



Based on the Guidelines for

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.

The American Academy of Neurology affirms the value of this guideline.

Possibly Modifiable Risk Factors

Possibly Modifiable Risk Factors	Recommendation	Class/Level of Evidence
Inflammation	There is currently no evidence to support the use of hs-CRP screening of the entire adult population as a marker of general vascular risk. Aggressive risk factor modification is recommended for patients at high risk for stroke given exposure to traditional risk factors regardless of hs-CRP level. In agreement with AHA/CDC guidelines, hs-CRP can be useful when considering the intensity of risk factor modification in those at moderate general cardiovascular risk based on traditional risk factors.	<i>Class IIa, Level of Evidence B</i>
Aspirin	Aspirin is not recommended for the prevention of a first stroke in men. Aspirin 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. The use of aspirin is recommended for cardiovascular (including but not specific to stroke) prophylaxis among persons whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment (a 10-year risk of cardiovascular events of 6% to 10%).	<i>Class III, Level of Evidence A</i> <i>Class IIa, Level of Evidence B</i> <i>Class I, Level of Evidence A</i>

Possibly Modifiable Risk Factors

Possibly Modifiable Risk Factors	Recommendation	Class/Level of Evidence
Hyperhomocysteinemia	Recommendations to meet current guidelines for daily intake of folate (400 µg/d), B6, (1.7 mg/d) and B12 (2.4 µg/d) may be useful in reducing the risk of stroke. There are insufficient data to recommend a specific treatment for reducing the risk of first stroke in patients with elevated homocysteine levels. Use of folic acid and B vitamins in patients with known elevated homocysteine levels their may be useful given safety and low cost.	<i>Class IIb, Level of Evidence C</i> <i>Class IIb, Level of Evidence C</i>
Elevated Lipoprotein (a)	Although no definitive recommendations regarding Lp(a) modification can be made because of an absence of outcome studies showing clinical benefit, treatment with niacin (extended-release or immediate-release formulation at a total daily dose of 2,000 mg/d as tolerated) can be considered because it reduces Lp(a) levels by approximately 25%.	<i>Class IIb, Level of Evidence C</i>
Elevated Lipoprotein-Associated Phospholipase A₂ (Lp-PLA₂)	No recommendations regarding Lp-PLA ₂ modification can be made because of an absence of outcome studies showing clinical benefit with reduction in its blood levels.	
Hypercoagulability	The majority of case-control studies have not found an association between hereditary hypercoagulable states and ischemic stroke. Young women with acquired antiphospholipid syndrome may represent a high risk group. There are insufficient data to support specific recommendations for primary stroke prevention in patients with a hereditary or acquired thrombophilia.	

Possibly Modifiable Risk Factors

Factors	Recommendation	Class/Level of Evidence
Alcohol Abuse	Reduction of alcohol consumption in heavy drinkers is endorsed. No more than 2 drinks per day for men and 1 drink per day for non-pregnant women— best reflects the state of the science for alcohol and stroke risk.	<i>Class IIb, Level of Evidence B</i>
Drug Abuse	When a patient is identified as having a drug addiction problem, referral for appropriate counseling may be considered.	<i>Class IIb, Level of Evidence C</i>
Oral Contraceptives	The incremental risk of stroke associated with use of low-dose oral contraceptives in women without additional risk factors, if one exists, appears low. It is suggested that oral contraceptives be discouraged in women with additional risk factors (e.g., cigarette smoking or prior thromboembolic events). For those who elect to assume the increased risk, aggressive therapy of stroke risk factors may be useful.	<i>Class III, Level of Evidence B</i> <i>Class III, Level of Evidence C</i> <i>Class IIb, Level of Evidence C</i>
Sleep-Disordered Breathing (SDB)	Questioning bed partners and patients, particularly those with obesity and hypertension, about symptoms of SDB (e.g., daytime sleepiness, snoring) and referral to a sleep specialist for further evaluation as appropriate may be useful, especially in the setting of drug-resistant hypertension.	<i>Class IIb, Level of Evidence C</i>
Migraine	There are insufficient data to recommend a specific treatment approach that would reduce the risk of first stroke in women with migraine, including migraine with aura.	

Less Well-Documented or Potentially Modifiable Risk Factors (continued)

Factor	Prevalence, %	Population-Attributable Risk, %*	RR or OR	Risk Reduction With Treatment
Inflammatory processes (continued)				
CD 40 ligand (CD 54) >3.71 ng/mL in females free of cardiovascular disease	6	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 (1.30–2.55)	
Elevated hs-CRP (>3 mg/L) in women age ≥45 y	28.13		RR 3.0, <i>P</i> <0.001 women ≥45 y for cardiovascular and cerebrovascular events combined (highest vs lowest quartile) RR 2.0 (CI 1.10–3.79) men age-adjusted for first ischemic stroke and TIA (highest vs lowest quartile) RR 2.7 (CI 1.59–4.79) women age-adjusted for first ischemic stroke and TIA (highest vs lowest quartile)	
Migraine	12	17 (women, 20–44 y)	2.1	
High Lp(a)	20, age ≥65 men	27	2.92 (1.53–5.57)	Unknown
High Lp-PLA₂			HR=1.97 (1.03–3.79) highest vs lowest quartile	Unknown
Sleep-disordered breathing				
Men	4	Unknown	1.2%/y	Unknown
Women	2			
IgA indicates immunoglobulin A; IgG , immunoglobulin G; IR , incidence rate; and hs-CRP , high-sensitivity C-reactive protein.				
* Adjusted for age, prior cardiovascular disease, systolic blood pressure, diabetes, smoking, plasma CRP, and serum total and HDL cholesterol.				
† Adjusted for age, smoking, hypertension, diabetes, angina, ethnicity, BMI, and HDL cholesterol.				
‡ Warfarin.				

Less Well-Documented or Potentially Modifiable Risk Factors

Factor	Prevalence, %	Population-Attributable Risk, %*	RR or OR	Risk Reduction With Treatment
Oral contraceptive use (women age 25–44 y)	13	19	2.8	None (and may increase risk)
Inflammatory processes				
Periodontal disease Age 25–74 y	16.8	16	2.11 (1.30–3.42)	Effects of medical therapy on periodontal disease remain to be studied
Age 60–64 y	15			
Age ≥65 y	45			
<i>C pneumoniae</i> Age ≥65 y	75–100 IgA	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	
Age <5 yr	0–5			
Age 5–20 y	50			
Cytomegalovirus Adults	69	82	OR 1.04; 95% CI 0.68–1.58 OR 7.6; 95% CI 3.21–17.96	
Males	62.5			
Females	72.8			
<i>H pylori</i> CagA seropositivity	Adults with vascular disease: IgG Ab >40 AU. 65.7	39	Atherothrombotic stroke: OR 1.97; CI 1.33–2.91	
		83	Carotid plaque irregularities: OR 8.42; CI 1.58–44.84	
Acute infection				
Systemic respiratory infection Days 1–3			Stroke IR 3.19; CI 2.81–3.62	
Days 29–91			Stroke IR 1.27; CI 1.15–1.41	
Urinary tract infection Days 1–3			Stroke IR 1.65 (CI 1.19–2.28)	
Days 19–91			Stroke IR 1.16 (CI 1.04–1.28)	

Asymptomatic Carotid Stenosis

It is recommended that patients with asymptomatic carotid artery stenosis be screened for other treatable causes of stroke and that intensive therapy of all identified stroke risk factors be pursued (*Class I, Level of Evidence C*). The use of aspirin is recommended unless contraindicated because aspirin was used in all of the cited trials as an antiplatelet drug except in the surgical arm of 1 study, in which there was a higher rate of MI in those who were not given aspirin (*Class I, Level of Evidence B*). Prophylactic carotid endarterectomy is recommended in highly selected patients with high-grade asymptomatic carotid stenosis performed by surgeons with <3% morbidity/mortality rates (Table 7) (*Class I, Level of Evidence A*).

Less Well-Documented or Potentially Modifiable Risk Factors

Factor	Prevalence, %	Population-Attributable Risk, %*	RR or OR	Risk Reduction With Treatment
Metabolic syndrome	23.7			
Alcohol abuse				
≥5 drinks/d	5–7	1–3	1.6†	Unknown
More than moderate (see text)	60	32	1.8†	Unknown
Hyperhomocysteinemia				
Age 40–59 y				
Men	29	26	1.3–2.3	Unknown
Women	21	37		
Age ≥60 y				
Men	43	35		
Women	47	37		
Drug abuse	3–14	Unknown	6.5	Unknown
Hypercoagulability				
Anticardiolipin antibody				
Men	19.7	6	1.3 (0.7–2.3)*	0.99 (0.69–1.41)‡
Women overall	17.6	14	1.9 (1.1–3.5)*	Warfarin
Women age 15–44 y	26.9	11	1.9 (1.24–2.83)†	
Lupus anticoagulant (women age 15–44 y)	12.8	9	1.80 (1.06–3.06)	0.78 (0.50–1.21)‡ 1.47 (0.91–2.36)‡ (anticardiolipin antibodies/lupus anticoagulant)
Factor V Leiden	7.7	0	0.92 (0.56–1.53)	Unknown
Prothrombin 20210 mutation	3.7	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

Introduction

Stroke remains a major healthcare problem. It is estimated that there are >700 000 incident strokes in the United States each year, resulting in >150 000 deaths annually, with 5.7 million stroke survivors alive today. Stroke ranks as the country's third leading cause of death and stroke incidence may be increasing. 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.

Primary prevention is particularly important because >70% of strokes are first events. Extensive evidence is available identifying a variety of specific factors that increase the risk of a first stroke and providing strategies for reducing that risk. This digest provides an overview of the evidence on various established and potential stroke risk factors and is an abbreviated version of the *AHA/ASA Guideline on Primary Prevention of Ischemic Stroke (Stroke, 2006)*. This guideline largely focuses on an individual patient-oriented approach to stroke prevention. This is in contrast to a population-based approach in which "...the entire distribution of risk factors in the population is shifted to lower levels through population-wide interventions," which is reflected in the *AHA Guide for Improving Cardiovascular Health at the Community Level*.

Please refer to full text online at <http://stroke.ahajournals.org/cgi/content/full/37/6/1583>

Levels of Evidence and Recommendations

Rating Levels of Evidence and Recommendations

Classification of 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.
IIa	The weight of evidence or opinion is in favor of the procedure or treatment.
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.

Level of Evidence

Level of Evidence A	Data derived from multiple randomized clinical trials.
Level of Evidence B	Data derived from a single randomized trial or nonrandomized studies.
Level of Evidence C	Expert opinion or case studies.

Assessing Risk

- Each patient should have an assessment of his or her stroke risk (*Class I, Level of Evidence A*).
- Risk assessment tools such as the Framingham Stroke Profile should be considered, as they can help identify individuals who could benefit from therapeutic interventions and who may not be treated based on any 1 risk factor (*Class IIa, Level of Evidence B*).
- Risk factors were categorized as either non-modifiable, modifiable or potentially modifiable.

Nonmodifiable Risk Factors

Factor	Prevalence (per 100 000)	RR
Age, y	Doubling of stroke rate each 10 y after age 55. Incidence:	...
	White	Black
	Men	Women
45–54	1.4	0.8
55–64	2.6	1.6
65–74	6.7	4.2
75–84	11.8	11.3
≥ 85	16.8	16.5
	24.7	21.8
	2.1	2.5
	4.9	4.6
	10.4	9.8
	23.3	13.5
	24.7	21.8
Race	...	
Blacks	233	
Hispanics	196	
Whites	93	
Sex	...	
Men	174	
Women	122	
Total	145	
Low birth weight	= 2 for birth weights < 2500 vs ≥ 4000 g	
Family history of stroke/TIA	RR paternal history 2.4 (95% CI 0.96–6.03); RR maternal history 1.4 (95% CI 0.60–3.25)	

- Referral for genetic counseling may be considered for patients with rare genetic causes of stroke (*Class IIb, Level of Evidence C*).
- There remain insufficient data to recommend genetic screening for the prevention of a first stroke.

Well-Documented and Modifiable Risk Factors

Factor	Prevalence, %	Population-Attributable Risk, %*	RR	Risk Reduction With Treatment
Cardiovascular disease				
Coronary heart disease				Overlap with risk factors for first stroke, see other relevant portions of this statement.
Men	8.4	5.8†	1.73 (1.68–1.78)	
Women	5.6	3.9†	1.55 (1.17–2.07)	
Heart failure				
Men	2.6	1.4†		
Women	2.1	1.1†		
Peripheral arterial disease	4.9	3.0†		
Hypertension				
Age 50 y	20	40	4.0	38%; See full text guidelines.
Age 60 y	30	35	3.	
Age 70 y	40	30	2.0	
Age 80 y	55	20	1.4	
Age 90 y	60	0	1.0	
Cigarette smoking	25	12–18	1.8	50% within 1 y; baseline after 5 y
Diabetes	7.31	5–27	1.8–6	Reduction of stroke risk in hypertensive diabetic patients with blood pressure control. No demonstrated benefit in stroke reduction with tight glycemic control; however, reduction in other complications does occur (see text). Reduction of stroke with statins (see text).
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).
Atrial fibrillation (nonvalvular)				
Age 50–59 y	0.5	1.5	4.0	Adjusted-dose warfarin vs control: 62% (CI 48% to 72%); 6 trials, 2900 patients.
Age 60–69 y	1.8	2.8	2.6	Aspirin vs placebo: 22% (CI 2% to 38%); 6 trials, 3119 patients.
Age 70–79 y	4.8	9.9	3.3	Adjusted-dose warfarin vs aspirin: 45% (CI 29% to 57%); 6 trials, 4025 patients.
Age 80–89 y	8.8	23.5	4.5	
Sickle cell disease	0.25 (of African Americans)		200–400§	91% with transfusion therapy (see text) .
Dyslipidemia				
High total cholesterol	25	15	2.0 for men and for women age 55 y	27% to 32% with statins in high-risk patients with coronary heart disease, hypertension, or diabetes; 25% reduction with high-dose vs low-dose statins (see text).
Low HDL cholesterol	25	10	1.5–2.5 for men	

Factor	Prevalence, %	Population-Attributable Risk, %*	RR	Risk Reduction With Treatment
Dietary factors				
Na intake >2300 mg	75–90	Unknown	Unknown	Note: Observational studies show an 8% reduction in stroke mortality from a 3-mm Hg reduction in systolic blood pressure. The extent of systolic blood pressure reduction from reduced Na and increased K intake can exceed 3 mm Hg according to baseline intake levels and factors.
K intake <4700 mg	90–99		Unknown	Unknown
Obesity	17.9	12–20‡	1.75–2.37	Unknown
Physical inactivity	25	30	2.7‡	Unknown
Postmenopausal hormone therapy	20 (women age 50–74 y)	7	1.4	None (and may increase risk).
Data derived from Hart et al and van Walraven et al. Stroke includes both ischemic and hemorrhagic stroke. Cardiovascular disease includes coronary heart disease, heart failure, and peripheral arterial disease.				
* Population-attributable risk is the proportion of ischemic stroke in the population that can be attributed to a particular risk factor (see text for formula).				
† Calculated on the basis of point estimates of referenced data provided in the table. For peripheral arterial disease, calculation was based on average RR for men and women.				
‡ Calculated based on referenced data provided in the table or text.				
§ Relative to stroke risk in children without sickle cell disease.				
For high-risk patients treated with transfusion.				
See Full Text Guideline, at http://stroke.ahajournals.org/cgi/content/full/37/6/1583 .				

There are several well-documented risk factors for first ischemic stroke with clear data showing a reduction in stroke risk with treatment. An important risk factor for a first stroke that is not adequately reflected in the organizational scheme used in this guideline is the presence of atherosclerotic vascular disease in another vascular bed. Those with a history of cardiovascular disease (coronary heart disease, cardiac failure, or symptomatic peripheral arterial disease) have a significant increased risk of a first stroke as compared with those without such a history, after adjustment for other risk factors (relative risk [RR]=1.73, 95% confidence interval [CI] 1.68 to 1.78 for men; RR=1.55, 95% CI 1.17 to 2.07 for women; adjusted for age, blood pressure, LV hypertrophy, cigarette smoking, atrial fibrillation, and diabetes). Treatments used in the management of these other conditions (eg, platelet antiaggregants) may also reduce the risk of stroke.

The risk factors for first stroke and the risk factors for cardiovascular disease overlap. The impact of management of these common risk factors is reviewed in the context of their specific impact on stroke throughout this statement but should also be considered in the context of global reduction of vascular disease.

Recommendations

Persons with evidence of noncerebrovascular atherosclerotic vascular disease (coronary heart disease, cardiac failure, or symptomatic peripheral arterial disease) are at increased risk for a first stroke. Treatments used in the management of these other conditions (eg, platelet antiaggregants) and as recommended in other sections of this guideline can reduce the risk of stroke (Class and Level of Evidence as indicated in the relevant sections).

Risk Factor	Recommendation	Class/Level of Evidence
Hypertension	Regular screening for hypertension (at least every 2 years in adults and more frequently in minority populations and the elderly) and appropriate management, including dietary changes, lifestyle modification, and pharmacological therapy as summarized in JNC 7, are recommended.	<i>Class I, Level of Evidence A</i>
Cigarette Smoking	Abstention from cigarette smoking and smoking cessation for current smokers are recommended. Avoidance of environmental tobacco smoke for stroke prevention should also be considered. The use of counseling, nicotine products, and oral smoking cessation medications should be considered.	<i>Class I, Level of Evidence B</i> <i>Class IIa, Level of Evidence C</i> <i>Class IIa, Level of Evidence B</i>
Diabetes	It is recommended that hypertension be tightly controlled in both type 1 and type 2 diabetes (the JNC 7 recommendation of <130/80 mmHg in diabetics is endorsed) as part of a comprehensive risk-reduction program. Treatment of adult diabetics, especially those with additional risk factors, with a statin to lower the risk of a first stroke is recommended.	<i>Class I, Level of Evidence A</i> <i>Class I, Level of Evidence A</i>
Carotid Disease	See full text guideline for recommendation.	
Asymptomatic Carotid Disease	It is recommended that patients with asymptomatic carotid artery stenosis be screened for other treatable causes of stroke and that intensive therapy of all identified stroke risk factors be pursued. The use of aspirin is recommended unless contraindicated because aspirin was used in all of the cited trials as an antiplatelet drug except in the surgical arm of 1 study, in which there was a higher rate of MI in those who were not given aspirin.	<i>Class I, Level of Evidence C</i> <i>Class I, Level of Evidence B</i>

Risk Factor	Recommendation	Class/Level of Evidence
Asymptomatic Carotid Disease (continued)	Prophylactic carotid endarterectomy is recommended in highly selected patients with high-grade asymptomatic carotid stenosis performed by surgeons with <3% morbidity/mortality rates.	<i>Class I, Level of Evidence A</i>
Atrial fibrillation	Anticoagulation of patients with AF and valvular heart disease (particularly those with mechanical heart valves) is recommended. Antithrombotic therapy is recommended to prevent stroke in patients with non-valvular atrial fibrillation based on assessment of their absolute stroke risk, estimated bleeding risk and considering patient preferences and access to high quality anticoagulation monitoring. Warfarin (INR 2.0 to 3.0) is recommended for high-risk (>4% annual risk of stroke) patients (and many moderate-risk patients based on patient preferences) with atrial fibrillation who have no clinically significant contraindications to oral anticoagulants.	<i>Class I, Level of Evidence A</i> <i>Class I, Level of Evidence A</i> <i>Class I, Level of Evidence A</i>
Sickle Cell Disease	It is recommended that children with sickle cell disease be screened with transcranial Doppler (TCD) ultrasound starting at 2 years of age. It is recommended that transfusion therapy be considered for those at elevated stroke risk. Although the optimal screening interval has not been established, it is reasonable that younger children and those with TCD velocities in the conditional range should be rescreened more frequently to detect development of high-risk TCD indications for intervention. Transfusion is reasonable to continue even in those whose TCD velocities revert to normal pending further studies. MRI/MRA criteria for selection of children for primary stroke prevention using transfusion have not been established, and these tests should not be substituted for TCD. Adults with SCD should be evaluated for known stroke risk factors and managed according to the general guidelines in this statement.	<i>Class I, Level of Evidence B</i> <i>Class I, Level of Evidence B</i> <i>Class IIa, Level of Evidence B</i> <i>Class III, Level of Evidence B</i> <i>Class I, Level of Evidence A</i>

Risk Factor	Recommendation	Class/Level of Evidence
Dyslipidemia	It is recommended that patients with known CHD and high-risk hypertensive patients, even with normal LDL-C levels, be treated with lifestyle measures and a statin. Suggested treatments for patients with known CHD and low HDL cholesterol include weight loss, increased physical activity, smoking cessation, and possibly niacin or gemfibrozil.	<i>Class I, Level of Evidence A</i> <i>Class IIa, Level of Evidence B</i>
Diet and Nutrition	A reduced intake of sodium and increased intake of potassium are recommended to lower blood pressure in persons with hypertension. The DASH diet, which emphasizes fruit, vegetables, and low-fat dairy products and is reduced in saturated fat, also lowers blood pressure and is recommended. A diet that is rich in fruits and vegetables may lower the risk of stroke and may be considered.	<i>Class I, Level of Evidence A</i> <i>Class I, Level of Evidence A</i> <i>Class IIb, Level of Evidence C</i>
Obesity	Obesity is classified by body mass index (BMI) > 30 kg/m ² . Clinically, abdominal obesity is defined by a waist circumference >102 cm (40 in) in men and 88 cm (35 in) in women. Weight reduction is recommended because it lowers blood pressure.	<i>Class I, Level of Evidence A</i>
Physical Inactivity	Increased physical activity is recommended because it is associated with a reduction in the risk of stroke. Exercise guidelines as recommended by the Centers for Disease Control and Prevention and the National Institutes of Health of regular exercise (30 min or more of moderate-intensity activity daily) as part of a healthy lifestyle are reasonable.	<i>Class I, Level of Evidence B</i> <i>Class IIa, Level of Evidence B</i>
Post-Menopausal Hormone Therapy	It is recommended that postmenopausal hormone therapy (with estrogen with or without a progestin) not be used for primary prevention of stroke. The use of hormone replacement therapy for other indications should be informed by the risk estimate for vascular outcomes provided by the reviewed clinical trials.	<i>Class III, Level of Evidence A</i>