Degraba TJ, Gorelick PB, Guyton JR, Hart RG, Howard G, Kelly-Hayes M, Nixon JV, Sacco RL. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Stroke*. 2006;37:1583–1633.
10. Pearson TA, Bazzarre TL, Daniels SR, Fair JM, Fortmann SP, Franklin BA, Goldstein LB, Hong Y, Mensah GA, Sallis JF Jr, Smith S Jr, Stone NJ, Taubert KA. American Heart Association guide for improving cardiovascular health at the community level: a statement for public health practitioners, healthcare providers, and health policy makers from the American Heart Association Expert Panel on Population and Prevention Science. *Circulation*. 2003;107:645–651.
11. Burt BA. Definitions of risk. *J Dent Educ*. 2001;65:1007–1008.
12. Whisnant JP. Modeling of risk factors for ischemic stroke: the Willis Lecture. *Stroke*. 1997;28:1840–1844.
13. Kleindorfer D, Khoury J, Kissela B, Alwell K, Woo D, Miller R, Schneider A, Moomaw C, Broderick JP. Temporal trends in the incidence and case fatality of stroke in children and adolescents. *J Child Neurol*. 2006;21:415–418.
14. Sofronas M, Ichord RN, Fullerton HJ, Lynch JK, Massicotte MP, Willan AR, deVeber G. Pediatric stroke initiatives and preliminary studies: what is known and what is needed? *Pediatr Neurol*. 2006;34:439–445.
15. Chong JY, Sacco RL. Epidemiology of stroke in young adults: race/ethnic differences. *J Thromb Thrombolysis*. 2005;20:77–83.
16. Ariesen MJ, Claus SP, Rinkel GJ, Algra A. Risk factors for intracerebral hemorrhage in the general population: a systematic review. *Stroke*. 2003;34:2060–2065.
17. Carandang R, Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Kannel WB, Wolf PA. Trends in incidence, lifetime risk, severity, and 30-day mortality of stroke over the past 50 years. *JAMA*. 2006;296:2939–2946.
18. Manolio TA, Kronmal RA, Burke GL, O'Leary DH, Price TR. Short-term predictors of incident stroke in older adults: the Cardiovascular Health Study. *Stroke*. 1996;27:1479–1486.
19. Sturgeon JD, Folsom AR, Longstreth WT Jr, Shahar E, Rosamond WD, Cushman M. Risk factors for intracerebral hemorrhage in a pooled prospective study. *Stroke*. 2007;38:2718–2725.
20. Wolf PA, D'Agostino RB, O'Neal MA, Sytkowski P, Kase CS, Belanger AJ, Kannel WB. Secular trends in stroke incidence and mortality: the Framingham Study. *Stroke*. 1992;23:1551–1555.
21. Pleis JR, Lethbridge-Cejku M Summary health statistics for U.S. adults: National Health Interview Survey, 2006. *Vital Health Stat. 10.* 2007:1–153.
22. Rosamond WD, Folsom AR, Chambless LE, Wang CH, McGovern PG, Howard G, Copper LS, Shahar E. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. *Stroke*. 1999;30:736–743.
23. Sacco RL, Boden-Albala B, Gan R, Chen X, Kargman DE, Shea S, Paik MC, Hauser WA. Stroke incidence among white, black, and Hispanic residents of an urban community: the Northern Manhattan Stroke Study. *Am J Epidemiol*. 1998;147:259–268.
24. Kissela B, Schneider A, Kleindorfer D, Khoury J, Miller R, Alwell K, Woo D, Szaflarski J, Gebel J, Moomaw C, Pancioli A, Jauch E, Shukla R, Broderick J. Stroke in a biracial population: the excess burden of stroke among blacks. *Stroke*. 2004;35:426–431.
25. Baillargeon JP, McClish DK, Essah PA, Nestler JE. Association between the current use of low-dose oral contraceptives and cardiovascular arterial disease: a meta-analysis. *J Clin Endocrinol Metab*. 2005; 90:3863–3870.

26. James AH, Bushnell CD, Jamison MG, Myers ER. Incidence and risk factors for stroke in pregnancy and the puerperium. *Obstet Gynecol*. 2005;106:509–516.
27. Kittner SJ, Stern BJ, Feeser BR, Hebel R, Nagey DA, Buchholz DW, Earley CJ, Johnson CJ, Macko RF, Sloan MA, Wityk RJ, Wozniak MA. Pregnancy and the risk of stroke. *N Engl J Med*. 1996;335:768–774.
28. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, Ford E, Furie K, Go A, Greenlund K, Haase N, Hailpern S, Ho M, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott M, Meigs J, Mozaffarian D, Nichol G, O'Donnell C, Roger V, Rosamond W, Sacco R, Sorlie P, Stafford R, Steinberger J, Thom T, Wasserthiel-Smoller S, Wong N, Wylie-Rosett J, Hong Y; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee [published correction appears in *Circulation.* 2009; 119:e182]. *Circulation.* 2009;119:480–486.
29. Bousser MG. Stroke in women: the 1997 Paul Dudley White International Lecture. *Circulation*. 1999;99:463–467.
30. Barker DJ, Lackland DT. Prenatal influences on stroke mortality in England and Wales. *Stroke*. 2003;34:1598–1602.
31. Lackland DT, Egan BM, Ferguson PL. Low birth weight as a risk factor for hypertension. *J Clin Hypertens (Greenwich)*. 2003;5:133–136.
32. Lackland DT, Egan BM, Jones PJ. Impact of nativity and race on "Stroke Belt" mortality. *Hypertension*. 1999;34:57–62.
33. Kleindorfer D, Broderick J, Khoury J, Flaherty M, Woo D, Alwell K, Moomaw CJ, Schneider A, Miller R, Shukla R, Kissela B. The unchanging incidence and case-fatality of stroke in the 1990s: a population-based study. *Stroke*. 2006;37:2473–2478.
34. Howard G, Anderson R, Sorlie P, Andrews V, Backlund E, Burke GL. Ethnic differences in stroke mortality between non-Hispanic whites, Hispanic whites, and blacks: the National Longitudinal Mortality Study. *Stroke*. 1994;25:2120–2125.
35. Morgenstern LB, Smith MA, Lisabeth LD, Risser JM, Uchino K, Garcia N, Longwell PJ, McFarling DA, Akuwumi O, Al-Wabil A, Al-Senani F, Brown DL, Moye LA. Excess stroke in Mexican Americans compared with non-Hispanic Whites: the Brain Attack Surveillance in Corpus Christi Project. *Am J Epidemiol*. 2004;160:376–383.
36. Zahuranec DB, Brown DL, Lisabeth LD, Gonzales NR, Longwell PJ, Eden SV, Smith MA, Garcia NM, Morgenstern LB. Differences in intracerebral hemorrhage between Mexican Americans and non-Hispanic whites. *Neurology*. 2006;66:30–34.
37. Giles WH, Kittner SJ, Hebel JR, Losonczy KG, Sherwin RW. Determinants of black-white differences in the risk of cerebral infarction: the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. *Arch Intern Med*. 1995;155:1319–1324.
38. Gillum RF. Risk factors for stroke in blacks: a critical review. *Am J Epidemiol*. 1999;150:1266–1274.
39. Kittner SJ, White LR, Losonczy KG, Wolf PA, Hebel JR. Black-white differences in stroke incidence in a national sample: the contribution of hypertension and diabetes mellitus. *JAMA*. 1990;264:1267–1270.
40. Liao Y, Greenlund KJ, Croft JB, Keenan NL, Giles WH. Factors explaining excess stroke prevalence in the US Stroke Belt. *Stroke*. 2009;40:3336–3341.
41. Zhang Y, Galloway JM, Welty TK, Wiebers DO, Whisnant JP, Devereux RB, Kizer JR, Howard BV, Cowan LD, Yeh J, Howard WJ, Wang W, Best L, Lee ET. Incidence and risk factors for stroke in American Indians: the Strong Heart Study. *Circulation*. 2008;118:1577–1584.
42. Flossmann E, Schulz UG, Rothwell PM. Systematic review of methods and results of studies of the genetic epidemiology of ischemic stroke. *Stroke*. 2004;35:212–227.
43. Schulz UG, Flossmann E, Rothwell PM. Heritability of ischemic stroke in relation to age, vascular risk factors, and subtypes of incident stroke in population-based studies. *Stroke*. 2004;35:819–824.
44. Touze E, Rothwell PM. Sex differences in heritability of ischemic stroke: a systematic review and meta-analysis. *Stroke*. 2008;39:16–23.
45. Rubattu S, Stanzione R, Gigante B, Bagalino A, Musumeci B, Volpe M. Genetic susceptibility to cerebrovascular accidents. *J Cardiovasc Pharmacol*. 2001;38(suppl 2):S71–S74.
46. Nicolaou M, DeStefano AL, Gavras I, Cupples LA, Manolis AJ, Baldwin CT, Gavras H, Farrer LA. Genetic predisposition to stroke in relatives of hypertensives. *Stroke*. 2000;31:487–492.
47. Turner ST, Boerwinkle E. Genetics of blood pressure, hypertensive complications, and antihypertensive drug responses. *Pharmacogenomics*. 2003; 4:53–65.
48. Hassan A, Hunt BJ, O'Sullivan M, Bell R, D'Souza R, Jeffery S, Bamford JM, Markus HS. Homocysteine is a risk factor for cerebral small vessel disease, acting via endothelial dysfunction. *Brain*. 2004; 127(Pt 1):212–219.
49. Ortel T. Genetics of coagulation disorders. In: Alberts M, ed. *Genetics of Cerebrovascular Disease.* Armonk, NY: Futura Publishing;1999:129–156.
50. Bertina RM, Koeleman BP, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, van der Velden PA, Reitsma PH. Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature*. 1994;369:64–67.
51. Deschiens MA, Conard J, Horellou MH, Ameri A, Preter M, Chedru F, Samama MM, Bousser MG. Coagulation studies, factor V Leiden, and anticardiolipin antibodies in 40 cases of cerebral venous thrombosis. *Stroke*. 1996;27:1724–1730.
52. Hillier CE, Collins PW, Bowen DJ, Bowley S, Wiles CM. Inherited prothrombotic risk factors and cerebral venous thrombosis. *QJM*. 1998; 91:677–680.
53. Kuwahara S, Abe T, Uga S, Mori K. Superior sagittal sinus and cerebral cortical venous thrombosis caused by congenital protein C deficiency–case report. *Neurol Med Chir (Tokyo)*. 2000;40:645–649.
54. Hankey GJ, Eikelboom JW, van Bockxmeer FM, Lofthouse E, Staples N, Baker RI. Inherited thrombophilia in ischemic stroke and its pathogenic subtypes. *Stroke*. 2001;32:1793–1799.
55. Juul K, Tybjaerg-Hansen A, Steffensen R, Kofoed S, Jensen G, Nordestgaard BG. Factor V Leiden: The Copenhagen City Heart Study and 2 meta-analyses. *Blood*. 2002;100:3–10.
56. Weber M, Hayem G, DeBandt M, Palazzo E, Roux S, Kahn MF, Meyer O. The family history of patients with primary or secondary antiphospholipid syndrome (APS). *Lupus*. 2000;9:258–263.
57. Goldberg SN, Conti-Kelly AM, Greco TP. A family study of anticardiolipin antibodies and associated clinical conditions. *Am J Med*. 1995; 99:473–479.
58. Begelman SM, Olin JW. Fibromuscular dysplasia. *Curr Opin Rheumatol*. 2000;12:41–47.
59. Shetty-Alva N, Alva S. Familial moyamoya disease in Caucasians. *Pediatr Neurol*. 2000;23:445–447.
60. Helgadottir A, Thorleifsson G, Manolescu A, Gretarsdottir S, Blondal T, Jonasdottir A, Sigurdsson A, Baker A, Palsson A, Masson G, Gudbjartsson DF, Magnusson KP, Andersen K, Levey AI, Backman VM, Matthiasdottir S, Jonsdottir T, Palsson S, Einarsdottir H, Gunnarsdottir S, Gylfason A, Vaccarino V, Hooper WC, Reilly MP, Granger CB, Austin H, Rader DJ, Shah SH, Quyyumi AA, Gulcher JR, Thorgeirsson G, Thorsteinsdottir U, Kong A, Stefansson K. A common variant on chromosome 9p21 affects the risk of myocardial infarction. *Science*. 2007;316:1491–1493.
61. McPherson R, Pertsemlidis A, Kavaslar N, Stewart A, Roberts R, Cox DR, Hinds DA, Pennacchio LA, Tybjaerg-Hansen A, Folsom AR, Boerwinkle E, Hobbs HH, Cohen JC. A common allele on chromosome 9 associated with coronary heart disease. *Science*. 2007;316:1488–1491.
62. Samani NJ, Erdmann J, Hall AS, Hengstenberg C, Mangino M, Mayer B, Dixon RJ, Meitinger T, Braund P, Wichmann HE, Barrett JH, Konig IR, Stevens SE, Szymczak S, Tregouet DA, Iles MM, Pahlke F, Pollard H, Lieb W, Cambien F, Fischer M, Ouwehand W, Blankenberg S, Balmforth AJ, Baessler A, Ball SG, Strom TM, Braenne I, Gieger C, Deloukas P, Tobin MD, Ziegler A, Thompson JR, Schunkert H. Genomewide association analysis of coronary artery disease. *N Engl J Med*. 2007;357:443–453.
63. Gschwendtner A, Bevan S, Cole JW, Plourde A, Matarin M, Ross-Adams H, Meitinger T, Wichmann E, Mitchell BD, Furie K, Slowik A, Rich SS, Syme PD, MacLeod MJ, Meschia JF, Rosand J, Kittner SJ, Markus HS, Muller-Myhsok B, Dichgans M. Sequence variants on chromosome 9p21.3 confer risk for atherosclerotic stroke. *Ann Neurol*. 2009;65:531–539.
64. Gudbjartsson DF, Arnar DO, Helgadottir A, Gretarsdottir S, Holm H, Sigurdsson A, Jonasdottir A, Baker A, Thorleifsson G, Kristjansson K, Palsson A, Blondal T, Sulem P, Backman VM, Hardarson GA, Palsdottir E, Helgason A, Sigurjonsdottir R, Sverrisson JT, Kostulas K, Ng MC, Baum L, So WY, Wong KS, Chan JC, Furie KL, Greenberg SM, Sale M, Kelly P, MacRae CA, Smith EE, Rosand J, Hillert J, Ma RC, Ellinor PT, Thorgeirsson G, Gulcher JR, Kong A, Thorsteinsdottir U, Stefansson K. Variants conferring risk of atrial fibrillation on chromosome 4q25. *Nature*. 2007;448:353–357.
65. Gretarsdottir S, Thorleifsson G, Manolescu A, Styrkarsdottir U, Helgadottir A, Gschwendtner A, Kostulas K, Kuhlenbaumer G, Bevan S, Jonsdottir T, Bjarnason H, Saemundsdottir J, Palsson S, Arnar DO, Holm H, Thor-

geirsson G, Valdimarsson EM, Sveinbjornsdottir S, Gieger C, Berger K, Wichmann HE, Hillert J, Markus H, Gulcher JR, Ringelstein EB, Kong A, Dichgans M, Gudbjartsson DF, Thorsteinsdottir U, Stefansson K. Risk variants for atrial fibrillation on chromosome 4q25 associate with ischemic stroke. *Ann Neurol*. 2008;64:402–409.
66. Tournier-Lasserve E, Joutel A, Chabriat H Clinical phenotypes and genetic data in 15 unrelated families. *Neurology.* 1995;45(suppl 4):A273.
67. Kalimo H, Viitanen M, Amberla K, Juvonen V, Marttila R, Poyhonen M, Rinne JO, Savontaus M, Tuisku S, Winblad B. CADASIL: hereditary disease of arteries causing brain infarcts and dementia. *Neuropathol Appl Neurobiol*. 1999;25:257–265.
68. Durlach J. A possible advance in arterial gene therapy for aortic complications in the Marfan syndrome by local transfer of an antisense Mg-dependent hammerhead ribozyme. *Magnes Res*. 14(1–2):65–67, 2001.
69. Desnick R, Ioannou Y, Eng C. Alpha-galactosidase A deficiency: Fabry disease. In: Scriver C, Beauder A, Sly W, et al, eds. *The Metabolic and Molecular Bases of Inherited Disease*. 8th ed. New York, NY: McGraw-Hill;2001:3733–3774.
70. De Schoenmakere G, Chauveau D, Grunfeld JP. Enzyme replacement therapy in Anderson-Fabry's disease: beneficial clinical effect on vital organ function. *Nephrol Dial Transplant*. 2003;18:33–35.
71. Eng CM, Guffon N, Wilcox WR, Germain DP, Lee P, Waldek S, Caplan L, Linthorst GE, Desnick RJ. Safety and efficacy of recombinant human alpha-galactosidase A– replacement therapy in Fabry's disease. *N Engl J Med*. 2001;345:9–16.
72. Schiffmann R, Kopp JB, Austin HA 3rd, Sabnis S, Moore DF, Weibel T, Balow JE, Brady RO. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. *JAMA*. 2001;285:2743–2749.
73. Moore DF, Altarescu G, Herscovitch P, Schiffmann R. Enzyme replacement reverses abnormal cerebrovascular responses in Fabry disease. *BMC Neurol*. 2002;2:4.
74. Vedder AC, Linthorst GE, Houge G, Groener JE, Ormel EE, Bouma BJ, Aerts JM, Hirth A, Hollak CE. Treatment of Fabry disease: outcome of a comparative trial with agalsidase alfa or beta at a dose of 0.2 mg/kg. *PLoS ONE*. 2007;2:e598.
75. De Braekeleer M, Perusse L, Cantin L, Bouchard JM, Mathieu J. A study of inbreeding and kinship in intracranial aneurysms in the Saguenay Lac-Saint-Jean region (Quebec, Canada). *Ann Hum Genet*. 1996;60(Pt 2):99–104.
76. Kissela BM, Sauerbeck L, Woo D, Khoury J, Carrozzella J, Pancioli A, Jauch E, Moomaw CJ, Shukla R, Gebel J, Fontaine R, Broderick J. Subarachnoid hemorrhage: a preventable disease with a heritable component. *Stroke*. 2002;33:1321–1326.
77. Schievink WI, Schaid DJ, Michels VV, Piepgras DG. Familial aneurysmal subarachnoid hemorrhage: a community-based study. *J Neurosurg*. 1995;83:426–429.
78. Wang PS, Longstreth WT Jr, Koepsell TD. Subarachnoid hemorrhage and family history: a population-based case-control study. *Arch Neurol*. 1995;52:202–204.
79. Broderick JP, Brown RD Jr, Sauerbeck L, Hornung R, Huston J 3rd, Woo D, Anderson C, Rouleau G, Kleindorfer D, Flaherty ML, Meissner I, Foroud T, Moomaw EC, Connolly ES. Greater rupture risk for familial as compared to sporadic unruptured intracranial aneurysms. *Stroke*. 2009;40:1952–1957.
80. Woo D, Hornung R, Sauerbeck L, Brown R, Meissner I, Huston J, Foroud T, Broderick J. Age at intracranial aneurysm rupture among generations: Familial Intracranial Aneurysm Study. *Neurology*. 2009; 72:695–698.
81. Grantham JJ. Clinical practice: autosomal dominant polycystic kidney disease. *N Engl J Med*. 2008;359:1477–1485.
82. Cloft HJ, Kallmes DF, Kallmes MH, Goldstein JH, Jensen ME, Dion JE. Prevalence of cerebral aneurysms in patients with fibromuscular dysplasia: a reassessment. *J Neurosurg*. 1998;88:436–440.
83. Germain DP. Ehlers-Danlos syndrome type IV. *Orphanet J Rare Dis*. 2007;2:32.
84. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th ed). *Chest.* 2008;133(suppl 6):160S–198S.
85. Link E, Parish S, Armitage J, Bowman L, Heath S, Matsuda F, Gut I, Lathrop M, Collins R. SLCO1B1 variants and statin-induced myopathy–a genomewide study. *N Engl J Med*. 2008;359:789–799.
86. Collet JP, Hulot JS, Pena A, Villard E, Esteve JB, Silvain J, Payot L, Brugier D, Cayla G, Beygui F, Bensimon G, Funck-Brentano C, Montalescot G. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. *Lancet*. 2009;373:309–317.
87. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, Walker JR, Antman EM, Macias W, Braunwald E, Sabatine MS. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med*. 2009;360:354–362.
88. Simon T, Verstuyft C, Mary-Krause M, Quteineh L, Drouet E, Meneveau N, Steg PG, Ferrieres J, Danchin N, Becquemont L. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med*. 2009;360:363–375.
89. Bederson JB, Awad IA, Wiebers DO, Piepgras D, Haley EC Jr, Brott T, Hademenos G, Chyatte D, Rosenwasser R, Caroselli C. Recommendations for the management of patients with unruptured intracranial aneurysms: a statement for healthcare professionals from the Stroke Council of the American Heart Association. *Circulation*. 2000;102:2300–2308.
90. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560–2572.
91. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903–1913.
92. Whelton PK, He J, Appel LJ, Cutler JA, Havas S, Kotchen TA, Roccella EJ, Stout R, Vallbona C, Winston MC, Karimbakas J. Primary prevention of hypertension: clinical and public health advisory from the National High Blood Pressure Education Program. *JAMA*. 2002;288:1882–1888.
93. Wolf PA. Cerebrovascular risk. In: Izzo JLJ, Black HR, eds. *Hypertension Primer: The Essentials of High Blood Pressure*. Baltimore, Md: Lippincott, Williams & Wilkins;1999:239.
94. Fields LE, Burt VL, Cutler JA, Hughes J, Roccella EJ, Sorlie P. The burden of adult hypertension in the United States 1999 to 2000: a rising tide. *Hypertension*. 2004;44:398–404.
95. Cutler JA, Sorlie PD, Wolz M, Thom T, Fields LE, Roccella EJ. Trends in hypertension prevalence, awareness, treatment, and control rates in United States adults between 1988–1994 and 1999–2004. *Hypertension*. 2008;52:818–827.
96. Baskin ML, Ard J, Franklin F, Allison DB. Prevalence of obesity in the United States. *Obes Rev*. 2005;6:5–7.
97. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics.* 2004;114(2 suppl IV report):555–576.
98. Burt VL, Whelton P, Roccella EJ, Brown C, Cutler JA, Higgins M, Horan MJ, Labarthe D. Prevalence of hypertension in the US adult population: results from the Third National Health and Nutrition Examination Survey, 1988–1991. *Hypertension*. 1995;25:305–313.
99. Vasan RS, Beiser A, Seshadri S, Larson MG, Kannel WB, D'Agostino RB, Levy D. Residual lifetime risk for developing hypertension in middle-aged women and men: the Framingham Heart Study. *JAMA*. 2002;287:1003–1010.
100. Psaty BM, Lumley T, Furberg CD, Schellenbaum G, Pahor M, Alderman MH, Weiss NS. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. *JAMA*. 2003;289:2534–2544.
101. Turnbull F. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet*. 2003;362:1527–1535.
102. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ*. 2009;338:b1665.
103. Wright JM, Musini VM. First-line drugs for hypertension. *Cochrane Database Syst Rev*. 2009:CD001841.
104. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;288:2981–2997.
105. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet*. 1998;351:1755–1762.
106. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, Belhani A,

Forette F, Rajkumar C, Thijs L, Banya W, Bulpitt CJ. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med*. 2008;358:1887–1898.
107. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA*. 1991;265:3255–3264.
108. Hyman DJ, Pavlik VN. Characteristics of patients with uncontrolled hypertension in the United States. *N Engl J Med*. 2001;345:479–486.
109. Black HR, Elliott WJ, Neaton JD, Grandits G, Grambsch P, Grimm RH Jr, Hansson L, Lacouciere Y, Muller J, Sleight P, Weber MA, White WB, Williams G, Wittes J, Zanchetti A, Fakouhi TD, Anders RJ. Baseline characteristics and early blood pressure control in the CONVINCE Trial. *Hypertension*. 2001;37:12–18.
110. Cushman WC, Ford CE, Cutler JA, Margolis KL, Davis BR, Grimm RH, Black HR, Hamilton BP, Holland J, Nwachuku C, Papademetriou V, Probstfield J, Wright JT Jr, Alderman MH, Weiss RJ, Piller L, Bettencourt J, Walsh SM. Success and predictors of blood pressure control in diverse North American settings: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *J Clin Hypertens (Greenwich)*. 2002;4:393–404.
111. Douglas JG, Bakris GL, Epstein M, Ferdinand KC, Ferrario C, Flack JM, Jamerson KA, Jones WE, Haywood J, Maxey R, Ofili EO, Saunders E, Schiffrin EL, Sica DA, Sowers JR, Vidt DG. Management of high blood pressure in African Americans: consensus statement of the Hypertension in African Americans Working Group of the International Society on Hypertension in Blacks. *Arch Intern Med*. 2003;163:525–541.
112. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke*. 1991;22:312–318.
113. Rodriguez BL, D'Agostino R, Abbott RD, Kagan A, Burchfiel CM, Yano K, Ross GW, Silbershatz H, Higgins MW, Popper J, Wolf PA, Curb JD. Risk of hospitalized stroke in men enrolled in the Honolulu Heart Program and the Framingham Study: a comparison of incidence and risk factor effects. *Stroke*. 2002;33:230–236.
114. Bhat VM, Cole JW, Sorkin JD, Wozniak MA, Malarcher AM, Giles WH, Stern BJ, Kittner SJ. Dose-response relationship between cigarette smoking and risk of ischemic stroke in young women. *Stroke*. 2008;39:2439–2443.
115. Feigin V, Parag V, Lawes CM, Rodgers A, Suh I, Woodward M, Jamrozik K, Ueshima H. Smoking and elevated blood pressure are the most important risk factors for subarachnoid hemorrhage in the Asia-Pacific region: an overview of 26 cohorts involving 306,620 participants. *Stroke*. 2005;36:1360–1365.
116. Feigin VL, Rinkel GJ, Lawes CM, Algra A, Bennett DA, van Gijn J, Anderson CS. Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. *Stroke*. 2005;36:2773–2780.
117. Kurth T, Kase CS, Berger K, Gaziano JM, Cook NR, Buring JE. Smoking and risk of hemorrhagic stroke in women. *Stroke*. 2003;34:2792–2795.
118. Kurth T, Kase CS, Berger K, Schaeffner ES, Buring JE, Gaziano JM. Smoking and the risk of hemorrhagic stroke in men. *Stroke*. 2003;34:1151–1155.
119. Feldmann E, Broderick JP, Kernan WN, Viscoli CM, Brass LM, Brott T, Morgenstern LB, Wilterdink JL, Horwitz RI. Major risk factors for intracerebral hemorrhage in the young are modifiable. *Stroke*. 2005;36:1881–1885.
120. Shinton R, Beevers G. Meta-analysis of relation between cigarette smoking and stroke. *BMJ*. 1989;298:789–794.
121. Thrift AG, McNeil JJ, Donnan GA. The risk of intracerebral haemorrhage with smoking. The Melbourne Risk Factor Study Group. *Cerebrovasc Dis*. 1999;9:34–39.
122. *Reducing the Health Consequences of Smoking: 25 Years of Progress. A Report of the Surgeon General.* Rockville, Md: US Dept of Health and Human Services, Public Health Service, Centers for Disease Control, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 1989. DHHS publication (CDC) 89–8411.
123. The surgeon general's 1989 report on reducing the health consequences of smoking: 25 years of progress. *MMWR Morb Mortal Wkly Rep.* 1989;38(suppl 2):1–32.
124. Thun MJ, Apicella LF, Henley SJ. Smoking vs other risk factors as the cause of smoking-attributable deaths: confounding in the courtroom. *JAMA*. 2000;284:706–712.
125. Smoking-attributable mortality, years of potential life lost, and productivity losses–United States, 2000–2004. *MMWR Morb Mortal Wkly Rep.* 2008;57:1226–1228.
126. Nakamura K, Barzi F, Lam TH, Huxley R, Feigin VL, Ueshima H, Woo J, Gu D, Ohkubo T, Lawes CM, Suh I, Woodward M. Cigarette smoking, systolic blood pressure, and cardiovascular diseases in the Asia-Pacific region. *Stroke*. 2008;39:1694–1702.
127. Schwartz SW, Carlucci C, Chambless LE, Rosamond WD. Synergism between smoking and vital exhaustion in the risk of ischemic stroke: evidence from the ARIC study. *Ann Epidemiol*. 2004;14:416–424.
128. Ischaemic stroke and combined oral contraceptives: results of an international, multicentre, case-control study. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. *Lancet.* 1996;348:498–505.
129. Haemorrhagic stroke, overall stroke risk, and combined oral contraceptives: results of an international, multicentre, case-control study. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. *Lancet.* 1996;348:505–510.
130. Pezzini A, Grassi M, Del Zotto E, Bazzoli E, Archetti S, Assanelli D, Akkawi NM, Albertini A, Padovani A. Synergistic effect of apolipoprotein E polymorphisms and cigarette smoking on risk of ischemic stroke in young adults. *Stroke*. 2004;35:438–442.
131. *The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General.* Atlanta, GA: US Dept of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2006.
132. Barnoya J, Glantz SA. Cardiovascular effects of secondhand smoke: nearly as large as smoking. *Circulation*. 2005;111:2684–2698.
133. Bonita R, Duncan J, Truelsen T, Jackson RT, Beaglehole R. Passive smoking as well as active smoking increases the risk of acute stroke. *Tob Control*. 1999;8:156–160.
134. He Y, Lam TH, Jiang B, Wang J, Sai X, Fan L, Li X, Qin Y, Hu FB. Passive smoking and risk of peripheral arterial disease and ischemic stroke in Chinese women who never smoked. *Circulation*. 2008;118:1535–1540.
135. Iribarren C, Darbinian J, Klatsky AL, Friedman GD. Cohort study of exposure to environmental tobacco smoke and risk of first ischemic stroke and transient ischemic attack. *Neuroepidemiology*. 23(1–2):38–44, 2004.
136. Qureshi AI, Suri MF, Kirmani JF, Divani AA. Cigarette smoking among spouses: another risk factor for stroke in women. *Stroke*. 2005;36:e74–76.
137. You RX, Thrift AG, McNeil JJ, Davis SM, Donnan GA. Ischemic stroke risk and passive exposure to spouses' cigarette smoking. Melbourne Stroke Risk Factor Study (MERFS) Group. *Am J Public Health*. 1999;89:572–575.
138. Zhang X, Shu XO, Yang G, Li HL, Xiang YB, Gao YT, Li Q, Zheng W. Association of passive smoking by husbands with prevalence of stroke among Chinese women nonsmokers. *Am J Epidemiol*. 2005;161:213–218.
139. Whincup PH, Gilg JA, Emberson JR, Jarvis MJ, Feyerabend C, Bryant A, Walker M, Cook DG. Passive smoking and risk of coronary heart disease and stroke: prospective study with cotinine measurement. *BMJ*. 2004;329:200–205.
140. Howard G, Thun MJ. Why is environmental tobacco smoke more strongly associated with coronary heart disease than expected? A review of potential biases and experimental data. *Environ Health Perspect.* 1999;107(suppl 6:853–858.
141. Burns DM. Epidemiology of smoking-induced cardiovascular disease. *Prog Cardiovasc Dis*. 2003;46:11–29.
142. Kool MJ, Hoeks AP, Struijker Boudier HA, Reneman RS, Van Bortel LM. Short- and long-term effects of smoking on arterial wall properties in habitual smokers. *J Am Coll Cardiol*. 1993;22:1881–1886.
143. Silvestrini M, Troisi E, Matteis M, Cupini LM, Bernardi G. Effect of smoking on cerebrovascular reactivity. *J Cereb Blood Flow Metab*. 1996;16:746–749.
144. Howard G, Wagenknecht LE, Burke GL, Diez-Roux A, Evans GW, McGovern P, Nieto FJ, Tell GS. Cigarette smoking and progression of atherosclerosis: the Atherosclerosis Risk in Communities (ARIC) Study. *JAMA*. 1998;279:119–124.
145. Karttunen V, Alfthan G, Hiltunen L, Rasi V, Kervinen K, Kesaniemi YA, Hillbom M. Risk factors for cryptogenic ischaemic stroke. *Eur J Neurol*. 2002;9:625–632.
146. Fagerstrom K. The epidemiology of smoking: health consequences and benefits of cessation. *Drugs.* 2002;62(suppl 2):1–9.
147. Robbins AS, Manson JE, Lee IM, Satterfield S, Hennekens CH. Cigarette smoking and stroke in a cohort of U.S. male physicians. *Ann Intern Med*. 1994;120:458–462.
148. Song YM, Cho HJ. Risk of stroke and myocardial infarction after reduction or cessation of cigarette smoking: a cohort study in Korean men. *Stroke*. 2008;39:2432–2438.

149. US Department of Health and Human Services. *The Health Consequences of Smoking: A Report of the Surgeon General.* Washington, DC: US Dept of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2004.
150. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev.* 2008:CD006103.
151. Stead LF, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev.* 2008:CD000146.
152. Counseling and interventions to prevent tobacco use and tobacco-caused disease in adults and pregnant women: U.S. Preventive Services Task Force reaffirmation recommendation statement. *Ann Intern Med.* 2009; 150:551–555.
153. Prevalence of diabetes and impaired fasting glucose in adults—United States, 1999–2000. *MMWR Morb Mortal Wkly Rep.* 2003;52:833–837. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5235a1.htm. Published September 5, 2003. Updated April 7, 2004. Accessed August 14, 2010.
154. *Guide to Clinical Preventive Services: Report of the U. S. Preventive Services Task Force.* Baltimore, MD: Williams and Wilkins; 1996. Available at: http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=hscps2ed1996&part=A19920. Accessed October 14, 2010.
155. Prevalence of self-reported cardiovascular disease among persons aged ≥35 years with diabetes—United States, 1997–2005. *MMWR Morb Mortal Wkly Rep.* 2007;56:1129–1132.
156. Kissela BM, Khoury J, Kleindorfer D, Woo D, Schneider A, Alwell K, Miller R, Ewing I, Moomaw CJ, Szaflarski JP, Gebel J, Shukla R, Broderick JP. Epidemiology of ischemic stroke in patients with diabetes: the Greater Cincinnati/Northern Kentucky Stroke Study. *Diabetes Care*. 2005;28:355–359.
157. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med*. 2008;358:580–591.
158. Anselmino M, Malmberg K, Ohrvik J, Ryden L. Evidence-based medication and revascularization: powerful tools in the management of patients with diabetes and coronary artery disease: a report from the Euro Heart Survey on diabetes and the heart. *Eur J Cardiovasc Prev Rehabil*. 2008;15:216–223.
159. Boden-Albala B, Cammack S, Chong J, Wang C, Wright C, Rundek T, Elkind MS, Paik MC, Sacco RL. Diabetes, fasting glucose levels, and risk of ischemic stroke and vascular events: findings from the Northern Manhattan Study (NOMAS). *Diabetes Care*. 2008;31:1132–1137.
160. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet.* 1998;352: 854–865.
161. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med.* 2008;359:1577–1589.
162. Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358:2545–2559.
163. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2008;358:2560–2572.
164. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. 2009;360:129–139.
165. Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EA, Howard BV, Kirkman MS, Kosiborod M, Reaven P, Sherwin RS. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *Circulation*. 2009;119:351–357.
166. Implementation of treatment protocols in the Diabetes Control and Complications Trial. *Diabetes Care.* 1995;18:361–376.
167. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med.* 2005;353: 2643–2653.
168. Tuomilehto J, Rastenyte D. Diabetes and glucose intolerance as risk factors for stroke. *J Cardiovasc Risk*. 1999;6:241–249.
169. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ*. 1998;317:703–713.
170. Curb JD, Pressel SL, Cutler JA, Savage PJ, Applegate WB, Black H, Camel G, Davis BR, Frost PH, Gonzalez N, Guthrie G, Oberman A, Rutan GH, Stamler J. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. Systolic Hypertension in the Elderly Program Cooperative Research Group. *JAMA*. 1996;276:1886–1892.
171. Holman RR, Paul SK, Bethel MA, Neil HA, Matthews DR. Long-term follow-up after tight control of blood pressure in type 2 diabetes. *N Engl J Med*. 2008;359:1565–1576.
172. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet.* 2000;355:253–259.
173. Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359:995–1003.
174. Wachtell K, Hornestam B, Lehto M, Slotwiner DJ, Gerdts E, Olsen MH, Aurup P, Dahlof B, Ibsen H, Julius S, Kjeldsen SE, Lindholm LH, Nieminen MS, Rokkedal J, Devereux RB. Cardiovascular morbidity and mortality in hypertensive patients with a history of atrial fibrillation: the Losartan Intervention for End Point Reduction in Hypertension (LIFE) study. *J Am Coll Cardiol*. 2005;45:705–711.
175. Patel A, MacMahon S, Chalmers J, Neal B, Woodward M, Billot L, Harrap S, Poulter N, Marre M, Cooper M, Glasziou P, Grobbee DE, Hamet P, Heller S, Liu LS, Mancia G, Mogensen CE, Pan CY, Rodgers A, Williams B. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet*. 2007;370:829–840.
176. Bangalore S, Parkar S, Grossman E, Messerli FH. A meta-analysis of 94,492 patients with hypertension treated with beta blockers to determine the risk of new-onset diabetes mellitus. *Am J Cardiol*. 2007; 100:1254–1262.
177. Barzilay JI, Davis BR, Cutler JA, Pressel SL, Whelton PK, Basile J, Margolis KL, Ong ST, Sadler LS, Summerson J. Fasting glucose levels and incident diabetes mellitus in older nondiabetic adults randomized to receive 3 different classes of antihypertensive treatment: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med*. 2006;166:2191–2201.
178. Ostergren J, Poulter NR, Sever PS, Dahlof B, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E. The Anglo-Scandinavian Cardiac Outcomes Trial: blood pressure-lowering limb: effects in patients with type II diabetes. *J Hypertens*. 2008;26:2103–2111.
179. ACCORD Study Group, Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, Katz L, Peterson KA, Friedewald WT, Buse JB, Bigger JT, Gerstein HC, Ismail-Beigi F. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med.* 2010;362:1575–1585.
180. Jamerson K, Weber MA, Bakris GL, Dahlof B, Pitt B, Shi V, Hester A, Gupte J, Gatlin M, Velazquez EJ. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med.* 2008;359:2417–2428.
181. Goldberg RB, Mellies MJ, Sacks FM, Moye LA, Howard BV, Howard WJ, Davis BR, Cole TG, Pfeffer MA, Braunwald E. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the cholesterol and recurrent events (CARE) trial. The Care Investigators. *Circulation*. 1998;98:2513–2519.
182. Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or

lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet*. 2003; 361:1149–1158.
183. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet.* 2002;360:7–22.
184. Collins R, Armitage J, Parish S, Sleigh P, Peto R. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet*. 2003;361:2005–2016.
185. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet*. 2004;364:685–696.
186. Shepherd J, Barter P, Carmena R, Deedwania P, Fruchart JC, Haffner S, Hsia J, Breazna A, LaRosa J, Grundy S, Waters D. Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study. *Diabetes Care*. 2006;29:1220–1226.
187. Rubins HB, Robins SJ, Collins D, Nelson DB, Elam MB, Schaefer EJ, Faas FH, Anderson JW. Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). *Arch Intern Med*. 2002;162:2597–2604.
188. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesaniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet*. 2005;366:1849–1861.
189. ACCORD Study Group, Ginsberg HN, Elam MB, Lovato LC, Crouse JR 3rd, Leiter LA, Linz P, Friedewald WT, Buse JB, Gerstein HC, Probstfield J, Grimm RH, Ismail-Beigi F, Bigger JT, Goff DC Jr, Cushman WC, Simons-Morton DG, Byington RP. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med*. 2010; 362:1563–1574.
190. Ogawa H, Nakayama M, Morimoto T, Uemura S, Kanauchi M, Doi N, Jinnouchi H, Sugiyama S, Saito Y. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA*. 2008;300:2134–2141.
191. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ.* 2002;324:71–86.
192. Iso H, Jacobs DR Jr, Wentworth D, Neaton JD, Cohen JD. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. *N Engl J Med*. 1989;320:904–910.
193. Leppala JM, Virtamo J, Fogelholm R, Albanes D, Heinonen OP. Different risk factors for different stroke subtypes: association of blood pressure, cholesterol, and antioxidants. *Stroke*. 1999;30:2535–2540.
194. Zhang X, Patel A, Horibe H, Wu Z, Barzi F, Rodgers A, MacMahon S, Woodward M. Cholesterol, coronary heart disease, and stroke in the Asia Pacific region. *Int J Epidemiol*. 2003;32:563–572.
195. Horenstein RB, Smith DE, Mosca L. Cholesterol predicts stroke mortality in the Women's Pooling Project. *Stroke*. 2002;33:1863–1868.
196. Kurth T, Everett BM, Buring JE, Kase CS, Ridker PM, Gaziano JM. Lipid levels and the risk of ischemic stroke in women. *Neurology*. 2007;68:556–562.
197. Shahar E, Chambless LE, Rosamond WD, Boland LL, Ballantyne CM, McGovern PG, Sharrett AR. Plasma lipid profile and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study. *Stroke*. 2003;34:623–631.
198. Bots ML, Elwood PC, Nikitin Y, Salonen JT, Freire de Concalves A, Inzitari D, Sivenius J, Benetou V, Tuomilehto J, Koudstaal PJ, Grobbee DE. Total and HDL cholesterol and risk of stroke. EUROSTROKE: a collaborative study among research centres in Europe. *J Epidemiol Community Health*. 2002;56(suppl 1):i19–i24.
199. O'Leary DH, Polak JF, Kronmal RA, Savage PJ, Borhani NO, Kittner SJ, Tracy R, Gardin JM, Price TR, Furberg CD. Thickening of the carotid wall: a marker for atherosclerosis in the elderly? Cardiovascular Health Study Collaborative Research Group. *Stroke*. 1996;27:224–231.
200. Sacco RL, Roberts JK, Boden-Albala B, Gu Q, Lin IF, Kargman DE, Berglund L, Hauser WA, Shea S, Paik MC. Race-ethnicity and determinants of carotid atherosclerosis in a multiethnic population: the Northern Manhattan Stroke Study. *Stroke*. 1997;28:929–935.
201. Sharrett AR, Patsch W, Sorlie PD, Heiss G, Bond MG, Davis CE. Associations of lipoprotein cholesterols, apolipoproteins A-I and B, and triglycerides with carotid atherosclerosis and coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) Study. *Arterioscler Thromb*. 1994;14:1098–1104.
202. Wasserman BA, Sharrett AR, Lai S, Gomes AS, Cushman M, Folsom AR, Bild DE, Kronmal RA, Sinha S, Bluemke DA. Risk factor associations with the presence of a lipid core in carotid plaque of asymptomatic individuals using high-resolution MRI: the multi-ethnic study of atherosclerosis (MESA). *Stroke*. 2008;39:329–335.
203. Wilson PW, Hoeg JM, D'Agostino RB, Silbershatz H, Belanger AM, Poehlmann H, O'Leary D, Wolf PA. Cumulative effects of high cholesterol levels, high blood pressure, and cigarette smoking on carotid stenosis. *N Engl J Med*. 1997;337:516–522.
204. Noda H, Iso H, Irie F, Sairenchi T, Ohtaka E, Doi M, Izumi Y, Ohta H. Low-density lipoprotein cholesterol concentrations and death due to intraparenchymal hemorrhage: the Ibaraki Prefectural Health Study. *Circulation*. 2009;119:2136–2145.
205. Iribarren C, Jacobs DR, Sadler M, Claxton AJ, Sidney S. Low total serum cholesterol and intracerebral hemorrhagic stroke: is the association confined to elderly men? The Kaiser Permanente Medical Care Program. *Stroke*. 1996;27:1993–1998.
206. Cui R, Iso H, Toyoshima H, Date C, Yamamoto A, Kikuchi S, Kondo T, Watanabe Y, Koizumi A, Inaba Y, Tamakoshi A. Serum total cholesterol levels and risk of mortality from stroke and coronary heart disease in Japanese: the J Am Coll Cardiol study. *Atherosclerosis*. 2007;194:415–420.
207. Suh I, Jee SH, Kim HC, Nam CM, Kim IS, Appel LJ. Low serum cholesterol and haemorrhagic stroke in men: Korea Medical Insurance Corporation Study. *Lancet*. 2001;357:922–925.
208. Sanossian N, Saver JL, Navab M, Ovbiagele B. High-density lipoprotein cholesterol: an emerging target for stroke treatment. *Stroke*. 2007;38: 1104–1109.
209. Lindenstrom E, Boysen G, Nyboe J. Influence of total cholesterol, high density lipoprotein cholesterol, and triglycerides on risk of cerebrovascular disease: the Copenhagen City Heart Study. *BMJ*. 1994;309:11–15.
210. Soyama Y, Miura K, Morikawa Y, Nishijo M, Nakanishi Y, Naruse Y, Kagamimori S, Nakagawa H. High-density lipoprotein cholesterol and risk of stroke in Japanese men and women: the Oyabe Study. *Stroke*. 2003;34:863–868.
211. Tanne D, Yaari S, Goldbourt U. High-density lipoprotein cholesterol and risk of ischemic stroke mortality: a 21-year follow-up of 8586 men from the Israeli Ischemic Heart Disease Study. *Stroke*. 1997;28:83–87.
212. Wannamethee SG, Shaper AG, Ebrahim S. HDL-cholesterol, total cholesterol, and the risk of stroke in middle-aged British men. *Stroke*. 2000;31:1882–1888.
213. Sacco RL, Benson RT, Kargman DE, Boden-Albala B, Tuck C, Lin IF, Cheng JF, Paik MC, Shea S, Berglund L. High-density lipoprotein cholesterol and ischemic stroke in the elderly: the Northern Manhattan Stroke Study. *JAMA*. 2001;285:2729–2735.
214. Psaty BM, Anderson M, Kronmal RA, Tracy RP, Orchard T, Fried LP, Lumley T, Robbins J, Burke G, Newman AB, Furberg CD. The association between lipid levels and the risks of incident myocardial infarction, stroke, and total mortality: the Cardiovascular Health Study. *J Am Geriatr Soc*. 2004;52:1639–1647.
215. Amarenco P, Labreuche J, Touboul PJ. High-density lipoprotein-cholesterol and risk of stroke and carotid atherosclerosis: a systematic review. *Atherosclerosis*. 2008;196:489–496.
216. Bowman TS, Sesso HD, Ma J, Kurth T, Kase CS, Stampfer MJ, Gaziano JM. Cholesterol and the risk of ischemic stroke. *Stroke*. 2003;34: 2930–2934.
217. Haheim LL, Holme I, Hjermann I, Leren P. Risk factors of stroke incidence and mortality: a 12-year follow-up of the Oslo Study. *Stroke*. 1993;24:1484–1489.
218. Patel A, Barzi F, Jamrozik K, Lam TH, Ueshima H, Whitlock G, Woodward M. Serum triglycerides as a risk factor for cardiovascular diseases in the Asia-Pacific region. *Circulation*. 2004;110:2678–2686.
219. Freiberg JJ, Tybjaerg-Hansen A, Jensen JS, Nordestgaard BG. Nonfasting triglycerides and risk of ischemic stroke in the general population. *JAMA*. 2008;300:2142–2152.

220. Bansal S, Buring JE, Rifai N, Mora S, Sacks FM, Ridker PM. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. *JAMA*. 2007;298:309–316.
221. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110:227–239.
222. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
223. Amarenco P, Labreuche J, Lavallee P, Touboul PJ. Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. *Stroke*. 2004;35:2902–2909.
224. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366:1267–1278.
225. Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. *Lancet Neurol*. 2009;8:453–463.
226. Crouse JR 3rd, Raichlen JS, Riley WA, Evans GW, Palmer MK, O'Leary DH, Grobbee DE, Bots ML. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. *JAMA*. 2007;297:1344–1353.
227. Smilde TJ, van Wissen S, Wollersheim H, Trip MD, Kastelein JJ, Stalenhoef AF. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial. *Lancet*. 2001;357:577–581.
228. Taylor AJ, Kent SM, Flaherty PJ, Coyle LC, Markwood TT, Vernalis MN. ARBITER: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol: a randomized trial comparing the effects of atorvastatin and pravastatin on carotid intima medial thickness. *Circulation*. 2002;106:2055–2060.
229. Canner PL, Berge KG, Wenger NK, Stamler J, Friedman L, Prineas RJ, Friedewald W. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol*. 1986;8:1245–1255.
230. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease: the Bezafibrate Infarction Prevention (BIP) study. *Circulation*. 2000;102:21–27.
231. Bloomfield Rubins H, Davenport J, Babikian V, Brass LM, Collins D, Wexler L, Wagner S, Papademetriou V, Rutan G, Robins SJ. Reduction in stroke with gemfibrozil in men with coronary heart disease and low HDL cholesterol: the Veterans Affairs HDL Intervention Trial (VA-HIT). *Circulation*. 2001;103:2828–2833.
232. Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF, Visseren FL, Sijbrands EJ, Trip MD, Stein EA, Gaudet D, Duivenvoorden R, Veltri EP, Marais AD, de Groot E. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med*. 2008;358:1431–1443.
233. Taylor AJ, Villines TC, Stanek EJ, Devine PJ, Griffen L, Miller M, Weissman NJ, Turco M. Extended-release niacin or ezetimibe and carotid intima-media thickness. *N Engl J Med*. 2009;361:2113–2122.
234. Cannon CP, Giugliano RP, Blazing MA, Harrington RA, Peterson JL, Sisk CM, Strony J, Musliner TA, McCabe CH, Veltri E, Braunwald E, Califf RM. Rationale and design of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimbe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes. *Am Heart J*. 2008;156:826–832.
235. Kannel WB, Benjamin EJ. Status of the epidemiology of atrial fibrillation. *Med Clin North Am*. 2008;92:17–40, ix.
236. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22:983–988.
237. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. *Neurology*. 2007;69:546–554.
238. Comparison of 12 risk stratification schemes to predict stroke in patients with nonvalvular atrial fibrillation. *Stroke*. 2008;39:1901–1910.
239. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*. 1998;98:946–952.
240. Marini C, De Santis F, Sacco S, Russo T, Olivieri L, Totaro R, Carolei A. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. *Stroke*. 2005;36:1115–1119.
241. Fitzmaurice DA, Hobbs FD, Jowett S, Mant J, Murray ET, Holder R, Raftery JP, Bryan S, Davies M, Lip GY, Allan TF. Screening versus routine practice in detection of atrial fibrillation in patients aged 65 or over: cluster randomised controlled trial. *BMJ*. 2007;335:383.
242. Hobbs FD, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, Raftery J, Davies M, Lip G. A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over: the SAFE study. *Health Technol Assess*. 2005;9:iii–iv, ix–x, 1–74.
243. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864–2870.
244. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Zamorano JL. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*. 2006;114:e257–354.
245. Hart RG, Pearce LA, Rothbart RM, McAnulty JH, Asinger RW, Halperin JL. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke Prevention in Atrial Fibrillation Investigators. *J Am Coll Cardiol*. 2000;35:183–187.
246. Hohnloser SH, Pajitnev D, Pogue J, Healey JS, Pfeffer MA, Yusuf S, Connolly SJ. Incidence of stroke in paroxysmal versus sustained atrial fibrillation in patients taking oral anticoagulation or combined antiplatelet therapy: an ACTIVE W substudy. *J Am Coll Cardiol*. 2007;50:2156–2161.
247. Singer DE, Albers GW, Dalen JE, Fang MC, Go AS, Halperin JL, Lip GY, Manning WJ. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest*. 2008;133(suppl 6):546S–592S.
248. Singer DE, Chang Y, Fang MC, Borowsky LH, Pomernacki NK, Udaltsova N, Go AS. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. *Ann Intern Med*. 2009;151:297–305.
249. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002;347:1825–1833.
250. Maisel WH. Left atrial appendage occlusion–closure or just the beginning? *N Engl J Med*. 2009;360:2601–2603.
251. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sick P. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet*. 2009;374:534–542.
252. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146:857–867.
253. ACTIVE Investigators, Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, Chrolavicius S, Yusuf S. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med*. 2009;360:2066–2078.
254. Bousser MG, Bouthier J, Buller HR, Cohen AT, Crijns H, Davidson BL, Halperin J, Hankey G, Levy S, Pengo V, Prandoni P, Prins MH, Tomkowski W, Thorp-Pedersen C, Wyse DG. Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomised, open-label, non-inferiority trial. *Lancet*. 2008;371:315–321.
255. Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, Murray E. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet*. 2007;370:493–503.
256. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD,

Wallentin L. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151.
257. Andersen KK, Olsen TS. Reduced poststroke mortality in patients with stroke and atrial fibrillation treated with anticoagulants: results from a Danish quality-control registry of 22,179 patients with ischemic stroke. *Stroke*. 2007;38:259–263.
258. Hylek EM, Go AS, Chang Y, Jensvold NG, Henault LE, Selby JV, Singer DE. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med*. 2003;349:1019–1026.
259. O'Donnell M, Oczkowski W, Fang J, Kearon C, Silva J, Bradley C, Guyatt G, Gould L, D'Uva C, Kapral M, Silver F. Preadmission antithrombotic treatment and stroke severity in patients with atrial fibrillation and acute ischaemic stroke: an observational study. *Lancet Neurol*. 2006;5:749–754.
260. Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, Yusuf S. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet*. 2006;367:1903–1912.
261. Usman MH, Notaro LA, Nagarakanti R, Brahin E, Dessain S, Gracely E, Ezekowitz MD. Combination antiplatelet therapy for secondary stroke prevention: enhanced efficacy or double trouble? *Am J Cardiol*. 2009; 103:1107–1112.
262. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation*. 2007;115: 2689–2696.
263. Arima H, Hart RG, Colman S, Chalmers J, Anderson C, Rodgers A, Woodward M, MacMahon S, Neal B. Perindopril-based blood pressure-lowering reduces major vascular events in patients with atrial fibrillation and prior stroke or transient ischemic attack. *Stroke*. 2005;36: 2164–2169.
264. Chapman N, Huxley R, Anderson C, Bousser MG, Chalmers J, Colman S, Davis S, Donnan G, MacMahon S, Neal B, Warlow C, Woodward M. Effects of a perindopril-based blood pressure-lowering regimen on the risk of recurrent stroke according to stroke subtype and medical history: the PROGRESS Trial. *Stroke*. 2004;35:116–121.
265. Lip GY, Frison L, Grind M. Effect of hypertension on anticoagulated patients with atrial fibrillation. *Eur Heart J*. 2007;28:752–759.
266. Joint Commission. 2010 National Patient Safety Goals (NPSGs). Available at: http://www.JointCommission.org/PatientSafety/NationalPatientSafetyGoals/. Accessed October 14, 2010.
267. Garcia DA, Witt DM, Hylek E, Wittkowsky AK, Nutescu EA, Jacobson A, Moll S, Merli GJ, Crowther M, Earl L, Becker RC, Oertel L, Jaffer A, Ansell JE. Delivery of optimized anticoagulant therapy: consensus statement from the Anticoagulation Forum. *Ann Pharmacother*. 2008; 42:979–988.
268. Shireman TI, Howard PA, Kresowik TF, Ellerbeck EF. Combined anticoagulant-antiplatelet use and major bleeding events in elderly atrial fibrillation patients. *Stroke*. 2004;35:2362–2367.
269. van Walraven C, Hart RG, Singer DE, Laupacis A, Connolly S, Petersen P, Koudstaal PJ, Chang Y, Hellemons B. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. *JAMA*. 2002;288:2441–2448.
270. Karjalainen PP, Porela P, Ylitalo A, Vikman S, Nyman K, Vaittinen MA, Airaksinen TJ, Niemela M, Vahlberg T, Airaksinen KE. Safety and efficacy of combined antiplatelet-warfarin therapy after coronary stenting. *Eur Heart J*. 2007;28:726–732.
271. Ruiz-Nodar JM, Marin F, Hurtado JA, Valencia J, Pinar E, Pineda J, Gimeno JR, Sogorb F, Valdes M, Lip GY. Anticoagulant and antiplatelet therapy use in 426 patients with atrial fibrillation undergoing percutaneous coronary intervention and stent implantation implications for bleeding risk and prognosis. *J Am Coll Cardiol*. 2008;51:818–825.
272. Francescone S, Halperin JL. "Triple therapy" or triple threat? Balancing the risks of antithrombotic therapy for patients with atrial fibrillation and coronary stents. *J Am Coll Cardiol*. 2008;51:826–827.
273. Rubboli A, Halperin JL, Juhani Airaksinen KE, Buerke M, Eeckhout E, Freedman SB, Gershlick AH, Schlitt A, Fat Tse H, Verheugt FW, Lip GY. Antithrombotic therapy in patients treated with oral anticoagulation undergoing coronary artery stenting: an expert consensus document with focus on atrial fibrillation. *Ann Med*. 2008;40:428–436.
274. King SB 3rd, Smith SC Jr, Hirshfeld JW Jr, Jacobs AK, Morrison DA, Williams DO, Feldman TE, Kern MJ, O'Neill WW, Schaff HV, Whitlow PL, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura R, Page RL, Riegel B, Tarkington LG, Yancy CW. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2008;51:172–209.
275. Olsson SB. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. *Lancet*. 2003; 362:1691–1698.
276. Albers GW, Diener HC, Frison L, Grind M, Nevinson M, Partridge S, Halperin JL, Horrow J, Olsson SB, Petersen P, Vahanian A. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. *JAMA*. 2005;293:690–698.
277. Gage BF. Can we rely on RE-LY? *N Engl J Med*. 2009;361:1200–1202.
278. Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB, Gorelick P, Halperin J, Harbaugh R, Johnston SC, Katzan I, Kelly-Hayes M, Kenton EJ, Marks M, Schwamm LH, Tomsick T. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention. *Circulation*. 2006;113:e409–449.
279. Doufekias E, Segal AZ, Kizer JR. Cardiogenic and aortogenic brain embolism. *J Am Coll Cardiol*. 2008;51:1049–1059.
280. Pinto A, Tuttolomondo A, Di Raimondo D, Fernandez P, Licata G. Risk factors profile and clinical outcome of ischemic stroke patients admitted in a Department of Internal Medicine and classified by TOAST classification. *Int Angiol*. 2006;25:261–267.
281. Arboix A, Oliveres M, Massons J, Pujades R, Garcia-Eroles L. Early differentiation of cardioembolic from atherothrombotic cerebral infarction: a multivariate analysis. *Eur J Neurol*. 1999;6:677–683.
282. Adams HP Jr. Secondary prevention of atherothrombotic events after ischemic stroke. *Mayo Clin Proc*. 2009;84:43–51.
283. Eagle KA, Guyton RA, Davidoff R, Edwards FH, Ewy GA, Gardner TJ, Hart JC, Herrmann HC, Hillis LD, Hutter AM Jr, Lytle BW, Marlow RA, Nugent WC, Orszulak TA. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). *Circulation*. 2004;110:e340–437.
284. Hogue CW Jr, Murphy SF, Schechtman KB, Davila-Roman VG. Risk factors for early or delayed stroke after cardiac surgery. *Circulation*. 1999;100:642–647.
285. Roach GW, Kanchuger M, Mangano CM, Newman M, Nussmeier N, Wolman R, Aggarwal A, Marschall K, Graham SH, Ley C. Adverse cerebral outcomes after coronary bypass surgery. Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation Investigators. *N Engl J Med*. 1996;335: 1857–1863.
286. Loh E, Sutton MS, Wun CC, Rouleau JL, Flaker GC, Gottlieb SS, Lamas GA, Moye LA, Goldhaber SZ, Pfeffer MA. Ventricular dysfunction and the risk of stroke after myocardial infarction. *N Engl J Med*. 1997;336:251–257.
287. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med*. 1992; 327:669–677.
288. Shindler DM, Kostis JB, Yusuf S, Quinones MA, Pitt B, Stewart D, Pinkett T, Ghali JK, Wilson AC. Diabetes mellitus, a predictor of morbidity and mortality in the Studies of Left Ventricular Dysfunction (SOLVD) Trials and Registry. *Am J Cardiol*. 1996;77:1017–1020.
289. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, Chavey WE 2nd, Fesmire FM, Hochman JS, Levin TN, Lincoff AM, Peterson ED, Theroux P, Wenger NK, Wright RS, Smith SC Jr, Jacobs AK, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular

Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol*. 2007;50:e1–e157.
290. Antman EM, Hand M, Armstrong PW, Bates ER, Green LA, Halasyamani LK, Hochman JS, Krumholz HM, Lamas GA, Mullany CJ, Pearle DL, Sloan MA, Smith SC Jr, Anbe DT, Kushner FG, Ornato JP, Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Halperin JL, Hunt SA, Lytle BW, Nishimura R, Page RL, Riegel B, Tarkington LG, Yancy CW. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2008;51:210–247.
291. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Zamorano JL. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation–executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). *J Am Coll Cardiol*. 2006;48:854–906.
292. Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2008;52:e1–142.
293. Coulshed N, Epstein EJ, McKendrick CS, Galloway RW, Walker E. Systemic embolism in mitral valve disease. *Br Heart J*. 1970;32:26–34.
294. Hanson MR, Hodgeman JR, Conomy JP. A study of stroke associated with prolapsed mitral valve. *Neurology*. 1978;23:341.
295. Benjamin EJ, Plehn JF, D'Agostino RB, Belanger AJ, Comai K, Fuller DL, Wolf PA, Levy D. Mitral annular calcification and the risk of stroke in an elderly cohort. *N Engl J Med*. 1992;327:374–379.
296. Kronzon I, Tunick PA. Aortic atherosclerotic disease and stroke. *Circulation*. 2006;114:63–75.
297. Cabell CH, Pond KK, Peterson GE, Durack DT, Corey GR, Anderson DJ, Ryan T, Lukes AS, Sexton DJ. The risk of stroke and death in patients with aortic and mitral valve endocarditis. *Am Heart J*. 2001;142:75–80.
298. Mylonakis E, Calderwood SB. Infective endocarditis in adults. *N Engl J Med*. 2001;345:1318–1330.
299. Rahmatullah AF, Rahko PS, Stein JH. Transesophageal echocardiography for the evaluation and management of patients with cerebral ischemia. *Clin Cardiol*. 1999;22:391–396.
300. Reynen K. Cardiac myxomas. *N Engl J Med*. 1995;333:1610–1617.
301. Berthet K, Lavergne T, Cohen A, Guize L, Bousser MG, Le Heuzey JY, Amarenco P. Significant association of atrial vulnerability with atrial septal abnormalities in young patients with ischemic stroke of unknown cause. *Stroke*. 2000;31:398–403.
302. Di Tullio MR, Sacco RL, Sciacca RR, Jin Z, Homma S. Patent foramen ovale and the risk of ischemic stroke in a multiethnic population. *J Am Coll Cardiol*. 2007;49:797–802.
303. Kizer JR, Devereux RB. Clinical practice. Patent foramen ovale in young adults with unexplained stroke. *N Engl J Med*. 2005;353:2361–2372.
304. Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology*. 2000;55:1172–1179.
305. Petty GW, Khandheria BK, Meissner I, Whisnant JP, Rocca WA, Christianson TJ, Sicks JD, O'Fallon WM, McClelland RL, Wiebers DO. Population-based study of the relationship between patent foramen ovale and cerebrovascular ischemic events. *Mayo Clin Proc*. 2006;81:602–608.
306. Meissner I, Khandheria BK, Heit JA, Petty GW, Sheps SG, Schwartz GL, Whisnant JP, Wiebers DO, Covalt JL, Petterson TM, Christianson TJ, Agmon Y. Patent foramen ovale: innocent or guilty? Evidence from a prospective population-based study. *J Am Coll Cardiol*. 2006;47:440–445.
307. Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. *Circulation*. 2002;105:2625–2631.
308. Massie BM, Collins JF, Ammon SE, Armstrong PW, Cleland JG, Ezekowitz M, Jafri SM, Krol WF, O'Connor CM, Schulman KA, Teo K, Warren SR. Randomized trial of warfarin, aspirin, and clopidogrel in patients with chronic heart failure: the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial. *Circulation*. 2009;119:1616–1624.
309. Amarenco P, Cohen A, Tzourio C, Bertrand B, Hommel M, Besson G, Chauvel C, Touboul PJ, Bousser MG. Atherosclerotic disease of the aortic arch and the risk of ischemic stroke. *N Engl J Med*. 1994;331:1474–1479.
310. Di Tullio MR, Sacco RL, Savoia MT, Sciacca RR, Homma S. Aortic atheroma morphology and the risk of ischemic stroke in a multiethnic population. *Am Heart J*. 2000;139(2 Pt 1):329–336.
311. Petty GW, Khandheria BK, Meissner I, Whisnant JP, Rocca WA, Sicks JD, Christianson TJ, O'Fallon WM, McClelland RL, Wiebers DO. Population-based study of the relationship between atherosclerotic aortic debris and cerebrovascular ischemic events. *Mayo Clin Proc*. 2006;81:609–614.
312. Bonow RO, Carabello B, de Leon AC Jr, Edmunds LH Jr, Fedderly BJ, Freed MD, Gaasch WH, McKay CR, Nishimura RA, O'Gara PT, O'Rourke RA, Rahimtoola SH. ACC/AHA guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Valvular Heart Disease). *J Am Coll Cardiol*. 1998;32:1486–1588.
313. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, Jones RH, Kereiakes D, Kupersmith J, Levin TN, Pepine CJ, Schaeffer JW, Smith EE 3rd, Steward DE, Théroux P, Gibbons RJ, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Smith SC Jr. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non–ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). *J Am Coll Cardiol*. 2002;40:1366–1374.
314. Gibbons RJ, Abrams J, Chatterjee K, Daley J, Deedwania PC, Douglas JS, Ferguson TB Jr, Fihn SD, Fraker TD Jr, Gardin JM, O'Rourke RA, Pasternak RC, Williams SV. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Chronic Stable Angina). *J Am Coll Cardiol*. 2003;41:159–168.
315. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC Jr, Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK, Ornato JP. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *J Am Coll Cardiol*. 2004;44:E1–E211.
316. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *JAMA*. 1995;273:1421–1428.
317. Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, Thomas D. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet*. 2004;363:1491–1502.
318. Hobson RW 2nd, Weiss DG, Fields WS, Goldstone J, Moore WS, Towne JB, Wright CB. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. The Veterans Affairs Cooperative Study Group. *N Engl J Med*. 1993;328:221–227.
319. Barnett HJ, Warlow CP. Carotid endarterectomy and the measurement of stenosis. *Stroke*. 1993;24:1281–1284.

320. Moore WS, Young B, Baker WH, Robertson JT, Toole JF, Vescera CL, Howard VJ. Surgical results: a justification of the surgeon selection process for the ACAS trial. The ACAS Investigators. *J Vasc Surg*. 1996;23:323–328.
321. Howard G, Chambless LE, Baker WH, Ricotta JJ, Jones AM, O'Leary D, Howard VJ, Elliott TJ, Lefkowitz DS, Toole JF. A multicenter validation study of Doppler ultrasound versus angiography. *J Stroke Cerebrovasc Dis*. 1991;1:166–173.
322. Johnston DC, Goldstein LB. Clinical carotid endarterectomy decision making: noninvasive vascular imaging versus angiography. *Neurology*. 2001;56:1009–1015.
323. Koelemay MJ, Nederkoorn PJ, Reitsma JB, Majoie CB. Systematic review of computed tomographic angiography for assessment of carotid artery disease. *Stroke*. 2004;35:2306–2312.
324. Fine-Edelstein JS, Wolf PA, O'Leary DH, Poehlman H, Belanger AJ, Kase CS, D'Agostino RB. Precursors of extracranial carotid atherosclerosis in the Framingham Study. *Neurology*. 1994;44:1046–1050.
325. Weber F. Risk factors for subclinical carotid atherosclerosis in healthy men. *Neurology*. 2002;59:524–528.
326. Ziegler DK, Zileli T, Dick A, Sebaugh JL. Correlation of bruits over the carotid artery with angiographically demonstrated lesions. *Neurology*. 1971;21:860–865.
327. David TE, Humphries AW, Young JR, Beven EG. A correlation of neck bruits and arteriosclerotic carotid arteries. *Arch Surg*. 1973;107:729–731.
328. McPhee JT, Hill JS, Ciocca RG, Messina LM, Eslami MH. Carotid endarterectomy was performed with lower stroke and death rates than carotid artery stenting in the United States in 2003 and 2004. *J Vasc Surg*. 2007;46:1112–1118.
329. Kresowik TF, Bratzler DW, Kresowik RA, Hendel ME, Grund SL, Brown KR, Nilasena DS. Multistate improvement in process and outcomes of carotid endarterectomy. *J Vasc Surg*. 2004;39:372–380.
330. Goodney PP, Lucas FL, Likosky DS, Malenka DJ, Fisher ES. Changes in the use of carotid revascularization among the medicare population. *Arch Surg*. 2008;143:170–173.
331. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, Whitlow P, Strickman NE, Jaff MR, Popma JJ, Snead DB, Cutlip DE, Firth BG, Ouriel K, the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Investigators. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med*. 2004;351:1493–1501.
332. Gurm HS, Yadav JS, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, Ansel G, Strickman NE, Wang H, Cohen SA, Massaro JM, Cutlip DE, SAPPHIRE Investigators. Long-term results of carotid stenting versus endarterectomy in high-risk patients. *N Engl J Med*. 2008;358:1572–1579.
333. Carotid Revascularization Using Endarterectomy or Stenting Systems (CaRESS) phase I clinical trial: 1-year results. *J Vasc Surg*. 2005;42:213–219.
334. Marine LA, Rubin BG, Reddy R, Sanchez LA, Parodi JC, Sicard GA. Treatment of asymptomatic carotid artery disease: similar early outcomes after carotid stenting for high-risk patients and endarterectomy for standard-risk patients. *J Vasc Surg*. 2006;43:953–958.
335. Goldstein LB. New data about stenting versus endarterectomy for symptomatic carotid artery stenosis. *Curr Treat Options Cardiovasc Med*. 2009;11:232–240.
336. Brott TG, Hobson RW 2nd, Howard G, Roubin GS, Clark WM, Brooks W, Mackey A, Hill MD, Leimgruber PP, Sheffet AJ, Howard VJ, Moore WS, Voeks JH, Hopkins LN, Cutlip DE, Cohen DJ, Popma JJ, Ferguson RD, Cohen SN, Blackshear JL, Silver FL, Mohr JP, Lal BK, Meschia JF. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med*. 2010;363:11–23.
337. US Preventive Services Task Force. Screening for carotid artery stenosis: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2007;147:854–859.
338. Abbott AL. Medical (nonsurgical) intervention alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis: results of a systematic review and analysis. *Stroke*. 2009;40:e573–583.
339. Marquardt L, Geraghty OC, Mehta Z, Rothwell PM. Low risk of ipsilateral stroke in patients with asymptomatic carotid stenosis on best medical treatment: a prospective, population-based study. *Stroke*. 2010;41:e11–17.
340. Woo K, Garg J, Hye RJ, Dilley RB. Contemporary results of carotid endarterectomy for asymptomatic carotid stenosis. *Stroke*. 2010;41:975–979.
341. Rothwell PM, Goldstein LB. Carotid endarterectomy for asymptomatic carotid stenosis: asymptomatic carotid surgery trial. *Stroke*. 2004;35:2425–2427.
342. Adams R. In: Embury S, ed. *Sickle Cell Disease: Basic Principles and Clinical Practice*. New York, NY: Raven Press;1994:599–621.
343. Armstrong FD, Thompson RJ Jr, Wang W, Zimmerman R, Pegelow CH, Miller S, Moser F, Bello J, Hurtig A, Vass K. Cognitive functioning and brain magnetic resonance imaging in children with sickle cell disease. Neuropsychology Committee of the Cooperative Study of Sickle Cell Disease. *Pediatrics*. 1996;97(6 Pt 1):864–870.
344. Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, Wethers DL, Pegelow CH, Gill FM. Cerebrovascular accidents in sickle cell disease: rates and risk factors. *Blood*. 1998;91:288–294.
345. Adams R, McKie V, Nichols F, Carl E, Zhang DL, McKie K, Figueroa R, Litaker M, Thompson W, Hess D. The use of transcranial ultrasonography to predict stroke in sickle cell disease. *N Engl J Med*. 1992;326:605–610.
346. Adams RJ, McKie VC, Carl EM, Nichols FT, Perry R, Brock K, McKie K, Figueroa R, Litaker M, Weiner S, Brambilla D. Long-term stroke risk in children with sickle cell disease screened with transcranial Doppler. *Ann Neurol*. 1997;42:699–704.
347. Adams RJ, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, Abboud M, Gallagher D, Kutlar A, Nichols FT, Bonds DR, Brambilla D. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *N Engl J Med*. 1998;339:5–11.
348. Kwiatkowski JL, Granger S, Brambilla DJ, Brown RC, Miller ST, Adams RJ. Elevated blood flow velocity in the anterior cerebral artery and stroke risk in sickle cell disease: extended analysis from the STOP trial. *Br J Haematol*. 2006;134:333–339.
349. Jones A, Granger S, Brambilla D, Gallagher D, Vichinsky E, Woods G, Berman B, Roach S, Nichols F, Adams RJ. Can peak systolic velocities be used for prediction of stroke in sickle cell anemia? *Pediatr Radiol*. 2005;35:66–72.
350. McCarville MB, Goodin GS, Fortner G, Li CS, Smeltzer MP, Adams R, Wang W. Evaluation of a comprehensive transcranial doppler screening program for children with sickle cell anemia. *Pediatr Blood Cancer*. 2008;50:818–821.
351. Raphael JL, Shetty PB, Liu H, Mahoney DH, Mueller BU. A critical assessment of transcranial doppler screening rates in a large pediatric sickle cell center: opportunities to improve healthcare quality. *Pediatr Blood Cancer*. 2008;51:647–651.
352. Kirkham FJ, Hewes DK, Prengler M, Wade A, Lane R, Evans JP. Nocturnal hypoxaemia and central-nervous-system events in sickle-cell disease. *Lancet*. 2001;357:1656–1659.
353. Bernaudin F, Verlhac S, Coic L, Lesprit E, Brugieres P, Reinert P. Long-term follow-up of pediatric sickle cell disease patients with abnormal high velocities on transcranial Doppler. *Pediatr Radiol*. 2005;35:242–248.
354. Hsu LL, Miller ST, Wright E, Kutlar A, McKie V, Wang W, Pegelow CH, Driscoll C, Hurlet A, Woods G, Elsas L, Embury S, Adams RJ. Alpha thalassemia is associated with decreased risk of abnormal transcranial Doppler ultrasonography in children with sickle cell anemia. *J Pediatr Hematol Oncol*. 2003;25:622–628.
355. Bernaudin F, Verlhac S, Chevret S, Torres M, Coic L, Arnaud C, Kamdem A, Hau I, Grazia Neonato M, Delacourt C. G6PD deficiency, absence of alpha-thalassemia, and hemolytic rate at baseline are significant independent risk factors for abnormally high cerebral velocities in patients with sickle cell anemia. *Blood*. 2008;112:4314–4317.
356. Rees DC, Dick MC, Height SE, O'Driscoll S, Pohl KR, Goss DE, Deane CR. A simple index using age, hemoglobin, and aspartate transaminase predicts increased intracerebral blood velocity as measured by transcranial Doppler scanning in children with sickle cell anemia. *Pediatrics*. 2008;121:e1628–1632.
357. Sebastiani P, Ramoni MF, Nolan V, Baldwin CT, Steinberg MH. Genetic dissection and prognostic modeling of overt stroke in sickle cell anemia. *Nat Genet*. 2005;37:435–440.
358. Hoppe C, Klitz W, D'Harlingue K, Cheng S, Grow M, Steiner L, Noble J, Adams R, Styles L. Confirmation of an association between the TNF(-308) promoter polymorphism and stroke risk in children with sickle cell anemia. *Stroke*. 2007;38:2241–2246.

359. Sampaio Silva G, Vicari P, Figueiredo MS, Filho AC, Valadi N, Massaro AR. Transcranial Doppler in adult patients with sickle cell disease. *Cerebrovasc Dis*. 21(1–2):38–41, 2006.
360. Valadi N, Silva GS, Bowman LS, Ramsingh D, Vicari P, Filho AC, Massaro AR, Kutlar A, Nichols FT, Adams RJ. Transcranial Doppler ultrasonography in adults with sickle cell disease. *Neurology*. 2006;67: 572–574.
361. Wayne AS, Kevy SV, Nathan DG. Transfusion management of sickle cell disease. *Blood*. 1993;81:1109–1123.
362. Vichinsky E, Luban N, Wright E, Olivieri N, Driscoll C, Pegelow C, Files B, Adams RJ Prospective cell phenotype matching in STOP—a multi-center transfusion trial. Paper presented at: 23rd Annual Meeting of the National Sickle Cell Disease Program; March 1999; San Francisco, CA.
363. Clinical Alert from the National Heart, Lung, and Blood Institute. NHLBI website. Available at: http://www.nhlbi.nih.gov/health/prof/blood/sickle/clinical-alert-scd.htm. Published December 5, 2004. Accessed August 14, 2010.
364. Adams RJ, Brambilla D. Discontinuing prophylactic transfusions used to prevent stroke in sickle cell disease. *N Engl J Med*. 2005;353: 2769–2778.
365. Miller ST, Macklin EA, Pegelow CH, Kinney TR, Sleeper LA, Bello JA, DeWitt LD, Gallagher DM, Guarini L, Moser FG, Ohene-Frempong K, Sanchez N, Vichinsky EP, Wang WC, Wethers DL, Younkin DP, Zimmerman RA, DeBaun MR. Silent infarction as a risk factor for overt stroke in children with sickle cell anemia: a report from the Cooperative Study of Sickle Cell Disease. *J Pediatr*. 2001;139:385–390.
366. Silent Infarct Transfusion (SIT) Study. Stroke Trials Registry website. Available at: http://www.strokecenter.org/trials/TrialDetail.aspx?tid=627. Updated June 8, 2010. Accessed August 14, 2010.
367. Bernaudin F, Socie G, Kuentz M, Chevret S, Duval M, Bertrand Y, Vannier JP, Yakouben K, Thuret I, Bordigoni P, Fischer A, Lutz P, Stephan JL, Dhedin N, Plouvier E, Margueritte G, Bories D, Verlhac S, Esperou H, Coic L, Vernant JP, Gluckman E. Long-term results of related myeloablative stem-cell transplantation to cure sickle cell disease. *Blood*. 2007;110:2749–2756.
368. Gulbis B, Haberman D, Dufour D, Christophe C, Vermylen C, Kagambega F, Corazza F, Devalck C, Dresse MF, Hunninck K, Klein A, Le PQ, Loop M, Maes P, Philippet P, Sariban E, Van Geet C, Ferster A. Hydroxyurea for sickle cell disease in children and for prevention of cerebrovascular events: the Belgian experience. *Blood*. 2005;105: 2685–2690.
369. Kratovil T, Bulas D, Driscoll MC, Speller-Brown B, McCarter R, Minniti CP. Hydroxyurea therapy lowers TCD velocities in children with sickle cell disease. *Pediatr Blood Cancer*. 2006;47:894–900.
370. Zimmerman SA, Schultz WH, Burgett S, Mortier NA, Ware RE. Hydroxyurea therapy lowers transcranial Doppler flow velocities in children with sickle cell anemia. *Blood*. 2007;110:1043–1047.
371. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy post-menopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288:321–333.
372. Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. *JAMA*. 2004;291:47–53.
373. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA*. 1998;280:605–613.
374. Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, Horwitz RI. A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med*. 2001;345:1243–1249.
375. The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. *JAMA*. 2004;291:1701–1712.
376. Mosca L, Banka C, Benjamin E, Berra K, Bushnell C, Dolor R, Ganiats T, Gomes A, Gornik H, Gracia C, Gulati M, Haan C, Judelson D, Keenan N, Kelepouris E, Michos E, Newby L, Oparil S, Ouyang P, Oz M, Petitti D, Pinn V, Redberg R, Scott R, Sherif K, Smith S, Sopko G, Steinhorn R, Stone N, Taubert K, Todd B, Urbina E, Wenger N. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. *Circulation*. 2007;115:1481–1501.
377. Hendrix SL, Wassertheil-Smoller S, Johnson KC, Howard B, Kooperberg C, Rossouw JE, Trevisan M, Aragaki AK, Baird A, Bray PF, Buring J, Criqui M, Herrington D, Lynch JK, Rapp SR, Torner J. Effects of conjugated equine estrogen on stroke in the Women's Health Initiative. *Circulation*. 2006;113:2425–2434.
378. Mendelsohn M, Karas R. Molecular and cellular basis of cardiovascular gender differences. *Science*. 2005;308:1583–1587.
379. Rossouw J, Prentice R, Manson J, Wu L, Barad D, Barnabei V, Ko M, LaCroix A, Margolis K, Stefanick M. Postmenopausal hormone therapy and risk of cardiovascular disase by age and years since menopause. *JAMA*. 2007;297:1465–1477.
380. Grodstein F, Manson J, Stampfer M, Rexrode K. Postmenopausal hormone therapy and stroke: role of time since menopause and age at initiation of hormone therapy. *Arch Intern Med*. 2008;168:861–866.
381. Veerus P, Hovi S-L, Fischer K, Rahu M, Hakama M, Hemmiki E. Results from the Estonian postmenopausal hormone therapy trial [ISRCTN35338757]. *Maturitas*. 2006;55:162–173.
382. Harman S, Brinton E, Cedars M, Lobo RA, Manson JE, Merriam G, Miller VM, Naftolin F, Santoro NF. KEEPS: The Kronos Early Estrogen Prevention Study. *Climacteric*. 2005;8:3–12.
383. Barrett-Connor E, Mosca L, Collins P, Geiger MJ, Grady D, Kornitzer M, McNabb MA, Wenger NK. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *N Engl J Med*. 2006;355:125–137.
384. Mosca L, Grady D, Barrett-Connor E, Collins P, Wenger N, Abramson B, Paganini-Hill A, Geiger M, Dowsett S, Amewou-Atisso M, Kornitzer M. Effect of raloxifene on stroke and venous thromboembolism according to subgroups in postmenopausal women at increased risk of coronary heart disease. *Stroke*. 2009;40:147–155.
385. Vogel V, Costantino JP, Wickerham DL, Cronin WM, Cecchini R, Atkins J, Bevers T, Fehrenbacher L, Pajon E. Effects of tamoxifen vs. raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 Trial. *JAMA*. 2006;295:2727–2741.
386. Cummings S, Ettinger B, Delmas P, Kenemans P, Stathopoulos V, Verweij P, Mol-Arts M, Kloosterboer L, Mosca L, Christiansen C, Bilezikian J, Kerzberg E, Johnson S, Zanchetta J, Grobbee D, Seifert W, Eastell R. The effects of tibolone in older postmenopausal women. *N Engl J Med*. 2008;359:697–708.
387. Hannaford P, Croft P, Kay C. Oral contraception and stroke: evidence from the Royal College of General Practitioners' Oral Contraception study. *Stroke*. 1994;25:935–942.
388. Lidegaard O. Oral contraception and risk of a cerebral thromboembolic attack: results of a case-control study. *BMJ*. 1993;306:956–963.
389. Gillum LA, Mamidipudi SK, Johnston SC. Ischemic stroke risk with oral contraceptives: a meta-analysis. *JAMA*. 2000;284:72–78.
390. Chan W-S, Ray J, Wai EK, Ginsburg S, Hannah ME, Corey PN, Ginsberg JS. Risk of stroke in women exposed to low-dose oral contraceptives: a critical evaluation of the evidence. *Arch Intern Med*. 2004; 164:741–747.
391. Chang C, Donaghy M, Poulter N. Migraine and stroke in young women: a case-control study. *BMJ*. 1999;318:13–18.
392. Kemmeren JM, Tanis BC, van den Bosch MA, Bollen EL, Helmerhorst FM, van der Graaf Y, Rosendaal FR. Risk of arterial thrombosis in Relation to Oral Contraceptives (RATIO) Study: oral contraceptives and the risk of ischemic stroke. *Stroke*. 2002;33:1202–1208.
393. Slooter AJ, Rosendaal FR, Tanis BC, Kemmeren JM, Van der Graaf Y. Prothrombotic conditions, oral contraceptives and the risk of ischemic stroke. *J Thromb Haemost*. 2005;3:1213–1217.
394. Kluft C, Lansink M. Effect of oral contraceptives on haemostasis variables. *Thromb Haemost*. 1997;78:315–326.
395. Chason-Taber L, Willett W, Manson J, Spiegelman D, Hunter D, Curhan G, Colditz G, Stampfer M. Prospective study of oral contraceptives and hypertension among women in the United States. *Circulation*. 1996;94: 483–489.
396. Schwartz SM, Pettiti DB, Siscovick DS, Longstreth WT Jr, Sidney S, Raghunathan TE, Quesenberry C, Kelaghan J. Stroke and use of low-dose oral contraceptives in young women: a pooled analysis of two US studies. *Stroke*. 1998;29:2277–2284.
397. Kristensen B, Malm J, Carlberg B, Stegmayr B, Backman C, Fagerlund M, Olsson T. Epidemiology and etiology of ischemic stroke in young adults aged 18 to 44 years in northern Sweden. *Stroke*. 1997;28: 1702–1709.
398. Farley T, Meirik O, Chang C, Poulter N. Combined oral contraceptives, smoking, and cardiovascular risk. *J Epidemiol Community Health*. 1998; 52:775–785.

399. Nightingale A, Farmer R. Ischemic stroke in young women: a nested case-control study using the UK General Practice Research Database. *Stroke*. 2004;35:1574–1578.
400. Deleted in proof.
401. Siritho S, Thrift AG, McNeil JJ, You RX, Davis SM, Donnan GA. Risk of ischemic stroke among users of the oral contraceptive pill. The Melbourne Risk Factor Study (MERFS) Group. *Stroke*. 2003;34:1575–1580.
402. Bousser M-G, Conrad J, Kittner S, de Lignieres B, MacGregor D, Massiou H, Silberstein S, Tzourio C. Recommendations on the risk of ischaemic stroke associated with use of combined oral contraceptives and hormone replacement therapy in women with migraine. *Cephalgia*. 2000;20:155–156.
403. Appel LJ, Brands MW, Daniels SR, Karanja N, Elmer PJ, Sacks FM. Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association. *Hypertension*. 2006;47:296–308.
404. He FJ, Nowson CA, MacGregor GA. Fruit and vegetable consumption and stroke: meta-analysis of cohort studies. *Lancet*. 2006;367:320–326.
405. Joshipura KJ, Ascherio A, Manson JE, Stampfer MJ, Rimm EB, Speizer FE, Hennekens CH, Spiegelman D, Willett WC. Fruit and vegetable intake in relation to risk of ischemic stroke. *JAMA*. 1999;282:1233–1239.
406. US Dept of Health and Human Services and US Dept of Agriculture. *Dietary Guidelines for Americans,* 2005. 6th ed. Washington, DC: US Government Printing Office; 2005.
407. Perry IJ, Beevers DG. Salt intake and stroke: a possible direct effect. *J Hum Hypertens*. 1992;6:23–25.
408. He J, Ogden LG, Vupputuri S, Bazzano LA, Loria C, Whelton PK. Dietary sodium intake and subsequent risk of cardiovascular disease in overweight adults. *JAMA*. 1999;282:2027–2034.
409. Nagata C, Takatsuka N, Shimizu N, Shimizu H. Sodium intake and risk of death from stroke in Japanese men and women. *Stroke*. 2004;35:1543–1547.
410. Ascherio A, Rimm EB, Hernan MA, Giovannucci EL, Kawachi I, Stampfer MJ, Willett WC. Intake of potassium, magnesium, calcium, and fiber and risk of stroke among US men. *Circulation*. 1998;98:1198–1204.
411. Khaw KT, Barrett-Connor E. Dietary potassium and stroke-associated mortality: a 12-year prospective population study. *N Engl J Med*. 1987;316:235–240.
412. Chang HY, Hu YW, Yue CS, Wen YW, Yeh WT, Hsu LS, Tsai SY, Pan WH. Effect of potassium-enriched salt on cardiovascular mortality and medical expenses of elderly men. *Am J Clin Nutr*. 2006;83:1289–1296.
413. Howard BV, Van Horn L, Hsia J, Manson JE, Stefanick ML, Wassertheil-Smoller S, Kuller LH, LaCroix AZ, Langer RD, Lasser NL, Lewis CE, Limacher MC, Margolis KL, Mysiw WJ, Ockene JK, Parker LM, Perri MG, Phillips L, Prentice RL, Robbins J, Rossouw JE, Sarto GE, Schatz IJ, Snetselaar LG, Stevens VJ, Tinker LF, Trevisan M, Vitolins MZ, Anderson GL, Assaf AR, Bassford T, Beresford SA, Black HR, Brunner RL, Brzyski RG, Caan B, Chlebowski RT, Gass M, Granek I, Greenland P, Hays J, Heber D, Heiss G, Hendrix SL, Hubbell FA, Johnson KC, Kotchen JM. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA*. 2006;295:655–666.
414. Tobian L, Lange JM, Ulm KM, Wold LJ, Iwai J. Potassium prevents death from strokes in hypertensive rats without lowering blood pressure. *J HypertensSuppl*. 1984;2:S363–366.
415. Johnson AG, Nguyen TV, Davis D. Blood pressure is linked to salt intake and modulated by the angiotensinogen gene in normotensive and hypertensive elderly subjects. *J Hypertens*. 2001;19:1053–1060.
416. MacGregor GA, Markandu ND, Sagnella GA, Singer DR, Cappuccio FP. Double-blind study of three sodium intakes and long-term effects of sodium restriction in essential hypertension. *Lancet*. 1989;2:1244–1247.
417. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER 3rd, Simons-Morton DG, Karanja N, Lin PH. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med*. 2001;344:3–10.
418. Vollmer WM, Sacks FM, Ard J, Appel LJ, Bray GA, Simons-Morton DG, Conlin PR, Svetkey LP, Erlinger TP, Moore TJ, Karanja N. Effects of diet and sodium intake on blood pressure: subgroup analysis of the DASH-sodium trial. *Ann Intern Med*. 2001;135:1019–1028.
419. Whelton PK, He J, Cutler JA, Brancati FL, Appel LJ, Follmann D, Klag MJ. Effects of oral potassium on blood pressure: meta-analysis of randomized controlled clinical trials. *JAMA*. 1997;277:1624–1632.
420. Morris RC Jr, Sebastian A, Forman A, Tanaka M, Schmidlin O. Normotensive salt sensitivity: effects of race and dietary potassium. *Hypertension*. 1999;33:18–23.
421. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, Lin PH, Karanja N. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med*. 1997;336:1117–1124.
422. Appel LJ, Sacks FM, Carey VJ, Obarzanek E, Swain JF, Miller ER 3rd, Conlin PR, Erlinger TP, Rosner BA, Laranjo NM, Charleston J, McCarron P, Bishop LM. Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. *JAMA*. 2005;294:2455–2464.
423. John JH, Ziebland S, Yudkin P, Roe LS, Neil HA. Effects of fruit and vegetable consumption on plasma antioxidant concentrations and blood pressure: a randomised controlled trial. *Lancet*. 2002;359:1969–1974.
424. Institute of Medicine. *Dietary Reference Intakes: Water, Potassium, Sodium, Chloride, and Sulfate*. Washington, DC: National Academies Press; 2004.
425. Sauvaget C, Nagano J, Hayashi M, Yamada M. Animal protein, animal fat, and cholesterol intakes and risk of cerebral infarction mortality in the adult health study. *Stroke*. 2004;35:1531–1537.
426. He K, Merchant A, Rimm EB, Rosner BA, Stampfer MJ, Willett WC, Ascherio A. Dietary fat intake and risk of stroke in male US healthcare professionals: 14 year prospective cohort study. *BMJ*. 2003;327:777–782.
427. *Physical Activity Guidelines Advisory Committee Report, 2008.* Washington, DC: US Dept of Health and Human Services; 2008. Available at: http://www.health.gov/paguidelines/. Accessed August 14, 2010.
428. Lee CD, Folsom AR, Blair SN. Physical activity and stroke risk: a meta-analysis. *Stroke*. 2003;34:2475–2481.
429. Wendel-Vos GC, Schuit AJ, Feskens EJ, Boshuizen HC, Verschuren WM, Saris WH, Kromhout D. Physical activity and stroke: a meta-analysis of observational data. *Int J Epidemiol*. 2004;33:787–798.
430. Gillum RF, Mussolino ME, Ingram DD. Physical activity and stroke incidence in women and men: the NHANES I Epidemiologic Follow-up Study. *Am J Epidemiol*. 1996;143:860–869.
431. Sacco RL, Gan R, Boden-Albala B, Lin IF, Kargman DE, Hauser WA, Shea S, Paik MC. Leisure-time physical activity and ischemic stroke risk: the Northern Manhattan Stroke Study. *Stroke*. 1998;29:380–387.
432. Manson JE, Colditz GA, Stampfer MJ, Willett WC, Krolewski AS, Rosner B, Arky RA, Speizer FE, Hennekens CH. A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. *Arch Intern Med*. 1991;151:1141–1147.
433. Blair SN, Kampert JB, Kohl HW 3rd, Barlow CE, Macera CA, Paffenbarger RS Jr, Gibbons LW. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *JAMA*. 1996;276:205–210.
434. Kokkinos PF, Holland JC, Pittaras AE, Narayan P, Dotson CO, Papademetriou V. Cardiorespiratory fitness and coronary heart disease risk factor association in women. *J Am Coll Cardiol*. 1995;26:358–364.
435. Lakka TA, Salonen JT. Moderate to high intensity conditioning leisure time physical activity and high cardiorespiratory fitness are associated with reduced plasma fibrinogen in eastern Finnish men. *J Clin Epidemiol*. 1993;46:1119–1127.
436. Wang HY, Bashore TR, Friedman E. Exercise reduces age-dependent decrease in platelet protein kinase C activity and translocation. *J Gerontol A Biol Sci Med Sci*. 1995;50A:M12–16.
437. Williams PT. High-density lipoprotein cholesterol and other risk factors for coronary heart disease in female runners. *N Engl J Med*. 1996;334:1298–1303.
438. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults. *Am J Clin Nutr*. 1998;68:899–917.
439. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA*. 2006;295:1549–1555.
440. Ogden CL, Carroll MD, Flegal KM. High body mass index for age among US children and adolescents, 2003–2006. *JAMA*. 2008;299:2401–2405.

441. Wang Y, Beydoun MA. The obesity epidemic in the United States–gender, age, socioeconomic, racial/ethnic, and geographic characteristics: a systematic review and meta-regression analysis. *Epidemiol Rev*. 2007;29:6–28.
442. Prospective Studies Collaboration, Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, Qizilbash N, Collins R, Peto R. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet*. 2009;373:1083–1096.
443. Flegal KM, Shepherd JA, Looker AC, Graubard BI, Borrud LG, Ogden CL, Harris TB, Everhart JE, Schenker N. Comparisons of percentage body fat, body mass index, waist circumference, and waist-stature ratio in adults. *Am J Clin Nutr*. 2009;89:500–508.
444. Folsom AR, Prineas RJ, Kaye SA, Munger RG. Incidence of hypertension and stroke in relation to body fat distribution and other risk factors in older women. *Stroke*. 1990;21:701–706.
445. Isozumi K. Obesity as a risk factor for cerebrovascular disease. *Keio J Med*. 2004;53:7–11.
446. Suk SH, Sacco RL, Boden-Albala B, Cheun JF, Pittman JG, Elkind MS, Paik MC. Abdominal obesity and risk of ischemic stroke: the Northern Manhattan Stroke Study. *Stroke*. 2003;34:1586–1592.
447. Walker SP, Rimm EB, Ascherio A, Kawachi I, Stampfer MJ, Willett WC. Body size and fat distribution as predictors of stroke among US men. *Am J Epidemiol*. 1996;144:1143–1150.
448. Neter JE, Stam BE, Kok FJ, Grobbee DE, Geleijnse JM. Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension*. 2003;42:878–884.
449. Tzourio C, Tehindrazanarivelo A, Iglesias S, Alperovitch A, Chedru F, d'Anglejan-Chatillon J, Bousser M-G. Case-control study of migraine and risk of ischaemic stroke in young women. *BMJ*. 1995;310:830–833.
450. Etminan M, Takkouche B, Isoma FC, Samii A. Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies. *BMJ*. 2005;330:63.
451. Kurth T, Slomke M, Kase C, Cook N, Lee I-M, Gaziano J, Diener H-C, Buring J. Migraine, headache, and the risk of stroke in women. *Neurology*. 2005;64:1020–1026.
452. Kurth T, Schurks M, Logroscino G, Gaziano J, Buring JE. Migraine, vascular risk, and cardiovascular events in women: prospective cohort study. *BMJ*. 2008;337:a636.
453. MacClellan LR, Giles WH, Cole JW, Wozniak MA, Stern BJ, Mitchell BD, Kittner SJ. Probable migraine with visual aura and risk of ischemic stroke: the stroke prevention in young women study. *Stroke*. 2007;38:2438–2445.
454. Swartz RH, Kern RZ. Migraine is associated with magnetic resonance imaging white matter abnormalities: a meta-analysis. *Arch Neurol*. 2004;61:1366–1368.
455. Schwaiger J, Kiechl S, Stockner H, Knoflach M, Werner P, Rungger G, Gasperi A, Willeit J. Burden of atherosclerosis and risk of venous thromboembolism in patients with migraine. *Neurology*. 2008;71:937–943.
456. Webster M, Chancellor A, Smith H, Swift D, Sharpe D, Bass N, Glasgow G. Patent foramen ovale in young stroke patients. *Lancet*. 1988;2:11–12.
457. Lechat P, Mas J, Lascault G, Loron P, Theard M, Klimczac M, Drobinski G, Thomas D, Grosgogeat Y. Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med*. 1988;318:1148–1152.
458. Deleted in proof.
459. Anzola G, Magoni M, Guindani M, Rozzini L, Dalla Volta G. Potential source of cerebral embolism in migraine with aura: a transcranial doppler study. *Neurology*. 1999;52:1622–1626.
460. Olesen J, Friberg L, Olsen T, Andersen A, Lassen N, Hansen P, Karle A. Ischaemia-induced (symptomatic) migraine attacks may be more frequent than migraine-induced ischaemic insults. *Brain*. 1993;116:187–202.
461. Zeller J, Frahm K, Baron R, Stingele R, Deuschl G. Platelet-leukocyte interaction and platelet activation in migraine: a link to ischemic stroke? *J Neurol Neurosurg Psychiatry*. 2004;75:984–987.
462. Dowson A, Mullen M, Peatfield R, Muir K, Khan A, Wells C, Lipscombe S, Rees T, De Giovanni J, Morrison W, Hildick-Smith D, Elrington G, Hillis W, Malik I, Rickards A. Migraine Intervention with STARFlex Technology (MIST) Trial. A prospective, multicenter, double-blinded, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache. *Circulation*. 2008;117:1397–1404.
463. Tobis J. Management of patients with refractory migraine and PFO: is MIST I relevant? *Catheter Cardiovasc Interv*. 2008;72:60–64.
464. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome–a new worldwide definition. *Lancet*. 2005;366:1059–1062.
465. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA*. 2002;288:2709–2716.
466. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet*. 2005;365:1415–1428.
467. Kay G, Kearns P. Monitoring central venous pressure: principles, procedures and problems. *Can Nurse*. 1976;72:15–17.
468. Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP. The continuing epidemics of obesity and diabetes in the United States. *JAMA*. 2001;286:1195–1200.
469. Cornier MA, Dabelea D, Hernandez TL, Lindstrom RC, Steig AJ, Stob NR, Van Pelt RE, Wang H, Eckel RH. The metabolic syndrome. *Endocr Rev*. 2008;29:777–822.
470. Bonora E, Willeit J, Kiechl S, Oberhollenzer F, Egger G, Bonadonna R, Muggeo M. Relationship between insulin and carotid atherosclerosis in the general population: the Bruneck Study. *Stroke*. 1997;28:1147–1152.
471. Haffner SM, D'Agostino R, Mykkanen L, Hales CN, Savage PJ, Bergman RN, O'Leary D, Rewers M, Selby J, Tracy R, Saad MF. Proinsulin and insulin concentrations in relation to carotid wall thickness: Insulin Resistance Atherosclerosis Study. *Stroke*. 1998;29:1498–1503.
472. Kaarisalo MM, Raiha I, Arve S, Lehtonen A. Impaired glucose tolerance as a risk factor for stroke in a cohort of non-institutionalised people aged 70 years. *Age Ageing*. 2006;35:592–596.
473. Kuusisto J, Mykkanen L, Pyorala K, Laakso M. Non-insulin-dependent diabetes and its metabolic control are important predictors of stroke in elderly subjects. *Stroke*. 1994;25:1157–1164.
474. Lindahl B, Dinesen B, Eliasson M, Roder M, Hallmans G, Stegmayr B. High proinsulin levels precede first-ever stroke in a nondiabetic population. *Stroke*. 2000;31:2936–2941.
475. Oizumi T, Daimon M, Jimbu Y, Wada K, Kameda W, Susa S, Yamaguchi H, Ohnuma H, Tominaga M, Kato T. Impaired glucose tolerance is a risk factor for stroke in a Japanese sample–the Funagata study. *Metabolism*. 2008;57:333–338.
476. Pyorala M, Miettinen H, Laakso M, Pyorala K. Hyperinsulinemia and the risk of stroke in healthy middle-aged men: the 22-year follow-up results of the Helsinki Policemen Study. *Stroke*. 1998;29:1860–1866.
477. Qureshi AI, Giles WH, Croft JB. Impaired glucose tolerance and the likelihood of nonfatal stroke and myocardial infarction: the Third National Health and Nutrition Examination Survey. *Stroke*. 1998;29:1329–1332.
478. Urabe T, Watada H, Okuma Y, Tanaka R, Ueno Y, Miyamoto N, Tanaka Y, Hattori N, Kawamori R. Prevalence of abnormal glucose metabolism and insulin resistance among subtypes of ischemic stroke in Japanese patients. *Stroke*. 2009;40:1289–1295.
479. Vermeer SE, Sandee W, Algra A, Koudstaal PJ, Kappelle LJ, Dippel DW. Impaired glucose tolerance increases stroke risk in nondiabetic patients with transient ischemic attack or minor ischemic stroke. *Stroke*. 2006;37:1413–1417.
480. Wang J, Ruotsalainen S, Moilanen L, Lepisto P, Laakso M, Kuusisto J. The metabolic syndrome predicts incident stroke: a 14-year follow-up study in elderly people in Finland. *Stroke*. 2008;39:1078–1083.
481. Wannamethee SG, Perry IJ, Shaper AG. Nonfasting serum glucose and insulin concentrations and the risk of stroke. *Stroke*. 1999;30:1780–1786.
482. Ninomiya JK, L'Italien G, Criqui MH, Whyte JL, Gamst A, Chen RS. Association of the metabolic syndrome with history of myocardial infarction and stroke in the Third National Health and Nutrition Examination Survey. *Circulation*. 2004;109:42–46.
483. Milionis HJ, Rizos E, Goudevenos J, Seferiadis K, Mikhailidis DP, Elisaf MS. Components of the metabolic syndrome and risk for first-ever acute ischemic nonembolic stroke in elderly subjects. *Stroke*. 2005;36:1372–1376.
484. Chen HJ, Bai CH, Yeh WT, Chiu HC, Pan WH. Influence of metabolic syndrome and general obesity on the risk of ischemic stroke. *Stroke*. 2006;37:1060–1064.
485. Koren-Morag N, Goldbourt U, Tanne D. Relation between the metabolic syndrome and ischemic stroke or transient ischemic attack: a prospective cohort study in patients with atherosclerotic cardiovascular disease. *Stroke*. 2005;36:1366–1371.

486. Kurl S, Laukkanen JA, Niskanen L, Laaksonen D, Sivenius J, Nyyssonen K, Salonen JT. Metabolic syndrome and the risk of stroke in middle-aged men. *Stroke*. 2006;37:806–811.
487. Najarian RM, Sullivan LM, Kannel WB, Wilson PW, D'Agostino RB, Wolf PA. Metabolic syndrome compared with type 2 diabetes mellitus as a risk factor for stroke: the Framingham Offspring Study. *Arch Intern Med*. 2006;166:106–111.
488. Ford ES. Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S. *Diabetes Care*. 2005;28:2745–2749.
489. Noto D, Barbagallo CM, Cefalu AB, Falletta A, Sapienza M, Cavera G, Amato S, Pagano M, Maggiore M, Carroccio A, Notarbartolo A, Averna MR. The metabolic syndrome predicts cardiovascular events in subjects with normal fasting glucose: results of a 15 years follow-up in a Mediterranean population. *Atherosclerosis*. 2008;197:147–153.
490. Waters DD, LaRosa JC, Barter P, Fruchart JC, Gotto AM Jr, Carter R, Breazna A, Kastelein JJ, Grundy SM. Effects of high-dose atorvastatin on cerebrovascular events in patients with stable coronary disease in the TNT (treating to new targets) study. *J Am Coll Cardiol*. 2006;48:1793–1799.
491. Deedwania P, Barter P, Carmena R, Fruchart JC, Grundy SM, Haffner S, Kastelein JJ, LaRosa JC, Schachner H, Shepherd J, Waters DD. Reduction of low-density lipoprotein cholesterol in patients with coronary heart disease and metabolic syndrome: analysis of the Treating to New Targets study. *Lancet*. 2006;368:919–928.
492. Gill JS, Zezulka AV, Shipley MJ, Gill SK, Beevers DG. Stroke and alcohol consumption. *N Engl J Med*. 1986;315:1041–1046.
493. Hillbom M, Numminen H, Juvela S. Recent heavy drinking of alcohol and embolic stroke. *Stroke*. 1999;30:2307–2312.
494. Klatsky AL, Armstrong MA, Friedman GD, Sidney S. Alcohol drinking and risk of hospitalization for ischemic stroke. *Am J Cardiol*. 2001;88:703–706.
495. Mazzaglia G, Britton AR, Altmann DR, Chenet L. Exploring the relationship between alcohol consumption and non-fatal or fatal stroke: a systematic review. *Addiction*. 2001;96:1743–1756.
496. Wannamethee SG, Shaper AG. Patterns of alcohol intake and risk of stroke in middle-aged British men. *Stroke*. 1996;27:1033–1039.
497. Berger K, Ajani UA, Kase CS, Gaziano JM, Buring JE, Glynn RJ, Hennekens CH. Light-to-moderate alcohol consumption and risk of stroke among U.S. male physicians. *N Engl J Med*. 1999;341:1557–1564.
498. Djousse L, Levy D, Benjamin EJ, Blease SJ, Russ A, Larson MG, Massaro JM, D'Agostino RB, Wolf PA, Ellison RC. Long-term alcohol consumption and the risk of atrial fibrillation in the Framingham Study. *Am J Cardiol*. 2004;93:710–713.
499. Elkind MS, Sciacca R, Boden-Albala B, Rundek T, Paik MC, Sacco RL. Moderate alcohol consumption reduces risk of ischemic stroke: the Northern Manhattan Study. *Stroke*. 2006;37:13–19.
500. Gorelick PB, Rodin MB, Langenberg P, Hier DB, Costigan J. Weekly alcohol consumption, cigarette smoking, and the risk of ischemic stroke: results of a case-control study at three urban medical centers in Chicago, Illinois. *Neurology*. 1989;39:339–343.
501. Iso H, Baba S, Mannami T, Sasaki S, Okada K, Konishi M, Tsugane S. Alcohol consumption and risk of stroke among middle-aged men: the JPHC Study Cohort I. *Stroke*. 2004;35:1124–1129.
502. Malarcher AM, Giles WH, Croft JB, Wozniak MA, Wityk RJ, Stolley PD, Stern BJ, Sloan MA, Sherwin R, Price TR, Macko RF, Johnson CJ, Earley CJ, Buchholz DW, Kittner SJ. Alcohol intake, type of beverage, and the risk of cerebral infarction in young women. *Stroke*. 2001;32:77–83.
503. Sacco RL, Elkind M, Boden-Albala B, Lin IF, Kargman DE, Hauser WA, Shea S, Paik MC. The protective effect of moderate alcohol consumption on ischemic stroke. *JAMA*. 1999;281:53–60.
504. Stampfer MJ, Colditz GA, Willett WC, Speizer FE, Hennekens CH. A prospective study of moderate alcohol consumption and the risk of coronary disease and stroke in women. *N Engl J Med*. 1988;319:267–273.
505. Klatsky AL, Armstrong MA, Friedman GD, Sidney S. Alcohol drinking and risk of hemorrhagic stroke. *Neuroepidemiology*. 2002;21:115–122.
506. Reynolds K, Lewis B, Nolen JD, Kinney GL, Sathya B, He J. Alcohol consumption and risk of stroke: a meta-analysis. *JAMA*. 2003;289:579–588.
507. Joosten MM, Beulens JW, Kersten S, Hendriks HF. Moderate alcohol consumption increases insulin sensitivity and ADIPOQ expression in postmenopausal women: a randomised, crossover trial. *Diabetologia*. 2008;51:1375–1381.
508. Mukamal KJ, Jensen MK, Gronbaek M, Stampfer MJ, Manson JE, Pischon T, Rimm EB. Drinking frequency, mediating biomarkers, and risk of myocardial infarction in women and men. *Circulation*. 2005;112:1406–1413.
509. Volcik KA, Ballantyne CM, Fuchs FD, Sharrett AR, Boerwinkle E. Relationship of alcohol consumption and type of alcoholic beverage consumed with plasma lipid levels: differences between Whites and African Americans of the ARIC study. *Ann Epidemiol*. 2008;18:101–107.
510. Miceli M, Alberti L, Bennardini F, Di Simplicio P, Seghieri G, Rao GH, Franconi F. Effect of low doses of ethanol on platelet function in long-life abstainers and moderate-wine drinkers. *Life Sci*. 2003;73:1557–1566.
511. Mukamal KJ, Massaro JM, Ault KA, Mittleman MA, Sutherland PA, Lipinska I, Levy D, D'Agostino RB, Tofler GH. Alcohol consumption and platelet activation and aggregation among women and men: the Framingham Offspring Study. *Alcohol Clin Exp Res*. 2005;29:1906–1912.
512. McKenzie CR, Abendschein DR, Eisenberg PR. Sustained inhibition of whole-blood clot procoagulant activity by inhibition of thrombus-associated factor Xa. *Arterioscler Thromb Vasc Biol*. 1996;16:1285–1291.
513. Mukamal KJ, Tolstrup JS, Friberg J, Jensen G, Gronbaek M. Alcohol consumption and risk of atrial fibrillation in men and women: the Copenhagen City Heart Study. *Circulation*. 2005;112:1736–1742.
514. Greenfield JR, Samaras K, Hayward CS, Chisholm DJ, Campbell LV. Beneficial postprandial effect of a small amount of alcohol on diabetes and cardiovascular risk factors: modification by insulin resistance. *J Clin Endocrinol Metab*. 2005;90:661–672.
515. Christie IC, Price J, Edwards L, Muldoon M, Meltzer CC, Jennings JR. Alcohol consumption and cerebral blood flow among older adults. *Alcohol*. 2008;42:269–275.
516. Kurth T, Moore SC, Gaziano JM, Kase CS, Stampfer MJ, Berger K, Buring JE. Healthy lifestyle and the risk of stroke in women. *Arch Intern Med*. 2006;166:1403–1409.
517. Bazzano LA, Gu D, Reynolds K, Wu X, Chen CS, Duan X, Chen J, Wildman RP, Klag MJ, He J. Alcohol consumption and risk for stroke among Chinese men. *Ann Neurol*. 2007;62:569–578.
518. US Preventive Services Task Force. Screening and behavioral counseling interventions in primary care to reduce alcohol misuse: recommendation statement. Rockville, MD: Agency for Healthcare Research and Quality. Available at: http://www.uspreventiveservicestaskforce.org/uspstf/uspsdrin.htm. Published April 2004. Accessed October 14, 2010.
519. US Dept of Health and Human Services and US Dept of Agriculture. *Dietary Guidelines for Americans,* 2005. Available at: http://www.health.gov/dietaryguidelines. Accessed August 14, 2010.
520. Lichtenstein AH, Appel LJ, Brands M, Carnethon M, Daniels S, Franch HA, Franklin B, Kris-Etherton P, Harris WS, Howard B, Karanja N, Lefevre M, Rudel L, Sacks F, Van Horn L, Winston M, Wylie-Rosett J. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. *Circulation*. 2006;114:82–96.
521. Cami J, Farre M. Drug addiction. *N Engl J Med*. 2003;349:975–986.
522. Brust JC. *Neurological Aspects of Substance Abuse.* II ed. Philadelphia, PA: Butterworth-Heinemann; 2004.
523. Kaufman MJ, Levin JM, Ross MH, Lange N, Rose SL, Kukes TJ, Mendelson JH, Lukas SE, Cohen BM, Renshaw PF. Cocaine-induced cerebral vasoconstriction detected in humans with magnetic resonance angiography. *JAMA*. 1998;279:376–380.
524. McEvoy AW, Kitchen ND, Thomas DG. Intracerebral haemorrhage and drug abuse in young adults. *Br J Neurosurg*. 2000;14:449–454.
525. McGee SM, McGee DN, McGee MB. Spontaneous intracerebral hemorrhage related to methamphetamine abuse: autopsy findings and clinical correlation. *Am J Forensic Med Pathol*. 2004;25:334–337.
526. Neiman J, Haapaniemi HM, Hillbom M. Neurological complications of drug abuse: pathophysiological mechanisms. *Eur J Neurol*. 2000;7:595–606.
527. Perez JA Jr, Arsura EL, Strategos S. Methamphetamine-related stroke: four cases. *J Emerg Med*. 1999;17:469–471.
528. Siegel AJ, Sholar MB, Mendelson JH, Lukas SE, Kaufman MJ, Renshaw PF, McDonald JC, Lewandrowski KB, Apple FS, Stec JJ, Lipinska I, Tofler GH, Ridker PM. Cocaine-induced erythrocytosis and increase in von Willebrand factor: evidence for drug-related blood

doping and prothrombotic effects. *Arch Intern Med*. 1999;159:1925–1929.
529. Kaku DA, Lowenstein DH. Emergence of recreational drug abuse as a major risk factor for stroke in young adults. *Ann Intern Med*. 1990;113:821–827.
530. Kittner SJ, Stern BJ, Wozniak M, Buchholz DW, Earley CJ, Feeser BR, Johnson CJ, Macko RF, McCarter RJ, Price TR, Sherwin R, Sloan MA, Wityk RJ. Cerebral infarction in young adults: the Baltimore-Washington Cooperative Young Stroke Study. *Neurology*. 1998;50:890–894.
531. Levine SR, Brust JC, Futrell N, Ho KL, Blake D, Millikan CH, Brass LM, Fayad P, Schultz LR, Selwa JF, et al. Cerebrovascular complications of the use of the "crack" form of alkaloidal cocaine. *N Engl J Med*. 1990;323:699–704.
532. Petitti DB, Sidney S, Quesenberry C, Bernstein A. Stroke and cocaine or amphetamine use. *Epidemiology*. 1998;9:596–600.
533. Sloan MA, Kittner SJ, Feeser BR, Gardner J, Epstein A, Wozniak MA, Wityk RJ, Stern BJ, Price TR, Macko RF, Johnson CJ, Earley CJ, Buchholz D. Illicit drug-associated ischemic stroke in the Baltimore-Washington Young Stroke Study. *Neurology*. 1998;50:1688–1693.
534. Westover AN, McBride S, Haley RW. Stroke in young adults who abuse amphetamines or cocaine: a population-based study of hospitalized patients. *Arch Gen Psychiatry*. 2007;64:495–502.
535. Herbeck DM, Hser YI, Teruya C. Empirically supported substance abuse treatment approaches: a survey of treatment providers' perspectives and practices. *Addict Behav*. 2008;33:699–712.
536. US Preventive Services Task Force. Screening for Illicit Drug Use. Rockville, MD: Agency for Healthcare Research and Quality. Available at: http://www.ahrq.gov/clinic/uspstf/uspsdrug.htm. Published in January 2008. Accessed August 14, 2010.
537. Palomaki H, Partinen M, Erkinjuntti T, Kaste M. Snoring, sleep apnea syndrome, and stroke. *Neurology*. 1992;42(suppl 6):75–81.
538. Partinen M, Palomaki H. Snoring and cerebral infarction. *Lancet*. 1985;2:1325–1326.
539. Lee SA, Amis TC, Byth K, Larcos G, Kairaitis K, Robinson TD, Wheatley JR. Heavy snoring as a cause of carotid artery atherosclerosis. *Sleep*. 2008;31:1207–1213.
540. Davies DP, Rodgers H, Walshaw D, James OF, Gibson GJ. Snoring, daytime sleepiness and stroke: a case-control study of first-ever stroke. *J Sleep Res*. 2003;12:313–318.
541. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med*. 2005;353:2034–2041.
542. Munoz R, Duran-Cantolla J, Martinez-Vila E, Gallego J, Rubio R, Aizpuru F, De La Torre G. Severe sleep apnea and risk of ischemic stroke in the elderly. *Stroke*. 2006;37:2317–2321.
543. Arzt M, Young T, Finn L, Skatrud JB, Bradley TD. Association of sleep-disordered breathing and the occurrence of stroke. *Am J Respir Crit Care Med*. 2005;172:1447–1451.
544. Valham F, Mooe T, Rabben T, Stenlund H, Wiklund U, Franklin KA. Increased risk of stroke in patients with coronary artery disease and sleep apnea: a 10-year follow-up. *Circulation*. 2008;118:955–960.
545. Culebras A. Cerebrovascular disease and sleep. *Curr Neurol Neurosci Rep*. 2004;4:164–169.
546. Hermann DM, Bassetti CL. Sleep-disordered breathing and stroke. *Curr Opin Neurol*. 2003;16:87–90.
547. Yaggi H, Mohsenin V. Sleep-disordered breathing and stroke. *Clin Chest Med*. 2003;24:223–237.
548. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D'Agostino RB, Newman AB, Lebowitz MD, Pickering TG. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. *JAMA*. 2000;283:1829–1836.
549. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med*. 2000;342:1378–1384.
550. Lavie P, Herer P, Hoffstein V. Obstructive sleep apnoea syndrome as a risk factor for hypertension: population study. *BMJ*. 2000;320:479–482.
551. Logan AG, Perlikowski SM, Mente A, Tisler A, Tkacova R, Niroumand M, Leung RS, Bradley TD. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. *J Hypertens*. 2001;19:2271–2277.
552. Guilleminault C, Connolly SJ, Winkle RA. Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. *Am J Cardiol*. 1983;52:490–494.
553. Mooe T, Gullsby S, Rabben T, Eriksson P. Sleep-disordered breathing: a novel predictor of atrial fibrillation after coronary artery bypass surgery. *Coron Artery Dis*. 1996;7:475–478.
554. Rostagno C, Taddei T, Paladini B, Modesti PA, Utari P, Bertini G. The onset of symptomatic atrial fibrillation and paroxysmal supraventricular tachycardia is characterized by different circadian rhythms. *Am J Cardiol*. 1993;71:453–455.
555. Yamashita T, Murakawa Y, Sezaki K, Inoue M, Hayami N, Shuzui Y, Omata M. Circadian variation of paroxysmal atrial fibrillation. *Circulation*. 1997;96:1537–1541.
556. Koshino Y, Satoh M, Katayose Y, Yasuda K, Tanigawa T, Takeyasu N, Watanabe S, Yamaguchi I, Aonuma K. Association of sleep-disordered breathing and ventricular arrhythmias in patients without heart failure. *Am J Cardiol*. 2008;101:882–886.
557. Stevenson IH, Teichtahl H, Cunnington D, Ciavarella S, Gordon I, Kalman JM. Prevalence of sleep disordered breathing in paroxysmal and persistent atrial fibrillation patients with normal left ventricular function. *Eur Heart J*. 2008;29:1662–1669.
558. Porthan KM, Melin JH, Kupila JT, Venho KK, Partinen MM. Prevalence of sleep apnea syndrome in lone atrial fibrillation: a case-control study. *Chest*. 2004;125:879–885.
559. Braga B, Poyares D, Cintra F, Guilleminault C, Cirenza C, Horbach S, Macedo D, Silva R, Tufik S, De Paola AA. Sleep-disordered breathing and chronic atrial fibrillation. *Sleep Med*. 2009;10:212–216.
560. Gami AS, Pressman G, Caples SM, Kanagala R, Gard JJ, Davison DE, Malouf JF, Ammash NM, Friedman PA, Somers VK. Association of atrial fibrillation and obstructive sleep apnea. *Circulation*. 2004;110:364–367.
561. Culebras A. Diaphragmatic insufficiency in REM sleep. *Sleep Med*. 2004;5:337–338.
562. Okosun IS, Prewitt TE, Cooper RS. Abdominal obesity in the United States: prevalence and attributable risk of hypertension. *J Hum Hypertens*. 1999;13:425–430.
563. Gami AS, Hodge DO, Herges RM, Olson EJ, Nykodym J, Kara T, Somers VK. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. *J Am Coll Cardiol*. 2007;49:565–571.
564. Minoguchi K, Yokoe T, Tazaki T, Minoguchi H, Oda N, Tanaka A, Yamamoto M, Ohta S, O'Donnell CP, Adachi M. Silent brain infarction and platelet activation in obstructive sleep apnea. *Am J Respir Crit Care Med*. 2007;175:612–617.
565. Becker HF, Jerrentrup A, Ploch T, Grote L, Penzel T, Sullivan CE, Peter JH. Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. *Circulation*. 2003;107:68–73.
566. Gotsopoulos H, Kelly JJ, Cistulli PA. Oral appliance therapy reduces blood pressure in obstructive sleep apnea: a randomized, controlled trial. *Sleep*. 2004;27:934–941.
567. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, Mullins R, Jenkinson C, Stradling JR, Davies RJ. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. *Lancet*. 2002;359:204–210.
568. Gami AS, Somers VK. Implications of obstructive sleep apnea for atrial fibrillation and sudden cardiac death. *J Cardiovasc Electrophysiol*. 2008;19:997–1003.
569. Buchner NJ, Sanner BM, Borgel J, Rump LC. Continuous positive airway pressure treatment of mild to moderate obstructive sleep apnea reduces cardiovascular risk. *Am J Respir Crit Care Med*. 2007;176:1274–1280.
570. Welch GN, Loscalzo J. Homocysteine and atherothrombosis. *N Engl J Med*. 1998;338:1042–1050.
571. Selhub J, Jacques PF, Wilson PW, Rush D, Rosenberg IH. Vitamin status and intake as primary determinants of homocysteinemia in an elderly population. *JAMA*. 1993;270:2693–2698.
572. Boushey CJ, Beresford SA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease: probable benefits of increasing folic acid intakes. *JAMA*. 1995;274:1049–1057.
573. Graham IM, Daly LE, Refsum HM, Robinson K, Brattstrom LE, Ueland PM, Palma-Reis RJ, Boers GH, Sheahan RG, Israelsson B, Uiterwaal CS, Meleady R, McMaster D, Verhoef P, Witteman J, Rubba P, Bellet H, Wautrecht JC, de Valk HW, Sales Luis AC, Parrot-Rouland FM, Tan KS, Higgins I, Garcon D, Andria G, et al. Plasma homocysteine as a risk factor for vascular disease: the European Concerted Action Project. *JAMA*. 1997;277:1775–1781.

574. Robinson K, Arheart K, Refsum H, Brattstrom L, Boers G, Ueland P, Rubba P, Palma-Reis R, Meleady R, Daly L, Witteman J, Graham I. Low circulating folate and vitamin B6 concentrations: risk factors for stroke, peripheral vascular disease, and coronary artery disease. European COMAC Group. *Circulation*. 1998;97:437–443.
575. Bostom AG, Rosenberg IH, Silbershatz H, Jacques PF, Selhub J, D'Agostino RB, Wilson PW, Wolf PA. Nonfasting plasma total homocysteine levels and stroke incidence in elderly persons: the Framingham Study. *Ann Intern Med*. 1999;131:352–355.
576. Das RR, Seshadri S, Beiser AS, Kelly-Hayes M, Au R, Himali JJ, Kase CS, Benjamin EJ, Polak JF, O'Donnell CJ, Yoshita M, D'Agostino RB, Sr, DeCarli C, Wolf PA. Prevalence and correlates of silent cerebral infarcts in the Framingham offspring study. *Stroke*. 2008;39:2929–2935.
577. Giles WH, Croft JB, Greenlund KJ, Ford ES, Kittner SJ. Total homocyst(e)ine concentration and the likelihood of nonfatal stroke: results from the Third National Health and Nutrition Examination Survey, 1988–1994. *Stroke*. 1998;29:2473–2477.
578. Tanne D, Haim M, Goldbourt U, Boyko V, Doolman R, Adler Y, Brunner D, Behar S, Sela BA. Prospective study of serum homocysteine and risk of ischemic stroke among patients with preexisting coronary heart disease. *Stroke*. 2003;34:632–636.
579. Malinow MR, Nieto FJ, Szklo M, Chambless LE, Bond G. Carotid artery intimal-medial wall thickening and plasma homocyst(e)ine in asymptomatic adults: the Atherosclerosis Risk in Communities Study. *Circulation*. 1993;87:1107–1113.
580. McQuillan BM, Beilby JP, Nidorf M, Thompson PL, Hung J. Hyperhomocysteinemia but not the C677T mutation of methylenetetrahydrofolate reductase is an independent risk determinant of carotid wall thickening: the Perth Carotid Ultrasound Disease Assessment Study (CUDAS). *Circulation*. 1999;99:2383–2388.
581. Selhub J, Jacques PF, Bostom AG, D'Agostino RB, Wilson PW, Belanger AJ, O'Leary DH, Wolf PA, Schaefer EJ, Rosenberg IH. Association between plasma homocysteine concentrations and extracranial carotid-artery stenosis. *N Engl J Med*. 1995;332:286–291.
582. Kelemen LE, Anand SS, Hegele RA, Stampfer MJ, Rosner B, Willett WC, Montague PA, Lonn E, Vuksan V, Teo KK, Devanesen S, Yusuf S. Associations of plasma homocysteine and the methylenetetrahydrofolate reductase C677T polymorphism with carotid intima media thickness among South Asian, Chinese and European Canadians. *Atherosclerosis*. 2004;176:361–370.
583. Held C, Sumner G, Sheridan P, McQueen M, Smith S, Dagenais G, Yusuf S, Lonn E. Correlations between plasma homocysteine and folate concentrations and carotid atherosclerosis in high-risk individuals: baseline data from the Homocysteine and Atherosclerosis Reduction Trial (HART). *Vasc Med*. 2008;13:245–253.
584. Potter K, Hankey GJ, Green DJ, Eikelboom JW, Arnolda LF. Homocysteine or renal impairment: which is the real cardiovascular risk factor? *Arterioscler Thromb Vasc Biol*. 2008;28:1158–1164.
585. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. *JAMA*. 2002;288:2015–2022.
586. Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. *BMJ*. 2002;325:1202.
587. Al-Delaimy WK, Rexrode KM, Hu FB, Albert CM, Stampfer MJ, Willett WC, Manson JE. Folate intake and risk of stroke among women. *Stroke*. 2004;35:1259–1263.
588. He K, Merchant A, Rimm EB, Rosner BA, Stampfer MJ, Willett WC, Ascherio A. Folate, vitamin B6, and B12 intakes in relation to risk of stroke among men. *Stroke*. 2004;35:169–174.
589. Van Guelpen B, Hultdin J, Johansson I, Stegmayr B, Hallmans G, Nilsson TK, Weinehall L, Witthoft C, Palmqvist R, Winkvist A. Folate, vitamin B12, and risk of ischemic and hemorrhagic stroke: a prospective, nested case-referent study of plasma concentrations and dietary intake. *Stroke*. 2005;36:1426–1431.
590. Weng LC, Yeh WT, Bai CH, Chen HJ, Chuang SY, Chang HY, Lin BF, Chen KJ, Pan WH. Is ischemic stroke risk related to folate status or other nutrients correlated with folate intake? *Stroke*. 2008;39:3152–3158.
591. Hodis HN, Mack WJ, Dustin L, Mahrer PR, Azen SP, Detrano R, Selhub J, Alaupovic P, Liu CR, Liu CH, Hwang J, Wilcox AG, Selzer RH. High-dose B vitamin supplementation and progression of subclinical atherosclerosis: a randomized controlled trial. *Stroke*. 2009;40:730–736.
592. Potter K, Hankey GJ, Green DJ, Eikelboom J, Jamrozik K, Arnolda LF. The effect of long-term homocysteine-lowering on carotid intima-media thickness and flow-mediated vasodilation in stroke patients: a randomized controlled trial and meta-analysis. *BMC Cardiovasc Disord*. 2008;8:24.
593. Zoungas S, McGrath BP, Branley P, Kerr PG, Muske C, Wolfe R, Atkins RC, Nicholls K, Fraenkel M, Hutchison BG, Walker R, McNeil JJ. Cardiovascular morbidity and mortality in the Atherosclerosis and Folic Acid Supplementation Trial (ASFAST) in chronic renal failure: a multicenter, randomized, controlled trial. *J Am Coll Cardiol*. 2006;47:1108–1116.
594. Bonaa KH, Njolstad I, Ueland PM, Schirmer H, Tverdal A, Steigen T, Wang H, Nordrehaug JE, Arnesen E, Rasmussen K. Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med*. 2006;354:1578–1588.
595. Ebbing M, Bleie O, Ueland PM, Nordrehaug JE, Nilsen DW, Vollset SE, Refsum H, Pedersen EK, Nygard O. Mortality and cardiovascular events in patients treated with homocysteine-lowering B vitamins after coronary angiography: a randomized controlled trial. *JAMA*. 2008;300:795–804.
596. Albert CM, Cook NR, Gaziano JM, Zaharris E, MacFadyen J, Danielson E, Buring JE, Manson JE. Effect of folic acid and B vitamins on risk of cardiovascular events and total mortality among women at high risk for cardiovascular disease: a randomized trial. *JAMA*. 2008;299:2027–2036.
597. Righetti M, Serbelloni P, Milani S, Ferrario G. Homocysteine-lowering vitamin B treatment decreases cardiovascular events in hemodialysis patients. *Blood Purif*. 2006;24:379–386.
598. Wrone EM, Hornberger JM, Zehnder JL, McCann LM, Coplon NS, Fortmann SP. Randomized trial of folic acid for prevention of cardiovascular events in end-stage renal disease. *J Am Soc Nephrol*. 2004;15:420–426.
599. Toole JF, Malinow MR, Chambless LE, Spence JD, Pettigrew LC, Howard VJ, Sides EG, Wang CH, Stampfer M. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. *JAMA*. 2004;291:565–575.
600. Lonn E, Yusuf S, Arnold MJ, Sheridan P, Pogue J, Micks M, McQueen MJ, Probstfield J, Fodor G, Held C, Genest J Jr. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med*. 2006;354:1567–1577.
601. Saposnik G, Ray JG, Sheridan P, McQueen M, Lonn E. Homocysteine-lowering therapy and stroke risk, severity, and disability: additional findings from the HOPE 2 trial. *Stroke*. 2009;40:1365–1372.
602. Bazzano LA, Reynolds K, Holder KN, He J. Effect of folic acid supplementation on risk of cardiovascular diseases: a meta-analysis of randomized controlled trials. *JAMA*. 2006;296:2720–2726.
603. Wang X, Qin X, Demirtas H, Li J, Mao G, Huo Y, Sun N, Liu L, Xu X. Efficacy of folic acid supplementation in stroke prevention: a meta-analysis. *Lancet*. 2007;369:1876–1882.
604. Marcovina SM, Koschinsky ML. Evaluation of lipoprotein(a) as a prothrombotic factor: progress from bench to bedside. *Curr Opin Lipidol*. 2003;14:361–366.
605. Danesh J, Collins R, Peto R. Lipoprotein(a) and coronary heart disease: meta-analysis of prospective studies. *Circulation*. 2000;102:1082–1085.
606. Foody JM, Milberg JA, Pearce GL, Sprecher DL. Lipoprotein(a) associated with coronary artery disease in older women: age and gender analysis. *Atherosclerosis*. 2000;153:445–451.
607. Hancock MA, Boffa MB, Marcovina SM, Nesheim ME, Koschinsky ML. Inhibition of plasminogen activation by lipoprotein(a): critical domains in apolipoprotein(a) and mechanism of inhibition on fibrin and degraded fibrin surfaces. *J Biol Chem*. 2003;278:23260–23269.
608. Ariyo AA, Thach C, Tracy R. Lp(a) lipoprotein, vascular disease, and mortality in the elderly. *N Engl J Med*. 2003;349:2108–2115.
609. Milionis HJ, Filippatos TD, Loukas T, Bairaktari ET, Tselepis AD, Elisaf MS. Serum lipoprotein(a) levels and apolipoprotein(a) isoform size and risk for first-ever acute ischaemic nonembolic stroke in elderly individuals. *Atherosclerosis*. 2006;187:170–176.
610. Ohira T, Schreiner PJ, Morrisett JD, Chambless LE, Rosamond WD, Folsom AR. Lipoprotein(a) and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study. *Stroke*. 2006;37:1407–1412.
611. Ridker PM, Stampfer MJ, Hennekens CH. Plasma concentration of lipoprotein(a) and the risk of future stroke. *JAMA*. 1995;273:1269–1273.
612. Klein JH, Hegele RA, Hackam DG, Koschinsky ML, Huff MW, Spence JD. Lipoprotein(a) is associated differentially with carotid stenosis,

occlusion, and total plaque area. *Arterioscler Thromb Vasc Biol*. 2008; 28:1851–1856.
613. Willeit J, Kiechl S, Santer P, Oberhollenzer F, Egger G, Jarosch E, Mair A. Lipoprotein(a) and asymptomatic carotid artery disease: evidence of a prominent role in the evolution of advanced carotid plaques: the Bruneck Study. *Stroke.* 1995;26:1582–1587.
614. Cerrato P, Imperiale D, Fornengo P, Bruno G, Cassader M, Maffeis P, Cavallo Perin P, Pagano G, Bergamasco B. Higher lipoprotein(a) levels in atherothrombotic than lacunar ischemic cerebrovascular disease. *Neurology*. 2002;58:653–655.
615. Smolders B, Lemmens R, Thijs V. Lipoprotein(a) and stroke: a meta-analysis of observational studies. *Stroke.* 2007;38:1959–1966.
616. Anticardiolipin antibodies are an independent risk factor for first ischemic stroke. The Antiphospholipid Antibodies in Stroke Study (APASS) Group. *Neurology.* 1993;43:2069–2073.
617. Erkan D, Harrison MJ, Levy R, Peterson M, Petri M, Sammaritano L, Unalp-Arida A, Vilela V, Yazici Y, Lockshin MD. Aspirin for primary thrombosis prevention in the antiphospholipid syndrome: a randomized, double-blind, placebo-controlled trial in asymptomatic antiphospholipid antibody-positive individuals. *Arthritis Rheum*. 2007;56:2382–2391.
618. Frances C, Papo T, Wechsler B, Laporte JL, Biousse V, Piette JC. Sneddon syndrome with or without antiphospholipid antibodies: a comparative study in 46 patients. *Medicine (Baltimore)*. 1999;78:209–219.
619. Ginsburg KS, Liang MH, Newcomer L, Goldhaber SZ, Schur PH, Hennekens CH, Stampfer MJ. Anticardiolipin antibodies and the risk for ischemic stroke and venous thrombosis. *Ann Intern Med*. 1992;117: 997–1002.
620. Brey RL, Abbott RD, Curb JD, Sharp DS, Ross GW, Stallworth CL, Kittner SJ. beta(2)-Glycoprotein 1-dependent anticardiolipin antibodies and risk of ischemic stroke and myocardial infarction: the honolulu heart program. *Stroke*. 2001;32:1701–1706.
621. Janardhan V, Wolf PA, Kase CS, Massaro JM, D'Agostino RB, Franzblau C, Wilson PW. Anticardiolipin antibodies and risk of ischemic stroke and transient ischemic attack: the Framingham cohort and offspring study. *Stroke*. 2004;35:736–741.
622. Levine SR, Brey RL, Tilley BC, Thompson JL, Sacco RL, Sciacca RR, Murphy A, Lu Y, Costigan TM, Rhine C, Levin B, Triplett DA, Mohr JP. Antiphospholipid antibodies and subsequent thrombo-occlusive events in patients with ischemic stroke. *JAMA*. 2004;291:576–584.
623. Heinzlef O, Abuaf N, Cohen A, Amarenco P. Recurrent stroke and vascular events in elderly patients with anticardiolipin antibodies: a prospective study. *J Neurol*. 2001;248:373–379.
624. Tanne D, D'Olhaberriague L, Trivedi AM, Salowich-Palm L, Schultz LR, Levine SR. Anticardiolipin antibodies and mortality in patients with ischemic stroke: a prospective follow-up study. *Neuroepidemiology*. 2002;21:93–99.
625. Galli M, Luciani D, Bertolini G, Barbui T. Anti-beta 2-glycoprotein I, antiprothrombin antibodies, and the risk of thrombosis in the antiphospholipid syndrome. *Blood*. 2003;102:2717–2723.
626. Brey RL, Stallworth CL, McGlasson DL, Wozniak MA, Wityk RJ, Stern BJ, Sloan MA, Sherwin R, Price TR, Macko RF, Johnson CJ, Earley CJ, Buchholz DW, Hebel JR, Kittner SJ. Antiphospholipid antibodies and stroke in young women. *Stroke*. 2002;33:2396–2400.
627. Wilson WA, Gharavi AE, Koike T, Lockshin MD, Branch DW, Piette JC, Brey R, Derksen R, Harris EN, Hughes GR, Triplett DA, Khamashta MA. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. *Arthritis Rheum*. 1999;42:1309–1311.
628. Petri M. Management of thrombosis in antiphospholipid antibody syndrome. *Rheum Dis Clin North Am.* 2001;27:633–642, viii.
629. Becker R, Chan M, Shah SH, Levine SR. Coagulopathy and stroke: evaluation and treatment. In: Goldstein LB, ed. *A Primer on Stroke Prevention and Treatment: An Overview Based on AHA/ASA Guidelines.* Dallas, TX: American Heart Association;2009:152–169.
630. Pezzini A, Del Zotto E, Magoni M, Costa A, Archetti S, Grassi M, Akkawi NM, Albertini A, Assanelli D, Vignolo LA, Padovani A. Inherited thrombophilic disorders in young adults with ischemic stroke and patent foramen ovale. *Stroke*. 2003;34:28–33.
631. Dalen JE. Should patients with venous thromboembolism be screened for thrombophilia? *Am J Med*. 2008;121:458–463.
632. Christiansen SC, Cannegieter SC, Koster T, Vandenbroucke JP, Rosendaal FR. Thrombophilia, clinical factors, and recurrent venous thrombotic events. *JAMA*. 2005;293:2352–2361.
633. Hron G, Kollars M, Binder BR, Eichinger S, Kyrle PA. Identification of patients at low risk for recurrent venous thromboembolism by measuring thrombin generation. *JAMA*. 2006;296:397–402.
634. Brouwer JL, Veeger NJ, Kluin-Nelemans HC, van der Meer J. The pathogenesis of venous thromboembolism: evidence for multiple interrelated causes. *Ann Intern Med*. 2006;145:807–815.
635. van Vlijmen EF, Brouwer JL, Veeger NJ, Eskes TK, de Graeff PA, van der Meer J. Oral contraceptives and the absolute risk of venous thromboembolism in women with single or multiple thrombophilic defects: results from a retrospective family cohort study. *Arch Intern Med*. 2007;167:282–289.
636. Wasay M, Bakshi R, Bobustuc G, Kojan S, Sheikh Z, Dai A, Cheema Z. Cerebral venous thrombosis: analysis of a multicenter cohort from the United States. *J Stroke Cerebrovasc Dis*. 2008;17:49–54.
637. Wu O, Robertson L, Twaddle S, Lowe GD, Clark P, Greaves M, Walker ID, Langhorne P, Brenkel I, Regan L, Greer I. Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis: the Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study. *Health Technol Assess*. 2006;10: 1–110.
638. Barnes C, Deveber G. Prothrombotic abnormalities in childhood ischaemic stroke. *Thromb Res*. 2006;118:67–74.
639. Libby P, Ridker PM. Inflammation and atherothrombosis: from population biology and bench research to clinical practice. *J Am Coll Cardiol*. 2006;48:A33–A46.
640. Oei HH, van der Meer IM, Hofman A, Koudstaal PJ, Stijnen T, Breteler MM, Witteman JC. Lipoprotein-associated phospholipase A2 activity is associated with risk of coronary heart disease and ischemic stroke: the Rotterdam Study. *Circulation*. 2005;111:570–575.
641. Garza CA, Montori VM, McConnell JP, Somers VK, Kullo IJ, Lopez-Jimenez F. Association between lipoprotein-associated phospholipase A2 and cardiovascular disease: a systematic review. *Mayo Clin Proc*. 2007;82:159–165.
642. Nambi V, Hoogeveen RC, Chambless L, Hu Y, Bang H, Coresh J, Ni H, Boerwinkle E, Mosley T, Sharrett R, Folsom AR, Ballantyne CM. Lipoprotein-associated phospholipase A2 and high-sensitivity C-reactive protein improve the stratification of ischemic stroke risk in the Atherosclerosis Risk in Communities (ARIC) study. *Stroke*. 2009; 40:376–381.
643. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC Jr, Taubert K, Tracy RP, Vinicor F. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation*. 2003;107: 499–511.
644. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med*. 1997;336:973–979.
645. Ridker PM, Buring JE, Shih J, Matias M, Hennekens CH. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation*. 1998;98:731–733.
646a. Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *NEJM*. 2008;359:2195–2207.
646. Rost NS, Wolf PA, Kase CS, Kelly-Hayes M, Silbershatz H, Massaro JM, D'Agostino RB, Franzblau C, Wilson PW. Plasma concentration of C-reactive protein and risk of ischemic stroke and transient ischemic attack: the Framingham study. *Stroke*. 2001;32:2575–2579.
647. Fischer LM, Schlienger RG, Matter C, Jick H, Meier CR. Effect of rheumatoid arthritis or systemic lupus erythematosus on the risk of first-time acute myocardial infarction. *Am J Cardiol*. 2004;93:198–200.
648. Gabriel SE. Cardiovascular morbidity and mortality in rheumatoid arthritis. *Am J Med*. 2008;121(suppl 1):S9–14.
649. Sodergren A, Stegmayr B, Lundberg V, Ohman ML, Wallberg-Jonsson S. Increased incidence of and impaired prognosis after acute myocardial infarction among patients with seropositive rheumatoid arthritis. *Ann Rheum Dis*. 2007;66:263–266.
650. Turesson C, Jarenros A, Jacobsson L. Increased incidence of cardiovascular disease in patients with rheumatoid arthritis: results from a community based study. *Ann Rheum Dis*. 2004;63:952–955.

651. Wolfe F, Freundlich B, Straus WL. Increase in cardiovascular and cerebrovascular disease prevalence in rheumatoid arthritis. *J Rheumatol*. 2003;30:36–40.
652. Esdaile JM, Abrahamowicz M, Grodzicky T, Li Y, Panaritis C, du Berger R, Cote R, Grover SA, Fortin PR, Clarke AE, Senecal JL. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. *Arthritis Rheum*. 2001; 44:2331–2337.
653. Manzi S, Selzer F, Sutton-Tyrrell K, Fitzgerald SG, Rairie JE, Tracy RP, Kuller LH. Prevalence and risk factors of carotid plaque in women with systemic lupus erythematosus. *Arthritis Rheum*. 1999;42:51–60.
654. Roman MJ, Moeller E, Davis A, Paget SA, Crow MK, Lockshin MD, Sammaritano L, Devereux RB, Schwartz JE, Levine DM, Salmon JE. Preclinical carotid atherosclerosis in patients with rheumatoid arthritis. *Ann Intern Med*. 2006;144:249–256.
655. Salmon JE, Roman MJ. Subclinical atherosclerosis in rheumatoid arthritis and systemic lupus erythematosus. *Am J Med*. 2008;121(suppl 1):S3–S8.
656. Pearson TA. Heightened risk of cardiovascular disease in patients with rheumatoid arthritis, heightened risk of cardiovascular disease in patients with rheumatoid arthritis. Introduction. *Am J Med*. 2008; 121(suppl 1):S1–S2.
657. Libby P, Egan D, Skarlatos S. Roles of infectious agents in atherosclerosis and restenosis: an assessment of the evidence and need for future research. *Circulation*. 1997;96:4095–4103.
658. Cercek B, Shah PK, Noc M, Zahger D, Zeymer U, Matetzky S, Maurer G, Mahrer P. Effect of short-term treatment with azithromycin on recurrent ischaemic events in patients with acute coronary syndrome in the Azithromycin in Acute Coronary Syndrome (AZACS) trial: a randomised controlled trial. *Lancet*. 2003;361:809–813.
659. Zahn R, Schneider S, Frilling B, Seidl K, Tebbe U, Weber M, Gottwik M, Altmann E, Seidel F, Rox J, Hoffler U, Neuhaus KL, Senges J. Antibiotic therapy after acute myocardial infarction: a prospective randomized study. *Circulation*. 2003;107:1253–1259.
660. Mamas MA, Fraser D, Neyses L. Cardiovascular manifestations associated with influenza virus infection. *Int J Cardiol*. 2008;130:304–309.
661. Warren-Gash C, Smeeth L, Hayward AC. Influenza as a trigger for acute myocardial infarction or death from cardiovascular disease: a systematic review. *Lancet Infect Dis*. 2009;9:601–610.
662. Madjid M, Curkendall S, Blumentals WA. The influence of oseltamivir treatment on the risk of stroke after influenza infection. *Cardiology*. 2009;113:98–107.
663. Lavallee P, Perchaud V, Gautier-Bertrand M, Grabli D, Amarenco P. Association between influenza vaccination and reduced risk of brain infarction. *Stroke*. 2002;33:513–518.
664. Nichol KL, Nordin J, Mullooly J, Lask R, Fillbrandt K, Iwane M. Influenza vaccination and reduction in hospitalizations for cardiac disease and stroke among the elderly. *N Engl J Med*. 2003;348: 1322–1332.
665. Wang CS, Wang ST, Lai CT, Lin LJ, Chou P. Impact of influenza vaccination on major cause-specific mortality. *Vaccine*. 2007;25: 1196–1203.
666. Davis MM, Taubert K, Benin AL, Brown DW, Mensah GA, Baddour LM, Dunbar S, Krumholz HM. Influenza vaccination as secondary prevention for cardiovascular disease: a science advisory from the American Heart Association/American College of Cardiology. *Circulation*. 2006;114: 1549–1553.
667. Hayden M, Pigone M, Phillips C, Mulrow C. Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the US Preventive Services Task Force. *Ann Intern Med*. 2002;136: 161–172.
668. Pearson TA, Blair SN, Daniels SR, Eckel RH, Fair JM, Fortmann SP, Franklin BA, Goldstein LB, Greenland P, Grundy SM, Hong Y, Miller NH, Lauer RM, Ockene IS, Sacco R, Sallis JF, Smith SC, Stone NJ, Taubert KA. AHA guidelines for primary prevention of cardiovascular disease and stroke: 2002 update. *Circulation*. 2002;106:388–391.
669. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy–I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ*. 1994;308:81–106.
670. Hart RG, Halperin JL, McBride R, Benavente O, Man-Son-Hing M, Kronmal RA. Aspirin for the primary prevention of stroke and other major vascular events: meta-analysis and hypotheses. *Arch Neurol*. 2000;57:326–332.
671. Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R, Lee R, Bancroft J, MacEwan S, Shepherd J, Macfarlane P, Morris A, Jung R, Kelly C, Connacher A, Peden N, Jamieson A, Matthews D, Leese G, McKnight J, O'Brien I, Semple C, Petrie J, Gordon D, Pringle S, MacWalter R. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ*. 2008;337:a1840.
672. Ridker PM, Cook NR, Lee I-M, Gordon D, Gaziano JM, Manson JE, Hennekens CH, Buring JE. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med*. 2005;352:1293–1304.
673. Grundy SM, Pasternak R, Greenland P, Smith S Jr, Fuster V. AHA/ACC scientific statement: assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *J Am Coll Cardiol*. 1999;34:1348–1359.
674. Pocock SJ, McCormack V, Gueyffier F, Boutitie F, Fagard RH, Boissel JP. A score for predicting risk of death from cardiovascular disease in adults with raised blood pressure, based on individual patient data from randomised controlled trials. *BMJ*. 2001;323:75–81.
675. D'Agostino RB, Wolf PA, Belanger AJ, Kannel WB. Stroke risk profile: adjustment for antihypertensive medication: the Framingham Study. *Stroke*. 1994;25:40–43.
676. Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D'Agostino RB, Larson MG, Kannel WB, Benjamin EJ. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA*. 2003;290:1049–1056.
677. Cappuccio FP, Oakeshott P, Strazzullo P, Kerry SM. Application of Framingham risk estimates to ethnic minorities in United Kingdom and implications for primary prevention of heart disease in general practice: cross sectional population based study. *BMJ*. 2002;325:1271.
678. Lumley T, Kronmal RA, Cushman M, Manolio TA, Goldstein S. A stroke prediction score in the elderly: validation and Web-based application. *J Clin Epidemiol*. 2002;55:129–136.
679. Simons LA, McCallum J, Friedlander Y, Simons J. Risk factors for ischemic stroke: Dubbo Study of the elderly. *Stroke*. 1998;29: 1341–1346.
680. Grundy SM, D'Agostino RB, Mosca L, Burke GL, Wilson PW, Rader DJ, Cleeman JI, Roccella EJ, Cutler JA, Friedman LM. Cardiovascular risk assessment based on US cohort studies: findings from a National Heart, Lung, and Blood institute workshop. *Circulation*. 2001;104: 491–496.
681. Wilson SL, Poulter NR. Cardiovascular risk: its assessment in clinical practice. *Br J Biomed Sci*. 2001;58:248–251.
682. Institute of Medicine. IOM report: the future of emergency care in the United States health system. *Acad Emerg Med*. 2006;13:1081–1085.
683. Pitts SR, Niska RW, Xu J, Burt CW. National Hospital Ambulatory Medical Care Survey: 2006 emergency department summary. *Natl Health Stat Report*. 2008:1–38.
684. Babcock Irvin C, Wyer PC, Gerson LW. Preventive care in the emergency department, part II: clinical preventive services–an emergency medicine evidence-based review. Society for Academic Emergency Medicine Public Health and Education Task Force Preventive Services Work Group. *Acad Emerg Med*. 2000;7:1042–1054.
685. Bernstein SL, Haukoos JS. Public health, prevention, and emergency medicine: a critical juxtaposition. *Acad Emerg Med*. 2008;15:190–193.
686. Reeves MJ, Hogan JG, Rafferty AP. Knowledge of stroke risk factors and warning signs among Michigan adults. *Neurology*. 2002;59: 1547–1552.
687. Marsden C, Pinell MC, Joyce SM. Emergency physicians and preventive medicine. *West J Med*. 1988;149:345.
688. Karras DJ, Kruus LK, Cienki JJ, Wald MM, Ufberg JW, Shayne P, Wald DA, Heilpern KL. Utility of routine testing for patients with asymptomatic severe blood pressure elevation in the emergency department. *Ann Emerg Med*. 2008;51:231–239.
689. Ginde AA, Cagliero E, Nathan DM, Camargo CA Jr. Value of risk stratification to increase the predictive validity of HbA1c in screening for undiagnosed diabetes in the US population. *J Gen Intern Med*. 2008;23:1346–1353.
690. George PM, Valabhji J, Dawood M, Henry JA. Screening for type 2 diabetes in the accident and emergency department. *Diabet Med*. 2005; 22:1766–1769.
691. Matchar DB, McCrory DC, Barnett HJ, Feussner JR. Medical treatment for stroke prevention. *Ann Intern Med*. 1994;121:41–53.

692. McDonald AJ, Pelletier AJ, Ellinor PT, Camargo CA Jr. Increasing US emergency department visit rates and subsequent hospital admissions for atrial fibrillation from 1993 to 2004. *Ann Emerg Med*. 2008;51:58–65.
693. Scott PA, Pancioli AM, Davis LA, Frederiksen SM, Eckman J. Prevalence of atrial fibrillation and antithrombotic prophylaxis in emergency department patients. *Stroke*. 2002;33:2664–2669.
694. Kelly AM, Kerr D, Hew R. Prevention of stroke in chronic and recurrent atrial fibrillation: role of the emergency department in identification of "at-risk" patients. *Aust Health Rev*. 2001;24:61–65.
695. Annual smoking-attributable mortality, years of potential life lost, and economic costs–United States, 1995–1999. *MMWR Morb Mortal Wkly Rep*. 2002;51:300–303.
696. Bernstein SL, Boudreaux ED, Cydulka RK, Rhodes KV, Lettman NA, Almeida SL, McCullough LB, Mizouni S, Kellermann AL. Tobacco control interventions in the emergency department: a joint statement of emergency medicine organizations. *Ann Emerg Med*. 2006;48:e417–e426.
697. D'Onofrio G, Degutis LC. Preventive care in the emergency department: screening and brief intervention for alcohol problems in the emergency department: a systematic review. *Acad Emerg Med*. 2002;9:627–638.
698. Wang TC, Kyriacou DN, Wolf MS. Effects of an intervention brochure on emergency department patients' safe alcohol use and knowledge. *J Emerg Med*. 2008 May 5. [Epub ahead of print.]
699. The impact of screening, brief intervention, and referral for treatment on emergency department patients' alcohol use. *Ann Emerg Med*. 2007;50:699–710.
700. Bernstein E, Bernstein J, Feldman J, Fernandez W, Hagan M, Mitchell P, Safi C, Woolard R, Mello M, Baird J, Lee C, Bazargan-Hejazi S, Broderick K, Laperrier KA, Kellermann A, Wald MM, Taylor RE, Walton K, Grant-Ervin M, Rollinson D, Edwards D, Chan T, Davis D, Buchanan Marshall J, Aseltine R, James A, Schilling E, Abu-Hasaballah K, Baumann BM, Boudreaux ED, Maio RF, Cunningham RM, Murrell T, Doezema D, Anglin D, Eliassen A, Martin M, Pines J, Buchanan L, Turner J, D'Onofrio G, Degutis LC, Owens P. An evidence based alcohol screening, brief intervention and referral to treatment (SBIRT) curriculum for emergency department (ED) providers improves skills and utilization. *Subst Abus*. 2007;28:79–92.
701. Williams JM, Chinnis AC, Gutman D. Health promotion practices of emergency physicians. *Am J Emerg Med*. 2000;18:17–21.
702. Bensberg M, Kennedy M. A framework for health promoting emergency departments. *Health Promot Int*. 2002;17:179–188.
703. Backer EL, Geske JA, McIlvain HE, Dodendorf DM, Minier WC. Improving female preventive health care delivery through practice change: an Every Woman Matters study. *J Am Board Fam Pract*. 2005;18:401–408.
704. Holloway RG, Benesch C, Rush SR. Stroke prevention: narrowing the evidence-practice gap. *Neurology*. 2000;54:1899–1906.
705. Shekelle PG. Why don't physicians enthusiastically support quality improvement programmes? *Qual Saf Health Care*. 2002;11:6.
706. Hyre AD, Muntner P, Menke A, Raggi P, He J. Trends in ATP-III-defined high blood cholesterol prevalence, awareness, treatment and control among U.S. adults. *Ann Epidemiol*. 2007;17:548–555.
707. Ong KL, Cheung BM, Wong LY, Wat NM, Tan KC, Lam KS. Prevalence, treatment, and control of diagnosed diabetes in the U.S. National Health and Nutrition Examination Survey 1999–2004. *Ann Epidemiol*. 2008;18:222–229.
708. Fine LJ, Cutler JA. Hypertension and the treating physician: understanding and reducing therapeutic inertia. *Hypertension*. 2006;47:319–320.
709. Muntner P, DeSalvo KB, Wildman RP, Raggi P, He J, Whelton PK. Trends in the prevalence, awareness, treatment, and control of cardiovascular disease risk factors among noninstitutionalized patients with a history of myocardial infarction and stroke. *Am J Epidemiol*. 2006;163:913–920.
710. Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA*. 2004;291:335–342.
711. Davis DA, Thomson MA, Oxman AD, Haynes RB. Changing physician performance: a systematic review of the effect of continuing medical education strategies. *JAMA*. 1995;274:700–705.
712. O'Brien MA, Rogers S, Jamtvedt G, Oxman AD, Odgaard-Jensen J, Kristoffersen DT, Forsetlund L, Bainbridge D, Freemantle N, Davis DA, Haynes RB, Harvey EL. Educational outreach visits: effects on professional practice and health care outcomes. *Cochrane Database Syst Rev*. 2007:CD000409.
713. Wright J, Bibby J, Eastham J, Harrison S, McGeorge M, Patterson C, Price N, Russell D, Russell I, Small N, Walsh M, Young J. Multifaceted implementation of stroke prevention guidelines in primary care: cluster-randomised evaluation of clinical and cost effectiveness. *Qual Saf Health Care*. 2007;16:51–59.
714. Shea S, DuMouchel W, Bahamonde L. A meta-analysis of 16 randomized controlled trials to evaluate computer-based clinical reminder systems for preventive care in the ambulatory setting. *J Am Med Inform Assoc*. 1996;3:399–409.
715. Baskerville NB, Hogg W, Lemelin J. Process evaluation of a tailored multifaceted approach to changing family physician practice patterns improving preventive care. *J Fam Pract*. 2001;50:W242–249.
716. Frijling B, Hulscher ME, van Leest LA, Braspenning JC, van den Hoogen H, Drenthen AJ, Grol RP. Multifaceted support to improve preventive cardiovascular care: a nationwide, controlled trial in general practice. *Br J Gen Pract*. 2003;53:934–941.
717. Stone EG, Morton SC, Hulscher ME, Maglione MA, Roth EA, Grimshaw JM, Mittman BS, Rubenstein LV, Rubenstein LZ, Shekelle PG. Interventions that increase use of adult immunization and cancer screening services: a meta-analysis. *Ann Intern Med*. 2002;136:641–651.
718. de Koning JS, Klazinga N, Koudstaal PJ, Prins AD, Borsboom GJ, Mackenbach JP. Quality of stroke prevention in general practice: relationship with practice organization. *Int J Qual Health Care*. 2005;17:59–65.
719. Sabatino SA, Habarta N, Baron RC, Coates RJ, Rimer BK, Kerner J, Coughlin SS, Kalra GP, Chattopadhyay S. Interventions to increase recommendation and delivery of screening for breast, cervical, and colorectal cancers by healthcare providers systematic reviews of provider assessment and feedback and provider incentives. *Am J Prev Med*. 2008;35(suppl 1):S67–S74.
720. LaBresh KA, Reeves MJ, Frankel MR, Albright D, Schwamm LH. Hospital treatment of patients with ischemic stroke or transient ischemic attack using the "Get With The Guidelines" program. *Arch Intern Med*. 2008;168:411–417.
721. California Acute Stroke Pilot Registry (CASPR) Investigators. The impact of standardized stroke orders on adherence to best practices. *Neurology*. 2005;65:360–365.
722. Hinchey JA, Shephard T, Tonn ST, Ruthazer R, Selker HP, Kent DM. Benchmarks and determinants of adherence to stroke performance measures. *Stroke*. 2008;39:1619–1620.
723. Shannon KC, Sinacore JM, Bennett SG, Joshi AM, Sherin KM, Deitrich A. Improving delivery of preventive health care with the comprehensive annotated reminder tool (CART). *J Fam Pract*. 2001;50:767–771.
724. Boulware LE, Marinopoulos S, Phillips KA, Hwang CW, Maynor K, Merenstein D, Wilson RF, Barnes GJ, Bass EB, Powe NR, Daumit GL. Systematic review: the value of the periodic health evaluation. *Ann Intern Med*. 2007;146:289–300.
725. Kiely DK, Wolf PA, Cupples LA, Beiser AS, Myers RH. Familial aggregation of stroke: the Framingham Study. *Stroke*. 1993;24:1366–1371.
726. Cigarette smoking among adults–United States, 2007. *MMWR Morb Mortal Wkly Rep*. 2008;57:1221–1226.
727. *Heart Disease and Stroke Statistics: 2009 Update*. Dallas, TX: American Heart Association; 2009.
728. Qureshi AI, Suri MF, Kirmani JF, Divani AA, Mohammad Y. Is prehypertension a risk factor for cardiovascular diseases? *Stroke*. 2005;36:1859–1863.
729. Majumdar S, Almasi E, Stafford R. Promotion and prescribing of hormone therapy after report of harm by the Women's Health Initiative. *JAMA*. 2004;282:1983–1988.
730. Haas J, Kaplan C, Gerstenberger E, Kerlikowske K. Changes in the use of postmenopausal hormone therapy after the publication of clinical trial results. *Ann Intern Med*. 2004;140:184–188.
731. Lundberg V, Tolonen H, Stegmayr B, Kuulasmaa K, Asplund K. Use of oral contraceptives and hormone replacement therapy in the WHO MONICA project. *Maturitas*. 2004;48:39–49.
732. Deleted in proof.
733. Ogden CL, Carroll MD, McDowell MA, Flegal KM. Obesity among adults in the United States—no change since 2003–2004. NCHS data brief no 1. Hyattsville, MD: National Center for Health Statistics; 2007.
734. Deleted in proof.
735. Fagerberg B, Gnarpe J, Gnarpe H, Agewall S, Wikstrand J. Chlamydia pneumoniae but not cytomegalovirus antibodies are associated with future risk of stroke and cardiovascular disease: a prospective study in middle-aged to elderly men with treated hypertension. *Stroke*. 1999;30:299–305.

AHA/ASA Guideline

脳卒中の一次予防

Guidelines for the Primary Prevention of Stroke

— A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

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はじめに：このガイドラインは，初発脳卒中のリスクを低減するため，エビデンスに基づいた推奨を提供することを目的とした脳卒中危険因子のオーバービューである。ガイドライン執筆委員会は前回 2006 年のレビュー以降 2009 年 4 月までの文献を用いて，現在知られているエビデンスを要約し，現在知識が欠如しているところを指摘し，適切なエビデンスには AHA の基準（**表 1**）に従った推奨を提唱した。2006 年のガイドライン（*Stroke* 日本語版 Vol.1, No.3 p27-36 参照）は虚血性脳卒中の一次予防に限定されていたが，今回のガイドラインは出血性脳卒中の一次予防も含む。危険因子は，前回と同様に，修正の可能性の程度（修正不可能，修正可能，修正の可能性あり）とエビデンスの強さ（明らかである，あまり明らかでない）で分類されている。このガイドラインの英文原著は 735 篇の引用文献を含む 67 ページにおよぶため，本要約では英文原著の表 14 に記載されているエビデンスに基づいた推奨文はすべて記載するが，本文の記載は 1）一般に修正が不可能な危険因子，2）根拠が明確で修正可能な危険因子，3）根拠が不十分，または修正の可能性がある危険因子，についての短い要約に止まることをお断りする。また原著では ischemic stroke が単に stroke と記載されていることが多いため，本要約でも単に脳卒中という記載は原則として虚血性脳卒中を意味するとご理解いただきたい。

I. 一般に修正が不可能な危険因子（表 2）

これらの因子は一般的に修正不可能であるが，脳卒中リスクが高い人を同定し，積極的な発症予防や他の修正可能な因子の治療をする可能性がある。低出生時体重と脳卒中リスクの関連はさらなる検討が必要である。

遺伝的要因ではファブリ病の酵素補充療法のように治療が可能な疾患があり，家族性頭蓋内未破裂動脈瘤は非家族性に比して破裂する危険が高く，症例によってはスクリーニングと脳外科的または血管内治療の適応がある。

薬理遺伝学領域ではビタミン K 拮抗薬の代謝が遺伝的影響を受けるが，遺伝子検索の臨床的有用性はまだ無作為試験で証明されていない。スタチン製剤による筋症の発症にも遺伝子異常が関与しているが，スクリーニングの臨床的有用性はまだ証明されていない。クロピドグレルは cytochrome P450 により代謝され活性化されるが，その遺伝子多型により活性化が低下することがあり，急性冠動脈疾患後の心血管合併症のリスクを増大させる。

II. 根拠が確立されて修正可能な危険因子（表 3）

高血圧はこの範疇で最も重要な危険因子であり，高血圧の治療が虚血性と出血性脳卒中の最も効果的な予防法であって，すべての年齢層で治療効果が明確である（JNC 7 による高血圧の分類と治療の推奨は英文原著 Table 6 を参照）。高血圧はまだ十分治療されておらず，治療遵守を改善する必要がある。

喫煙は虚血性脳卒中とくも膜下出血のリスクを増大させるが，脳内出血ではまだ結論が得られていない。禁煙を促進させるプログラムはあるが，それにより長期に脳卒中を低減させるというデータはない。

糖尿病患者では，アンジオテンシン変換酵素阻害薬（ACEI）やアンジオテンシン受容体拮抗薬（ARB）による高血圧の厳密なコントロールを含む総合的なプログラム

により脳卒中リスクを低減させることができる。血糖のコントロールは微小血管の合併症を低下させるが，血糖値の改善が脳卒中発症リスクを低下させるエビデンスはない。スタチン製剤による糖尿病患者の治療が初発脳卒中リスクを低下させることが統計学的パワーをもった臨床試験で示されている。一方フィブラート系薬剤による糖尿病患者の脳卒中予防については有効性がまだ確立されていない。

脂質異常症の治療にはNCEP ATP-IIIの推奨が使われる（英文原著Table 8参照）。スタチンはLDLコレステロールを30～50％減少させ，動脈硬化症患者の脳卒中リスクを低減させる。一方，スタチン以外の脂質治療薬では，ナイアシンはHDLコレステロールを増加させてリポ蛋白(a)を減少させ，フィブラート系薬剤（フィブリン酸誘導体）であるゲムフィブロジル，フェノフィブラート，ベザフィブラートは中性脂肪を減少させHDLコレステロールを増加させるが，スタチン以外の薬物の虚血性脳卒中リスクに対する効果はまだ確立されていない。

心房細動は虚血性脳卒中の重要な危険因子であり，プライマリケアで65歳以上の患者の脈拍を調べ，適応があれば心電図検査を施行することで心房細動の診断が60％増加するとされる。高リスク患者の脳卒中予防には用量調節をしたワルファリンが非常に効果的である。しかしガイドラインによって脳卒中リスクの層別化（英文原著Table 9参照）が異なっているため，抗血栓薬による予防が一律には行われていない。

その他の心疾患で脳卒中のリスクが高い病態には心房性不整脈（心房粗動，洞不全症候群），左房血栓，原発性心腫瘍，疣（vegetation），人工心臓弁が含まれ，その他に拡張型心筋症，冠動脈疾患，弁膜症，心内膜炎などが含まれ，急性冠動脈症候群や左心室瘤もリスクを高める。卵円孔開存（PFO），心房中隔欠損，心房中隔瘤は特に若年者の脳卒中に関与するが，疫学調査ではPFOが初発脳卒中のリスクを高めることは示されていない。そのため脳血管徴候を伴わないPFOに対する薬物または侵襲的治療を評価をした臨床試験がない。原因不明の脳卒中の危険因子としてのアテローム動脈硬化性大動脈プラークの役割はまだ不明であり，一次予防の臨床試験はされていない。

無症候性頸動脈狭窄症（ACS）の内科的治療は頸動脈内膜剥離術（CEA）と内科的治療が比較された頃と比較して進歩しており，最近の研究では内科的治療による脳卒中の年間発症率は≦1％とされている。症候性の場合にはCEAと血管内治療（CAS）の選択があるが，無症候性の場合にはさらに長期の比較が必要であり，米国食品医薬品局（FDA）はACSへのCASをまだ認可していない。女性のACSに対する外科的治療の効果には議論がある。

鎌状赤血球症を有し，高い脳卒中発症リスクがあり，輸血効果が期待できる子供の同定には経頭蓋ドプラ超音波法（TCD）が有用である。しかし，脳卒中の一次予防にヒドロキシウレアが有効である可能性が第II相試験で示唆されており，第III相試験でその有効性を輸血療法と比較する必要がある。また成人に対する脳卒中予防法も確立されるべきである。

閉経後ホルモン補充療法は，標準的なエストロゲン/プロゲステロン製剤を含めて脳卒中のリスクを高める。また選択的エストロゲン受容体調節薬（SERM）であるラロキシフェンやタモキシフェンには脳卒中予防効果はなく，ラロキシフェンでは死亡に至る脳卒中リスクが高くなる可能性がある。チボロンも脳卒中リスクを高める。他の目的のためのホルモン療法については，それぞれの臨床試験で得られた血管系リスクの評価に基づいて告知する必要がある。

経口避妊薬による脳卒中リスクについては，研究によるばらつきや無作為試験の欠如などによりまだ議論がある。虚血性脳卒中についてはメタ解析でオッズ比2.1が報告されているが，年長（35歳以上）女性，喫煙，片頭痛，高血圧，糖尿病，肥満，高コレステロール血症，血栓性素因などのある女性では脳卒中リスクがより高くなることが考えられる。他の脳卒中危険因子がない女性が低用量経口避妊薬を用いることによる脳卒中リスクは低いと考えられる。

食事と栄養についての疫学調査と無作為試験は，DASH（Dietary Approaches to Stop Hypertension：高血圧予防）食のような低ナトリウムで果物と野菜に富んだ食事が脳卒中リスクを減少させることを示唆している。「アメリカ人のための食事ガイドライン」では1日にナトリウム2.3 g（100 mmol）以下とカリウム最低4.7 g（120 mmol）の摂取を推奨している。

運動不足は脳卒中リスクを含む種々の健康に有害な影響をもたらし，観察研究では脳卒中予防に日々の運動を推奨するためのエビデンスが得られているが，これまで規則正しい運動で初発脳卒中リスクの低減を示した臨床試験はない。2008年の「アメリカ人のための運動ガイドライン」では最低で毎週150分以上の中等度の運動（速歩，ジョギング，サイクリング，その他の有酸素運動），または毎週75分の激しい有酸素運動が推奨されている。

肥満と体脂肪の増加が脳卒中リスクを高めるとことが報告されている。これまで体重減少による脳卒中転帰の改善を示した臨床試験はないが，血圧低下との関連が示されており，それによって脳卒中リスクを減少させるかもしれない。

III. 根拠が不十分であるか，修正の可能性がある危険因子（表４）

片頭痛については，恐らく前兆を伴う片頭痛に限られるが，55歳以下の女性において脳卒中との関連が疑われる。脳卒中リスクは前兆を伴う片頭痛の頻度と関連があるかもしれないが，片頭痛の予防が脳卒中リスクを低減するというデータはない。

メタボリックシンドロームの個々の病態は虚血性脳卒中リスクを高めるため，適切に治療されるべきである。メタボリックシンドロームそのものの脳卒中リスクはより高いと考えられるがまだ確定していない。

飲酒については，軽度または適量の飲酒，特にワインは，すべての脳卒中と虚血性脳卒中リスクを低減するが，過度の飲酒は脳卒中リスクを増大させる。これらの関連を示す前向き無作為試験は存在しないが，このような無作為試験をすることは不可能である。

薬物乱用の対象となる薬物のなかで，コカイン，アンフェタミン，ヘロインは脳卒中リスクを高める。これらの薬物は急激な血圧上昇，脳血管攣縮，心内膜炎による塞栓，止血異常などにより虚血性と出血性脳卒中を起こす。

睡眠時呼吸障害は独立した脳卒中リスクと考えられる。習慣的ないびきや過剰な眠気を訴える患者，血管系危険因子，特にBMI 30 kg/m^{2}以上や薬剤抵抗性高血圧がある患者は特別な睡眠検査が必要である。

高ホモシステイン血症は脳卒中リスクを高めるが，ビタミンB群（葉酸，B6，B12）による血中ホモシステイン値低下の効果は一定していない。全般的には，ビタミンB群による3年以上の治療，血中ホモシステイン値の20％以上の低下，および脳卒中既往のない被検者において脳卒中リスクの低減がみられている。

リポ蛋白(a)［Lp(a)］はLDLに似ており，冠動脈疾患のリスクを高める。疫学調査では脳卒中リスクの増大が認められているがすべての調査ではない。高Lp(a)血症は頸動脈狭窄・閉塞症との関連も報告されている。31件の研究のメタ解析ではLp(a)値が脳卒中患者で高く，上位3分の1群では下位3分の1群に比して脳卒中発症が22％高かった。

凝固亢進状態は遺伝性であれ後天性であれ静脈血栓症を起こすが，動脈性脳梗塞を起こすものは少ない。そのうち抗リン脂質抗体（aPLs）の多くは後天的に陽性となり，動脈血栓と関連が強い。抗カルジオリピン抗体（aCL）とループス抗凝固因子が検出に用いられるが，aCLのELISA法は感度が低く，aPL結合のコファクターであるβ_2GPIの抗体測定が血栓症には特異性が高いかもしれない。凝固亢進状態のリスクを詳細に検討し，血栓性素因と静脈性血栓および虚血性脳卒中との関連を確立するには大規模な前向き調査が必要である。

炎症と感染症はアテローム動脈硬化病変の形成に関与するとされる。炎症マーカーとしては高感度C反応性蛋白（hs-CRP）が最もよく使われる（英文原著Table 5参照）。JUPITER試験ではhs-CRP 2 mg/dL以上の症例でスタチンの効果を無作為試験で検討し，脳卒中を含む心血管系評価項目の低減（RR＝0.52）を認めた。慢性関節リウマチ（RA）では脳卒中を含む心血管疾患（CVD）のリスクが上昇して（オッズ比＝1.4～2.0），特に35～55歳の女性で明らかであった。全身性エリテマトーデス（SLE）でもCVDの相対的リスクが2～52倍と非常に高かった。

感染症のうち*Helicobacter pylori*を含む数種の細菌とウイルス（英文原著Table 5参照）がアテローム動脈硬化症を助長するとされる。急性感染症では，インフルエンザに対する発症後2日以内の抗インフルエンザ薬の投与が脳卒中/TIAのリスクを低減し，インフルエンザワクチンも脳卒中リスクを低減すると報告されている。

アスピリンによる脳卒中一次予防については，2006年のAHA/ASAガイドライン（*Stroke* 日本語版 Vol.1, No.3 p27-36参照）でUS Preventive Service Task Forceの勧告に従い脳卒中リスクの高い男性にはアスピリン75mg/日が推奨されていたが，この勧告は脳卒中ではなく，CVDの予防効果に基づいていた。その後2件の臨床試験（JPAD，POPADAD）において脳卒中を含む心血管系評価項目でアスピリンの効果が認められなかった。一方女性を対象としたWHS試験では，脳卒中一次予防に低用量アスピリンの効果があったが心疾患には効果がなかった。

初発脳卒中リスクの評価にはフラミンガム脳卒中プロフィール（FSP；英文原著Table 13参照）や他のリスク評価スケールが用いられるが，一次予防効果を改善させるか否かはまだ充分検討されておらず，新しく同定された危険因子を加えて精度を改善する必要がある。

救急外来における一次予防はスクリーニング，初期介入，他施設・部門への紹介を通して重要な場となり得るが，人的資源，効果，費用の面で今後検討する必要がある。

ガイドライン遵守改善のための予防医療サービス/戦略は実行可能な手段を検討する必要があり，リスクをもつ患者の特定を改善するだけではなく，予防処置の実施とガイドライン遵守の向上を評価する手段が含まれる。

（文責：柳原　武彦）

表1 AHA ガイドラインにおける各推奨のクラスとエビデンスレベルの定義

クラス I	検査や治療法の有用性および有効性を示すエビデンスまたは一般的合意がある。
クラス II	検査や治療法の有用性および有効性に関して相反するエビデンスまたは見解の相違が認められる。
クラス IIa	検査や治療法の有用性および有効性を支持するエビデンスまたは見解が多数を占める。
クラス IIb	有用性および有効性を支持するエビデンスや見解は十分ではない。
クラス III	検査や治療法が有用または有効でなく，場合によっては有害となり得ることを示すエビデンスまたは一般的合意がある。
治療の推奨	
エビデンスレベル A	複数の無作為試験またはメタ解析により得られたデータがある。
エビデンスレベル B	1 つの無作為試験または複数の非無作為試験より得られたデータがある。
エビデンスレベル C	専門家の合意した見解，症例研究，または標準治療法。
診断の推奨	
エビデンスレベル A	参照基準を用いてマスクされた評価者により施行された複数の前向きコホート研究のデータがある。
エビデンスレベル B	1 つのグレード A の研究，または 1 つ以上の症例対照研究のデータ，あるいは参照基準を使ってマスクされていない評価者により施行された研究のデータがある。
エビデンスレベル C	専門家の合意した見解。

表2 一般に修正不可能な危険因子

危険因子	推　奨	エビデンスの分類とレベル
年齢	該当なし	
性別	該当なし	
低出生時体重	該当なし	
人種 / 民族	該当なし	
遺伝的要因	●家族歴は，脳卒中リスクが高いと考えられる人の特定に役立つ可能性がある。	クラス IIa，エビデンスレベル A
	●初回脳卒中の予防を目的とした一般集団の遺伝子スクリーニングは推奨されない。	クラス III，エビデンスレベル C
	●稀な脳卒中の遺伝的要因がある患者には，遺伝カウンセリングへの紹介を検討してもよい。	クラス IIb，エビデンスレベル C
	●脳卒中の素因となる特定の遺伝子疾患の治療（ファブリ病における酵素補充療法など）は妥当かもしれないが，脳卒中リスクの低減は示されておらず，その有効性は不明である。	クラス IIb，エビデンスレベル C
	● HMG-CoA 還元酵素阻害薬（スタチン）療法を考慮する際，現時点ではスタチン誘発性ミオパチーのリスクがある患者のスクリーニングは推奨されない。	クラス III，エビデンスレベル C
	●SAH の既往または脳動内動脈瘤がある近親者が 1 名いる患者を対象とした未破裂脳動内動脈瘤の非侵襲的スクリーニングは推奨されない。	クラス III，エビデンスレベル C
	●SAH の既往または脳動内動脈瘤がある第一度近親者が 2 名またはそれ以上いる患者では，未破裂脳動内動脈瘤の非侵襲的スクリーニングは妥当であろう。	クラス IIb，エビデンスレベル C
	●動脈瘤を伴うメンデル型遺伝子変異の保有者すべてに対する脳動内動脈瘤のスクリーニングは推奨されない。	クラス III，エビデンスレベル C
	●ADPKD があり，かつ ADPKD および SAH / 脳動内動脈瘤がある近親者が 1 名以上いる患者では，未破裂脳動内動脈瘤の非侵襲的スクリーニングを検討してもよい。	クラス IIb，エビデンスレベル C
	●頸動脈に線維筋性形成異常のみられる患者では，未破裂脳動内動脈瘤の非侵襲的スクリーニングを検討してもよい。	クラス IIb，エビデンスレベル C
	●薬理遺伝学に基づくビタミン K 拮抗薬の投与は今のところ推奨されない。	クラス III，エビデンスレベル C

SAH：くも膜下出血，ADPKD：常染色体優性多発性嚢胞腎。

表3 根拠が確立されて修正可能な危険因子

危険因子	推　奨	エビデンスの分類とレベル
高血圧	●JNC 7 の報告に従って，定期的な血圧スクリーニングと適切な治療（生活習慣の改善および薬理学的療法の両者を含む）が推奨される。	クラス I，エビデンスレベル A
	●収縮期血圧と拡張期血圧の治療目標値は，それぞれの値と脳卒中および心血管系イベントのリスク低減の間に関連がみられるため，< 140 mmHg および< 90 mmHg とする。	クラス I，エビデンスレベル A
	糖尿病や腎疾患を合併している高血圧患者の血圧目標値は< 130/80 mmHg とする（糖尿病の項も参照）。	クラス I，エビデンスレベル A

（次ページに続く）

表3 根拠が確立されて修正可能な危険因子（続き）

危険因子	推　奨	エビデンスの分類とレベル
喫煙	●喫煙と虚血性脳卒中およびSAHとの強い関連を示した疫学研究に基づき，非喫煙者の喫煙回避と現喫煙者の禁煙が推奨される。	クラスⅠ，エビデンスレベルB
	●間接喫煙の回避が脳卒中の発症を低減させることを示すデータはないが，脳卒中リスクの上昇と，その他の心血管系イベントリスクに対する間接喫煙回避による効果を示した疫学データに基づき，間接喫煙への曝露を回避することは妥当である。	クラスⅡa，エビデンスレベルC
	●患者の禁煙時には，必ず喫煙状況について話し合うべきである。カウンセリング，ニコチン補充療法，経口禁煙補助薬など多様な手法を使用することは，包括的な禁煙戦略の一環として有用である。	クラスⅠ，エビデンスレベルB
糖尿病	●JNC 7ガイドラインで言及されているとおり，包括的な心血管系リスク低減プログラムの一環として，1型または2型糖尿病患者の血圧コントロールが推奨される。	クラスⅠ，エビデンスレベルA
	●糖尿病がある成人患者では，ACEIまたはARBによる降血圧治療が有用である。	クラスⅠ，エビデンスレベルA
	●糖尿病がある成人，特に他の危険因子も有する患者では，初回脳卒中リスクを低減させるためにスタチンによる治療が推奨される。	クラスⅠ，エビデンスレベルA
	●糖尿病患者では，脳卒中リスクの低減を目的としてフィブラート系薬剤による単剤療法の施行を考慮してもよい。	クラスⅡb，エビデンスレベルB
	●スタチンにフィブラート系薬剤を追加しても，糖尿病患者の脳卒中リスクの低減に有用ではない。	クラスⅢ，エビデンスレベルB
	●脳卒中リスクの低減に対するアスピリンの有益性は，糖尿病患者では十分に確立されていない。しかし，CVDリスクの重い患者へのアスピリンの投与は考慮されてもよい。（アスピリンの推奨も参照。）	クラスⅡb，エビデンスレベルB
脂質異常症	●冠動脈疾患や糖尿病など特定の重リスク疾患がある患者では，NCEPガイドラインで言及されているように，虚血性脳卒中の一次予防を目的として，生活習慣の改善とLDLコレステロールの目標値達成に加えてスタチンによる治療を行うことが推奨される。	クラスⅠ，エビデンスレベルA
	●重トリグリセリド血症患者では，フィブラート系薬剤を検討してもよいが，虚血性脳卒中の予防に対するフィブラート系薬剤の有効性は確立されていない。	クラスⅡb，エビデンスレベルC
	●HDLコレステロール低値またはリポ蛋白（a）高値の患者では，ナイアシンを検討してもよいが，このような病態の患者におけるナイアシンの虚血性脳卒中予防に対する有効性は確立されていない。	クラスⅡb，エビデンスレベルC
	●スタチンではLDLコレステロール目標値を達成できないか，スタチンに忍容性がない患者には，フィブラート系薬剤，胆汁酸吸着薬，ナイアシン，エゼチミブなど他の脂質低下療法による治療を検討してもよいが，脳卒中リスクの低減に対するこれらの治療法の有効性は確立されていない。	クラスⅡb，エビデンスレベルC
心房細動	●65歳を超える患者を対象に，脈拍測定と心電図検査（適応となる場合）を用いたプライマリケア現場での心房細動の積極的なスクリーニングは有用と考えられる。	クラスⅡa，エビデンスレベルB
	●重リスクと判定されたすべての非弁膜症性心房細動患者と，脳卒中リスクが中等度でワルファリンを安全に投与できると判定された多くの患者には，ワルファリンの用量調節（INR目標値2.0～3.0）が推奨される。	クラスⅠ，エビデンスレベルA
	●低リスクの心房細動患者と一部の中等度リスクの心房細動患者には，患者の希望，抗凝固療法により予想される出血リスク，厳重な抗凝固モニタリングの有無に応じてアスピリンによる抗血小板療法が推奨される。	クラスⅠ，エビデンスレベルA
	●抗凝固療法に不適格と判定された重リスクの心房細動患者については，アスピリン単独よりもクロピドグレルとアスピリンによる2剤併用抗血小板療法の方が，大出血リスクは重いものの脳卒中の予防効果が高く，妥当かもしれない。	クラスⅡb，エビデンスレベルB
	●高齢の心房細動患者には，血圧の積極的管理に加えて抗血栓薬の予防的投与が有用と考えられる。	クラスⅡa，エビデンスレベルB
その他の心疾患	●ACC / AHA診療ガイドラインは，心臓弁膜症，不安定狭心症，慢性安定狭心症，急性心筋梗塞など，種々の心疾患をもつ患者の脳卒中リスクの低減策を提示しており，推奨される。	
	●神経症状や特異的な心原性疾患がない場合は，PFOなどの心疾患のスクリーニングは推奨されない。	クラスⅢ，エビデンスレベルA
	●左心室に壁在血栓や無収縮セグメントを伴ったST部上昇心筋梗塞後の患者に対する脳卒中予防を目的としたワルファリンの処方は妥当である。	クラスⅡa，エビデンスレベルA
無症候性頸動脈狭窄症	●無症候性頸動脈狭窄症患者については，他の治療可能な脳卒中危険因子のスクリーニングを行い，適切な生活習慣の改善と薬物療法を始めるべきである。	クラスⅠ，エビデンスレベルC
	●頸動脈血行再建術の候補となる無症候性患者の選択にあたっては，併存疾患，余命，他の個別的因子を評価するほか，患者の希望を把握したうえで手術のリスクと有益性を充分に検討すべきである。	クラスⅠ，エビデンスレベルC
	●これまで引用されたすべてのCEAの臨床試験においてアスピリンが抗血小板薬として使用されているため，禁忌である場合を除きCEA施行時にはアスピリンの併用が推奨される。	クラスⅠ，エビデンスレベルC
	●予防的CEAは，合併症および死亡率が3%未満であれば，厳選された無症候性頸動脈狭窄症患者（血管造影で60%以上，超音波ドプラ検査で70%以上）において適応があるだろう。 外科手術の有益性が無作為臨床試験の成績から期待されたものより実際は低く，また事物療法が進歩したことにより，引用された3%という合併症発現率の閾値は高い可能性があることに注目すべきである。	クラスⅡa，エビデンスレベルA

（次ページに続く）

表3 根拠が確立されて修正可能な危険因子（続き）

危険因子	推　奨	エビデンスの分類とレベル
無症候性頭蓋内動脈狭窄症	●予防的頭蓋内ステント留置術は，厳選された無症候性頭蓋内動脈狭窄症患者（血管造影で 60%以上，確認された超音波ドプラ検査で 70%以上，または超音波検査での狭窄が 50～69%の場合は CT 血管造影または MRA で 80%以上）を対象として検討するのが適当かもしれない。現行の薬物療法のみの治療を上回る血行再建術の利点は十分に確立されていない。	クラス IIb，エビデンスレベル B
	●外科手術のリスクが高い無症候性患者における CEA の代替療法としての CAS の有用性は明らかではない。	クラス IIb，エビデンスレベル C
	●無症候性頭蓋内動脈狭窄症の集団スクリーニングは推奨されない。	クラス III，エビデンスレベル B
鎌状赤血球症	●SCD 患児については，2 歳から TCD によるスクリーニングを行うべきである。	クラス I，エビデンスレベル B
	●最適なスクリーニング間隔は確立されていないが，年少児および TCD による血流速度が境界域異常である小児については，頻回のスクリーニングを行うことにより，高リスク TCD 徴候を検出して介入を行うのが妥当である。	クラス IIa，エビデンスレベル B
	●輸血療法（ヘモグロビン S をベースライン値の 90%超から目標値の 30%未満に減少させる）は，脳卒中リスクの高いこれら小児の脳卒中リスクの低減に有効である。	クラス I，エビデンスレベル B
	●追加の臨床試験の結果がでるまでは，TCD による血流速度が正常値に回復している小児であっても，輸血継続の適応があるだろう。	クラス IIa，エビデンスレベル B
	●脳卒中リスクが高いが，定期的な赤血球輸血による治療を施行できないかその意志のない小児では，ヒドロキシウレア治療または骨髄移植が考慮されてもよい。	クラス IIb，エビデンスレベル C
	●輸血により初発脳卒中を予防する小児を選択するための MRI および MRA の判定基準は確立されておらず，この目的でこれらの検査を TCD の代わりに行うことは推奨されない。	クラス III，エビデンスレベル B
	●成人の SCD 患者は，既知の脳卒中危険因子について評価を行い，本声明の一般的ガイドラインに従って管理するべきである。	クラス I，エビデンスレベル A
閉経後ホルモン療法	●閉経後女性における脳卒中の一次予防を目的としてホルモン療法（CEE 単独または CEE＋MPA 併用）を用いてはならない。	クラス III，エビデンスレベル A
	●脳卒中の一次予防を目的としてラロキシフェン，タモキシフェン，チボロンなどの SERM を用いてはならない。	クラス III，エビデンスレベル A
経口避妊薬	●他の危険因子（喫煙，血栓塞栓症の既往など）がある女性では，OC は有害と考えられる。	クラス III，エビデンスレベル C
	●OC の使用によりリスクが上昇しても OC の使用を選択する女性については，脳卒中の危険因子に対する積極的な治療が妥当であろう。	クラス IIb，エビデンスレベル C
食事および栄養	●「アメリカ人のための食事ガイドライン」に示されているとおり，血圧低下にはナトリウム摂取量を減らしカリウム摂取量を増やすことが推奨される。	クラス I，エビデンスレベル A
	●果物，野菜，低脂肪乳製品の消費に重点を置き飽和脂肪を抑えた DASH 食（本文参照）も，血圧を低下させることから推奨される。	クラス I，エビデンスレベル A
	●果物や野菜に富み結果的にカリウムの多い食事は有益であり，脳卒中リスクを低減すると考えられる。	クラス I，エビデンスレベル B
運動不足	●運動の増強は，脳卒中リスクの低下と関連するため推奨される。	クラス I，エビデンスレベル B
	2008 年の「アメリカ人のための運動ガイドライン」で推奨されている，成人には週に 150 分以上の中等度の有酸素運動か，週に 75 分以上の激しい有酸素運動を支持する。	クラス I，エビデンスレベル B
肥満および体脂肪分布	●過体重の肥満者では，血圧を低下させる手段として体重減少が推奨される。	クラス I，エビデンスレベル A
	●過体重の肥満者では，脳卒中リスクの低減策として体重減少が妥当であろう。	クラス IIa，エビデンスレベル B

SAH：くも膜下出血，*JNC 7: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*，ACEI：アンジオテンシン変換酵素阻害薬，ARB：アンジオテンシン II 受容体拮抗薬，CVD：心血管疾患，NCEP：*the National Cholesterol Education Program*，ACC/AHA：*American College of Cardiology / American Heart Association*，PFO：卵円孔開存，CEA：頭蓋外内膜剥離術，CAS：頭蓋外血管形成・ステント留置術，SCD：鎌状赤血球症，TCD：経頭蓋ドプラ検査，CEE：結合型ウマエストロゲン，MPA：酢酸メドロキシプロゲステロン，SERM：選択的エストロゲン受容体調節薬，OC：経口避妊薬。

表4 根拠が不十分であるか修正の可能性がある危険因子

危険因子	推　奨	エビデンスの分類とレベル
片頭痛	●頻回の片頭痛と脳卒中リスクには関連があるため，片頭痛の発症頻度を低下させる治療は妥当かもしれないが，こうした治療が初回脳卒中リスクを低減することを示したデータはない。	クラス IIb，エビデンスレベル C
メタボリックシンドローム	●NCEP ATP III および JNC 7 で勧奨され，また，本ガイドラインの他の項で支持または推奨されているとおり，生活習慣の改善（すなわち運動，体重減少，適切な食事）や薬物療法（すなわち降圧薬，脂質低下薬，血糖降下薬，抗血小板療法）など，メタボリックシンドロームの個々の要素の管理が推奨される（各項目の推奨のクラスおよびエビデンスレベルの項目を参照）。	
	●インスリン抵抗性症候群の種々の構成要素を改善する薬剤の，脳卒中リスク低減に関する有効性は不明である。	クラス IIb，エビデンスレベル C

（次ページに続く）

表4 根拠が不十分であるか修正の可能性がある危険因子（続き）

危険因子	推　奨	エビデンスの分類とレベル
飲酒	●2004年の US Preventive Services Task Forceの推奨に記述されているとおり，健康に関する多くの課題の克服に向けて，確立されたスクリーニングおよびカウンセリングによる大量飲酒者の飲酒または節酒が推奨される。	クラスⅠ，エビデンスレベルA
	●飲酒者の飲酒量は，男性で1日2杯以下，非妊娠女性で1日1杯以下が適当であろう。	クラスⅡb，エビデンスレベルB
薬物乱用	●薬物乱用患者には適切な治療プログラムの紹介が妥当である。	クラスⅡa，エビデンスレベルC
睡眠呼吸障害	●SDBはその他の血管系危険因子や心血管疾患との関連がみられるため，特に腹部肥満，高血圧，心疾患，薬剤抵抗性高血圧を呈する患者では，詳細な病歴聴取と，もし適応があれば，特定の検査によるSDBの評価が推奨される。	クラスⅠ，エビデンスレベルA
	●脳卒中リスクを低減するために睡眠時無呼吸の治療を行うことを考慮してもよいが，その有効性は不明である。	クラスⅡb，エビデンスレベルC
高ホモシステイン血症	●高ホモシステイン血症患者では虚血性脳卒中の予防にビタミンB群［ピリドキシン（B_6），コバラミン（B_{12}），葉酸］の使用を考慮してもよいが，その有効性は十分に確立されていない。	クラスⅡb，エビデンスレベルB
リポ蛋白（a）高値	●リポ蛋白（a）高値の患者における虚血性脳卒中の予防には，ナイアシンの使用を考慮してもよいが，その有効性は十分に確立されていない。	クラスⅡb，エビデンスレベルB
線維素溶解状態	●初回脳卒中の予防を目的とした遺伝性線維素溶解状態を検出する遺伝子スクリーニングの有用性は十分に確立されていない。	クラスⅡb，エビデンスレベルC
	●遺伝性または後天性の血栓性素因をもつ無症候性患者の脳卒中一次予防を目的とした特定の治療の有用性は十分に確立されていない。	クラスⅡb，エビデンスレベルC
	●aPL陽性が持続する患者には，脳卒中の一次予防を目的とした低用量アスピリン（81 mg/日）の適応はない。	クラスⅢ，エビデンスレベルB
炎症および感染	●脳卒中リスクが高いと考えられる患者の同定を目的として，CVDのみられない患者を対象にhs-CRPやLp-PLA2などの炎症マーカーの測定を検討してもよいが，その有効性（すなわち，日常診療における有用性）は十分に確立されていない。	クラスⅡb，エビデンスレベルB
	●RAやSLEなどの慢性炎症性疾患患者は，脳卒中リスクが高いと考えるべきである。	クラスⅠ，エビデンスレベルB
	●慢性感染症に対する抗生物質による治療は，脳卒中の予防手段としては推奨されない。	クラスⅢ，エビデンスレベルA
	●hs-CRP高値の患者では，脳卒中リスクを低減するためスタチンによる治療を考慮してもよい。	クラスⅡb，エビデンスレベルB
	●年1回のインフルエンザワクチンの接種は，脳卒中リスクのある患者に有用と考えられる。	クラスⅡa，エビデンスレベルB
脳卒中の一次予防を目的としたアスピリン	●リスクが十分に高く治療による有益性がリスクを上回る患者（心血管系イベントの10年リスクが6～10%）では，心血管疾患（脳卒中を含むがこれに限定されない）の予防を目的としたアスピリンの使用が推奨される。	クラスⅠ，エビデンスレベルA
	●リスクが十分に高く治療による有益性がリスクを上回る女性では，初回脳卒中の予防にアスピリン（81 mg連日または100 mg隔日）が有用と考えられる。	クラスⅡa，エビデンスレベルB
	●アスピリンは，低リスク患者における初回脳卒中の予防には有用ではない。	クラスⅢ，エビデンスレベルA
	●アスピリンは，糖尿病または糖尿病＋無症候性末梢動脈疾患（足関節上腕血圧比≦0.99と定義）がある患者では，他に確立されたCVDがない場合は，初回脳卒中の予防に有用ではない。	クラスⅢ，エビデンスレベルB
	●その他の特定の状況（心房細動，頸動脈狭窄など）に対するアスピリンの使用については，本声明の関連する項において検討されている。	
初回脳卒中リスクの評価	●各患者について脳卒中リスクの評価を行うべきである。	クラスⅠ，エビデンスレベルA
	●治療的介入が有効と考えられる患者や，個々の危険因子だけでは治療されない可能性がある患者の同定には，FSPのようなリスク評価ツールの使用が妥当である。	クラスⅡa，エビデンスレベルB
救急外来における一次予防	●EDでの禁煙プログラムと介入が推奨される。	クラスⅠ，エビデンスレベルB
	●EDで心房細動を診断し，抗凝固療法の評価をすることが推奨される。	クラスⅠ，エビデンスレベルB
	●EDにおける高血圧のスクリーニングは妥当である。	クラスⅡa，エビデンスレベルC
	●患者に薬物またはアルコール乱用の懸念が認められる場合は，EDから適切な治療プログラムへ紹介するのが妥当である。	クラスⅡa，エビデンスレベルC
	●糖尿病治療や脳卒中リスクである生活習慣因子（肥満，アルコール／薬物乱用，運動不足）の改善を目的としたEDにおけるスクリーニング，初期介入ならびに紹介の有効性は確立されていない。	クラスⅡb，エビデンスレベルC
ガイドラインの遵守を向上させる予防医療サービス／戦略	●脳卒中リスクのある全患者を対象に，危険因子を体系的に同定および治療する方法を導入することは有用と考えられる。	クラスⅡa，エビデンスレベルC

JNC 7: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, NCEP ATP Ⅲ：*the National Cholesterol Education Program (NCEP)- Adult Treatment Panel*，SDB：睡眠呼吸障害，CVD：心血管疾患，aPL：抗リン脂質抗体，hs-CRP：高感度C反応性蛋白，Lp-PLA2：リポ蛋白関連ホスホリパーゼA2，RA：関節リウマチ，SLE：全身性エリテマトーデス，FSP：フラミンガム脳卒中プロファイル，ED：救急外来。

卒中一级预防指南

美国心脏病学会 / 美国卒中协会对于专业医务人员的指南

经美国神经病学学会批准此指南作为神经科医师教育材料 (摘译)

Guidelines for the Primary Prevention of Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

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背景和目的：本指南概览了目前已证实的和新发现的卒中危险因素的相关证据，提出循证医学推荐，以降低首次卒中的风险。

方法：指南制定委员会成员由委员会主席根据他们既往在相关领域的工作成绩而任命，并得到美国心脏病学会 (American Heart Association，AHA) 卒中协会科学声明监督委员会和 AHA 稿件监督委员会批准。委员会系统性综述 (涵盖时间自上次 2006 版指南发表后至 2009 年 4 月) 了所有发表的指南、个人经验和专家意见，并总结为目前的证据，提出现有知识的缺陷，并在合适的情况下，根据规范的 AHA 标准制定推荐。所有成员均有机会对推荐给予评价，并批准最终稿。本指南还得到卒中协会领导和 AHA 科学声明监督委员会的广泛评议，再提交 AHA 科学监督和协调委员会审核和批准。

结果：评价了个体首发卒中的各种风险。首次卒中的危险因素或危险因子按照是否可改变 (不可改变、可改变、潜在可改变) 以及证据级别 (资料完整或资料尚不完整) 进行分类。不可改变的危险因素包括年龄、性别、低出生体重、种族 / 人种和遗传易感性。资料完整的可改变的危险因素包括高血压、吸烟暴露、糖尿病、房颤及其他特定心脏病、血脂异常、颈动脉狭窄、镰状细胞病、绝经后激素治疗、营养不良、缺乏体育活动及肥胖或体脂分布异常。资料不全的或潜在可改变的危险因素包括：代谢综合症、酗酒、药物滥用、使用口服避孕药、睡眠呼吸障碍、偏头痛、高同型半胱氨酸血症、脂蛋白 (a) 增高、高凝状态、炎症和感染。此外，本文综述了使用阿司匹林作为卒中一级预防的数据。

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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The online-only Data Supplement is available at http://stroke.ahajournals.org/cgi/content/full/10.1161/STR.0b013e3181fcb238.

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结论：大量证据表明各种特定的因素可增加首次卒中的风险，通过各种治疗策略可降低此风险。

关键词：美国心脏病学会科学声明，卒中，危险因素，一级预防
(*Stroke*. 2011;42:517-584.　复旦大学附属华山医院神经内科　董漪 摘译 程忻 董强 校)

卒中仍是影响健康的主要问题之一，其所消耗的人力和财力巨大。美国每年大约有 795 000 人发生卒中，其中 610 000 人为首次卒中患者，目前有 640 万卒中幸存者[1]。每年死于卒中的患者约 134 000 人，是美国人第三位的死亡原因，仅次于心脏病及癌症[1]。美国心脏病学会 (American Heart Association，AHA) 与其他卫生组织协作，设立的目标是 10 年内使心血管疾病和卒中的死亡率降低 25%[1]。1996 至 2006 年期间，卒中死亡率降低了 33.5%，总体卒中死亡数降低了 18.4%[1]，至 2008 年卒中死亡率下降已超过了 25% 的目标。卒中死亡率的降低在男性中更明显 (经年龄校正，男女比从 1.11 降低至 1.03)[1]。尽管整体卒中死亡率在下降，卒中发生率可能在增加[2]。从 1988 年至 1997 年，经年龄校正的卒中住院率上升了 18.6%(每万人从 560 人上升至 664 人)，而总体卒中住院次数增加了 38.6%(每年从 592 811 增加至 821 760)[3]。2010 年，卒中治疗成本约 737 亿美元 (包括直接及间接花费)[1]，平均每个生命的花费约 140 048 美元[1]。

卒中也是造成功能障碍的主要原因，20% 的幸存者在卒中 3 个月时需要机构照料，15-30% 的患者可能永久致残[1]。卒中也是足以改变生活的事件，不仅卒中患者，而且他们的家庭成员及监护人的生活也会受到影响。效用分析表明对一半以上的卒中高危患者来说，重症卒中甚至比死亡更坏[4]。尽管缺血性卒中患者急性期可选择性给予静脉组织型纤溶酶原激活剂或其它有效的急性期治疗，有效的预防仍是减轻卒中负担的最佳方式[5-7]。由于超过 77% 的卒中为首次事件[1]，故一级预防尤为重要。英国牛津郡的研究发现通过使用预防性治疗和减少危险因素，其重症卒中的年龄特异性发病率在 20 年间降低了 40%[9]。拥有健康生活方式的个体较无健康生活方式者，首次卒中风险减少 80%[8]。需识别高危或易于卒中的患者并予针对性干预，具体内容会在下文中提及。

本指南概览了目前已证实的和新发现的卒中危险因素的相关证据，对 2006 年卒中一级预防指南进行了完全的更新[9]，主要是拓宽了指南的适用范围。2006 版的指南关注缺血性卒中，由于缺血性和出血性卒中在危险因素和预防措施方面有部分交叉，因此本版卒中指南加入了出血性卒中方面的内容，更倾向于患者个体化的卒中预防。这与基于人群的预防，即“通过整体人群的干预使其危险因素的分布调整至较低的水平”相反，并在 AHA 在社区水平提高心血管健康声明中有所体现[10]。

指南制定委员会成员由委员会主席根据他们既往在相关领域的工作成绩而任命，并得到 AHA 卒中协会科学声明监督委员会和 AHA 稿件监督委员会批准。委员会系统性综述 (涵盖时间自上次 2006 版指南发表后至 2009 年 4 月) 了所有发表的指南、个人经验和专家意见，并总结为目前的证据，提出现有知识的缺陷，并在合适的情况下，根据规范的 AHA 标准制定推荐。所有成员均有机会对推荐给予评价，并批准最终稿。本指南还得到卒中协会领导和 AHA 科学声明监督委员会的广泛评议，再提交 AHA 科学监督和协调委员会审核和批准。由于各标题下的内容多样，每条推荐无法采用统一的系统性格式。在选择任一治疗性推荐时，需考虑患者个体的需求。首次卒中的危险因素 (直接增加发病的可能性，或假如缺乏或去除时可减少发病的可能性) 或危险标记物 (暴露量与发病可能性增加相关，但因果关系尚不明确)[11] 根据他们是否可改变 (不可改变、可改变、潜在可改变) 以及证据级别 (资料完整或资料尚不完整) 进行分类[7]。虽然这个分类方法相对主观，但是资料完整的可改变因素，其资料明确、有支持性流行病学证据且有随机临床研究证据证明可通过调整危险因素降低风险。资料欠缺或潜在可改变的危险因素，其流行病学证据不明确或缺乏随机临床研究的证据说明危险因素调整后可使得卒中风险降低。表格列出了预计的患病率、人群归因危险度 (即人群中因某种特定的危险因素导致缺血性卒中的比例，计算公式为 100×([患病率 ×(相对危险度 -1)]/[患病率 ×(相对危险度 -1)+1][12]、相对危险度、以及各项公认危险因素经治疗后风险降低的程度。目前尚不清楚的内容以问号标记。引用这些研究数据时需注意，由于临床试验的设计和研究人群的不同，

表 14 推荐建议总结 (部分)

危险因素	推荐
不可改变的一般危险因素	
年龄	N/A
性别	N/A
低出生体重	N/A
人种 / 种族	N/A
遗传性因素	● 询问家族史有助于发现卒中风险增加的个体 (*IIa 类，A 级推荐*)。 ● *为预防首次卒中不推荐对所有人进行基因筛查 (III 类，C 级推荐*)。 ● 对于罕见基因原因引起卒中的患者可进行遗传咨询 (*IIb 类，C 级推荐*)。 ● 治疗引起卒中的特定基因 (如 Fabry 病和酶替代治疗) 可能合理，但未发现治疗可以减少卒中风险，且其有效性尚不明确 (*IIb 类，C 级推荐*)。 ● 启动他汀治疗前不推荐筛查患者有无他汀引起的肌病风险 (*III 类，C 级推荐*)。 ● 1 个亲属患蛛网膜下腔出血 (SAH) 或颅内动脉瘤，不推荐对未破裂的颅内动脉瘤进行非创伤性筛查 (*III 类，C 级推荐*)。 ● ≥ 2 个一级亲属患 SAH 或颅内动脉瘤，对未破裂的颅内动脉瘤进行非创伤性筛查可能合理 (*IIb 类，C 级推荐*)。 ● 携带动脉瘤相关的孟德尔疾病基因突变的患者，不推荐进行颅内动脉瘤的全面筛查 (*III 类，C 级推荐*)。 ● 常染色体显性多囊肾病 (ADPKD) 患者，并且≥ 1 个亲属患 ADPKD 和 SAH 或颅内动脉瘤的，可考虑对未破裂的颅内动脉瘤进行非创伤性筛查 (*IIb 类，C 级推荐*)。 ● 颈动脉肌纤维发育不良的患者，可考虑对未破裂的颅内动脉瘤进行非创伤性筛查 (*IIb 类，C 级推荐*)。 ● 不推荐根据药物遗传学调整维生素 K 拮抗剂的剂量 (*III 类，C 级推荐*)。
资料完整的可改变的危险因素	
高血压	● 与 JNC 7 报告一致，推荐血压常规筛查及适宜的治疗，包括生活方式的调整和药物治疗 (*I 类，A 级推荐*)。 ● 收缩压目标值 <140 mmHg，舒张压目标值 <90 mmHg，此血压水平与减少卒中及心血管事件相关 (I 类，A 级推荐)。高血压合并糖尿病或肾病的患者，血压控制目标 <130/80 mmHg (*I 类，A 级推荐*)。
吸烟	● 流行病学证据充分表明吸烟与缺血性卒中和 SAH 均相关，推荐不吸烟或戒烟 (*I 类，B 级推荐*)。 ● 虽然缺乏避免吸烟环境可以减少卒中发生的数据，但流行病学研究发现吸烟环境可增加卒中风险，而避免吸烟环境可减少其它心血管事件的发生，故推荐减少环境中的烟草接触 (*IIa 类，C 级推荐*)。 ● 应询问每个患者的吸烟史，采用多种手段有助于患者的全程戒烟，包括咨询、尼古丁替代治疗及口服戒烟药物 (*I 类，B 级推荐*)。
糖尿病	● 按照 JNC7 指南推荐，不论是 1 型或 2 型糖尿病患者均应将控制血压作为全面降低心血管危险因素项目的一部分 (*I 类，A 级推荐*)。 ● 伴有糖尿病的高血压患者推荐予 ACEI 或 ARB 治疗 (*I 类，B 级推荐*)。 ● 糖尿病患者合并其它危险因素时，推荐他汀药物治疗以降低首次卒中的发生风险 (*I 类，A 级推荐*)。 ● 糖尿病的患者可考虑予贝特类单药治疗降低卒中风险 (*IIb 类，B 级推荐*)。 ● 贝特类与他汀类联合治疗无法减少糖尿病患者的卒中风险 (*III 类，B 级推荐*)。 ● 糖尿病患者使用阿司匹林减少卒中风险的作用并不理想，但是，具有心血管疾病 (CVD) 高风险的患者可以考虑阿司匹林治疗 (*IIb 类，B 级推荐*)。
血脂异常	● 除了生活方式改变外，使用 HMG-CoA 还原酶抑制剂 (他汀) 治疗可降低 LDL- 胆固醇，其目标按照 NCEP 指南，推荐用于冠心病或特定高风险人群如糖尿病的卒中一级预防 (*I 类，A 级推荐*)。 ● 苯氧酸类衍生物可考虑治疗高甘油三酯血症，但其预防缺血性卒中的作用尚不明确 (*IIb 类，C 级推荐*)。 ● 低 HDL 胆固醇或高脂蛋白 (a) 的患者可考虑给予烟酸治疗，但其预防存在上述情况患者的缺血性卒中的作用尚不明确 (*IIb 类，C 级推荐*)。 ● 他汀治疗后未达到 LDL 目标水平或不能耐受他汀的患者，可给予其它降脂治疗，如苯氧酸类衍生物、胆汁酸螯合剂、烟酸、依折麦布，但其降低卒中风险的有效性尚不明确 (*IIb 类，C 级推荐*)。
房颤	● 一级预防机构对 65 岁以上人群应积极筛查房颤，包括先了解脉搏，随后行心电图检查 (*IIa 类，B 级推荐*)。 ● 所有非瓣膜性病变房颤的患者伴有卒中的高或中度风险，推荐根据 INR(目标值 2.0-3.0) 校正华法林剂量，安全服用 (*I 类，A 级推荐*)。 ● 基于患者的偏好、抗凝后出血风险的评估、以及是否可得到高质量抗凝监测，在低风险和部分中度风险的房颤患者中可推荐阿司匹林的抗血小板治疗 (*I 类，A 级推荐*)。 ● 高风险的房颤患者若不适合抗凝治疗的话，可选用双联抗血小板治疗即氯吡格雷联合阿司匹林，可能较阿司匹林单药治疗更具有预防卒中的作用，但可能带来出血增加的风险 (*IIb 类，B 级推荐*)。 ● 对于老年房颤患者来说，应严格控制血压联合抗栓治疗 (*IIa 类，B 级推荐*)。
其它心脏病	● ACC/AHA 指南中介绍了患有各种心脏疾病时如何降低卒中风险，包括瓣膜性心脏病，不稳定性心绞痛，慢性稳定性心绞痛，及急性心肌梗塞。

(续)

表 14 续

危险因素	推荐
	● 缺乏神经系统表现或特定的心脏病因时，不推荐筛查如卵圆孔未闭 (PFO) 之类的心脏情况 (*III 类，A 级推荐*)。
	● ST 段抬高性心肌梗塞后伴有左室附壁血栓或左室壁节段性活动不良的患者可考虑予华法林治疗预防卒中 (*IIa 类，A 级推荐*)。
无症状性颈动脉狭窄	● 无症状性颈动脉狭窄的患者应接受其它可治疗的卒中危险因素的筛查，包括适宜的生活方式改变和药物治疗 (*I 类，C 级推荐*)。
	● 应对无症状患者合并的其它疾病和预期寿命评估后，并在考虑患者意愿的情况下全面讨论手术的利弊，再进行血管再通手术 (*I 类，C 级推荐*)。
	● 鉴于所有颈动脉内膜剥脱术 (CEA) 的临床研究均使用阿司匹林抗血小板治疗，推荐 CEA 时联合应用阿司匹林，除非阿司匹林禁忌 (*I 类，C 级推荐*)。
	● 手术病死率 <3% 的预防性 CEA 手术可用于高度选择性的无症状性颈动脉狭窄的病人 (血管造影显示≥ 60% 狭窄，可靠的多普勒超声显示≥ 70% 狭窄)(*IIa 类，A 级推荐*)。根据既往的随机对照研究，应注意 CEA 手术的获益度可能较预想的要低。因为药物治疗的发展，3% 的手术并发症可能较高。
	● 预防性颈动脉支架手术可用于高度选择性的无症状性颈动脉狭窄的病人 (血管造影显示≥ 60% 狭窄，可靠的多普勒超声显示≥ 70% 狭窄，或超声显示 50-69% 的狭窄但 CT 血管造影或 MRA 显示≥ 80% 狭窄)。血管再通较单独药物治疗的优势尚不明确 (*IIb 类，B 级推荐*)。
	● 手术高风险的无症状性患者，颈动脉血管成形及支架置入术 (CAS) 作为 CEA 的替代治疗疗效不肯定 (*IIb 类，C 级推荐*)。
	● 不推荐对人群进行无症状性颈动脉狭窄的筛查 (*III 类，B 级推荐*)。
镰状细胞病	● 患镰状细胞病的儿童应从 2 岁起接受经颅多普勒超声 (TCD) 筛查 (*I 类，B 级推荐*)。
	● 尽管理想的筛查频率尚不明确，但对于低龄儿童和 TCD 血流速度临界的儿童应增加筛查频率，以发现可干预的高危 TCD 适应症 (*IIa 类，B 级推荐*)。
	● 卒中风险增高的儿童可接受输血治疗 (目标是使血红蛋白 S 从基线 >90% 降低至 <30%)，以降低卒中风险 (*I 类，B 级推荐*)。
	● TCD 血流速度恢复正常的病人可考虑接受持续输血，但仍需进一步研究 (*IIa 类，B 级推荐*)。
	● 卒中高危的患儿，如无法或不愿接受正常红细胞输注治疗，可考虑羟基脲或骨髓移植治疗 (*IIb 类，C 级推荐*)。
	● 根据 MRI 或核磁共振血管造影 (MRA) 选择患儿予输注治疗用于卒中一级预防尚不明确，不推荐因此目的将这些检查取代 TCD(*III 类，B 级推荐*)。
	● 对患镰状细胞病的成人，应评估已知的卒中风险因素，并根据本指南给予相应的处理 (*I 类，A 级推荐*)。
绝经后激素治疗	● 绝经后妇女的卒中一级预防，不可予激素治疗 (共轭雌激素合用或不合用醋酸甲羟孕酮)(*III 类，A 级推荐*)。
	● 选择性雌激素受体调节剂，如：雷洛昔芬、他莫西芬、替勃龙，不可用于卒中一级预防 (*III 类，A 级推荐*)。
口服避孕药	● 口服避孕药可能对合并其它危险因素 (如：吸烟，既往血栓栓塞事件) 的妇女有害 (*III 类，C 级推荐*)。
	● 尽管卒中风险增加但仍选择口服避孕药者，可能需要更积极地治疗卒中危险因素 (*IIb 类，C 级推荐*)。
饮食和营养	● 美国饮食指南推荐减少钠摄入并增加钾摄入，可降低血压 (*I 类，A 级推荐*)。
	● 推荐 DASH 式饮食，即注重水果、蔬菜和低脂奶制品的摄入，减少饱和脂肪的摄入，可降低血压 (*I 类，A 级推荐*)。
	● 富含水果和蔬菜，即高钾含量的饮食有益，可能有助于降压 (*I 类，B 级推荐*)。
体力活动少	● 推荐增加体力活动，因其可降低卒中风险 (*I 类，B 级推荐*)。
	● 美国 2008 体力活动指南推荐成年人必须每周参加至少 150 分钟 (2 小时 30 分钟) 中等强度或 75 分钟 (1 小时 15 分钟) 高强度的有氧体力活动 (*I 类，B 级推荐*)。
肥胖和体脂分布异常	● 超重和肥胖的病人，推荐减轻体重以降压 (*I 类，A 级推荐*)。
	● 超重和肥胖的病人，可考虑减轻体重以降低卒中风险 (*IIa 类，B 级推荐*)。

比较不同研究的相对危险度和人群归因危险度时需谨慎。由于风险评估的差异和患病率的变化，无法精确预计危险因素 (如激素替代治疗) 的归因风险度。

参考文献(部分)

1. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger VL, Rosamond W, Sacco R, Sorlie P, Stafford R, Thom T, Wasserthiel-Smoller S, Wong ND, Wylie-Rosett J. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation.* 2010;121:e46–e215. Epub December 17, 2009.
2. Brown RD, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Stroke incidence, prevalence, and survival: secular trends in Rochester, Minnesota, through 1989. *Stroke*. 1996;27:373–380.
3. Fang J, Alderman MH. Trend of stroke hospitalization, United States, 1988–1997. *Stroke*. 2001;32:2221–2226.
4. Samsa GP, Matchar DB, Goldstein L, Bonito A, Duncan PW, Lipscomb J, Enarson C, Witter D, Venus P, Paul JE, Weinberger M. Utilities for major stroke: results from a survey of preferences among persons at increased risk for stroke. *Am Heart J*. 1998;136:703–713.
5. Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, Grubb RL, Higashida RT, Jauch EC, Kidwell C, Lyden PD, Morgenstern LB, Qureshi

AI, Rosenwasser RH, Scott PA, Wijdicks EF. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups. *Stroke*. 2007;38:1655–1711.

6. Gorelick PB. Stroke prevention. *Arch Neurol*. 1995;52:347–355.
7. Sacco RL, Benjamin EJ, Broderick JP, Dyken M, Easton JD, Feinberg WM, Goldstein LB, Gorelick PB, Howard G, Kittner SJ, Manolio TA, Whisnant JP, Wolf PA. American Heart Association Prevention Conference, IV: prevention and rehabilitation of stroke. Risk factors. *Stroke*. 1997;28:1507–1517.
8. Chiuve SE, Rexrode KM, Spiegelman D, Logroscino G, Manson JE, Rimm EB. Primary prevention of stroke by healthy lifestyle. *Circulation*. 2008;118:947–954.
9. Goldstein LB, Adams R, Alberts MJ, Appel LJ, Brass LM, Bushnell CD, Culebras A, Degraba TJ, Gorelick PB, Guyton JR, Hart RG, Howard G, Kelly-Hayes M, Nixon JV, Sacco RL. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Stroke*. 2006;37:1583–1633.
10. Pearson TA, Bazzarre TL, Daniels SR, Fair JM, Fortmann SP, Franklin BA, Goldstein LB, Hong Y, Mensah GA, Sallis JF Jr, Smith S Jr, Stone NJ, Taubert KA. American Heart Association guide for improving cardiovascular health at the community level: a statement for public health practitioners, healthcare providers, and health policy makers from the American Heart Association Expert Panel on Population and Prevention Science. *Circulation*. 2003;107:645– 651.
11. Burt BA. Definitions of risk. *J Dent Educ*. 2001;65:1007–1008.
12. Whisnant JP. Modeling of risk factors for ischemic stroke: the Willis Lecture. *Stroke*. 1997;28:1840–1844.

Executive Summary: 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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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. 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. Stroke is also a leading cause of functional impairments and is a life-changing event that affects not only stroke patients themselves but their family members and caregivers as well. 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. As discussed in detail in the full text, persons at high risk 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. Recommendations follow the American Heart Association (AHA) and the American College of Cardiology (ACC) methods of classifying the level of certainty of the treatment effect and the class of evidence (Tables 1 and 2).

Recommendations

Generally Nonmodifiable Risk Factors

(Age, Sex, Low Birth Weight, Race/Ethnicity, Genetic Factors)

- 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*).
- Genetic screening of the general population for prevention of a first stroke is not recommended (*Class III; Level of Evidence C*).
- Referral for genetic counseling may be considered for patients with rare genetic causes of stroke (*Class IIb; Level of Evidence C*).
- 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*).
- 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*).
- Noninvasive screening for unruptured intracranial aneurysms in patients with 1 relative with subarachnoid hem-

The full-text version is available online at: http://stroke.ahajournals.org/cgi/reprint/STR.0b013e3181fcb238.

The American Heart Association requests that the full-text version of this document be used when cited: Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, Creager MA, Culebras A, Eckel RH, Hart RG, Hinchey JA, Howard VJ, Jauch EC, Levine SR, Meschia JF, Moore WS, Nixon JV, Pearson TA; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Epidemiology and Prevention, Council for High Blood Pressure Research, Council on Peripheral Vascular Disease, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2011;42:517-584.

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Table 1. Applying Classification of Recommendations and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT →			
	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/administered	**CLASS IIa** *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	**CLASS IIb** *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	**CLASS III** *Risk ≥ Benefit* Procedure/Treatment should **NOT** be performed/administered **SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL**
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ 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	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ 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	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ 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.

orrhage (SAH) or intracranial aneurysms is not recommended (*Class III; Level of Evidence C*).

- 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*).
- Universal screening for intracranial aneurysms in carriers of mutations for aneurysm-associated Mendelian disorders is not recommended (*Class III; Level of Evidence C*).
- Noninvasive screening for unruptured intracranial aneurysms in patients with autosomal dominant polycystic kidney disease (ADPKD) and ≥1 relative with ADPKD and SAH or intracranial aneurysm may be considered (*Class IIb; Level of Evidence C*).
- Noninvasive screening for unruptured intracranial aneurysms in patients with cervical fibromuscular dysplasia may be considered (*Class IIb; Level of Evidence C*).
- 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, Cigarette Smoking, Diabetes, Dyslipidemia, Atrial Fibrillation, Other Cardiac Conditions, Asymptomatic Carotid Stenosis, Sickle Cell Disease, Postmenopausal Hormone Therapy, Oral Contraceptives, Diet and Nutrition, Physical Inactivity, Obesity and Body Fat Distribution)

- In agreement with the Joint National Committee (JNC 7) report, regular blood pressure (BP) screening and appropriate treatment, including both lifestyle modification and pharmacological therapy, are recommended (*Class I; Level of Evidence A*) (Table 6 in the full text of the guideline).

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.
Therapeutic recommendations	
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
Diagnostic recommendations	
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

- 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*).
- 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*).
- 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 (*Class IIa; Level of Evidence C*).
- 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*).
- 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*).
- Treatment of hypertension in adults with diabetes with an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) is useful (*Class I; Level of Evidence A*).
- 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*).
- The use of monotherapy with a fibrate to lower stroke risk might be considered for patients with diabetes (*Class IIb; Level of Evidence B*).
- 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*).
- 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 cardiovascular disease (CVD) risk (also see section on aspirin) (*Class IIb; Level of Evidence B*).
- Treatment with an HMG coenzyme-A (HMG-CoA) reductase inhibitor (statin) medication in addition to therapeutic lifestyle changes with low-density lipoprotein (LDL) cholesterol goals as reflected in the National Cholesterol Education Program (NCEP) guidelines 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*).
- Fibric 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*).
- Niacin may be considered for patients with low high-density lipoprotein (HDL) cholesterol or elevated lipoprotein(a) (Lp[a]), but its efficacy in prevention of ischemic stroke in patients with these conditions is not established (*Class IIb; Level of Evidence C*).
- Treatment with other lipid-lowering therapies, such as fibric 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*).
- Active screening for atrial fibrillation in patients >65 years of age in primary care settings using pulse taking followed by an ECG (ECG) as indicated can be useful (*Class IIa; Level of Evidence B*).
- Adjusted-dose warfarin (target international normalized ratio [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*).
- ACC/AHA practice guidelines providing strategies to reduce the risk of stroke in patients with a variety of cardiac conditions, including valvular heart disease, unstable angina, chronic stable angina, and acute myocardial infarction (MI) are endorsed.
- Screening for cardiac conditions such as patent foramen ovale (PFO) in the absence of neurological conditions or a specific cardiac cause is not recommended (*Class III; Level of Evidence A*).
- 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 stroke (*Class IIa; Level of Evidence A*).
- 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*).
- 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*).
- The use of aspirin in conjunction with carotid endarterectomy (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*).
- 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.
- Prophylactic carotid artery stenting (CAS) 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 magnetic resonance angiography [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*).
- 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*).
- Population screening for asymptomatic carotid artery stenosis is not recommended (*Class III; Level of Evidence B*).
- Children with sickle cell disease (SCD) should be screened with transcranial Doppler ultrasound (TCD) starting at age 2 years (*Class I; Level of Evidence B*).
- 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*).
- 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*).
- Pending further studies, continued transfusion, even in those with TCD velocities that revert to normal, is probably indicated (*Class IIa; Level of Evidence B*).
- 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*).
- Magnetic resonance imaging (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*).
- 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*).
- Hormone therapy (conjugated equine estrogens [CEE] with or without medroxyprogesterone) should not be used for primary prevention of stroke in postmenopausal women (*Class III; Level of Evidence A*).
- Selective estrogen receptor modulators (SERMs), such as raloxifene, tamoxifen, or tibolone, should not be used for primary prevention of stroke (*Class III; Level of Evidence A*).
- Oral contraceptives (OCs) may be harmful in women with additional risk factors (eg, cigarette smoking, prior thromboembolic events) (*Class III; Level of Evidence C*).
- 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*).
- 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*).
- A Dietary Approaches to Stop Hypertension (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*).
- 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*).
- Increased physical activity is recommended because it is associated with a reduction in risk of stroke (*Class I; Level of Evidence B*).
- 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*).
- Among overweight and obese persons, weight reduction is recommended as a means to lower BP (*Class I; Level of Evidence A*).
- 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, Metabolic Syndrome, Alcohol Consumption, Drug Abuse, Sleep-Disordered Breathing, Hyperhomocysteinemia, Elevated Lipoprotein(a), Hypercoagulability, Inflammation and Infection)

- 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*).
- 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–Adult Treatment Panel (ATP) III and the JNC 7, and as endorsed or indicated in other sections of this guideline. (Refer to relevant sections for Classes 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 (*Class IIb; Level of Evidence C*).
- 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 recommended (*Class I; Level of Evidence A*).
- For persons who choose to consume alcohol, consumption of $\leq$2 drinks per day for men and $\leq$1 drink per day for nonpregnant women might be reasonable (*Class IIb; Level of Evidence B*).
- Referral to an appropriate therapeutic program is reasonable for patients with drug abuse (*Class IIa; Level of Evidence C*).
- Because of its association with other vascular risk factors and cardiovascular morbidity, evaluation for sleep-disordered breathing (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*).
- Treatment of sleep apnea to reduce risk of stroke might be reasonable, although its effectiveness is unknown (*Class IIb; Level of Evidence C*).
- The use of the B-complex vitamins, pyridoxine (B_6), cobalamin (B_{12}), 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*).
- 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*).
- 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*).
- 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*).
- Low-dose aspirin (81 mg/d) is not indicated for primary stroke prevention in persons who are persistently antiphospholipid antibody (aPL) positive (*Class III; Level of Evidence B*).
- 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*).
- Patients with chronic inflammatory disease such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) should be considered at increased risk for stroke (*Class I; Level of Evidence B*).
- Treatment with antibiotics for chronic infections as a means to prevent stroke is not recommended (*Class III; Level of Evidence A*).
- Treatment of patients with elevated hs-CRP with a statin to decrease stroke risk might be considered (*Class IIb; Level of Evidence B*).
- Annual influenza vaccination can be useful for patients at risk for stroke (*Class IIa; Level of Evidence B*).

Aspirin for Primary Stroke Prevention

- 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*).
- 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*).
- Aspirin is not useful for preventing a first stroke in persons at low risk (*Class III; Level of Evidence A*).
- 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 $\leq$0.99) in the absence of other established CVD (*Class III; Level of Evidence B*).

- 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

- Each patient should undergo an assessment of stroke risk (*Class I; Level of Evidence A*).
- The use of a risk-assessment tool such as the Framingham Stroke Profile (FSP) is reasonable as 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

- Emergency department (ED)–based smoking cessation programs and interventions are recommended (*Class I; Level of Evidence B*).
- Identification of atrial fibrillation and evaluation for anticoagulation in the ED is recommended (*Class I; Level of Evidence B*).
- ED population screening for hypertension is reasonable (*Class IIa; Level of Evidence C*).
- 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*).
- 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

- 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*).

References

References are available in the full text of this guideline: http://stroke.ahajournals.org/cgi/reprint/STR.0b013e3181fcb238.