Guidelines for the Primary Prevention of Stroke

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

The American Academy of Neurology affirms the value of these guidelines as an educational tool for neurologists.

Endorsed by the American Association of Neurological Surgeons, the Congress of Neurological Surgeons, and the Preventive Cardiovascular Nurses Association

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Abstract—The aim of this updated statement is to provide comprehensive and timely evidence-based recommendations on the prevention of stroke among individuals who have not previously experienced a stroke or transient ischemic attack. Evidence-based recommendations are included for the control of risk factors, interventional approaches to atherosclerotic disease of the cervicocephalic circulation, and antithrombotic treatments for preventing thrombotic and thromboembolic stroke. Further recommendations are provided for genetic and pharmacogenetic testing and for the prevention of stroke in a variety of other specific circumstances, including sickle cell disease and patent foramen ovale. **(*Stroke*. 2014;45:3754-3832.)**

Key Words: AHA Scientific Statements ■ atrial fibrillation ■ diabetes mellitus ■ hyperlipidemias ■ hypertension ■ intracranial aneurysm ■ ischemia ■ prevention and control ■ smoking ■ stroke

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Approximately 795 000 people in the United States have a stroke each year, ≈610 000 of whom have had first attacks, resulting in 6.8 million stroke survivors >19 years of age.[1] Stroke ranks as the fourth-leading cause of death in the United States.[2] Globally, over the past 4 decades, stroke incidence rates have fallen by 42% in high-income countries and increased by >100% in low- and middle-income countries.[3] Stroke incidence rates in low- and middle-income countries now exceed those in high-income countries.[3]

Stroke is a leading cause of functional impairment. For patients who are ≥65 years of age, 6 months after stroke, 26% are dependent in their activities of daily living, and 46% have

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cognitive deficits.[1] Stroke changes the lives not only of those who experience a stroke but also of their family and other caregivers. A major stroke is viewed by more than half of those at risk as being worse than death.[4] Despite the advent of reperfusion therapies for selected patients with acute ischemic stroke, effective prevention remains the best approach for reducing the burden of stroke.[5–7] Primary prevention is particularly important because >76% of strokes are first events.[1] Fortunately, there are enormous opportunities for preventing stroke. An international case-control study of 6000 individuals found that 10 potentially modifiable risk factors explained 90% of the risk of stroke.[8] As detailed in the sections that follow, stroke-prone individuals can readily be identified and targeted for effective interventions.

This guideline summarizes the evidence on established and emerging stroke risk factors and represents an update of the last American Heart Association (AHA) statement on this topic, published in 2011.[9] Targets for stroke prevention have been reordered to align with the AHA's public health campaign for ideal cardiovascular health known as Life's Simple 7.[10] As with the earlier document, the guideline addresses prevention of both hemorrhagic and ischemic stroke. The traditional definition of ischemic stroke as a clinical event is used in most instances out of necessity because of the design of most stroke prevention studies; however, where permitted by the evidence, the Writing Group has adopted the updated tissue-based definition of ischemic stroke as infarction of central nervous system tissue.[11]

Differences in stroke risk among men and women are well recognized, and certain risk factors are specific to women's health (eg, oral contraceptives [OCs] and hormone replacement therapy). To increase awareness of these important issues and to provide sufficient coverage of the topic, the AHA has issued a guideline on the prevention of stroke in women.[11a] Key recommendations are summarized in the current document but not reiterated in full. Readers are encouraged to review the new guideline.

The committee chair nominated Writing Group members on the basis of their previous work in relevant topic areas. The AHA Stroke Council's Scientific Statement Oversight Committee and the AHA's Manuscript Oversight Committee approved all Writing Group members. In consultation with 2 research librarians, we developed individual search strategies for each topic section and for each database to identify potentially relevant studies from the PubMed, Ovid MEDLINE, Ovid Cochrane Database of Systematic Reviews, and Ovid Central Register of Controlled Trials databases. The Internet Stroke Center/Clinical Trials Registry (http://www.strokecenter.org/trials/) and National Guideline Clearinghouse (http://guideline.gov/) were also searched. Articles included were limited to those that were randomized, controlled trials; systematic reviews; meta-analyses; and in some cases, cohort studies. The database searches were also limited to articles with English-language citations, with human subjects, and published between January 1, 2009, and varying end dates, (between October 2, 2012, and December 6, 2012). Medical subject headings (MeSH) and key words, including stroke; ischemic attack, transient; cerebral infarction; cerebral hemorrhage; ischemia; and cerebrovascular disorders, in addition to select MeSH and key words on each topic, were used in the search strategy. The writers used systematic literature reviews covering the time period since the last review published in 2011 to October 2012. They also reviewed contemporary published evidence-based guidelines, personal files, and published expert opinion to summarize existing evidence, to indicate gaps in current knowledge, and, when appropriate, to 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, including review by the Stroke Council Leadership and Scientific Statements Oversight Committees, before consideration and approval by the AHA Science Advisory and Coordinating Committee. Because of the diverse nature of the topics covered, it was not possible to provide a systematic, uniform summary of the magnitude of the effect associated with each of the recommendations. As with all therapeutic recommendations, patient preferences must be considered. Risk factors, which directly increase disease probability and if absent or removed reduce disease probability, or risk markers, which are attributes or exposures associated with increased probability of disease but are not necessarily causal[12] of a first stroke, were classified according to their potential for modification.[7] Although this distinction is somewhat subjective, risk factors considered both well documented and modifiable were those with clear, supportive epidemiological evidence and evidence of risk reduction when modified in the context of randomized clinical trials. Less well-documented or potentially modifiable risk factors were those either with less clear epidemiological evidence or without evidence from randomized clinical trials demonstrating a reduction of stroke risk when modified.

Assessing the Risk of First Stroke

It may be helpful for healthcare providers and patients to be able to estimate risk for a first stroke for an individual patient. Patients prefer being told their own individual risk through the use of a global risk assessment tool, although it has only a small effect on preferences for reducing risk and no effect on patient beliefs or behavior compared with standard risk factor education.[13] As detailed in other sections, numerous individual factors can contribute to stroke risk. The levels of evidence supporting a causal relationship among several of these factors and stroke vary, and specific or proven treatments for some 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 taking into account the effect of multiple risk factors have been used in community stroke screening programs and in some guideline statements to select certain treatments for primary stroke prevention.[14,15] Some of the goals of such risk assessment tools are to identify people at elevated risk who might be unaware of their risk, to assess risk in the presence of >1 condition, to measure an individual's risk that can be tracked and lowered by appropriate modifications, to estimate risk for selecting treatments or stratification in clinical trials, and to 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

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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 *No Benefit* or CLASS III *Harm* Procedure/Test / Treatment COR III: No benefit — Not Helpful / No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful / Harmful to Patients
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	COR III: No Benefit is not recommended is not indicated should not be performed/administered/other is not useful/beneficial/effective COR III: Harm potentially harmful causes harm associated with excess morbidity/mortality should not be performed/administered/other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

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. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

risk factors stratified by age, sex, race/ethnicity, and geography are incompletely captured by available global risk assessment tools. 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.[16] Independent stroke predictors include age, systolic blood pressure (SBP), hypertension, diabetes mellitus, current smoking, established cardiovascular disease (CVD; myocardial infarction [MI], angina or coronary insufficiency, congestive heart failure, and intermittent claudication), atrial fibrillation (AF), and left ventricular hypertrophy on ECG. Additional refinements include a measure of carotid intima-media thickness (IMT); however, these refinements result in only a small improvement in 10-year risk prediction of first-time MI or stroke that is unlikely to be of clinical importance.[17] FSP scores can be calculated to estimate sex-specific, 10-year cumulative stroke risk. The initial FSP has been updated to account for the use of antihypertensive therapy and the risk of stroke and stroke or death among individuals with new-onset AF.[18,19] Despite its widespread use, the validity of the FSP among individuals of different age ranges or belonging to different race/ethnic groups has been inadequately studied. The FSP has been applied to ethnic minorities in the United

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Table 2. Definition of Classes and Levels of Evidence Used in AHA/ASA 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 one or more case-control studies, or studies using a reference standard applied by an unmasked evaluator
Level of Evidence C	Consensus opinion of experts

AHA/ASA indicates American Heart Association/American Stroke Association

Kingdom and found to vary across groups, but the suitability of the scale to predict outcomes has not been fully established.[20]

Alternative prediction models have been developed using other cohorts and different sets of stroke risk factors. Retaining most of the Framingham covariates, one alternative stroke risk scoring system omits cigarette smoking and antihypertensive medication and adds "time to walk 15 feet" and serum creatinine.[21] Another score is derived from a mixed cohort of stroke and stroke-free patients and includes history of stroke, marital status, blood pressure (BP) as a categorical variable, high-density lipoprotein (HDL) cholesterol, impaired expiratory flow, physical disability, and a depression score.[22] Several studies have generated risk assessment tools for use in patients with AF (see Atrial Fibrillation). Risk models have also been developed for other populations. For example, a stroke prediction model derived for use in Chinese adults in Taiwan included age, sex, SBP, diastolic BP (DBP), family history of stroke, AF, and diabetes mellitus and was found to have a discriminative capacity similar to or better than those of other available stroke models.[23] The model, however, has not been independently validated.

Recent guideline statements from the AHA/American Stroke Association have emphasized the importance of including both stroke and coronary heart disease events as outcomes in risk prediction instruments intended for primary prevention.[24] The AHA/American College of Cardiology (ACC) CV Risk Calculator is available online for use in estimating risk at http://my.americanheart.org/cvriskcalculator.

Assessing the Risk of First Stroke: Summary and Gaps

An ideal stroke risk assessment tool that is simple, is widely applicable and accepted, and takes into account the effects of multiple risk factors does not exist. Each available tool has limitations. Newer risk factors for stroke such as obstructive sleep apnea, not collected in older studies, need to be considered.[25] Risk assessment tools should be used with care because they do not include all the factors that contribute to disease risk.[25] Some potential for harm exists from unnecessary application of interventions that may result from inappropriate use of risk assessment tools or from the use of poorly adjudicated tools. The utility of the FSP or other stroke risk assessment scales as a way of improving the effectiveness of primary stroke prevention is not well studied. Research is needed to validate risk assessment tools across age, sex, and race/ethnic groups; to evaluate whether any of the more recently identified risk factors add to the predictive accuracy of existing scales; and to determine whether the use of these scales improves primary stroke prevention.

Assessing the Risk of First Stroke: Recommendations

1. **The use of a risk assessment tool such as the AHA/ACC CV Risk Calculator (http://my.americanheart.org/cvriskcalculator) is reasonable because these tools can help identify individuals who could benefit from therapeutic interventions and who may not be treated on the basis of any single risk factor. These calculators are useful to alert clinicians and patients of possible risk, but basing treatment decisions on the results needs to be considered in the context of the overall risk profile of the patient (*Class IIa; Level of Evidence B*).**

Generally Nonmodifiable Risk Factors and Risk Assessment

Age

The cumulative effects of aging on the cardiovascular system and the progressive nature of stroke risk factors over a prolonged period substantially increase the risk of ischemic stroke and intracerebral hemorrhage (ICH). An analysis of data from 8 European countries found that the combined risk of fatal and nonfatal stroke increased by 9%/y in men and 10%/y in women.[26] The incidence of ICH increases with age from <45 years to >85 years, and the incidence rates did not decrease between 1980 and 2006.[27] Disturbing trends have been observed in the risk of stroke in younger individuals. In Greater Cincinnati/Northern Kentucky, the mean age of stroke decreased from 71.2 years in 1993 to 1994 to 69.2 years in 2005 because of an increase in the proportion of stroke in

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individuals between 20 to 54 years of age.[28] The Nationwide Inpatient Sample showed that the rates of stroke hospitalization increased for individuals between 25 and 34 years of age and between 35 and 44 years of age from 1998 to 2007.[29] Stroke occurring at younger ages has the potential to cause greater lifetime impairment and disability. The Framingham Heart Study estimated the lifetime risk of stroke to be 1 in 6 or more for middle-aged adults.[30]

Low Birth Weight

Low birth weight has been associated in several populations with risk of stroke in later life. Stroke mortality rates among adults in England and Wales are higher among people with lower birth weights.[31] The mothers of these low-birth-weight babies were typically poor, were malnourished, had poor overall health, and were generally socially disadvantaged.[31] A similar study compared a group of South Carolina Medicaid beneficiaries <50 years of age who had stroke with population control subjects.[32] The odds of stroke was more than double for those with birth weights <2500 g compared with those weighing 4000 g (with a significant linear trend for intermediate birth weights). A US nationally representative longitudinal study found an odds ratio (OR) of 2.16 (P<0.01) for low-birth-weight babies compared with normal-birth-weight babies for the risk of stroke, MI, or heart disease by 50 years of age.[33] Differences in birth weight may reflect differences in birthplace, and these geographic differences may relate to differences in stroke mortality.[34] Whether the association of birth weight with stroke risk is causal remains to be clarified.

Race/Ethnicity

Epidemiological studies support racial and ethnic differences in the risk of stroke.[35] Blacks[36-38] and some Hispanic/Latino Americans[38-41] 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.[36,37] In the Atherosclerosis Risk in Communities (ARIC) study, blacks had an incidence of all stroke types that was 38% (95% confidence interval [CI], 1.01–1.89) higher than that of whites.[42] American Indians have an incidence rate for stroke of 679 per 100 000 person-years, which is high relative to non-Hispanic whites.[43] It remains unclear whether these racial differences are genetic, environmental, or an interaction between the two. Possible reasons for the higher incidence and mortality rates of stroke in blacks include a higher prevalence of prehypertension, hypertension, obesity, and diabetes mellitus.[44–49] A higher prevalence of these risk factors, however, may not explain all of the excess risk.[50] Several studies have suggested that race/ethnic differences may be the result of social determinants, including neighborhood characteristics,[51–53] geography,[50] language, access to and use of health care,[35] and nativity.[54]

Genetic Factors

A meta-analysis of cohort studies showed that a positive family history of stroke increases the risk of stroke by ≈30% (OR, 1.3; 95% CI, 1.2–1.5; P<0.00001).[55] The Framingham study showed that a documented parental history of stroke before 65 years of age was associated with a 3-fold increase in the risk of stroke in offspring.[56] The odds of both monozygotic twins having strokes is 1.65-fold higher than for dizygotic twins.[55] Stroke heritability estimates vary with age, sex, and stroke subtype.[57,58] Younger stroke patients are more likely to have a first-degree relative with stroke.[57] Women with stroke are more likely than men to have a parental history of stroke.[58] Recent estimates of heritability using genome-wide common variant single-nucleotide polymorphism (SNP) data show similar heritability for cardioembolic (32.6%) and large-vessel disease (40.3%) but lower heritability for small-vessel disease (16.1%).[59] These estimates, however, do not consider the potential contribution of rare variants.

Genetic influences on stroke risk can be considered on the basis of their influence on individual risk factors, the genetics of common stroke types, and uncommon or rare familial causes of stroke. Many of the established and emerging risk factors that are described in the sections that follow such as arterial hypertension, diabetes mellitus, and hyperlipidemia have both genetic and environmental or behavioral components.[60–62] Genome-wide association studies have identified common genetic variants for these risk factors. Studies that assess the effect of the cumulative burden of risk alleles of stroke risk factors, as measured by a so-called genetic risk score, are beginning to emerge. For example, the burden of risk alleles for elevated BP was associated with a modest but significant increase in risk for ICH (OR, 1.11; 95% CI, 1.02–1.21; P=0.01) in 1025 cases and 1247 controls of European ancestry.[63] Whether a genetic risk score will provide clinically useful information beyond that afforded by clinical risk factors remains uncertain. Arguably, estimating genetic risk remains crude because only a few loci influencing stroke risk factors or stroke susceptibility have been identified.

Common variants on chromosome 9p21 adjacent to the tumor suppressor genes *CDKN2A* and *CDKN2B*, which were initially found to be associated with MI,[64–66] have also been associated with large-artery ischemic stroke.[67] Common variants on 4q25 and 16q22, adjacent to genes involved in cardiac development (*PITX2* and *ZFHX3*, respectively), which were initially found to be associated with AF,[68,69] were subsequently associated with ischemic stroke, particularly cardioembolic stroke.[69,70] Although tests are commercially available for the 9p21, 4q25, and 16q22 risk loci, studies have yet to prove that altering preventive therapies on the basis of genotypes leads to improved patient outcomes.

Genome-wide association studies have identified novel genetic variants influencing risk of stroke. A meta-analysis of genome-wide association studies from prospective cohorts identified a locus on 12p13 near the *NINJ2* gene associated with incident ischemic stroke,[71] but large case-control studies have not replicated this finding.[72,73] This inconsistency may be because of a possible effect of this locus on stroke mortality,[74] a synthetic association from rare variants not well represented in the subsequent replication studies, or a false-positive association. Recent meta-analyses of large case-control studies have identified novel genetic associations with specific stroke subtypes, suggesting that risk factor profiles and pathological mechanisms may differ across subtypes. Two loci have been associated with large-vessel stroke in individuals of European ancestry: a locus on 6p21.1[75] and a locus on 7q21

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near the *HDAC9* gene, encoding a protein involved in histone deacetylation.[76,77] A variant in the *PRKCH* gene encoding a protein kinase has been associated with small-vessel stroke in Asians.[78] The genetic variants described to date account for only a small proportion of stroke risk. Even combined, their predictive value is likely to be low.

Personalizing medicine through genetic testing has the potential to improve the safety of primary prevention pharmacotherapies. For example, genetic variability in cytochrome P450 2C9 (*CYP2C9*), vitamin K oxide reductase complex 1 (*VKORC1*), and rare missense mutations in the factor IX propeptide affect sensitivity of patients to vitamin K antagonists. This has led to testing of various genotype-guided dosing protocols. A 12-week randomized trial of 455 patients treated with warfarin showed significantly more time in therapeutic range for the international normalized ratio (INR) for patients assigned to the genotype-guided dosing regimen versus standard dosing (67.4% versus 60.3%; $P<0.001$).[79] A 4-week randomized trial of 1015 patients treated with warfarin showed no significant difference in the time in therapeutic range for the INR (45.2% versus 45.4%; $P=0.91$).[80] A 12-week randomized trial of 548 patients treated with acenocoumarol or phencoumon showed no significant difference in the time in therapeutic range for the INR (61.6% versus 60.2%; $P=0.52$).[81]

A genome-wide association study of individuals taking 80 mg simvastatin identified common variants on *SLCO1B1* that are associated with myopathy.[82] This may prove useful in screening for patients being considered for simvastatin therapy, although randomized validation studies demonstrating the clinical and cost-effectiveness of its use are lacking.

Several monogenic disorders are associated with stroke. Although rare, their effect on the individual patient is substantial because individuals carrying a mutation are likely to develop stroke or other clinical characteristics of disease. Thus, identification of the underlying gene for these disorders is important for diagnosis, counseling, and patient management. With the exception of sickle cell disease (SCD; discussed below), no treatment based specifically on genetic factors has yet been shown to reduce incident stroke. Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy is characterized by subcortical infarcts, dementia, migraine headaches, and white matter changes that are readily apparent on brain magnetic resonance imaging (MRI).[83] Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy is caused by any one of a series of mutations in the *NOTCH3* gene.[83,84] Genetic testing for *NOTCH3* mutations is available. Retinal vasculopathy with cerebral leukodystrophy is caused by mutation in the *TREX1* gene, a DNA exonuclease involved in the response to oxidative DNA damage.[85] Mutations in the *COL4A1* gene can cause leukoaraiosis and microbleeds and can present with ischemic or hemorrhagic stroke or as the hereditary angiopathy with nephropathy, aneurysm, and muscle cramps syndrome.[86,87]

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.[88] Deposition affects mostly small vessels in the brain and other organs, although involvement of the larger vessels has been reported. Enzyme replacement therapy appears to improve cerebral vessel function. Two prospective, randomized studies using human recombinant lysosomal α-galactosidase A found a reduction in microvascular deposits and reduced plasma levels of globotriaosylceramide.[89–91] These studies had short follow-up periods, and no reduction in stroke incidence was found. Agalsidase-α and agalsidase-β given at the same dose of 0.2 mg/kg have similar short-term effects in reducing left ventricular mass.[85,92]

Many coagulopathies are inherited as autosomal-dominant traits.[93] These disorders, including protein C and S deficiencies, the factor V Leiden mutation, and various other factor deficiencies, can lead to an increased risk of cerebral venous thrombosis.[94–97] As discussed below, there has not been a strong association between several of these disorders and arterial events such as MI and ischemic stroke.[98,99] Some apparently acquired coagulopathies such as the presence of a lupus anticoagulant or anticardiolipin antibody (aCL) can be familial in ≈10% of cases.[100,101] 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 infancy and childhood.[102] Arterial dissections, moyamoya syndrome, and fibromuscular dysplasia have a familial component in 10% to 20% of cases.[103,104]

Intracranial aneurysms are a feature of certain mendelian disorders, including autosomal-dominant polycystic kidney disease and Ehlers-Danlos type IV syndrome (so-called vascular Ehlers-Danlos). Intracranial aneurysms occur in ≈8% of individuals with autosomal-dominant polycystic kidney disease and 7% with cervical fibromuscular dysplasia.[105,106] Ehlers-Danlos type IV is associated with dissection of vertebral and carotid arteries, carotid-cavernous fistulas, and intracranial aneurysms.[107]

Loss-of-function mutations in *KRIT1*, malcavernin, and *PDCD10* genes cause cerebral cavernous malformation syndromes CCM1, CCM2, and CCM3, respectively.[108] Mutations in the amyloid precursor protein gene, cystatin C, gelsolin, and BRI2 can cause inherited cerebral amyloid angiopathy syndromes.[109]

Genetic Factors: Summary and Gaps

The cause of ischemic stroke remains unclear in as many as 35% of patients. The use of DNA sequence information, in conjunction with other "omics" (eg, transcriptomics, epigenomics) and clinical information to refine stroke origin, although promising, has not yet proven useful for guiding preventive therapy. Genetic factors could arguably be classified as potentially modifiable, but because specific gene therapy is not presently available for most conditions, genetic factors have been classified as nonmodifiable. It should be recognized that treatments are available for some, such as Fabry disease and SCD.

Genetic Factors: Recommendations

1. **Obtaining a family history can be useful in identifying people who may have increased stroke risk (*Class IIa; Level of Evidence A*).**
2. **Referral for genetic counseling may be considered for patients with rare genetic causes of stroke (*Class IIb; Level of Evidence C*).**

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3. **Treatment of Fabry disease with enzyme replacement therapy might be considered, but has not been shown to reduce the risk of stroke, and its effectiveness is unknown (*Class IIb; Level of Evidence C*).**
4. **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*).[110]**
5. **Noninvasive screening may be considered for unruptured intracranial aneurysms in patients with autosomal-dominant polycystic kidney disease and ≥1 relatives with autosomal-dominant polycystic kidney disease and SAH or ≥1 relatives with autosomal-dominant polycystic kidney disease and intracranial aneurysm (*Class IIb; Level of Evidence C*).**
6. **Noninvasive screening for unruptured intracranial aneurysms in patients with cervical fibromuscular dysplasia may be considered (*Class IIb; Level of Evidence C*).**
7. **Pharmacogenetic dosing of vitamin K antagonists may be considered when therapy is initiated (*Class IIb; Level of Evidence C*).**
8. **Noninvasive screening for unruptured intracranial aneurysms in patients with no more than 1 relative with SAH or intracranial aneurysms is not recommended (*Class III; Level of Evidence C*).**
9. **Screening for intracranial aneurysms in every carrier of autosomal-dominant polycystic kidney disease or Ehlers-Danlos type IV mutations is not recommended (*Class III; Level of Evidence C*).**
10. **Genetic screening of the general population for the prevention of a first stroke is not recommended (*Class III; Level of Evidence C*).**
11. **Genetic screening to determine risk for myopathy is not recommended when initiation of statin therapy is being considered (*Class III; Level of Evidence C*).**

Well-Documented and Modifiable Risk Factors

Physical Inactivity

Physical inactivity is associated with numerous adverse health effects, including an increased risk of total mortality, cardiovascular morbidity and mortality, and stroke. The 2008 physical activity guidelines for Americans provide an extensive review and conclude that physically active men and women generally have a 25% to 30% lower risk of stroke or mortality than the least active.[111] Two meta-analyses of physical activity reached the same conclusion.[112,113] The benefits appear to occur from a variety of activities, including leisure-time physical activity, occupational activity, and walking. Overall, the relationship between activity and stroke is not influenced by age or sex, but some data suggest linkages between these factors and activity levels.[114–116]

The relationship between the amount or intensity of physical activity and stroke risk remains unsettled and includes the possibility of a sex interaction. One study suggested an increasing benefit with greater intensity in women (median relative risk [RR], 0.82 for all strokes for moderate-intensity versus no or light activity; RR, 0.72 for high-intensity versus no or light activity). In men, there was no apparent benefit of higher intensity (median RR, 0.65 for moderate intensity versus no or light activity; RR, 0.72 for high intensity versus no or light activity).[111] In contrast, the prospective Northern Manhattan Study (NOMAS) suggested that moderate- to high-intensity physical activity was protective against risk of ischemic stroke in men (hazard ratio [HR], 0.37; 95% CI, 0.18–0.78) but not women (HR, 0.93; 95% CI, 0.57–1.50).[117] Increased physical activity has also been associated with a lower prevalence of brain infarcts.[118] Vigorous physical activity, regardless of sex, was associated with a decreased incidence of stroke in the National Runners' Health Study.[119]

The protective effect of physical activity may be partly mediated through its role in reducing BP[120] and controlling other risk factors for CVD,[121,122] including diabetes mellitus[120] and excess body weight. Physical activity also reduces plasma fibrinogen and platelet activity and elevates plasma tissue plasminogen activator activity and HDL cholesterol concentrations.[123–125] Physical activity may also exert positive health effects by increasing circulating anti-inflammatory cytokines, including interleukin-1 receptor antagonist and interleukin-10, and modulating immune function in additional ways.[126]

A large and generally consistent body of evidence from prospective, observational studies indicates that routine physical activity prevents stroke. The 2008 physical activity guidelines for Americans recommend that adults should engage in ≥150 min/wk of moderate-intensity (eg, fast walking) or 75 min/wk of vigorous-intensity aerobic physical activity (eg, running) 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.[111] The 2013 AHA/ACC guideline on lifestyle to reduce cardiovascular risk encourages moderate to vigorous aerobic physical activity for at least 40 minutes at a time to be done at least 3 to 4 d/wk for the purpose of reducing BP and improving lipid profile.[127]

Physical Inactivity: Summary and Gaps

A sedentary lifestyle is associated with several adverse health effects, including an increased risk of stroke. Indeed, the global vascular risk prediction scale including the addition of physical activity, waist circumference, and alcohol consumption improved prediction of 10-year event rates in multiethnic communities compared with traditional Framingham variables.[128] Clinical trials documenting a reduction in risk of a first or recurrent stroke with regular physical activity have not been conducted. Evidence from observational studies is sufficiently strong to make recommendations for routine physical activity to prevent stroke.[127]

Physical Inactivity: Recommendations

1. **Physical activity is recommended because it is associated with a reduction in the risk of stroke (*Class I; Level of Evidence B*).**
2. **Healthy adults should perform at least moderate- to vigorous-intensity aerobic physical activity at least 40 min/d 3 to 4 d/wk[127] (*Class I; Level of Evidence B*).**

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Dyslipidemia

Total Cholesterol

Most studies have found high total cholesterol to be a risk factor for ischemic stroke. In the Multiple Risk Factor Intervention Trial (MRFIT), comprising >350 000 men, the RR of death resulting from nonhemorrhagic stroke increased progressively with each higher level of cholesterol.[129] In the Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) study, which included >28 000 cigarette-smoking men, the risk of cerebral infarction was increased among those with total cholesterol levels of ≥7 mmol/L (≥271 mg/dL).[130] In the Asia Pacific Cohort Studies Collaboration (APCSC), which included 352 033 individuals, there was a 25% (95% CI, 13–40) increase in ischemic stroke rates for every 1-mmol/L (38.7-mg/dL) increase in total cholesterol.[131] In the Women's Pooling Project, which included 24 343 US women <55 years of age with no previous CVD, and in the Women's Health Study (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.[132,133] In other studies, the association between cholesterol and stroke was less clear. In the ARIC study, including 14 175 middle-aged men and women free of clinical CVD, the relationships between lipid values and incident ischemic stroke were weak.[134]

Most studies have found an inverse relationship between cholesterol levels and risk of hemorrhagic stroke. In MRFIT, the risk of death resulting from ICH was increased 3-fold in men with total cholesterol concentrations <4.14 mmol/L (160 mg/dL) compared with higher levels.[129] In a pooled cohort analysis of the ARIC study and the Cardiovascular Health Study (CHS), lower levels of low-density lipoprotein (LDL) cholesterol were inversely associated with incident intracranial hemorrhage.[135] In the APCSC, there was a 20% (95% CI, 8–30) decreased risk of hemorrhagic stroke for every 1-mmol/L (38.7-mg/dL) increase in total cholesterol.[131] 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 people with LDL cholesterol of ≥140 mg/dL was about half of that in people with LDL cholesterol <80 mg/dL (OR, 0.45; 95% CI, 0.30–0.69).[136] The Kaiser Permanente Medical Care Program reported that serum cholesterol <178 mg/dL increased the risk of ICH among men ≥65 years (RR, 2.7; 95% CI, 1.4–5.0).[137] In a Japanese nested case-control study, patients with intraparenchymal hemorrhage had lower cholesterol levels than control subjects.[138] In contrast, in the Korean Medical Insurance Corporation Study of ≈115 000 men, low serum cholesterol was not an independent risk factor for ICH.[139] Overall, epidemiological studies suggest competing stroke risk related to total cholesterol levels in the general population: low levels of total cholesterol increasing risk of ICH and high levels of total cholesterol increasing risk of ischemic stroke.

Given the complex relationship between total cholesterol and stroke, it is noteworthy that there appears to be no positive association between total cholesterol and stroke mortality.[140]

HDL Cholesterol

Some epidemiological studies have shown an inverse relationship between HDL cholesterol and risk of stroke,[141–145] whereas others have not.[134] The Emerging Risk Factors Collaboration performed a meta-analysis involving individual records on 302 430 people without vascular disease from 68 long-term prospective studies.[146] Collectively, there were 2.79 million person-years of follow-up. The aggregated data set included 2534 ischemic strokes, 513 hemorrhagic strokes, and 2536 unclassified strokes. The analysis adjusted for risk factors other than lipid levels and corrected for regression dilution. The adjusted HRs were 0.93 (95% CI, 0.84–1.02) for ischemic stroke, 1.09 (95% CI, 0.92–1.29) for hemorrhagic stroke, and 0.87 (95% CI, 0.80–0.94) for unclassified stroke. There was modest heterogeneity among studies of ischemic stroke (I^2=27%). The absence of an association between HDL and ischemic stroke and between HDL and hemorrhagic stroke contrast with the clear inverse association between HDL cholesterol and coronary heart disease observed in the same meta-analysis.

Triglycerides

Epidemiological studies that have evaluated the relationship between triglycerides and ischemic stroke have been inconsistent, in part because some have used fasting and others used nonfasting levels. Fasting triglyceride levels were not associated with ischemic stroke in ARIC.[134] Triglycerides did not predict the risk of ischemic stroke among healthy men enrolled in the Physicians' Health Study.[147] Similarly, in the Oslo study of healthy men, triglycerides were not related to the risk of stroke.[148] 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.[149] The Copenhagen City Heart Study, a prospective, population-based cohort study comprising ≈14 000 people, found that elevated nonfasting triglyceride levels increased the risk of ischemic stroke in both men and women. After multivariate adjustment, there was a 15% (95% CI, 9–22) increase in the risk of ischemic stroke for each 89-mg/dL increase in nonfasting triglycerides. HRs for ischemic stroke among men and women with the highest (≥443 mg/dL) compared with the lowest (<89 mg/dL) nonfasting triglyceride levels were 2.5 (95% CI, 1.3–4.8) and 3.8 (95% CI, 1.3–11), respectively. The 10-year risks of ischemic stroke were 16.7% and 12.2%, respectively, in men and women ≥55 years of age with triglyceride levels of ≥443 mg/dL.[150] 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.[151] A meta-analysis of 64 randomized clinical trials that tested lipid-modifying drugs found an adjusted RR of stroke of 1.05 (95% CI, 1.03–1.07) for each 10-mg/dL increase in baseline triglycerides, although fasting status is not specified.[152] In the Emerging Risk Factors Collaboration meta-analysis, triglyceride levels were not associated with either ischemic or hemorrhagic stroke risk, and determination of fasting status did not appear to change the lack of association.[146]

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Treatment of Dyslipidemia

Treatment with statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) reduces the risk of stroke in patients with or at high risk for atherosclerosis.[153,154] One meta-analysis of 26 trials that included >90 000 patients found that statins reduced the risk of all strokes by ≈21% (95% CI, 15–27).[153] Baseline mean LDL cholesterol in the studies ranged from 124 to 188 mg/dL and averaged 149 mg/dL. The risk of all strokes was estimated to decrease by 15.6% (95% CI, 6.7–23.6) for each 10% reduction in LDL cholesterol. Another meta-analysis of randomized trials of statins in combination with other preventive strategies that included 165 792 individuals showed that each 1-mmol/L (39-mg/dL) decrease in LDL cholesterol was associated with a 21.1% (95% CI, 6.3–33.5; P=0·009) reduction in stroke.[155] Several meta-analyses also found that beneficial effects are greater with greater lipid lowering. One meta-analysis of 7 randomized, controlled trials of primary and secondary prevention reported that more intensive statin therapy that achieved an LDL cholesterol of 55 to 80 mg/dL resulted in a lower risk of stroke than less intensive therapy that achieved an LDL cholesterol of 81 to 135 mg/dL (OR, 0.80; 95% CI, 0.71–0.89).[156] Another meta-analysis of 10 randomized, controlled trials of patients with atherosclerosis and coronary artery disease reported a significant reduction in the composite of fatal and nonfatal strokes with higher versus lower statin doses (RR, 0.86; 95% CI, 0.77–0.96).[157]

A meta-analysis of 22 trials involving 134 537 patients assessed the association of LDL cholesterol lowering with a statin and major cardiovascular events, including stroke, according to risk categories ranging from <5% to >30% 5-year risk of a major cardiovascular event.[158] The risk of major vascular events was lowered by 21% (95% CI, 23–29) for each 39-mg/dL reduction in LDL cholesterol. For every 39-mg/dL reduction in LDL, there was a 24% (95% CI, 5–39) reduction in the risk of stroke in participants with an estimated 5-year risk of major vascular events <10%, which was similar to the relationship seen in higher-risk categories. Similarly, another meta-analysis, which included 14 trials reporting stroke outcomes in patients with an estimated 10-year risk of cardiovascular events of <20%, found that the RR of stroke was significantly lower among statin recipients than among control subjects (RR, 0.83; 95% CI, 0.74–0.94).[159] In addition, in Justification for the Use of statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), statin treatment reduced the incidence of fatal and nonfatal stroke compared with placebo (HR, 0.52; 95% CI, 0.34–0.79) in healthy men and women with LDL cholesterol levels <130 mg/dL and high-sensitivity C-reactive protein (hs-CRP) levels ≥2.0 mg/L.[160]

Concerns about lowering of LDL cholesterol by statin therapy increasing the risk of hemorrhagic stroke are not supported. One meta-analysis of 31 trials comparing statin therapy with a control reported that statin therapy decreased total stroke (OR, 0.84; 95% CI, 0.78–0.91) and found no difference in the incidence of ICH (OR, 1.08; 95% CI, 0.88–1.32).[161] These findings are consistent with another meta-analysis that included 23 randomized trials and found that statins were not associated with an increased risk of ICH (RR, 1.10; 95% CI, 0.86–1.41).[162] The intensity of cholesterol lowering did not correlate with risk of ICH.

The beneficial effect of statins on ischemic stroke is most likely related to their capacity to reduce progression or to induce regression of atherosclerosis. Meta-analyses of statin trials found that statin therapy slows the progression of carotid IMT and that the magnitude of LDL cholesterol reduction correlates inversely with the progression of carotid IMT.[153,163] Moreover, beneficial effects on carotid IMT are greater with higher-intensity statin therapy.[164–166] In addition, plaque characteristics appear to improve with statin therapy. One study using high-resolution MRI reported that intensive lipid therapy depleted carotid plaque lipid,[167] and another found that high-dose atorvastatin reduced carotid plaque inflammation as determined by ultrasmall superparamagnetic iron oxide–enhanced MRI.[168]

Statins should be prescribed in accordance with the 2013 "ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults."[169] These guidelines represent a dramatic shift away from specific LDL cholesterol targets. Instead, the guidelines call for estimating the 10-year risk for atherosclerotic CVD and, based on the estimated risk, prescribing a statin at low, moderate, or high intensity. The intensity of statin therapy depends on the drug and the dose. For example, lovastatin at 20 mg/d is considered low-intensity therapy, and lovastatin at 40 mg/d is considered moderate-intensity therapy. Atorvastatin at 10 mg/d is considered moderate-intensity therapy, and atorvastatin at 80 mg/d is considered high-intensity therapy. A cardiovascular risk calculator to assist in estimating 10-year risk can be found online at http://my.americanheart.org/cvriskcalculator. Although the new guidelines shift focus away from specific lipid targets, values for total cholesterol and HDL are incorporated into the cardiovascular risk calculator, along with age, sex, race, SBP, hypertension treatment, diabetes mellitus, and cigarette smoking.

The benefits of lipid-modifying therapies other than statins on the risk of ischemic stroke are not established. A meta-analysis of 78 lipid-lowering trials involving 266 973 patients reported that statins decreased the risk of total stroke (OR, 0.85; 95% CI, 0.78–0.92), whereas the benefits of other lipid-lowering interventions were not significant, including diet (OR, 0.92; 95% CI, 0.69–1.23), fibrates (OR, 0.98; 95% CI, 0.86–1.12), and other treatments (OR, 0.81; 95% CI, 0.61–1.08).[170] Reduction in the risk of stroke is proportional to the reduction in total and LDL cholesterol; each 1% reduction in total cholesterol is associated with a 0.8% reduction in the risk of stroke. Similarly, another meta-analysis of 64 randomized, controlled trials reported that treatment-related decreases in LDL cholesterol were associated with decreases in all strokes (RR reduction, 4.5% per 10-mg/dL reduction; 95% CI, 1.7–7.2); however, there was no relationship between triglycerides and stroke.[152]

Niacin increases HDL cholesterol and decreases plasma levels of lipoprotein(a) [Lp(a)]. The Coronary Drug Project found that treatment with niacin reduced mortality in men with prior MI.[171] In the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) study of patients with established CVD, the addition of extended-release niacin to intensive simvastatin therapy did not reduce the risk of a composite of cardiovascular

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events, which included ischemic stroke.[172] In a meta-analysis of 11 studies comprising 9959 subjects, niacin use was associated with a significant reduction in cardiovascular events, including a composite of cardiac death, nonfatal MI, hospitalization for acute coronary syndrome, stroke, or revascularization procedure (OR, 0.66; 95% CI, 0.49–0.89). There was an association between niacin therapy and coronary heart disease event (OR, 0.75; 95% CI, 0.59–0.96) but not with the incidence of stroke (OR, 0.88; 95% CI, 0.5–1.54).[173] However, there are serious safety concerns about niacin therapy. The Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial involving 25 693 patients at high risk for vascular disease showed that extended-release niacin with laropiprant (a prostaglandin D2 signal blocker) caused a significant 4-fold increase in the risk of myopathy in patients taking simvastatin.[174]

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 ≤45 mg/dL, found that bezafibrate did not significantly decrease either the risk of MI or sudden death (primary end point) or stroke (secondary end point).[175] The Veterans Administration HDL Intervention Trial of men with coronary artery disease and low HDL cholesterol found that gemfibrozil reduced the risk of all strokes, primarily ischemic strokes.[176] In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, fenofibrate neither decreased the composite primary end point of coronary heart disease death or nonfatal MI nor decreased the risk of stroke. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study of patients with type 2 diabetes mellitus, adding fenofibrate to simvastatin did not reduce fatal cardiovascular events, nonfatal MI, or nonfatal stroke compared with simvastatin alone.[177] A meta-analysis of 18 trials found that fibrate therapy produced a 10% (95% CI, 0–18) relative reduction in the risk for major cardiovascular but no benefit on the risk of stroke (RR reduction, −3%; 95% CI, −16 to 9).[178]

Ezetimibe lowers blood cholesterol by reducing intestinal absorption of cholesterol. In a study of familial hypercholesterolemia, adding ezetimibe to simvastatin did not affect the progression of carotid IMT more than simvastatin alone.[179] In another trial of subjects receiving a statin, niacin led to greater reductions in mean carotid IMT than ezetimibe over 14 months (P=0.003).[180] Counterintuitively, patients receiving ezetimibe who had greater reductions in the LDL cholesterol had an increase in the carotid IMT (r=–0.31; P<0.001).[180] 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 ezetimibe and simvastatin with simvastatin alone on cardiovascular outcomes is in progress.[181] Ezetimibe has not been shown to decrease cardiovascular events or stroke.

Dyslipidemia: Recommendations

1. **In addition to therapeutic lifestyle changes, treatment with an HMG coenzyme-A reductase inhibitor (statin) medication is recommended for the primary prevention of ischemic stroke in patients estimated to have a high 10-year risk for cardiovascular events as recommended in the 2013 "ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults"[169] (*Class I; Level of Evidence A*).**
2. **Niacin may be considered for patients with low HDL cholesterol or elevated Lp(a), but its efficacy in preventing ischemic stroke in patients with these conditions is not established. Caution should be used with niacin because it increases the risk of myopathy (*Class IIb; Level of Evidence B*).**
3. **Fibric acid derivatives may be considered for patients with hypertriglyceridemia, but their efficacy in preventing ischemic stroke is not established (*Class IIb; Level of Evidence C*).**
4. **Treatment with nonstatin lipid-lowering therapies such as fibric acid derivatives, bile acid sequestrants, niacin, and ezetimibe may be considered in patients who cannot tolerate statins, but their efficacy in preventing stroke is not established (*Class IIb; Level of Evidence C*).**

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 scientific statement from the AHA concluded that several aspects of diet lead to elevated BP.[182] Specifically, dietary risk factors that are causally related to elevated BP include excessive salt intake, low potassium intake, excessive 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.[182] In this setting, dietary changes have the potential to substantially reduce racial disparities in BP and stroke.[182,183]

Nutrition science is generally limited because randomized trials involving long-term follow-up are challenging to conduct. Nutritional epidemiology faces challenges of measurement error, confounders, variable effects of food items, variable reference groups, interactions, and multiple testing.[184] Keeping these limitations in mind, it is worth noting that several aspects of diet have been associated with stroke risk. A meta-analysis found a strong inverse relationship between servings of fruits and vegetables and subsequent stroke.[185] Compared with individuals who consumed <3 servings per day, the RR of ischemic stroke was less in those who consumed 3 to 5 servings per day (RR, 0.88; 95% CI, 0.79–0.98) and in those who consumed >5 servings per day (RR, 0.72; 95% CI, 0.66–0.79). The dose-response relationship extends into the higher ranges of intake.[186] Specifically, in analyses of the Nurses' Health Study and the Health Professionals' Follow-Up Study,[186] the RR of incident stroke was 0.69 (95% CI, 0.52–0.92) for people 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 in women. For each serving-per-day increase in fruit and vegetable intake, the risk of stroke was reduced by 6% (95% CI, 1–10). A subsequent analysis of the Nurses' Health Study[187] showed that increased intake of flavonoids, primarily from citrus fruits, was associated with a reduced risk of ischemic stroke (RR, 0.81; 95% CI, 0.66–0.99; P=0.04). As highlighted in the 2010 US Dietary Guidelines, most Americans

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obtain only 64% and 50% of the recommended daily consumption of vegetables and fruits, respectively.[188]

A randomized, controlled trial of the Mediterranean diet performed in 7447 individuals at high cardiovascular risk showed that those on an energy-unrestricted Mediterranean diet supplemented by nuts (walnuts, hazelnuts, and almonds) had a lower risk of stroke than people on a control diet (3.1 versus 5.9 strokes per 1000 person-years; P=0.003) and that those on an energy-unrestricted Mediterranean diet supplemented by extra virgin olive oil had a lower risk of stroke than people on a control diet (4.1 strokes per 1000 person-years; P=0.03).[189]

In ecological studies,[190] prospective studies,[191,192] and meta-analyses,[193,194] a higher level of sodium intake was associated with an increased risk of stroke. In prospective studies, a higher level of potassium intake was also associated with a reduced risk of stroke.[195–198] 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.[199] In addition to increased overall survivorship and reduced costs, the potassium-enriched salt reduced the risk of mortality 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 the Women's Health Initiative, 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 increase in fruit and vegetable consumption (mean difference, only 1.1 servings per day) or decrease in BP (mean difference, <0.5 mm Hg for both SBP and DBP).[200]

The effects of sodium and potassium on stroke risk are likely mediated through direct effects on BP and effects independent of BP.[201] In clinical trials, particularly dose-response studies, the relationship between sodium intake and BP is direct and progressive, without an apparent threshold.[202–204] Blacks, hypertensives, and middle-aged and older adults are especially sensitive to the BP-lowering effects of a reduced sodium intake.[205] In other trials, an increased intake of potassium was shown to lower BP[206] and to blunt the pressor effects of sodium.[207] 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.[208–210] As documented in a study by the Institute of Medicine,[211] sodium intake remains high and potassium intake quite low in the United States.

Other dietary factors may affect the risk of stroke, but the evidence is insufficient to make specific recommendations.[182] In Asian countries, a low intake of animal protein, saturated fat, and cholesterol has been associated with a decreased risk of stroke,[212] but such relationships have been less apparent in Western countries.[213] A recent prospective study[214] showed that higher intake of red meat was associated with a higher risk of stroke, but a higher intake of poultry was associated with a lower risk of stroke. Additionally, a meta-analysis of prospective studies concluded that intake of fresh, processed, and total red meat is associated with an increased risk of ischemic stroke.[215] Potentially, the source of dietary protein may affect stroke risk. In the absence of a clinical syndrome of a specific vitamin or nutrient deficiency, there is no conclusive evidence that vitamins or other supplements prevent incident stroke.

Diet and Nutrition: Summary and Gaps

From epidemiological studies and randomized trials, it is likely that diets low in sodium and rich in fruits and vegetables, such as the Mediterranean and DASH-style diets, reduce stroke risk. Few randomized trials with clinical outcomes have been conducted. US Dietary Guidelines for Americans recommend a sodium intake of <2300 mg/d (100 mmol/d) for the general population. In blacks, individuals with hypertension, those with diabetes mellitus, those with chronic kidney disease, and individuals ≥51 years of age, a sodium intake of <1500 mg is recommended.[188] The AHA recommends <1500 mg sodium per day.[216] The ideal lower limit of dietary salt intake remains ill defined and may depend on comorbidities such as diabetes mellitus and heart failure managed with diuretic medications.[217] US Dietary Guidelines for Americans recommend that potassium intake be at least 4700 mg/d (120 mmol/d).[188]

Diet and Nutrition: Recommendations

1. **Reduced intake of sodium and increased intake of potassium as indicated in the US Dietary Guidelines for Americans are recommended to lower BP (*Class I; Level of Evidence A*).**
2. **A DASH-style diet, which emphasizes fruits, vegetables, and low-fat dairy products and reduced saturated fat, is recommended to lower BP[127,218] (*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 the risk of stroke (*Class I; Level of Evidence B*).**
4. **A Mediterranean diet supplemented with nuts may be considered in lowering the risk of stroke (*Class IIa; Level of Evidence B*).**

Hypertension

The Seventh Joint National Committee defined hypertension as SBP >140 mm Hg and DBP >90 mm Hg.[219] The most recent panel appointed by the National Heart, Lung, and Blood Institute to review hypertension management guidelines was silent on the issue of defining hypertension but chose instead to focus on defining BP thresholds for initiating or modifying therapy.[220] Hypertension is a major risk factor for both cerebral infarction and ICH. The relationship between BP and stroke risk is strong, continuous, graded, consistent, independent, predictive, and etiologically significant.[221] Throughout the usual range of BPs, including the nonhypertensive range, the higher the BP is, the greater the risk of stroke.[222]

The prevalence of hypertension has plateaued over the past decade. On the basis of national survey data from 1999

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to 2000 and 2007 to 2008, the prevalence of hypertension in the United States remained stable at 29%.[223,224] Hypertension control has also improved over the past 25 years, with control rates of 27.3% measured in 1988 to 1994 and 50.1% measured in 2007 to 2008. The improved control is likely attributable to heightened awareness and treatment. Awareness of hypertension among US residents significantly increased from 69% in 1988 to 1994 to 81% in 2007 to 2008, and treatment improved from 54% to 73% over the same period. Despite the improvements, however, rates of control were lower among Hispanics compared with whites and among those 18 to 39 years of age compared with older individuals.

BP, particularly SBP, rises with increasing age in both children[225] and adults.[226] Individuals who are normotensive at 55 years of age have a 90% lifetime risk for developing hypertension.[227] More than two thirds of people ≥65 years of age are hypertensive.[221]

Because the risk of stroke increases progressively with increasing BP and because many individuals have a BP level below current drug treatment thresholds,[220] nondrug or lifestyle approaches are recommended as a means of reducing BP in nonhypertensive individuals with an elevated BP (ie, pre-hypertension: 120 to 139 mm Hg SBP or 80 to 89 mm Hg DBP).[228] Pharmacological treatment of prehypertension appears to reduce the risk of stroke. In a meta-analysis of 16 trials involving 70 664 prehypertensive patients, prehypertensive patients randomized to active antihypertensive treatment had a consistent and statistically significant 22% reduction in the risk of stroke compared with those taking placebo (P<0.000001).[229]

Behavioral lifestyle changes are recommended by the Seventh Joint National Committee as part of a comprehensive treatment strategy for hypertension.[221] Compelling evidence from >40 years of clinical trials has documented that drug treatment of hypertension prevents stroke and other BP-related target-organ damage, including heart failure, coronary heart disease, and renal failure.[221] A meta-analysis of 23 randomized trials showed that antihypertensive drug treatment reduced the risk of stroke by 32% (95% CI, 24–39; P=0.004) compared with no drug treatment.[230] The use of antihypertensive therapies among those with mild hypertension (SBP, 140 to 159 mm Hg; DBP, 90 to 99 mm Hg; or both), however, was not clearly shown to reduce the risk of first stroke in a Cochrane Database Systematic Review, although a trend of clinically important magnitude was present (RR, 0.51; 95% CI, 0.24–1.08). Because 9% of patients stopped therapy as a result of side effects, the authors recommended further trials be conducted.[231]

Several trials have addressed the potential role of antihypertensive treatment among patients with prevalent CVD but without hypertension. In a meta-analysis of 25 trials of antihypertensive therapy for patients with prevalent CVD (including stroke) but without hypertension, patients receiving antihypertensive medications had a pooled RR for stroke of 0.77 (95% CI, 0.61–0.98) compared with control subjects.[232] The magnitude of the RR reduction was greater for stroke than for most other cardiovascular outcomes, although the absolute risk reductions were greater for other outcomes because of their greater relative frequency.

In a separate meta-analysis of 13 trials involving 80 594 individuals, among those either with prevalent atherosclerotic disease or at high risk for developing it, angiotensin-converting enzyme (ACE) inhibitors (ACEIs) or angiotensin receptor blocker (ARB) therapy reduced the risk of a composite primary outcome including stroke by 11%, without variability by baseline BP.[233] There was also a significant reduction in fatal and nonfatal strokes (OR, 0.91; 95% CI, 0.86–0.97). Non–ACEI/ARB therapies were allowed, but meta-regression analyses provided evidence that the benefits were not due solely to BP reductions during the trial. Several other meta-analyses have evaluated whether specific classes of antihypertensive agents offer protection against stroke beyond their BP-lowering effects.[230,234–237] In one of these meta-analyses evaluating different classes of agents used as first-line therapy in subjects with a baseline BP >140/90 mm Hg, thiazide diuretics (RR, 0.63; 95% CI, 0.57–0.71), β-blockers (RR, 0.83; 95% CI, 0.72–0.97), ACEIs (RR, 0.65; 95% CI, 0.52–0.82), and calcium channel blockers (RR, 0.58; 95% CI, 0.41–0.84) each reduced the risk of stroke compared with placebo or no treatment.[236] Compared with thiazides, β-blockers, ACEIs, and ARBs, calcium channel blockers appear to have a slightly greater effect on reducing the risk of stroke, although the effect is not seen for other cardiovascular outcomes and was of small magnitude (8% relative reduction in risk).[235] One meta-analysis found that diuretic therapy was superior to ACEI therapy,[230] and another found that calcium channel blockers were superior to ACEIs.[237] Another found that β-blockers were less effective in reducing stroke risk than calcium channel blockers (RR, 1.24; 95% CI, 1.11–1.40) or inhibitors of the renin-angiotensin system (RR, 1.30; 95% CI, 1.11–1.53).[238] Subgroup analyses from 1 major trial suggest that the benefit of diuretic therapy over ACEI therapy is especially prominent in blacks,[239] and subgroup analysis from another large trial found that β-blockers were significantly less effective than thiazide diuretics and ARBs at preventing stroke in those ≥65 years of age than in younger patients.[240] The results of a recent trial of the direct renin inhibitor aliskiren in patients with type 2 diabetes mellitus plus chronic kidney disease or prevalent CVD did not find evidence that aliskiren reduced cardiovascular end points, including stroke.[241] In general, therefore, although the benefits of lowering BP as a means to prevent stroke are undisputed, there is no definitive evidence that any particular class of antihypertensive agents offers special protection against stroke in all patients. Further hypothesis-driven trials are warranted, however, to test differences in efficacy of individual agents in specific subgroups of patients.

BP control can be achieved in most patients, but most patients require therapy with ≥2 drugs.[242,243] In 1 open-label trial conducted in Japan, among patients taking a calcium channel blocker who had not yet achieved a target BP, the addition of a thiazide diuretic significantly reduced the risk of stroke compared with the addition of either a β-blocker (P=0.0109) or an ARB (P=0.0770).[244] The advantage of the combination of a calcium channel blocker and thiazide was not seen, however, for other cardiovascular end points.

Meta-analyses support that more intensive control of BP (SBP <130 mm Hg) reduces risk of stroke more than less intensive control (SBP, 130–139 mm Hg), although the effects

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on other outcomes and in all subgroups of patients remain unclear. Among 11 trials with 42572 participants, the RR of stroke for those whose SBP was <130 mm Hg was 0.80 (95% CI, 0.70–0.92). The effect was greater among those with cardiovascular risk factors but without established CVD.[245] This benefit of intensive BP lowering may be more specific to stroke than to other cardiovascular outcomes, at least among certain subgroups of patients. Among patients with diabetes mellitus at high cardiovascular risk enrolled in the ACCORD Blood Pressure Trial, more intensive BP control (SBP <120 mm Hg) compared with standard control (<140 mm Hg) led to a significant reduction in risk of stroke, a prespecified secondary outcome (HR, 0.59; 95% CI, 0.39–0.89).[246,247] However, there was no effect on either the primary composite outcome or overall mortality. This absence of benefit on nonstroke outcomes was not attributable to obesity because effects were similar across levels of obesity. A meta-analysis of 31 trials with 73913 individuals with diabetes mellitus demonstrated that more intensive BP reduction significantly reduced the risk of stroke but not MI.[248] For every 5-mm Hg reduction in SBP, the risk of stroke decreased by 13% (95% CI, 5–20). In a secondary analysis of the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial, however, among 9193 hypertensive patients with left ventricular hypertrophy by ECG criteria, achieving intensive BP control to <130 mm Hg was not associated with a reduction in stroke after multivariable adjustment, and there was a significant increase in all-cause mortality (HR, 1.37; 95% CI, 1.10–1.71).[249] The target for BP reduction, therefore, may differ by patient characteristics and comorbidities.

Pharmacogenomics may contribute to improving individualized selection of antihypertensive medications for stroke prevention. For example, in genetic studies ancillary to the Antihypertensive and Lipid Lowering to Prevent Heart Attack Trial (ALLHAT), individuals with the stromelysin (matrix metalloproteinase-3) genotype 6A/6A had higher stroke rates on lisinopril than on chlorthalidone, and those with the 5A/6A genotype had lower stroke rates on lisinopril.[250] The 5A/5A homozygotes had the lowest stroke rates compared with those taking chlorthalidone (HR for interaction=0.51; 95% CI, 0.31–0.85). The effect was not seen for other medications. Carriers of mutations of the fibrinogen-β gene also had a lower risk of stroke on lisinopril compared with amlodipine than those who were homozygous for the usual allele, potentially because ACEIs lower fibrinogen levels and this effect is more clinically important among those with mutations associated with higher fibrinogen levels.[251] The role of genetic testing in hypertension management remains undefined at present, however.

Recent evidence suggests that intraindividual variability in BP may confer risk beyond that caused by mean elevations in BP alone.[252] There is further observational evidence that calcium channel blockers may have benefits in reducing BP variability that are not present with β-blockers and that these benefits may provide additional benefits in stroke risk reduction.[253,254] Twenty-four–hour ambulatory BP monitoring provides additional insight into risk of stroke and cardiovascular events. Measurements of nocturnal BP changes ("reverse dipping" or "extreme dipping") and the ratio of nocturnal to daytime BPs may provide data about risk beyond that provided by mean 24-hour SBP.[255,256] Further study of the benefits on stroke risk reduction of treatments focused on reducing intraindividual variability in BP and nocturnal BP changes seem warranted.

Controlling isolated systolic hypertension (SBP ≥160 mm Hg and DBP <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% (95% CI, 18–60; *P*=0.02) risk reduction in the actively treated group.[257] The Systolic Hypertension in the Elderly Program (SHEP) Trial found a 36% reduction (95% CI, 18–50; *P*=0.003) in the incidence of stroke from a diuretic-based regimen.[258] In the Hypertension in the Very Elderly (HYVET) trial, investigators randomized 3845 patients ≥80 years of age with SBP ≥160 mm Hg to placebo or indapamide, with perindopril or placebo added as needed to target a BP <150/80 mm Hg. After 2 years, there was a reduction in SBP of 15 mm Hg, associated with a 30% reduction in risk of stroke (*P*=0.06), a 39% reduction in fatal stroke (*P*=0.046), and a 21% reduction in overall mortality (*P*=0.02).[257] No trial has focused on individuals with lesser degrees of isolated systolic hypertension (SBP=140–159 mm Hg; DBP <90 mm Hg).

The most recent National Heart, Lung, and Blood Institute–appointed panel provides an evidence-based approach to pharmacological treatment of hypertension.[220] The report focuses on age as a guide for therapeutic targets, with recommendations to lower BP pharmacologically to a target of <150/90 mm Hg for patients >60 years of age and target a BP of <140/90mm Hg for younger patients. However, these recommendations differ from the 2014 science advisory on high BP control endorsed by the AHA, ACC, and Centers for Disease Control and Prevention in which more aggressive BP targets are recommended (<140/90 mm Hg) regardless of age.[218] There is concern that raising the SBP threshold from 140 to 150 mm Hg might reverse some of the gains that have been achieved in reducing stroke by tighter BP control. For patients with diabetes mellitus who are at least 18 years of age, the panel originally appointed by the National Heart, Lung, and Blood Institute to review the evidence on treatment of hypertension recommends initiating pharmacologic treatment to lower BP at SBP of ≥140 mm Hg or DBP of ≥90 mm Hg and to treat to a goal SBP of <140 mm Hg and a goal DBP <90 mm Hg.[220]

The International Society on Hypertension in Blacks revised its recommendations for managing BP in this at-risk population in 2010.[259] In the absence of target-organ damage, the target should be <135/85 mm Hg; in the presence of target-organ damage, the target should be <130/80 mm Hg. For patients who are within 10 mm Hg above target, monotherapy with diuretic or calcium channel blocker is preferred, and for patients >15/10 mm Hg above target, 2-drug therapy is preferred either with a calcium channel blocker plus renin-angiotensin system blocker or, in edematous or volume-overloaded states, with a thiazide diuretic plus a renin-angiotensin system blocker. Largely on the basis of a prespecified subgroup analysis of the ALLHAT trial, the National Heart, Lung, and Blood Institute panel originally appointed to address hypertension management recommend that in the general black population, including those with diabetes mellitus, initial antihypertensive therapy should include a thiazide-type diuretic or a calcium channel blocker.[220]

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Population-wide approaches to reducing BP have also been advocated as more effective than approaches focused on screening individual patients for the presence of hypertension and treating them.[235,260] Because the benefits of BP reduction can be seen across the range of measurements in the population, with and without pre-existing CVD, it may be reasonable to provide BP-lowering medications to all patients above a certain age (eg, 60 years of age).[235] Similarly, on the basis of observational data from 19 cohorts with 177 025 participants showing lower salt intake to be associated with a lower risk of stroke and other cardiovascular outcomes, population-wide reductions in salt intake may be advocated as a way to reduce stroke risk.[194] Self-measured BP monitoring is recommended because with or without additional support such monitoring lowers BP compared with usual care.[261]

Hypertension: Summary and Gaps

Hypertension remains the most important, well-documented modifiable stroke risk factor, and treatment of hypertension is among the most effective strategies for preventing both ischemic and hemorrhagic stroke. Across 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. Optimal BP targets for reducing stroke risk are uncertain. Although the benefits of BP reduction on stroke risk continue to be seen at progressively lower pressures, adverse effects on mortality and other outcomes may limit the lower level to which BP targets can be pushed, particularly among certain subgroups of patients such as patients with diabetes mellitus. Future studies are needed to determine the effects of treating BP variability beyond the effects of treatment of mean BP levels. Hypertension remains undertreated in the community, and additional programs to improve treatment adherence need to be developed, tested, and implemented. Both personalized approaches to pharmacotherapy based on pharmacogenetics and population-level approaches to reducing BP require further study.

Hypertension: Recommendations

1. **Regular BP screening and appropriate treatment of patients with hypertension, including lifestyle modification and pharmacological therapy, are recommended (*Class I; Level of Evidence A*).**
2. **Annual screening for high BP and health-promoting lifestyle modification are recommended for patients with prehypertension (SBP of 120 to 139 mm Hg or DBP of 80 to 89 mm Hg) (*Class I; Level of Evidence A*).**
3. **Patients who have hypertension should be treated with antihypertensive drugs to a target BP of <140/90 mm Hg (*Class I; Level of Evidence A*).**
4. **Successful reduction of BP is more important in reducing stroke risk than the choice of a specific agent, and treatment should be individualized on the basis of other patient characteristics and medication tolerance (*Class I; Level of Evidence A*).**
5. **Self-measured BP monitoring is recommended to improve BP control. (*Class I; Level of Evidence A*).**

Obesity and Body Fat Distribution

Stroke, along with hypertension, heart disease, and diabetes mellitus, is associated with being overweight or obese. The prevalence of obesity in the United States has tripled for children and doubled for adults since 1980.[262] Only in the last 3 years has a leveling off been seen.[263–265] Increasing public awareness and government initiatives have placed this public health issue in the forefront.

According to the National Center for Health Statistics data from the Department of Health and Human Services, in 2009 and 2010, the prevalence of obesity was 35.7% among adults and 16.9% among children, with a higher prevalence in adults >60 years of age and adolescents.[263–265] Among the race/ethnic groups surveyed in the United States, age-adjusted rates of obesity indicate the highest rates in non-Hispanic blacks (49.5%), followed by Mexican Americans (40.45%) and then all Hispanics (39.1%), with the lowest rate being among non-Hispanic whites (34.3%).[263–265]

A patient's body mass index (BMI), defined as weight in kilograms divided by the square of the height in meters, is used to distinguish overweight (BMI, 25 to 29 kg/m^2) from obesity (BMI >30 kg/m^2) and morbid obesity (BMI >40 kg/m^2).[266] Men presenting with a waist circumference of >102 cm (40 in) and women with a waist circumference >88 cm (35 in) are categorized as having abdominal obesity.[267] Abdominal obesity can also be measured as the waist-to-hip ratio. For every 0.01 increase in waist-to-hip ratio, there is a 5% increase in risk of CVD.[268]

Abdominal body fat has proved to be a stronger predictor of stroke risk than BMI.[269,270] In contrast, another study reported that in men only BMI was significantly associated with stroke, whereas for women it was waist-to-hip ratio.[271] Adiposity, however, correlated with risk of ischemic heart disease for both sexes. When fat distribution measured by dual-energy x-ray absorptiometry in relation to incidence of stroke was studied, there was a significant association in both men and women between stroke and abdominal fat mass. This association, however, was not independent of diabetes mellitus, smoking, and hypertension.[272]

Mounting evidence shows a graded positive relationship between stroke and obesity independent of age, lifestyle, or other cardiovascular risk factors. Prospective studies of the relationship between weight (or measures of adiposity) and incident stroke indicate that in the BMI range of 25 to 50 kg/m^2 there was a 40% increased stroke mortality with each 5-kg/m^2 increase in BMI. However, in the BMI range of 15 to 24 kg/m^2, there was no relationship between BMI and mortality.[273]

A meta-analysis of data from 25 studies involving >2.2 million people and >30 000 events found an RR for ischemic stroke of 1.22 (95% CI, 1.05–1.41) for overweight people and 1.64 (95% CI, 1.36–1.99) for obese people.[274] For hemorrhagic stroke, the RR was 1.01 (95% CI, 0.88–1.17) for overweight people and 1.24 (95% CI, 0.99–1.54) for obese people. This meta-analysis showed an increased risk of ischemic stroke compared with normal-weight individuals of 22% in overweight individuals and 64% in obese individuals. When diabetes mellitus, hypertension, dyslipidemia, and other confounders were taken into account, there was no significant increase in the incidence of hemorrhagic stroke. These findings have been subsequently borne out in a Chinese study of

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27 000 patients.[275] In Japan, a meta-analysis of 44 000 patients found a positive correlation in both sexes of elevated BMI with both ischemic and hemorrhagic events.[276] ARIC examined a population of 13 000 black and white participants and found that obesity was a risk factor for ischemic stroke independently of race.[277] Adjustments for covariates in all these studies significantly reduced these associations.

The effects of stroke risk and weight reduction have not been studied extensively. A Swedish study that followed 4000 patients over 10 to 20 years, comparing individuals with weight loss through bariatric surgery and obese subjects receiving usual care, showed significant reductions in diabetes mellitus, MI, and stroke.[278] Thirty-six thousand Swedish subjects followed for >13 years again showed a significant decrease in stroke incidence when more than 3 healthy lifestyle goals, including normal weight, were met.[279] The Sibutramine Cardiovascular Outcomes (SCOUT) trial followed up 10 000 patients with CVD or type 2 diabetes mellitus and found that even modest weight loss reduced cardiovascular mortality in the following 4 to 5 years.[280] Reduction in body weight improves control of hypertension. A meta-analysis of 25 trials showed mean SBP and DBP reductions of 4.4 and 3.6 mm Hg, respectively, with a 5.1-kg weight loss.[281]

The US Preventive Services Task Force currently recommends that all adults be screened for obesity and that patients with a BMI of ≥30 kg/m^2 be referred for intensive multicomponent behavioral interventions for weight loss.[282]

Obesity and Body Fat Distribution: Summary and Gaps

Although there is ample evidence that increased weight is associated with an increased incidence of stroke, with stronger associations for ischemic events, many questions remain unanswered. There is no clear and compelling evidence that weight loss in isolation reduces the risk of stroke because of the difficulty in isolating the effects of weight loss as a single contributing factor rather than as a component contributing to better control of hypertension, diabetes mellitus, metabolic syndrome, and other stroke risk factors. It remains to be determined whether the disparities among studies stem from choosing BMI, waist-to-hip ratio, or waist circumference as the measure of obesity.

Obesity and Body Fat Distribution: Recommendations

1. **Among overweight (BMI=25 to 29 kg/m^2) and obese (BMI >30 kg/m^2) individuals, weight reduction is recommended for lowering BP (*Class I; Level of Evidence A*).**
2. **Among overweight (BMI=25 to 29 kg/m^2) and obese (BMI >30 kg/m^2) individuals, weight reduction is recommended for reducing the risk of stroke (*Class I; Level of Evidence B*).**

Diabetes Mellitus

People with diabetes mellitus have both an increased susceptibility to atherosclerosis and an increased prevalence of atherogenic risk factors, notably hypertension and abnormal blood lipids. In 2010, an estimated 20.7 million adults or 8.2% of adult Americans had diabetes mellitus.[283] Moreover, the prevalence of prediabetes among Americans >65 years of age tested in 2005 through 2008 was estimated to be 50%.[283]

Diabetes mellitus is an independent risk factor for stroke.[284] Diabetes mellitus more than doubles the risk for stroke, and ≈20% of patients with diabetes mellitus will die of stroke. Duration of diabetes mellitus also increases the risk of nonhemorrhagic stroke (by 3%/y of diabetes duration).[284] For those with prediabetes, fasting hyperglycemia is associated with stroke.[285] In a study of 43 933 men (mean age, 44.3±9.9 years) free of known CVD and diabetes mellitus at baseline between 1971 and 2002, a total of 595 stroke events (156 fatal and 456 nonfatal strokes) occurred. Age-adjusted fatal, nonfatal, and total stroke event rates per 10 000 person-years for normal fasting plasma glucose (80–109 mg/dL), impaired fasting glucose (110–125 mg/dL), and undiagnosed diabetes mellitus (≥126 mg/dL) were 2.1, 3.4, and 4.0 (P_{trend}=0.002); 10.3, 11.8, and 18.0 (P_{trend}=0.008); and 8.2, 9.6, and 12.4 (P_{trend}=0.008), respectively.[285]

In the Greater Cincinnati/Northern Kentucky Stroke Study, ischemic stroke patients with diabetes mellitus were younger, more likely to be black, and more likely to have hypertension, MI, and high cholesterol than patients without diabetes mellitus.[286] Age-specific incidence rates and rate ratios showed that diabetes mellitus increased ischemic stroke incidence for all ages but that the risk was most prominent before 55 years of age in blacks and before 65 years of age in whites. Although Mexican Americans had a substantially greater incidence rate for the combination of ischemic stroke and ICH than non-Hispanic whites,[40] there is insufficient evidence that the presence of diabetes mellitus or other forms of glucose intolerance influenced this rate. In the Strong Heart Study (SHS), 6.8% of 4549 Native American participants 45 to 74 years of age at baseline without prior stroke had a first stroke over 12 to 15 years, and diabetes mellitus and impaired glucose tolerance increased the HR to 2.05.[43]

In NOMAS, which included 3298 stroke-free community residents, 572 reported a history of diabetes mellitus, and 59% (n=338) had elevated fasting blood glucose.[287] Those subjects with an elevated fasting glucose had an increased stroke risk (HR, 2.7; 95% CI, 2.0–3.8), but those with a fasting blood glucose level of <126 mg/dL were not at increased risk.

Stroke risk can be reduced in patients with diabetes mellitus. In the Steno-2 Study, 160 patients with type 2 diabetes mellitus and persistent microalbuminuria were assigned to receive either intensive therapy, including behavioral risk factor modification and the use of a statin, an ACEI, an ARB, or an antiplatelet drug as appropriate, or conventional therapy with a mean treatment period of 7.8 years.[288] Patients were subsequently followed up for an average of 5.5 years. The primary end point was time to death resulting from any cause. The risk of cardiovascular events was reduced by 60% (HR, 0.41; 95% CI, 0.25–0.67; P<0.001) with intensive versus conventional therapy, and strokes were 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, 0.19–0.94; P=0.04). Eighteen of the 30 strokes were fatal in the conventional group, and all 6 were fatal in the intensive group.

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In the Euro Heart Survey on Diabetes and the Heart, 3488 patients were enrolled, 59% without and 41% with diabetes mellitus.[289] Evidence-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 mellitus, the use of evidence-based medicine (RR, 0.37; 95% CI, 0.20–0.67; *P*=0.001) had an independent protective effect on 1-year mortality and on cardiovascular events (RR, 0.61; 95% CI, 0.40–0.91; *P*=0.015) compared with those without diabetes mellitus. Although stroke rates were not changed, there was an ≈50% reduction in cerebrovascular revascularization procedures.

Glycemic Control

The effect of previous randomization of the UK Prospective Diabetes Study (UKPDS)[290] 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 post-trial monitoring, 3277 patients were asked to attend UKPDS clinics annually for 5 years; however, there were no attempts to maintain their previously assigned therapies.[291] 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 major recent trials have evaluated the effects of reduced glycemia on CVD events in patients with type 2 diabetes mellitus. The ACCORD recruited 10 251 patients (mean age, 62 years) with a mean glycated hemoglobin of 8.1%.[292] Participants were then randomized to receive intensive (glycated hemoglobin goal, <6.0%) or standard (goal, 7.0%–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 mellitus and used a number of strategies to reduce glycemia in an intensive treatment group.[293] Mean glycated hemoglobin levels were 6.5% versus 7.4% at 5 years, with no effect of more intensive therapy on the risk of CVD events or on the risk of nonfatal strokes between groups. In another study, 1791 US veterans (Veterans Affairs Diabetes Trial) with an average duration of diabetes mellitus of >10 years (mean age, 60.4 years) were randomized to a regimen to decrease glycated hemoglobin by 1.5% or standard care.[294] After 5.6 years, the mean levels of glycated hemoglobin were 6.9% versus 8.4%, with no difference in the number of macrovascular events, including stroke, between the 2 groups.[295] From the available clinical trial results, there is no evidence that reduced glycemia decreases the short-term risk of macrovascular events, including stroke, in patients with type 2 diabetes mellitus. A glycated hemoglobin goal of <7.0% has been recommended by the American Diabetes Association to prevent long-term microangiopathic complications in patients with type 2 diabetes mellitus.[296] Whether control to this level also reduces the long-term risk of stroke requires further study. In patients with recent-onset type I diabetes mellitus, intensive diabetes therapy aimed at achieving near-normal glycemia can be accomplished with good adherence but with more frequent episodes of severe hypoglycemia.[297] Although glycemia was similar between the groups over a mean 17 years of follow-up in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study, intensive treatment reduced the risk of any CVD event by 42% (95% CI, 9–63; *P*=0.02) and the combined risk nonfatal MI, stroke, or death from CVD events by 57% (95% CI, 12–79; *P*=0.02).[298] The decrease in glycated hemoglobin was associated with the positive effects of intensive treatment on the overall risk of CVD. There were too few strokes, however, to evaluate the effect of improved glycemia during the trial, and as with type 2 diabetes mellitus, there remains no evidence that tight glycemic control reduces risk of stroke.

Despite the lack of convincing support from any individual clinical trial for intensified glycemic control to reduce stroke incidence in patients with diabetes mellitus, a recent meta-analysis provided some supportive evidence in a subgroup of patients with diabetes mellitus. From 649 identified studies, the authors identified 9 relevant trials, which provided data for 59 197 patients and 2037 stroke events.[299] Overall, intensive control of glucose compared with usual care had no effect on incident stroke (RR, 0.96; 95% CI, 0.88–1.06; *P*=0.445); however, in a stratified analyses, a beneficial effect was seen in patients with diabetes mellitus and a BMI >30 kg/m^2 (RR, 0.86; 95% CI, 0.75–0.99; *P*=0.041).

Diabetes Mellitus and Hypertension

More aggressive lowering of BP in patients with diabetes mellitus and hypertension reduces stroke incidence.[300] In addition to comparing the effects of more intensive glycemic control and standard care on the complications of type 2 diabetes mellitus, the UKPDS found that tight BP control (mean BP, 144/82 mm Hg) resulted in a 44% reduction (95% CI, 11–65; *P*=0.013) in the risk of stroke compared with more liberal control (mean BP, 154/87 mm Hg).[301] There was also a nonstatistically significant 22% (RR, 0.78; 95% CI, 0.45–1.34) risk reduction with antihypertensive treatment in subjects with diabetes mellitus in SHEP.[302] In UKPDS, 884 patients with type 2 diabetes mellitus who attended annual UKPDS clinics for 5 years after study completion were evaluated.[303] Differences in BP between the 2 groups, standard of care and more aggressive BP lowering, disappeared within 2 years. There was a nonsignificant trend toward reduction in stroke with more intensive BP control (RR, 0.77; 95% CI, 0.55–1.07; *P*=0.12). Continued efforts to maintain BP targets might have led to maintenance of the 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 mellitus with a previous cardiovascular event or an additional cardiovascular risk factor (total population, 9541 participants) showed a reduction in the ACEI group in the primary combined outcome of MI, stroke, and cardiovascular death by 25% (95% CI, 12–36; *P*=0.0004) and stroke by 33% (95% CI, 10–50; *P*=0.0074).[304] Whether these benefits represent a specific effect of the ACEI or were simply the result of BP lowering remains unclear. The LIFE study compared the

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effects of an ARB with a β-adrenergic receptor blocker in 9193 people with essential hypertension (160–200/95–115 mm Hg) and electrocardiographically determined left ventricular hypertrophy over 4 years.[305] BP reductions were similar for each group. The 2 regimens were compared among the subgroup of 1195 people who also had diabetes mellitus in a prespecified analysis.[306] There was a 24% reduction (RR, 0.76; 95% CI, 0.58–0.98) in major vascular events and a nonsignificant 21% reduction (RR, 0.79; 95% CI, 0.55–1.14) 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 mellitus would decrease major macrovascular and microvascular events.[307] 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 composite of major macrovascular and microvascular events was reduced by 9% (HR, 0.91; 95% CI, 0.83–1.00; *P*=0.04), but there was no reduction in the incidence of major macrovascular events, including stroke.

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 addition of thiazide as required [atenolol-based]) for the prevention of major cardiovascular events were compared in 5137 patients with diabetes mellitus.[308] 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, 0.76–0.98; *P*=0.026), including a 25% reduction (*P*=0.017) in fatal and nonfatal strokes.

The open-label ACCORD trial randomized trial 4733 participants to 1 of 2 groups with different treatment goals: SBP <120 mm Hg as the more intensive goal and SBP <140 mm Hg as the less intensive goal. Randomization to the more intensive goal did not reduce the rate of the composite outcome of fatal and nonfatal major CVD events (HR, 0.88; 95% CI, 0.73–1.06; *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, 0.39–0.89; *P*=0.01).[247]

In the Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, 11 506 patients (6746 with diabetes mellitus) with hypertension were randomized to treatment with benazepril plus amlodipine or benazepril plus hydrochlorothiazide.[309] The primary end point was the composite of death resulting 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, 0.72–0.90; *P*<0.001). There was, however, no difference in stroke between the groups. Of the participants in the ACCOMPLISH trial with diabetes mellitus, the primary outcome results were similar.

Two recent meta-analyses investigated the effect of BP lowering in patients with type 2 diabetes mellitus. The first included 37 760 patients with type 2 diabetes mellitus or impaired fasting glucose/impaired glucose tolerance with achieved SBP of ≤135 versus ≤140 mm Hg, and the follow-up was at least 1 year.[310] Intensive BP control was associated with a 10% reduction in all-cause mortality (OR, 0.90; 95% CI, 0.83–0.98) and a 17% reduction in stroke, but there was a 20% increase in serious adverse effects. Meta-regression analysis showed continued risk reduction for stroke to a SBP of <120 mm Hg. However, at levels of <130 mm Hg, there was a 40% increase in serious adverse events with no benefit for other outcomes.

In the second meta-analysis, 73 913 patients with diabetes mellitus (295 652 patient-years of exposure) were randomized in 31 intervention trials.[248] Overall, more aggressive treatment reduced stroke incidence by 9% (*P*=0.006), and lower versus less aggressive BP control reduced the risk of stroke by 31% (RR, 0.61; 95% CI, 0.48–0.79). In a meta-regression analysis, the risk of stroke decreased by 13% (95% CI, 0.05–0.20; *P*=0.002) for each 5-mm Hg reduction in SBP and by 11.5% (95% CI, 0.05–0.17; *P*<0.001) for each 2-mm Hg reduction in DBP.

Lipid-Altering Therapy and Diabetes Mellitus

Although secondary subgroup analyses of some studies did not find a benefit of statins in patients with diabetes mellitus,[311,312] 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 (95% CI, 19–28) in the rate of major CVD events.[313] A 22% reduction (95% CI, 13–30) in major vascular events (regardless of the presence of known coronary heart disease or cholesterol levels) and a 24% reduction (95% CI, 6–39; *P*=0.01) in strokes were found among 5963 diabetic individuals treated with the statin in addition to best medical care.[314] The Collaborative Atorvastatin Diabetes Study (CARDS) reported that in patients with type 2 diabetes mellitus, at least 1 additional risk factor (retinopathy, albuminuria, current smoking, or hypertension), and an LDL cholesterol level <160 mg/dL but without a history of CVD, treatment with a statin resulted in a 48% reduction (95% CI, 11–69) in stroke.[315]

In a post hoc analysis of the Treating to New Targets (TNT) study, the effects of intensive lowering of LDL cholesterol with high-dose (80 mg daily) versus low-dose (10 mg daily) atorvastatin on CVD events were compared for patients with coronary heart disease and diabetes mellitus.[316] After a median follow-up of 4.9 years, higher-dose treatment was associated with a 40% reduction in the time to a CVD event (HR, 0.69; 95% CI, 0.48–0.98; *P*=0.037).

Clinical trials with a statin or any other single intervention in patients with high CVD risk, including the presence of diabetes mellitus, are often insufficiently powered to determine an effect on incident stroke. In 2008, data from 18 686 individuals with diabetes mellitus (1466 with type 1 and 17 220 with type 2 diabetes mellitus) were assessed to determine the impact of a 1.0-mmol/l (≈40-mg/dL) reduction in LDL cholesterol.[317] During a mean follow-up of 4.3 years, there were 3247 major cardiovascular events with a 9% proportional reduction

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in all-cause mortality per 1-mmol/L LDL cholesterol reduction (RR, 0.91; 95% CI, 0.82–1.01; *P*=0.02) and a 13% reduction in vascular death (RR, 0.87; 95% CI, 0.76–1.00; *P*=0.008). There were also reductions in MI or coronary death (RR, 0.78; 95% CI, 0.69–0.87; *P*<0.0001) and stroke (RR, 0.79; 95% CI, 0.67–0.93; *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.[318] Compared with those with normal fasting plasma glucose, the risk for major cardiovascular events was higher in subjects with either known (HR, 1.87; 95% CI, 1.44–2.43; *P*=0.001) or newly diagnosed (HR, 1.72; 95% CI, 1.10–2.68; *P*=0.02) diabetes mellitus. Gemfibrozil treatment did not affect the risk of stroke among subjects without diabetes mellitus, but treatment was associated with a 40% reduction in stroke in those with diabetes mellitus (HR, 0.60; 95% CI, 0.37–0.99; *P*= 0.046).

The FIELD study assessed the effect of fenofibrate on cardiovascular events in 9795 subjects 50 to 75 years of age with type 2 diabetes mellitus who were not taking a statin therapy at study entry.[319] The study population included 2131 people with and 7664 people without previous CVD. Over 5 years, 5.9% of patients (n=288) on placebo and 5.2% (n=256) on fenofibrate had a coronary event (*P*=0.16). There was a 24% (RR, 0.76; 95% CI, 0.62–0.94; *P*=0.010) reduction in nonfatal MI. There was no effect on stroke with fenofibrate. A higher rate of statin therapy initiation occurred in patients allocated to placebo, which might have masked a treatment effect. The ACCORD trial randomized 5518 patients with type 2 diabetes mellitus who were being treated with open-label simvastatin to double-blind treatment with fenofibrate or placebo.[177] 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, 0.79–1.08; *P*=0.32]) and no effect on any secondary outcome, including stroke (HR, 1.05; 95% CI, 0.71–1.56; *P*=0.80).

A recent meta-analysis examining the effects of fibrates on stroke in 37 791 patients included some patients with diabetes mellitus.[320] Overall, fibrate therapy was not associated with a significant reduction on the risk of stroke (RR, 1.02; 95% CI, 0.90–1.16; *P*=0.78). However, a subgroup analysis suggested that fibrate therapy reduced fatal stroke (RR, 0.49; 95% CI, 0.26–0.93; *P*=0.03) in patients with diabetes mellitus, CVD, or stroke.

Diabetes Mellitus, Aspirin, and Stroke

The benefit of aspirin in the primary prevention of cardiovascular events, including stroke in patients with diabetes mellitus, remains unclear. A recent study at 163 institutions throughout Japan enrolled 2539 patients with type 2 diabetes mellitus and no history of atherosclerotic vascular disease.[321] Patients were assigned to receive low-dose aspirin (81 or 100 mg/d) or 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, 0.58–1.10; *P*=0.16]). Only a single fatal stroke occurred in the aspirin group, but 5 strokes occurred in the nonaspirin group; thus, the study was insufficiently powered to detect an effect on stroke.

Several large primary prevention trials have included subgroup analyses of patients with diabetes mellitus. The Antithrombotic Trialists' Collaboration meta-analysis of 287 randomized trials reported effects of antiplatelet therapy (mainly aspirin) versus control in 135 000 patients.[322] There was a nonsignificant 7% reduction in serious vascular events, including stroke, in the subgroup of 5126 patients with diabetes mellitus.

A meta-analysis covering the interval between 1950 and 2011 included 7 studies in patients with diabetes mellitus without previous CVD and helps to shed new light on this controversial topic.[323] A total of 11 618 participants were included in the analysis. The overall relative risk for major cardiovascular events was 0.91 (95% CI, 0.82–1.00), but an effect on stroke incidence was not found (RR, 0.84; 95% CI, 0.64–1.11). Because hyperglycemia reduces platelet sensitivity to aspirin,[324] an important consideration in patients with diabetes mellitus is aspirin dose. In another meta-analysis, there was no evidence that aspirin dose explained the lack of an aspirin effect on cardiovascular and stroke mortality in patients with diabetes mellitus.[325] However, the systematic review identified an important gap in randomized, controlled trials for using anywhere between 101 to 325 mg aspirin daily in patients with diabetes mellitus.

Diabetes: Summary and Gaps

A comprehensive program that includes tight control of hypertension with ACEI or ARB treatment reduces the risk of stroke in people with diabetes mellitus. Glycemic control reduces microvascular complications, but there remains no evidence that improved glycemic control reduces the risk of incident stroke. Adequately powered studies show that treatment of patients with diabetes mellitus with a statin decreases the risk of a first stroke. Although a subgroup analysis of VA-HIT suggests that gemfibrozil reduces stroke in men with diabetes mellitus and dyslipidemia, a fibrate effect was not seen in FIELD, and ACCORD found no benefit of adding fenofibrate to statin. However, the subgroup analysis from fibrate trials suggests a benefit of fibrates in patients with diabetes mellitus and a BMI >30 kg/m^2.

Diabetes: Recommendations

1. **Control of BP in accordance with an AHA/ACC/CDC Advisory[218] to a target of <140/90 mm Hg is recommended in patients with type 1 or type 2 diabetes mellitus (*Class I; Level of Evidence A*).**
2. **Treatment of adults with diabetes mellitus with a statin, especially those with additional risk factors, is recommended to lower the risk of first stroke (*Class I; Level of Evidence A*).**
3. **The usefulness of aspirin for primary stroke prevention for patients with diabetes mellitus but low 10-year risk of CVD is unclear (*Class IIb; Level of Evidence B*).**
4. **Adding a fibrate to a statin in people with diabetes mellitus is not useful for decreasing stroke risk (*Class III; Level of Evidence B*).**

Cigarette Smoking

Virtually every multivariable assessment of stroke risk factors (eg, Framingham,[16] CHS,[326] and the Honolulu Heart Study[327]) has identified cigarette smoking as a potent risk factor for ischemic

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stroke, associated with an approximate doubling of risk. 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.[328] Smoking is also associated with a 2- to 4-fold increased risk for SAH.[329–332] The data for ICH (apart from SAH), however, are inconsistent. A multicenter case-control study found an adjusted OR of 1.58 (95% CI, 1.02–2.44)[333] for ICH, and analyses from the Physicians' Health Study[332] and WHS[331] also found such an association, but other studies, including a pooled analysis of the ARIC and CHS cohorts, found no relationship between smoking and ICH risk.[135,334–336] A meta-analysis of 32 studies estimated the RR for ischemic stroke to be 1.9 (95% CI, 1.7–2.2) for smokers versus nonsmokers, the RR for SAH to be 2.9 (95% CI, 2.5–3.5), and the RR for ICH to be 0.74 (95% CI, 0.56–0.98).[335]

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.[337] From data available from the National Health Interview Survey and death certificate data for 2000 through 2004, the Centers for Disease Control and Prevention estimated that smoking resulted in an annual average of 61 616 stroke deaths among men and 97 681 stroke deaths among women.[338]

Cigarette smoking may potentiate the effects of other stroke risk factors, including SBP[339] and OCs.[340,341] For example, a synergistic effect exists between the use of OCs and smoking on the risk of cerebral infarction. With nonsmoking, non-OC users serving as the reference group, the odds of cerebral infarction were 1.3 times greater (95% CI, 0.7–2.1) for women who smoked but did not use OCs, 2.1 times greater (95% CI, 1.0–4.5) for nonsmoking OC users, and 7.2 times greater (95% CI, 3.2–16.1) for OC users who smoked.[340] 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, 1.2–2.0) for women who smoked but did not use OCs, 1.5 times greater (95% CI, 1.1–2.1) for nonsmoking OC users, and 3.7 times greater (95% CI, 2.4–5.7) for OC users who smoked.[341]

Exposure to environmental tobacco smoke (also referred to as passive or second-hand smoke) is an established risk factor for heart disease.[342,343] Exposure to environmental tobacco smoke may also be a risk factor for stroke, with a risk approaching the doubling found for active smoking,[344–349] although 1 study found no association.[350] 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 is surprising. This apparent lack of a dose-response relationship may be explained in part by physiological studies suggesting a tobacco smoke exposure threshold rather than a linear dose-response relationship.[351] Recent studies of the effects of smoking bans in communities have also shown that these bans are associated with a reduction in the risk of stroke. After Arizona enacted a statewide ban on smoking in most indoor public places. including workspaces, restaurants, and bars, there was a 14% reduction in strokes in counties that had not previously had a ban in place.[352] A study of New York State did not find a reduction in strokes despite a decrease in risk of MI when it enacted a comprehensive smoking ban in enclosed workspaces, restaurants, and construction sites.[353]

Smoking likely contributes to increased stroke risk through both short-term effects on the risk of thrombus generation in atherosclerotic arteries and long-term effects related to increased atherosclerosis.[354] Smoking as little as a single cigarette increases heart rate, mean BP, and cardiac index and decreases arterial distensibility.[355,356] Beyond the immediate effects of smoking, both active and passive exposure to cigarette smoke is associated with the development of atherosclerosis.[357] In addition to placing individuals at increased risk for both thrombotic and embolic stroke, cigarette smoking approximately triples the risk of cryptogenic stroke among individuals with a low atherosclerotic burden and no evidence of a cardiac source of emboli.[358,359]

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 the risk of stroke and other cardiovascular events to a level that approaches, but does not reach, that of those who never smoked.[354,360–362]

Although sustained smoking cessation is difficult to achieve, effective behavioral and pharmacological treatments for nicotine dependence are available.[363–365] Comprehensive reviews and recommendations for smoking cessation are provided in the 2008 Surgeon General's report,[363] the 2008 update from the Public Health Service,[366] and the 2009 affirmation of these recommendations from the US Preventive Services Task Force.[367] The combination of counseling and medications is more effective than either therapy alone.[367]

With regard to specific pharmacotherapy, in a meta-analysis current to January 2012, nicotine replacement therapy, bupropion, and varenicline were all superior to inert control medications, but varenicline was superior to each of the other active interventions in direct comparisons.[368] Emerging evidence suggests that varenicline may be more cost-effective than nicotine replacement therapy.[369]

Cigarette Smoking: 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 and with community-wide smoking bans. 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.

Cigarette Smoking: Recommendations

1. **Counseling, in combination with drug therapy using nicotine replacement, bupropion, or varenicline, is recommended for active smokers to assist in quitting smoking (*Class I; Level of Evidence A*).**
2. **Abstention from cigarette smoking is recommended for patients who have never smoked on the basis of epidemiological studies showing a consistent and overwhelming relationship between smoking and both ischemic stroke and SAH (*Class I; Level of Evidence B*).**

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3. Community-wide or statewide bans on smoking in public spaces are reasonable for reducing the risk of stroke and MI (*Class IIa; Level of Evidence B*).

Atrial Fibrillation

AF, even in the absence of cardiac valvular disease, is associated with a 4- to 5-fold increased risk of ischemic stroke resulting from embolism of stasis-induced thrombi forming in the left atrial appendage (LAA).[370] About 2.3 million Americans have either sustained or paroxysmal AF.[370] Embolism of appendage thrombi associated with AF accounts for ≈10% of all ischemic strokes and an even higher fraction in the very elderly in the United States.[371] The absolute stroke rate averages ≈3.5%/y for 70-year-old individuals with AF, but the risk varies 20-fold among patients, depending on age and other clinical features (see below).[372,373] AF is also an independent predictor of increased mortality.[374] Paroxysmal AF increases stroke risk similar to sustained AF.[375]

There is an important opportunity for primary stroke prevention in patients with AF because the dysrhythmia is diagnosed before stroke in many patients. However, a substantial minority of AF-related stroke occurs in patients without a prior diagnosis of the condition. Studies of active screening of patients >65 years of age for AF in primary care settings show that pulse assessment by trained personnel increases the detection of undiagnosed AF.[376,377] Systematic pulse assessment during routine clinic visits followed by 12-lead ECG in those with an irregular pulse resulted in a 60% increase in the detection of AF.[376]

Risk Stratification in Patients With AF

Once the diagnosis of AF is established, the next step is to estimate an individual's risks for cardioembolic stroke and for hemorrhagic complications of antithrombotic therapy. For estimating risk of AF-related cardioembolic stroke, more than a dozen risk stratification schemes have been proposed on the basis of various combinations of clinical and echocardiographic predictors.[373] The widely used $CHADS_2$ scheme (Table 3) yields a score of 0 to 6, with 1 point each given for congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus and with 2 points given for prior stroke or transient ischemic attack (TIA).[378]

This scheme has been tested in multiple independent cohorts of AF patients, with 0 points corresponding to low risk (0.5%–1.7%), 1 point reflecting moderate risk (1.2%/y–2.2%/y), and ≥2 points indicating high risk (1.9%/y–7.6%/y).[373] The CHA_2DS_2-VASc scheme (Table 3) modifies $CHADS_2$ by adding an age category (1 point for age 65 to 74 years, 2 points for age ≥75 years) and adding 1 point each for diagnosis of vascular disease (such as peripheral artery disease, MI, or aortic plaque) and for female sex. The main advantage of the more cumbersome CHA_2DS_2-VASc scheme for primary stroke prevention is improved stratification of individuals estimated to be at low to moderate risk using $CHADS_2$ (scores of 0 to 1). A study of 45 576 such patients found combined stroke and thromboembolism rates per 100 person-years ranging from 0.84 for $CHADS_2$ of 0 to 1 or CHA_2DS_2-VASc of 0 to 1.79, 3.67, 5.75, and 8.18 for CHA_2DS_2-VASc of 1, 2, 3, and 4, respectively, resulting in significantly improved prediction.[383]

Table 3. Stroke Risk Stratification Schemes for Patients With Atrial Fibrillation

$CHADS_2$[378]	CHA_2DS_2-VASc[379]
Scoring system	Scoring system
Congestive heart failure–1 point	Congestive heart failure–1 point
Hypertension–1 point	Hypertension–1 point
Age ≥75 y–1 point	Age 65–74 y–1 point
Diabetes mellitus–1 point	≥75 y–2 points
Stroke/TIA–2 points	Diabetes mellitus–1 point
Risk scores range: 0–6 points	Stroke/TIA–2 points
Levels of risk for thromboembolic stroke	Vascular disease (eg, peripheral artery disease, myocardial infarction, aortic plaque)–1 point
Low risk for stroke=0 points	Female sex–1 point
Moderate risk=1 point	Risk scores range: 0–9 points
High risk ≥2 points	Levels of risk for thromboembolic stroke
	Low risk=0 points
	Moderate risk=1 point
	High risk ≥2 points
ACCP treatment guidelines based on estimated risk for thromboembolic stroke[380]	HAS-BLED[381]
Low risk: no therapy	Hypertension–1 point
Moderate risk: OAC	Abnormal renal function–1 point
High risk: OAC	Abnormal liver function–1 point
	Prior stroke–1 point
	Prior major bleeding or bleeding predisposition–1 point
	INR in therapeutic range <60% of time–1 point
	Age >65 y–1 point
	Use of antiplatelet or nonsteroidal drugs–1 point
	Excessive alcohol use–1 point
	Risk scores range: 0–9 points
	Score >2 associated with clinically relevant and major bleeding.[382]

ACCP indicates American College of Chest Physicians; INR, international normalized ratio; OAC, oral anticoagulation; and TIA, transient ischemic attack.

Instruments have also been proposed for stratifying risk of bleeding associated with warfarin treatment for AF. In the HAS-BLED scheme (Table 3), 1 point is assigned each for hypertension, abnormal renal or liver function, past stroke, past bleeding history or predisposition, labile INR (ie, poor time in therapeutic range), older age (age >65 years), and use of certain drugs (concomitant antiplatelet or nonsteroidal anti-inflammatory agent use, alcohol abuse).[381] In a validation analysis of data from 2293 subjects randomized to idraparinux or vitamin K antagonist therapy, the HAS-BLED score was moderately predictive (HAS-BLED >2: HR, 1.9 for clinically relevant bleeding; HR, 2.4 for major bleeding).[382] The ATRIA Risk Score[384] derived its point scheme from the Anticoagulation and Risk Factors in Atrial Fibrillation study, assigning 3 points for anemia or severe renal disease (estimated glomerular filtration rate <30 mL/min or dialysis dependent), 2 for age ≥75 years, and 1 for any prior hemorrhage diagnosis or hypertension. Subjects in a validation cohort were successfully divided into groups at low (ATRIA score of 0 to 3, <1%/y) and high (ATRIA score of 5 to 10, >5%/y) risk for major hemorrhage.

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Most of these analyses stratifying risk of future bleeding have not focused on intracranial hemorrhages, the category of major bleeding with the greatest long-term effect on quality of life. Another limitation of prediction scales for hemorrhage is that several of their components such as age and hypertension are also risks for cardioembolic stroke.

Selecting Treatment to Reduce Stroke Risk in Patients With AF

Adjusted-dose warfarin has generally been the treatment of choice for patients at high risk for cardioembolic stroke and acceptably low risk of hemorrhagic complications, particularly intracranial hemorrhage. Treatment with adjusted-dose warfarin (target INR, 2 to 3) robustly protects against stroke (RR reduction, 64%; 95% CI, 49–74), virtually eliminating the excess risk of ischemic stroke associated with AF if the intensity of anticoagulation is adequate and reducing all-cause mortality by 26% (95% CI, 3–23).[385] In addition, anticoagulation reduces stroke severity and poststroke mortality.[386–388] Compared with aspirin, adjusted-dose warfarin reduces stroke by 39% (95% CI, 22–52).[385,389]

Three newer oral anticoagulants have been approved in the United States for stroke prevention in patients with nonvalvular AF: the direct thrombin inhibitor dabigatran (dosed at 150 mg twice daily in patients with creatinine clearance ≥30 mL/min) and the direct factor Xa inhibitors rivaroxaban (20 mg once daily for patients with creatinine clearance ≥50 mL/min) and apixaban (5 mg twice daily for patients with no more than 1 of the following characteristics: age ≥80 years, serum creatinine ≥1.5 mg/dL, or body weight ≤60 kg). Clinical trial data and other information for these agents were recently reviewed in an AHA/American Stroke Association science advisory[390] and are briefly summarized here.

The Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial[391] randomized 18 113 patients to dabigatran 150 mg or 110 mg twice daily or adjusted-dose warfarin (target INR, 2 to 3). The study enrolled patients with and without a history of prior stroke but with overall moderate to high risk of stroke (mean $CHADS_2$ score, 2.1) and excluded patients who had stroke within 14 days (6 months for severe stroke), increased bleeding risk, creatinine clearance <30 mL/min, or active liver disease. The primary outcome of stroke or systemic embolism during the mean 2-year follow-up occurred at a rate of 1.7%/y in the warfarin (INR, 2 to 3) group compared with 1.11%/y in the 150 mg dabigatran group (RR=0.66 versus warfarin; 95% CI, 0.53–0.82; $P<0.001$ for superiority). Intracranial hemorrhage rates were strikingly lower with 150 mg dabigatran relative to adjusted-dose warfarin (0.30%/y versus 0.74%/y; RR, 0.40; 95% CI, 0.27–0.60). However, the overall rates of major bleeding were not different between the groups (3.11%/y versus 3.36%/y; $P=0.31$), and gastrointestinal bleeding was more frequent on 150 mg dabigatran (1.51%/y versus 1.12%/y; RR, 1.50; 95% CI, 1.19–1.89). MI was also increased in the 150 mg dabigatran group (0.74%/y versus 0.53%/y; RR, 1.38; 95% CI, 1.00–1.91),[392] although this difference was no longer significant when silent MIs or unstable angina, cardiac arrest, and cardiac death were included.[391] Meta-analysis of 7 trials of dabigatran use for various indications has supported the possibility of a small but consistent increased risk of MI or acute coronary syndrome versus the risk observed in various control arms of these studies (OR, 1.33; 95% CI, 1.03–1.71; $P=0.03$).[393] Finally, analyses of multiple patient subgroups, categorized by nationality,[394] $CHADS_2$ score,[395] and the presence or absence of prior TIA/stroke, have not found evidence for differences in the risk/benefit profile for dabigatran. In the subgroup of patients ≥75 years of age,[396] dabigatran 150 mg was associated with increased gastrointestinal hemorrhage relative to warfarin (OR, 1.79; 95% CI, 1.35–2.37) but reduced ICH (OR, 0.42; 95% CI, 0.25–0.70).

The Rivaroxaban Versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET AF) Trial[397] randomized 14 264 patients with nonvalvular AF to rivaroxaban 20 mg/d or adjusted-dose warfarin (target INR, 2 to 3). A $CHADS_2$ score of ≥2 was required, yielding a mean score for enrolled subjects of 3.5, which was higher than in the RE-LY and ARISTOTLE trials; more than half of the participants had a stroke, TIA, or systemic embolism before enrollment. Over a median follow-up of 707 days, the primary end point of ischemic and hemorrhagic stroke and systemic embolism in patients as actually treated (the prespecified analysis plan for efficacy in this study) occurred in 1.7%/y in those receiving rivaroxaban and 2.2%/y in those on warfarin (HR, 0.79; 95% CI, 0.66–0.96; $P<0.001$ for noninferiority; analyzed by intention to treat, HR, 0.88; 95% CI, 0.74–1.03; $P<0.001$ for noninferiority; $P=0.12$ for superiority). The primary safety end point of major or nonmajor bleeding occurred in 14.9% of patients per year in those receiving rivaroxaban and 14.5% in those on warfarin (HR, 1.03; 95% CI, 0.96–1.11; $P=0.44$). ICH (0.5% versus 0.7%; HR, 0.67; 95% CI, 0.47–0.93) and fatal bleeding (0.2% versus 0.5%; HR, 0.50; 95% CI, 0.31–0.79), however, were reduced on rivaroxaban relative to warfarin. Subsequent subgroup analysis of the 6796 subjects without previous stroke or TIA[398] found rivaroxaban to have borderline superiority to warfarin in intention-to-treat analysis of efficacy (HR, 0.77; 95% CI, 0.58–1.01), supporting its use in primary prevention. Other subgroup analyses[397] found no differences in the effectiveness of rivaroxaban according to age, sex, $CHADS_2$ score, or the presence of moderate renal insufficiency[399] (creatinine clearance, 30 to 49 mL/min; these subjects were randomized to rivaroxaban 15 rather than 20 mg/d). Important concerns have been raised about the interpretation of ROCKET AF, most notably the relatively poor management of warfarin (mean time in therapeutic range, 55%) and the relatively high number of outcomes (stroke or systemic embolism) beyond the 2-day monitoring period after drug cessation.[400]

Apixaban has been studied in 2 phase III trials. The Apixaban Versus Acetylsalicylic Acid to Prevent Strokes in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial[401] compared apixaban 5 mg twice daily with aspirin 81 to 324 mg daily in 5599 subjects with nonvalvular AF unsuitable for warfarin therapy. The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial[402] compared the same dose of apixaban with adjusted-dose warfarin (target INR, 2 to 3) among 18 201 patients with nonvalvular AF. Subjects in each study had at least 1 additional risk factor for stroke (prior stroke or TIA,

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age ≥75 years, hypertension, diabetes mellitus, heart failure, or peripheral artery disease). A reduced dose of apixaban 2.5 mg twice daily was used in both studies for subjects with at least 2 of the following: ≥80 years, body mass ≤60 kg, or serum creatinine ≥1.5 mg/dL. AVERROES was terminated after a mean follow-up of 1.1 years when an interim analysis found apixaban to be markedly superior to aspirin for the prevention of stroke or systemic embolism (1.6%/y versus 3.7%/y; HR, 0.45; 95% CI, 0.32–0.62) with similar rates of major bleeding (1.4%/y versus 1.2%/y). Germane to primary prevention, apixaban was also superior to aspirin in subjects without prior TIA or stroke (HR, 0.51; 95% CI, 0.35–0.74).[403] Over a median 1.8 years of follow-up in ARISTOTLE, the primary outcome occurred in 1.27%/y in the apixaban group (analyzed as intention to treat) and 1.60%/y in the warfarin group (HR, 0.79; 95% CI, 0.66–0.95; $P<0.001$ for noninferiority; $P=0.01$ for superiority). Much of the difference between the groups could be attributed to a reduction in ICH in the apixaban group (0.24%/y versus 0.47%/y); the differences in ischemic or uncertain type of stroke were minimal (0.97%/y versus 1.05%/y). Major bleeding events were similarly less frequent on apixaban (2.13%/y versus 3.09%/y; HR, 0.69; 95% CI, 0.60–0.80). Subgroup analysis[404] found a similar magnitude effect for primary prevention of stroke or systemic embolism in subjects without prior stroke or TIA (1.01%/y versus 1.23%/y; HR, 0.82; 95% CI, 0.65–1.03), with the sharpest difference again in risk of ICH (0.29%/y versus 0.65%/y; HR, 0.44; 95% CI, 0.30–0.66). Another secondary analysis found consistent efficacy of apixaban in subjects with impaired renal function (estimated glomerular filtration rate <80 mL/min) and significantly greater reduction in major bleeding among those with more advanced dysfunction (estimated glomerular filtration rate ≤50 mL/min).[405] Because of the clustering of stroke observed after discontinuation of apixaban, a black box warning was required for this agent (as for rivaroxaban), indicating that coverage with another anticoagulant should be strongly considered at the time of cessation unless there is pathological bleeding.

Early analyses[406-409] suggest that the newer oral anticoagulants can be cost-effective, particularly for patients at high risk of cardioembolism or hemorrhage. A Markov decision model using data from RE-LY, for example, found that dabigatran 150 mg twice daily provided 0.36 additional quality-adjusted life-years at a cost of $9000,[407] representing an incremental cost-effectiveness ratio ($25 000 per quality-adjusted life-year) that is within the range tolerated by many healthcare systems. These analyses are based on only a single trial of dabigatran, however, and similar evaluations have yet to be performed for rivaroxaban and apixaban. The cost-effectiveness of newer anticoagulants relative to adjusted-dose warfarin is predicted to be sensitive to the cost of the medications, the risk for cardioembolism or hemorrhage (cost-effectiveness improving with increasing risk), and the quality of INR control on warfarin.

There are many factors to consider in the selection of an anticoagulant for patients with nonvalvular AF. The newer agents offer clearly attractive features such as fixed dose, lack of required blood monitoring, absence of known interaction with the immune complexes associated with heparin-induced thrombocytopenia,[410] and fewer identified drug interactions than warfarin. Most notably, each appears to confer lower risk than adjusted-dose warfarin for ICH, arguably the strongest determinant of long-term safety for anticoagulation (Table 4).

These agents also raise important concerns, however, including substantial cost to the healthcare system, renal clearance, short half-lives, general unavailability of a monitoring test to ensure compliance, and lack of a specific agent to reverse their anticoagulant effects.[412] Although a dabigatran dose of 75 mg twice daily was approved for patients with creatinine clearance of 15 to 30 mL/min, such subjects were in fact excluded from RE-LY and have not been extensively studied. The short half-lives of the newer anticoagulants raise the possibility of increased risk of cardioembolism if doses are missed, a concern heightened by the relatively large number of events in ROCKET AF occurring between 2 and 7 days after discontinuation of rivaroxaban.[400] In assessments of the lack of reversing agent for the newer anticoagulants, it is important to consider that even warfarin-related ICH mortality rates are extremely high despite the availability of reversing agents.[413] An analysis of ICH events occurring on dabigatran 150 mg twice daily and adjusted-dose warfarin in RE-LY found no difference in mortality (35% versus 36%) and, because of the lower overall risk of bleeding with dabigatran, significantly fewer deaths caused by ICH (13 versus 32; $P<0.01$).

In studies of antiplatelet agents for nonvalvular AF, aspirin offers modest protection against stroke (RR reduction, 22%; 95% CI, 6–35).[385] No convincing data favor 1 dose of aspirin (50–325 mg daily) over another. Two randomized trials assessed the potential role of the combination of clopidogrel (75 mg daily) plus aspirin (75–100 mg daily) for preventing stroke in patients with AF. The AF Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE) investigators compared this combination antiplatelet regimen with adjusted-dose warfarin (target INR, 2 to 3) in AF patients with 1 additional risk factor for stroke in ACTIVE W and found a reduction in stroke risk with warfarin compared with the dual antiplatelet regimen (RR reduction, 40%; 95% CI, 18–56; $P=0.001$) and no significant difference in risk of major bleeding.[385,414] ACTIVE A compared the combination of clopidogrel and aspirin with aspirin alone in AF patients who were deemed unsuitable for warfarin anticoagulation and who had at least 1 additional risk factor for stroke (≈25%

Table 4. Odds ratios of intracranial hemorrhage relative to warfarin with an INR of 2.0 to 3.0

Drug	Dose(s)	OR (95% CI)	Reference
Apixaban	5 mg twice daily	0.42 (0.30 to 0.58)	Granger[402]
	2.5 or 5 mg twice daily	0.17 (0.01 to 4.30)	Ogawa[321]
Dabigatran	110 to 150 mg twice daily	0.36 (0.26 to 0.49)	Connolly[392]
Rivaroxaban	20 mg daily	0.65 (0.46 to 0.92)	Patel[397]
	15 mg daily	0.50 (0.17 to 1.46)	Hori[394]

CI indicates confidence interval; INR, international normalized ratio; and OR, odds ratio. Adapted with permission from Chatterjee et al.[411] Copyright © 2013, American Medical Association. All rights reserved. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

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were deemed unsuitable because of concern for warfarin-associated bleeding).[415] Dual antiplatelet therapy resulted in a significant reduction in all strokes (including parenchymal ICH) over treatment with aspirin alone (RR reduction, 28%; 95% CI, 17–38; *P*=0.0002) but also resulted in a significant increase in major bleeding (RR increase, 57%; 95% CI, 29–92; *P*<0.001). Overall and in absolute terms, major vascular events (the study primary end point) were decreased 0.8%/y, but major hemorrhages increased 0.7%/y (RR for major vascular events and major hemorrhages, 0.97; 95% CI, 0.89–1.06; *P*=0.54). Disabling/fatal stroke, however, was decreased by dual antiplatelet therapy (RR reduction, 26%; 95% CI, 11–38; *P*=0.001). A post hoc analysis of randomized trial data that used relative weighting of events suggested a modest net benefit from the combination of aspirin and clopidogrel over aspirin alone.[416]

Recommendations for the selection of antithrombotic therapy for patients with nonvalvular AF have had to adjust for 2 emerging trends: a decreasing rate of stroke for any given $CHADS_2$ risk category,[417] possibly related to improving control of other stroke risk factors, and the appearance of the newer oral anticoagulants with a lower risk of ICH. These 2 trends tend to have opposing effects on the tipping point at which the benefits of anticoagulation outweigh its risks: A lower stroke risk argues for more limited use of anticoagulation, and safer agents argue for more extensive use.[418] On the basis of the decreasing risk of AF-related stroke, the 2012 American College of Chest Physicians evidence-based practice guidelines[380] suggested that patients with nonrheumatic AF at low stroke risk (ie, $CHADS_2$=0) be treated with no therapy rather than any antithrombotic agent (American College of Chest Physicians grade 2B; ie, weak recommendation, moderate evidence); for those patients preferring antithrombotic treatment, aspirin rather than anticoagulation was recommended (grade 2B). These guidelines also favored oral anticoagulation rather than antiplatelet therapy for those at moderate risk (ie, $CHADS_2$=1; grade 2B) and for those at high risk (ie, $CHADS_2$ ≥2; American College of Chest Physicians grade 1B, ie strong recommendation, moderate evidence) and the use of dabigatran (the only approved newer anticoagulant when the guidelines were formulated) rather than warfarin as oral anticoagulant (grade 2B). For patients in these groups who select antiplatelet rather than anticoagulant therapy, the guidelines recommended combination aspirin plus clopidogrel rather than aspirin alone (grade 2B). Of these clinical scenarios, the greatest uncertainty surrounds the management of patients at moderate risk ($CHADS_2$=1). A large cohort study did not find net clinical benefit of warfarin for AF patients with a $CHADS_2$ score of 1,[417] and a decision-analysis model predicted that anticoagulation would be beneficial in this group only when the lower risk of ICH associated with the newer agents was assumed.[418]

Most guidelines have not explicitly incorporated risk for anticoagulant-related hemorrhagic complications, largely because of the paucity of precise data on the risk of bleeding. Some of the risks for hemorrhage are also risks for cardioembolism and thus do not necessarily argue against anticoagulation. Age >75 years, for example, is a factor favoring rather than opposing anticoagulation.[377] One bleeding risk that appears sufficient to tip the balance away from anticoagulation in nonvalvular AF is a history of lobar ICH suggestive of cerebral amyloid angiopathy.[419] Other risks for ICH such as certain genetic profiles or the presence of asymptomatic cerebral microbleeds on neuroimaging do not currently appear sufficient by themselves to outweigh the benefits of anticoagulation in patients at average risk of cardioembolism.[420]

For patients treated with adjusted-dose warfarin, the initial 3-month period is a particularly high-risk period for bleeding[421] and requires especially close anticoagulation monitoring. ICH is the most devastating complication of anticoagulation, but the absolute increase in risk is small for INR ≤3.5.[387] Treatment of hypertension in AF patients reduces the risk of both ICH and ischemic stroke and hence has dual benefits for anticoagulated patients with AF.[422–424] A consensus statement on the delivery of optimal anticoagulant care (focusing primarily on warfarin) has been published.[425] The combined use of warfarin with antiplatelet therapy increases the risk of intracranial and extracranial hemorrhage.[426] Because adjusted-dose warfarin (target INR, 2 to 3) appears to offer protection against MI comparable to that provided by aspirin in AF patients,[427] the addition of aspirin is not recommended for most patients with AF and stable coronary artery disease.[428,429] There are meager data on the type and duration of optimal antiplatelet therapy when combined with warfarin in AF patients with recent coronary angioplasty and stenting.[430,431] The combination of clopidogrel, aspirin, and warfarin has been suggested for at least 1 month after placement of bare metal coronary stents in patients with AF.[432] Because drug-eluting stents require even more prolonged antiplatelet therapy, bare metal stents are generally preferred for AF patients taking warfarin.[433,434] 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.[435]

Closure of the LAA has been evaluated as an alternative approach to stroke prevention in nonvalvular AF.[436] In a trial of 707 subjects randomized 2:1 to percutaneous LAA closure with the WATCHMAN device (in which patients were treated with warfarin for at least 45 days after device placement, then aspirin plus clopidogrel from echocardiographically demonstrated closure of the LAA until 6 months after placement, then aspirin alone) versus adjusted-dose warfarin (target INR, 2 to 3), LAA closure was noninferior to warfarin for preventing the primary outcome of ischemic or hemorrhagic stroke, cardiac or unexplained death, or systemic embolism during the mean 18-month follow-up (RR, 0.62; 95% CI, 0.35–1.25; *P*<0.001 for noninferiority). Hemorrhagic stroke was less frequent in the LAA closure group (RR, 0.09; 95% CI, 0–0.45), but ischemic stroke was insignificantly more frequent (RR, 1.34; 95% CI, 0.60–4.29), in part because of procedure-related strokes (occurring in 5 of the 449 patients in whom LAA closure was attempted, including 2 with long-term residual deficits). At 1588 patient-years of follow-up, the rate of the primary efficacy end point of stroke, systemic embolism, and cardiovascular death was not inferior for the WATCHMAN device compared with warfarin.[437] Although this approach appears promising, there are substantial reasons for proceeding cautiously with this treatment, including the

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relatively modest power of the trial, the exclusion of subjects with firm contraindications to anticoagulation (who would otherwise appear to be ideal candidates for LAA closure), and the lack of comparison to the newer, potentially more effective oral anticoagulants. Other potential nonpharmacological approaches such as therapeutic cardioversion and rhythm control do not reduce stroke risk.[438] Intervals of asymptomatic AF also persist after apparently successful radiofrequency ablation,[439] suggesting a persistent need for antithrombotic treatment after this procedure.

Several randomized, clinical trials have consistently shown that rhythm control does not protect against stroke relative to rate control.[438,440–442] For patients with AF of ≥48 hours or when duration is unknown, it is recommended that patients receive warfarin to an INR of 2.0 to 3.0 for 3 weeks before and 4 weeks after chemical or electrical cardioversion.[443] Subgroup analyses of ROCKET AF[444] and RE-LY[445] suggest that protection from cardioembolism around the time of cardioversion appears to be comparable for warfarin and the novel oral anticoagulants.

AF: Summary and Gaps

AF is a prevalent, potent, and treatable risk factor for embolic stroke. Knowing which treatment offers the optimal balance of benefits and risks for a particular patient remains challenging, however. Complicating the decision is that the field is rapidly changing, with ongoing changes in the epidemiology of AF-related stroke, improvements in the ability to predict risk of stroke and hemorrhage, and a growing armamentarium of effective therapies. This fluid environment has contributed to a proliferation of proposed guidelines, which can vary substantially.

One clear goal is therefore to continue to collect sufficient data on risk stratification and treatment effects to strengthen the foundation for future recommendations. A key step toward this goal is head-to-head comparison of the newer anticoagulants with each other and with emerging alternatives such as LAA closure.

Despite improving public awareness, anticoagulation for suitable AF patients remains underused, particularly among the very elderly. A potential benefit of the newer anticoagulants would be to improve use and compliance for appropriate patients. Another step toward optimizing the use of anticoagulants is large-scale MRI studies of cerebral microbleeds to determine whether and when they should alter the decision to prescribe anticoagulants, especially in the elderly. Risk for future ICH may be particularly important in selecting one of the newer anticoagulants because the major advantage of these agents may be their reduced risk for this complication.

AF: Recommendations

1. **For patients with valvular AF at high risk for stroke, defined as a CHA_2DS_2-VASc score of ≥2 and acceptably low risk for hemorrhagic complications, long-term oral anticoagulant therapy with warfarin at a target INR of 2.0 to 3.0 is recommended (*Class I; Level of Evidence A*).**
2. **For patients with nonvalvular AF, a CHA_2DS_2-VASc score of ≥2, and acceptably low risk for hemorrhagic complications, oral anticoagulants are recommended (*Class I*). Options include warfarin (INR, 2.0 to 3.0) (*Level of Evidence A*), dabigatran (*Level of Evidence B*), apixaban (*Level of Evidence B*), and rivaroxaban (*Level of Evidence B*). The selection of antithrombotic agent should be individualized on the basis of patient risk factors (particularly risk for intracranial hemorrhage), cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including the time that the INR is in therapeutic range for patients taking warfarin.**
3. **Active screening for AF in the primary care setting in patients >65 years of age by pulse assessment followed by ECG as indicated can be useful (*Class IIa; Level of Evidence B*).**
4. **For patients with nonvalvular AF and CHA_2DS_2-VASc score of 0, it is reasonable to omit antithrombotic therapy (*Class IIa; Level of Evidence B*).**
5. **For patients with nonvalvular AF, a CHA_2DS_2-VASc score of 1, and an acceptably low risk for hemorrhagic complication, no antithrombotic therapy, anticoagulant therapy, or aspirin therapy may be considered (*Class IIb; Level of Evidence C*). The selection of antithrombotic agent should be individualized on the basis of patient risk factors (particularly risk for intracranial hemorrhage), cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including the time that the INR is in the therapeutic range for patients taking warfarin.**
6. **Closure of the LAA may be considered for high-risk patients with AF who are deemed unsuitable for anticoagulation if performed at a center with low rates of periprocedural complications and the patient can tolerate the risk of at least 45 days of postprocedural anticoagulation (*Class IIb; Level of Evidence B*).**

Other Cardiac Conditions

Cardiac conditions other than AF that are associated with an increased risk for stroke include acute MI; ischemic and nonischemic cardiomyopathy; valvular heart disease, including prosthetic valves and infective endocarditis; patent foramen ovale (PFO) and atrial septal aneurysms (ASAs); cardiac tumors; and aortic atherosclerosis.

Acute MI

A meta-analysis of population-based studies published between 1970 and 2004 found that the risk of ischemic stroke after acute MI was 11.1 per 1000 (95% CI, 10.7–11.5) during the index hospitalization, 12.2 per 1000 (95% CI, 10.4–14.0) at 30 days, and 21.4 (95% CI, 14.1–28.7) at 1 year.[446] Factors associated with increased stroke risk included advanced age, hypertension, diabetes mellitus, anterior MI, AF, and congestive heart failure. Importantly, the risk of embolic stroke is increased in patients with anterior MI and left ventricular thrombus. Contemporary studies have found that left ventricular thrombus affects ≈6% to 15% of patients with anterior MI and ≈27% with anterior MI and left ventricular ejection

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fraction <40%.[447–449] Systemic embolism occurs in ≈11% of patients with left ventricular thrombus.[450] In the Warfarin, Aspirin Reinfarction Study, (WARIS II), warfarin, combined with aspirin or given alone, compared with aspirin alone reduced the risk of thromboembolic stroke but was associated with a greater risk of bleeding.[451] A meta-analysis of 14 trials comprising 25 307 patients with an acute coronary syndrome reported that aspirin plus warfarin, in which the achieved INR was 2.0 to 3.0, compared with aspirin alone reduced the risk of death, nonfatal MI, and nonfatal thromboembolic stroke but doubled the risk of major bleeding.[452] A meta-analysis of 24 542 patients in 10 randomized trials that evaluated the efficacy of warfarin after acute MI found a stroke incidence over 5 years of 2.4%. In this meta-analysis, warfarin decreased the risk of stroke (OR, 0.75; 95% CI, 0.63–0.89) but increased the risk of bleeding. The 2013 ACCF/AHA guideline for the management of ST-segment–elevation MI (STEMI) states that anticoagulant therapy with a vitamin K antagonist is reasonable for patients with STEMI and asymptomatic left ventricular mural thrombi (*Class IIa; Level of Evidence C*) and that anticoagulant therapy may be considered for patients with STEMI and anterior apical akinesis or dyskinesis (*Class IIb; Level of Evidence C*).[453]

Cardiomyopathy

The incidence of stroke in patients with cardiomyopathy and sinus rhythm is ≈1 per 100 patient-years.[454–456] The Warfarin/Aspirin Study in Heart Failure (WASH) randomized patients with heart failure, reduced left ventricular systolic function, and no other indications for anticoagulant therapy to warfarin, aspirin, or no treatment.[454] There was no difference between groups in the primary composite cardiovascular end point, which included stroke. The Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial randomized patients with heart failure, reduced left ventricular systolic function, and sinus rhythm to warfarin, clopidogrel, or aspirin. The study was terminated early because of slow enrollment. There was no difference in the composite primary end point of death, nonfatal MI, or nonfatal stroke, but warfarin was associated with fewer nonfatal strokes than aspirin or clopidogrel.[455] The Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial randomized 2305 patients with reduced left ventricular ejection fraction and sinus rhythm to warfarin or aspirin and followed them up for up to 6 years.[457] There was no difference in the primary composite outcome of ischemic stroke, ICH, or death resulting from any cause (HR, 0.93; 95% CI, 0.79–1.10), but there was a significant reduction in the rate of ischemic stroke with warfarin compared with aspirin (0.72 versus 1.36 events per 100 patient-years; HR, 0.52; 95% CI, 0.33–0.82). The rate of major hemorrhage, however, was greater in the warfarin than in the aspirin group. The 2009 ACCF/AHA guideline for the diagnosis and management of heart failure in adults states that the usefulness of anticoagulation is not well established in patients with heart failure who do not have AF or a previous thromboembolic event.[458] The American College of Chest Physicians guidelines on antithrombotic therapy and prevention of thrombosis state that the usefulness of anticoagulation is not well established in patients with heart failure who do not have AF or a previous thromboembolic event (*Class IIb; Level of Evidence B*).[458] Based on the more recent WARCEF trial,[457] this recommendation is upgraded in this document to state that anticoagulants or antiplatelet agents are reasonable for patients with heart failure who do not have AF or a previous thromboembolic event (*Class IIa; Level of Evidence B*).

Valvular Heart Disease

The risk of embolic stroke is increased in patients with rheumatic mitral valve disease, even in the absence of AF, and in patients with prosthetic heart valves. Rheumatic carditis is the most common cause of mitral stenosis. Studies from the middle part of the last century found an annual incidence of systemic embolism among patients with rheumatic mitral valve disease of 1.5% to 4.7% (reviewed by Whitlock et al[459]). Thrombus and subsequent embolism may be more likely to occur in large left atria. The ACCF/AHA guidelines for the management of valvular heart disease recommend anticoagulation in patients with mitral stenosis and a prior embolic event, even in sinus rhythm (*Class I; Level of Evidence B*), and in patients with mitral stenosis with left atrial thrombus (*Class I; Level of Evidence B*).[460] Reports on the association of embolic stroke with mitral valve prolapse have been inconsistent.[461–463] A population-based study of patients from Olmsted County, Minnesota, found an increased RR of stroke or TIA among patients with mitral valve prolapse who were initially in sinus rhythm (RR, 2.2; 95% CI, 1.5–3.2).[464] Independent factors associated with stroke included older age, mitral valve thickening, and the development of AF. The ACCF/AHA guidelines for the management of valvular heart disease recommend aspirin therapy for patients with mitral valve prolapse who experience TIAs (*Class I; Level of Evidence C*) and warfarin for these patients with a history of stroke and mitral regurgitation, AF, or left atrial thrombus (*Class I; Level of Evidence C*).[460] The risk of stroke is also increased in patients with mitral annular calcification. There was an increased risk of stroke (RR, 2.1; 95% CI, 1.2–3.6) among participants in the Framingham study who had mitral annular calcification.[465] Risk of stroke was associated with the severity of mitral annular calcification. Similarly, in the SHS, a cohort study of American Indians, stroke incidence was increased among those with mitral annular calcification (RR, 3.1; 95% CI, 1.8–5.2).[466] In contrast, in the multiethnic NOMAS, mitral annular calcification was associated with an increased risk of MI and vascular death but not ischemic stroke.[467] There is no evidence that anticoagulant therapy reduces the risk of stroke in patients with mitral annular calcification. Calcific aortic stenosis is an uncommon cause of embolic stroke, unless disrupted by valvuloplasty, transcatheter aortic valve replacement, or open surgical aortic valve replacement.[468]

Prosthetic heart valves can serve as a source of thromboembolism. The risk of embolic stroke is greater in patients with mechanical valves than bioprosthetic valves. The annual incidence of thromboembolism in patients with bioprosthetic valves and sinus rhythm is ≈0.7% (reviewed by Bonow et al[460]). Among patients with bioprosthetic valves, the risk of embolism is greatest within the first 3 months after implantation and is higher with mitral than aortic bioprosthetic valves.[469] ACCF/AHA guidelines for the management of patients with

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valvular heart disease recommend aspirin after aortic or mitral valve replacement with a bioprosthesis in patients with no risk factors (ie, AF, previous thromboembolism, left ventricular dysfunction, and hypercoagulable condition) and warfarin (INR, 2.0 to 3.0) after aortic or mitral valve replacement with a bioprosthesis in patients with additional risk factors (*Class I; Level of Evidence C*). During the first 3 months after aortic or mitral valve replacement with a bioprosthesis, the guidelines indicate that it is reasonable to give warfarin to achieve an INR of 2.0 to 3.0 (*Class IIa; Level of Evidence C*).

In the first 3 months after bioprosthetic valve implantation, aspirin is recommended for aortic valves; the combination of aspirin and clopidogrel is recommended if the aortic valve is transcatheter; and vitamin K antagonist therapy with a target INR of 2.5 is recommended for mitral valves. After 3 months, aspirin is recommended.[459]

A meta-analysis of 46 studies comprising 13 088 patients who received mechanical mitral or aortic valve prostheses reported an incidence of valve thrombosis or embolism in the absence of antithrombotic therapy of 8.6 per 100 patient-years (95% CI, 7.0–10.4). Risk of embolism was lower in patients with tilting disk and bileaflet valves than in those with caged ball valves (no longer used).[470] Antithrombotic therapy with a vitamin K antagonist reduced the risk of thromboembolic events to 1.8 per 100 patient-years (95% CI, 1.7–1.9). Even among anticoagulated patients, the risk of embolism is higher among those with mechanical mitral valves than mechanical aortic valves.[471,472] ACC/AHA guidelines for the management of patients with valvular heart disease recommend warfarin (INR, 2.0 to 3.0) after aortic valve replacement with bileaflet mechanical or Medtronic Hall prostheses in patients with no risk factors (*Class I; Level of Evidence B*), warfarin (INR, 2.5 to 3.5) in patients with risk factors (*Class I; Level of Evidence B*), and warfarin (INR, 2.5 to 3.5) after mitral valve replacement with any mechanical valve (*Class IIa; Level of Evidence C*).[460] The addition of low-dose aspirin to warfarin is recommended for all patients with mechanical valves (*Class IIa; Level of Evidence C*).

The novel oral anticoagulants (factor Xa inhibitors and direct thrombin inhibitors) are not indicated for the prevention of thromboembolism associated with mechanical heart valves. The randomized, phase II study to evaluate the safety and pharmacokinetics of oral dabigatran etexilate in patients after heart valve replacement (RE-ALIGN) trial showed an increase in thromboembolic and bleeding complications with dabigatran compared to warfarin in patients with mechanical heart valves.[473]

About 20% to 40% of patients with endocarditis suffer embolic events, the majority of which affect the central nervous system.[474,475] The rate of embolic events decreases rapidly after the initiation of antibiotic therapy.[476–478] The risk of embolic stroke is associated with the size of the vegetation, involvement of the mitral valve, and infection by *Staphylococcus aureus*.[475,476,479] Anticoagulant therapy does not reduce the risk of embolic stroke and may increase the risk of cerebral hemorrhage.[474] Anticoagulant therapy should not be used to treat patients with infective endocarditis unless indicated for other cardiovascular conditions.[459] Nonbacterial thrombotic endocarditis, also known as marantic endocarditis, is associated with malignant neoplasms, antiphospholipid antibodies (aPLs), and systemic lupus erythematosus (SLE) and may be a source of an embolic stroke.[480] Anticoagulant therapy is indicated for patients with nonbacterial thrombotic endocarditis and systemic embolism.[459]

PFO and ASAs

A PFO is present in ≈15% to 25% of the adult population, and ASA occurs in 1% to 4%. A PFO serves as a right-to-left conduit for paradoxical emboli originating in the veins, whereas ASA may be a nidus for thrombus formation. PFO and ASA have been associated with stroke in many, but not all, studies.[481–487] In the Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS), a PFO was detected by transesophageal echocardiography more often in patients with cryptogenic stroke than in those with known causes of stroke (39.2% versus 29.9%, respectively).[482] Another study also found that the prevalence of PFO was greater among patients with cryptogenic stroke than among those with known causes of stroke, including patients <55 years of age (OR, 4.70; 95% CI, 1.89–11.68; $P<0.001$) and patients ≥55 years of age (OR, 2.92; 95% CI, 1.70–5.01).[488] A meta-analysis of case-control studies of patients who have had an ischemic stroke found that among patients ≤55 years of age there are significant associations with PFO (OR, 3.10; 95% CI, 2.29–4.21), ASA (OR, 6.14; 95% CI, 2.47–15.22), and PFO plus ASA (OR, 15.59; 95% CI, 2.83–85.87).[486] In patients >55 years of age, the association with PFO was not significant (OR, 1.27; 95% CI, 0.80–2.01), although it was for ASA (OR, 3.43; 95% CI, 1.89–6.22) and for PFO plus ASA (OR, 5.09; 95% CI, 1.25–20.74). In a population-based study from Olmstead County, Minnesota, in which the mean participant age was 66.9±13.3 years, PFO was not associated with increased risk of stroke (HR, 1.46; 95% CI, 0.74–2.88), whereas there was an association with ASA (HR, 3.72; 95% CI, 0.88–15.71).[489] In the multiethnic NOMAS, in which the mean age was 68.7±10.0 years, PFO was not associated with increased risk of stroke (HR, 1.64; 95% CI, 0.87–3.09), nor was the coexistence of PFO and ASA (HR, 1.25; 95% CI, 0.17–9.24).[483] Another study examining the characteristics of PFO observed larger PFOs, longer tunnels, and a greater frequency of ASA in patients with stroke than in those without stroke.[490] One study of patients with cryptogenic stroke found that the risk of recurrent stroke was 2.3% (95% CI, 0.3–4.3) among patients with PFO alone, 0% in those with ASA alone, 15.2% (95% CI, 1.8–28.6) in patients with both PFO and ASA, and 4.2% (95% CI, 1.8–6.6) in patients with neither.[491] Further analyses from NOMAS with longer follow-up also failed to find evidence for an increased risk of first stroke with PFO (adjusted HR, 1.10; 95% CI, 0.64–1.91) and provided further evidence that PFO is not associated with subclinical cerebrovascular disease.[492]

No study has examined treatments to prevent initial strokes in patients with PFO or ASA. Accordingly, given the uncertainties and relatively low risk of initial stroke caused by PFO or ASA and the potential risk of antithrombotic therapy or invasive treatments, no treatment is recommended for the primary prevention of stroke in people with PFO or ASA. Several studies have examined the treatment of PFO with antithrombotic therapy or percutaneous closure devices in patients with cryptogenic stroke, but a discussion of secondary prevention exceeds the scope of this document.[482,493–495]

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Cardiac Tumors

Benign primary cardiac tumors such as myxomas, papillary fibroelastomas, and primary malignant cardiac neoplasms such as sarcomas may embolize to the brain and cause ischemic stroke.[496,497] Embolic stroke is most likely to occur with intracavitary tumors that have friable surfaces. Myxoma is the most common cardiac tumor, and the majority of them occur in the left atrium.[498] About 30% to 40% of myxomas embolize.[499] Stroke or TIA is the presenting symptoms in half of the patients with papillary fibroelastomas.[500] Surgical excision of atrial myxomas is recommended. Surgical intervention, including removal or occasionally valve replacement, is recommended for symptomatic fibroelastomas and for fibroelastomas that are >1 cm in diameter or appear mobile, even if asymptomatic, because they pose a risk for embolism.[501] Recommendations for the treatment of malignant cardiac neoplasms depend on the precise nature and extent of the tumor and are beyond the scope of this document.[502]

Aortic Atherosclerosis

Plaques ≥4 mm in size, particularly large, complex plaques, are associated with an increased risk of cryptogenic strokes.[503–506] In the French Study of Aortic Plaques in Stroke, plaques >4 mm were found to be independent predictors of recurrent stroke (RR, 3.8; 95% CI, 1.8–7.8).[507] Among patients with cryptogenic stroke who participated in PICSS, large plaques detected by transesophageal echocardiography were associated with an increased risk of recurrent ischemic stroke or death over a 2-year follow-up (HR, 6.42; 95% CI, 1.62–25.46), as were those with complex morphology (HR, 9.50; 95% CI, 1.92–47.10).[504] Atheroembolism from aortic plaques is also a cause of stroke associated with cardiac surgery.[505,506,508] There are no prospective, randomized trials examining the efficacy of medical therapy to reduce the risk of stroke caused by embolic events from large thoracic aortic plaques. One nonrandomized study found that warfarin reduced the risk of recurrent stroke in patients with mobile thoracic atheroma detected by transesophageal echocardiography.[509] In another nonrandomized study, patients with aortic plaques >4 mm thick treated with oral anticoagulants had fewer stroke and peripheral embolic events than those treated with antiplatelet therapy.[510] A retrospective analysis of patients with severe thoracic aortic plaque found that statin therapy (OR, 0.3; 95% CI, 0.2–0.6), but not warfarin (OR, 0.7; 95% CI, 0.4–1.2) or antiplatelet therapy (OR, 1.4; 95% CI, 0.8–2.4), reduced the risk of stroke, TIA, and peripheral emboli.[511]

Other Cardiac Conditions: Summary and Gaps

Cardiac conditions, including MI, cardiomyopathy, valvular heart disease, PFO and ASAs, cardiac tumors, and aortic atherosclerosis, are associated with an increased risk for stroke. Therapies to prevent stroke in many of these conditions are based on well-reasoned consensus of opinion, but randomized, prospective trials to support these decisions are often lacking. For example, therapy with a vitamin K antagonist is reasonable for patients with STEMI and left ventricular mural thrombi, but clinical trials could inform the duration of treatment. Prospective trials are lacking to determine whether antithrombotic therapy is useful for the primary prevention of stroke in patients with mitral valve prolapse and mitral regurgitation who do not have AF. Comparative-effectiveness trials would be useful to determine which antithrombotic would be most effective in reducing the risk of stroke in patients with large aortic plaques.

Other Cardiac Conditions: Recommendations

1. **Anticoagulation is indicated in patients with mitral stenosis and a prior embolic event, even in sinus rhythm (*Class I; Level of Evidence B*).**
2. **Anticoagulation is indicated in patients with mitral stenosis and left atrial thrombus (*Class I; Level of Evidence B*).**
3. **Warfarin (target INR, 2.0–3.0) and low-dose aspirin are indicated after aortic valve replacement with bileaflet mechanical or current-generation, single-tilting-disk prostheses in patients with no risk factors* (*Class I; Level of Evidence B*); warfarin (target INR, 2.5–3.5) and low-dose aspirin are indicated in patients with mechanical aortic valve replacement and risk factors* (*Class I; Level of Evidence B*); and warfarin (target INR, 2.5–3.5) and low-dose aspirin are indicated after mitral valve replacement with any mechanical valve (*Class I; Level of Evidence B*).**
4. **Surgical excision is recommended for the treatment of atrial myxomas (*Class I; Level of Evidence C*).**
5. **Surgical intervention is recommended for symptomatic fibroelastomas and for fibroelastomas that are >1 cm or appear mobile, even if asymptomatic (*Class I; Level of Evidence C*).**
6. **Aspirin is reasonable after aortic or mitral valve replacement with a bioprosthesis (*Class IIa; Level of Evidence B*).**
7. **It is reasonable to give warfarin to achieve an INR of 2.0 to 3.0 during the first 3 months after aortic or mitral valve replacement with a bioprosthesis (*Class IIa; Level of Evidence C*).**
8. **Anticoagulants or antiplatelet agents are reasonable for patients with heart failure who do not have AF or a previous thromboembolic event (*Class IIa; Level of Evidence A*).**
9. **Vitamin K antagonist therapy is reasonable for patients with STEMI and asymptomatic left ventricular mural thrombi (*Class IIa; Level of Evidence C*).**
10. **Anticoagulation may be considered for asymptomatic patients with severe mitral stenosis and left atrial dimension ≥55 mm by echocardiography (*Class IIb; Level of Evidence B*).**
11. **Anticoagulation may be considered for patients with severe mitral stenosis, an enlarged left atrium, and spontaneous contrast on echocardiography (*Class IIb; Level of Evidence C*).**
12. **Anticoagulant therapy may be considered for patients with STEMI and anterior apical akinesis or dyskinesis (*Class IIb; Level of Evidence C*).**
13. **Antithrombotic treatment and catheter-based closure are not recommended in patients with PFO for primary prevention of stroke (*Class III; Level of Evidence C*).**

*Risk factors include AF, previous thromboembolism, left ventricular dysfunction, and hypercoagulable condition.

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Asymptomatic Carotid Artery Stenosis

Atherosclerotic stenosis in the extracranial internal carotid artery or carotid bulb has been associated with an increased risk of stroke. What follows is a summary of recommendations for managing asymptomatic patients with carotid atherosclerotic stenosis. Further details are available in an earlier guideline endorsed by the AHA that is dedicated to this topic.[512]

Previous randomized trials have shown that prophylactic carotid endarterectomy (CEA) in appropriately selected patients with carotid stenosis results in a relative risk reduction of stroke of 53% and an absolute 5-year risk reduction of 6% compared with patients treated by medical management alone.[513–515] However, since these trials were performed, medical management has improved. The question has been raised if invasive treatment of carotid bifurcation disease remains an effective way to reduce stroke risk compared to contemporary medical management alone.

Assessment of Carotid Stenosis

A hemodynamically significant carotid stenosis produces a pressure drop across the lesion, a flow reduction distal to the lesion, or both. This generally corresponds to a 60% diameter-reducing stenosis as reflected by catheter angiography as measured with the North American method. This method was first described in publications from the Joint Study of Extracranial Arterial Occlusive Disease of the 1960s[516] and has been used in multiple trials carried out in North America. This 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 first become parallel. It uses the following formula: stenosis=(1−N/D)×100%, where N is the diameter at point of maximum stenosis and D is the diameter of the arterial segment distal to the stenosis where the arterial walls first become parallel. This method is in contrast to the European method, which estimates stenosis of the internal carotid bulb.

Because the randomized trials of CEA for symptomatic and asymptomatic disease in North America used catheter angiography, this has become the gold standard against which other imaging technologies are compared. Historically, catheter angiography carried an ≈1% risk of causing a stroke in patients with atherosclerotic disease.[513,517–519] The complication rate has been dropping over the past several years, and the permanent stroke complication rate is <0.2%.[519] Duplex ultrasound is the noninvasive method of screening the extracranial carotid artery for an atherosclerotic stenosis with the lowest cost and risk. Although there can be considerable variation in the accuracy of duplex scanning among laboratories,[520] 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. MR 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, and as with duplex ultrasound, there may be errors when high-grade stenosis is differentiated from complete occlusion. MR contrast material may cause debilitating nephrogenic systemic fibrosis in patients with renal dysfunction. When concordant, the combination of duplex ultrasound and MRA is more accurate than either test alone.[521] Computed tomographic angiography is another means of identifying and measuring stenosis of the extracranial carotid artery.[522] Like MRA, it has the advantage of being able to evaluate the intracranial circulation. Disadvantages of computed tomographic angiography include radiation exposure and the need for intravenous injection of contrast material. Atherosclerotic calcification may confound accurate measurement of stenosis with computed tomographic angiography.

A variety of vascular risk factors reviewed in this guideline are associated with carotid atherosclerosis.[523,524] Carotid bruit can reflect an underlying carotid stenosis. However, the sensitivity for detecting carotid stenosis is low. In NOMAS, auscultation had a sensitivity of 56% and a specificity of 98%.[525]

Endarterectomy for Asymptomatic Carotid Stenosis

The first study with >1000 patients comparing CEA plus best medical therapy to medical therapy alone was the Asymptomatic Carotid Atherosclerosis Study (ACAS).[513] The primary outcome was the composite of any stroke or death occurring in the perioperative period and ipsilateral cerebral infarction thereafter. During follow-up after 34 centers randomized 1662 patients, the Data and Safety Monitoring Committee called a halt to the trial because of a clear benefit in favor of CEA. Patients randomized to surgery had contrast angiography showing diameter-reducing lesions of ≥60% using the North American method of measurement. Both treatment groups received what at the time was considered best medical management. The aggregate risk over 5 years for ipsilateral stroke, any perioperative stroke, and death was 5.1% for the surgical patients and 11% for the medical patients (RR reduction, 53%; 95% CI, 22–72). The 30-day stroke morbidity and all-cause mortality for CEA was 2.3%, which included a 1.2% stroke complication rate for catheter angiography. It was suggested that the complications of angiography should be considered part of the risk of surgery because an angiogram would not have been performed if surgery were not contemplated. It should be noted that ACAS was conducted at a time when best medical management was limited to control of BP, the control of diabetes mellitus, and the use of daily aspirin. The value of statins and newer antiplatelet drugs had not been established.

The Asymptomatic Carotid Surgery Trial (ACST), carried out primarily in European centers,[514] included 3120 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 end points that were different from those used in ACAS (perioperative stroke, MI or death, and nonperioperative stroke). The net 5-year risks were 6.4% in the immediate surgery group and 11.8% in the deferred surgery group for any stroke or perioperative death (net gain, 5.4%; 95% CI, 3.0–7.8; $P<0.0001$). In subgroup analysis, the benefits of CEA were confined to patients <75 years of age.

The National Institute of Neurological Disorders and Stroke–sponsored Carotid Revascularization of Primary Prevention of Stroke (CREST-2) trial will be comparing centrally managed, intensive medical therapy with or without CEA.[526]

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Careful screening of surgeons participating in clinical trials might lead to results that cannot be generalized to the community. This is particularly evident when the complications from angiography are removed from the surgical group. When this is done, the 30-day rate of stroke and death for CEA in ACAS was 1.54%.[517] 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.[527] The rate of the combination of stroke and death for CEA was 1.16%. This compares favorably with the rate of the combination of stroke and death for carotid artery stent/angioplasty during the same interval, which was 2.24%. These estimates, however, are based on administrative data and are 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).[528] Thus, it would appear the perioperative complication rates for CEA found in the ACAS trial could be similar or better in the community; however, in at least some areas, rates may be higher. More recently, complication rates from the CREST trial were reported.[529] CEA in asymptomatic patients carried a combined risk of stroke and death of 1.4%. Additionally, a registry maintained by the Society for Vascular Surgery documented a 30-day postoperative combined rate of stroke and death of 1.35%.[530] This rate among unselected surgeons was comparable to the rate seen among surgeons selected to participate in a trial.

Endovascular Treatment for Asymptomatic Carotid Stenosis

Carotid angioplasty and stenting (CAS) is being performed more frequently.[531] 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 resulting from neurological cause or ipsilateral stroke between 31 and 365 days) in a group of patients considered to be at high risk for CEA.[532] About 70% of the subjects had an 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 the CAS patients and 21.5% of the CEA patients (*P*=0.02). Three-year outcomes from the SAPPHIRE trial showed that patients receiving CAS had a significantly higher death rate (20.0%) than stroke rate (10.1%),[533] raising questions about the long-term value of the procedure in this high-risk cohort. In addition, there was no medically treated control group, and the complication rates in both treatment arms were high enough to raise questions about the benefit of either intervention over medical therapy alone.

Several industry-supported registries have reported periprocedural complication rates of 2.1% to 8.3%.[534] The lack of medically treated control groups makes the results of these registries difficult to interpret.

CREST enrolled both symptomatic and asymptomatic patients with carotid stenosis who could technically undergo either CEA or CAS.[535] Asymptomatic patients could be included if they had a stenosis of ≥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 primary end point was a composite of stroke, MI, or death resulting 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 composite primary end point between stenting (7.2%) and endarterectomy (6.8%; HR, 1.11; 95% CI, 0.81–1.51; *P*=0.51), with no significant heterogeneity based on symptom status. CREST demonstrated an interaction of age on the primary end point, with age >70 years showing a significant benefit for CEA over CAS. CAS had a higher periprocedural stroke/death rate for patients >64 years of age.[529] Patient age may be among the factors to consider when choosing between the 2 procedures. The periprocedural rate of stroke was higher with CAS than with CEA (4.1% versus 2.3%; *P*=0.01), and the periprocedural rate of MI was lower with CAS than with CEA (1.1% versus 2.3%; *P*=0.03). In the periprocedural period, point estimates for the rates of any stroke or death among asymptomatic patients were low (2.5% in CAS versus 1.4% for CEA; HR, 1.88; 95% CI, 0.79–4.42; *P*=0.15). The overall estimated 4-year rate of any periprocedural stroke or death or postprocedural ipsilateral stroke, however, was higher with stenting compared with endarterectomy (HR, 1.50; 95% CI, 1.05–2.15; *P*=0.03). Although the trial was not powered to evaluate symptomatic and asymptomatic patients separately, there was a trend favoring CEA over CAS in both the symptomatic (HR, 1.37; 95% CI, 0.90–2.09; *P*=0.14) and asymptomatic (HR, 1.86; 95% CI, 0.95–3.66; *P*=0.07) groups. Post hoc analysis found that major and minor stroke negatively affected quality of life at 1 year (Short Form-36, physical component scale), with minor stroke affecting mental health at 1 year (Short Form-36, mental component scale), but the effect of periprocedural MI did not negatively affect quality of life. Having MI or stroke, including minor stroke, was associated with a higher mortality rate.

The advantage of revascularization over medical therapy by itself was not addressed by CREST, which did not randomize a group of asymptomatic subjects to medical therapy without revascularization. Hospital costs for CAS tend to be greater than for CEA.[536–538] The National Institute of Neurological Disorders and Stroke–sponsored CREST-2 trial will be comparing centrally managed, intensive medical therapy with or without carotid stenting with embolic protection.[539]

Screening of Asymptomatic Carotid Stenosis

Although carotid artery stenosis is a risk factor for stroke, not every carotid stenosis carries the same risk for future stroke. There have been attempts to identify those patients with carotid stenosis who are at high risk for future events. Two methods have shown promise. The first method uses transcranial Doppler (TCD) to count the number of presumed embolic events, known as high-intensity transient signals per unit time. Although this technique has shown that patients with frequent high-intensity transient signals have a higher subsequent stroke rate than those without high-intensity transient signals, the test

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is time-consuming to perform and has not received uniform acceptance. Additionally, the effect of intensive medical therapy on high-intensity transient signals has not been adequately assessed. Another method of study uses plaque analysis in a computerized algorithm using B-mode insonation of the carotid plaque. 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."[540] Screening for other risk factors is addressed in relevant sections of this guideline.

Asymptomatic Carotid Stenosis: Summary and Gaps

Medical therapy has advanced since clinical trials have been completed comparing endarterectomy plus best medical therapy with best medical therapy alone in patients with an asymptomatic carotid artery stenosis.[541] Recent studies suggest that the annual rate of stroke in medically treated patients with an asymptomatic carotid artery stenosis has fallen to ≤1%.[541–543] In the ACST, the rate of absolute benefit from CEA per year was lower in patients on lipid-lowering therapy (0.6%/y) compared with patients not on lipid lowering therapy (1.5%/y).[544] ACST had no explicit targets for LDL, and intensive targets (eg, LDL <70 mg/dL) may further reduce the benefit of revascularization. Statin therapy is appropriate for patients with asymptomatic carotid stenosis, whether or not they undergo revascularization.

Interventional therapy has also advanced, particularly in terms of perioperative management and device design. Because the absolute reduction in stroke risk with CEA in patients with an asymptomatic stenosis is small, however, the benefit of revascularization may be reduced or eliminated with current medical therapy.[541] The benefit of CEA for carotid stenosis in asymptomatic women remains controversial.[545] 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 after CEA and CAS. Currently, the Centers for Medicare & Medicaid Services cover CAS for asymptomatic stenosis only in patients with >80% stenosis at high risk for CEA who are participating in postmarket approval studies.

For patients with asymptomatic carotid stenosis who defer revascularization, periodic reassessment of degree of stenosis may be helpful in identifying patients at higher risk of stroke. A retrospective ultrasound-based study of the deferred surgery arm of the ACST trial found that patients who had carotid stenosis that worsened in 1 year by 1 stenosis category did not have an increased risk of ipsilateral ischemic events, with categories being 0% to 49%, 50% to 69%, 70% to 89%, 90% to 99%, and 100%.[546] Patients who had a progression of ≥2 categories in 1 year were at high risk of ipsilateral ischemic events relative to nonprogressors.

The recommendations below reflect current best evidence. However, modern optimal medical therapy may obviate the need for carotid revascularization. The balance of risks and benefits of revascularization in the setting of modern optimal medical therapy is being assessed in ongoing multicenter clinical trials in the United States and elsewhere.

Asymptomatic Carotid Stenosis: Recommendations

1. **Patients with asymptomatic carotid stenosis should be prescribed daily aspirin and a statin. Patients should also be screened for other treatable risk factors for stroke, and appropriate medical therapies and lifestyle changes should be instituted (*Class I; Level of Evidence C*).**
2. **In patients who are to undergo CEA, aspirin is recommended perioperatively and postoperatively unless contraindicated (*Class I; Level of Evidence C*).**
3. **It is reasonable to consider performing CEA in asymptomatic patients who have >70% stenosis of the internal carotid artery if the risk of perioperative stroke, MI, and death is low (<3%). However, its effectiveness compared with contemporary best medical management alone is not well established (*Class IIa; Level of Evidence A*).**
4. **It is reasonable to repeat duplex ultrasonography annually by a qualified technologist in a certified laboratory to assess the progression or regression of disease and response to therapeutic interventions in patients with atherosclerotic stenosis >50% (*Class IIa; Level of Evidence C*).**
5. **Prophylactic CAS might be considered in highly selected patients with asymptomatic carotid stenosis (minimum, 60% by angiography, 70% by validated Doppler ultrasound), but its effectiveness compared with medical therapy alone in this situation is not well established (*Class IIb; Level of Evidence B*).**
6. **In asymptomatic patients at high risk of complications for carotid revascularization by either CEA or CAS, the effectiveness of revascularization versus medical therapy alone is not well established (*Class IIb; Level of Evidence B*).**
7. **Screening low-risk populations for asymptomatic carotid artery stenosis is not recommended (*Class III; Level of Evidence C*).**

Sickle Cell Disease

SCD, an autosomal-recessive disorder in which the abnormal gene product is an altered hemoglobin β-chain, typically manifests very early in life. Signs and symptoms associated with SCD are the result of chronic anemia or acute vaso-occlusive crises, most commonly manifesting as painful episodes. Complications of SCD include acute chest syndrome, pulmonary hypertension, bacterial infections, and organ infarctions, especially stroke. Other effects include cognitive deficits related to MRI-demonstrated strokes and otherwise asymptomatic white matter hyperintensities.[547,548]

Stroke is a major complication of SCD, with the highest stroke rates occurring in early childhood. The prevalence of stroke by 20 years of age is at least 11%,[549] with a substantial number of strokes being silent strokes on brain MRI.[548] Stroke prevention is most important for patients with homozygous SCD because the majority of the SCD-associated strokes occur in these patients. TCD ultrasound identifies those at high risk of stroke, allowing evidence-based decisions about optimal primary stroke prevention.[550,551] Although the exact mechanism by which high blood flow velocities increase the

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risk for ischemic stroke is not known, the association is well established. The risk of stroke during childhood in those with SCD is 1%/y, but patients with TCD evidence of high cerebral blood flow velocities (time-averaged mean velocity >200 cm/s) have stroke rates >10%/y.[551,552] Retrospective analysis of the Stroke Prevention Trial in Sickle Cell Anemia (STOP) data suggested that velocity >170 cm/s in the anterior cerebral artery is associated with increased stroke risk after controlling for the middle cerebral artery/internal carotid artery velocities.[553] TCD surveillance of children with SCD remains the gold standard for stroke risk prediction, and its increased use coincides with a decrease in stroke among the pediatric SCD population.[554,555]

The optimal frequency of screening to detect patients at high risk has not been 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. Additionally, peak systolic velocity may be used, in which case a measurement of 250 cm/s is used as a threshold for prophylactic transfusion.[556] 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 velocities in younger patients and in those with TCD velocities closer to 200 cm/s.[557] Despite strong evidence of its value, overall TCD screening rates continue to be suboptimal as a result of patient and provider factors.[558,559] The National Institutes of Health and the American Academy of Pediatrics recommend annual TCD screening from 2 to 16 years of age.[560,561]

Few studies have been done to determine whether TCD also predicts stroke in adults with SCD. One study comparing TCD velocities in SCD adults with those of healthy control subjects found that velocities in SCD adults were lower than those found in children, higher than in healthy control subjects, and negatively correlated with the hematocrit in both SCD groups.[562] Another study found no examples of high TCD (>200 cm/s) in adults with SCD. The mean velocity was 110 cm/s, which is higher than in normal adults but lower than in children with SCD.[563] At present, there are no validated TCD criteria for predicting stroke in adults with SCD.

Although TCD remains the most extensively validated stroke prediction tool, other clinical characteristics are also associated with increased risk of stroke. One study found that nocturnal desaturation predicted neurological events in 95 patients with SCD (median age, 7.7 years; range, 1 to 23 years) followed up for a median of 6 years.[564] There were 7 strokes among 19 individuals with events. Mean overnight oxygen saturation and TCD independently predicted events.[564] Nocturnal oxygen desaturation appears to place children at risk for developing executive dysfunction, which was not associated with MRI-demonstrable infarcts.[565] There is no proven therapy for the cognitive impairment associated with nocturnal desaturation.

MRI has also been used to identify children with SCD who are at high risk of stroke. 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.[566] The Silent Cerebral Infarct Multicenter Clinical Trial (SIT), a randomized, controlled trial MRI-guided prophylactic transfusion, found that regular blood transfusion significantly reduced the incidence of the recurrence of cerebral infarction in children with sickle cell anemia.[567] In a cohort of 67 patients with indication for cervical internal carotid artery MRA, 15% of patients had occlusions or stenoses.[568] The role of cervical MRA in stroke risk prediction remains undefined.

Additional clinical features identify children at risk for developing elevated TCD velocities and stroke. G6PD deficiency, absence of α-thalassemia (OR, 6.45; 95% CI, 2.21–18.87; *P*=0.001), hemoglobin levels (OR, 0.63 per 1 g/dL; 95% CI, 0.41–0.97; *P*=0.038), and lactate dehydrogenase levels (OR, 1.001 per 1 IU/L; 95% CI, 1.000–1.002; *P*=0.047) are independent risk factors for abnormally high velocities.[569] This confirmed a previously reported protective effect of α-thalassemia[570] and found for the first time that G6PD deficiency and hemolysis independently increased the risk of abnormal TCD.[571] Another study found independent effects of hemoglobin and aspartate transaminase levels on TCD velocities, whereas age had an unclear association.[572] Several recent studies of children with SCD identified increased lactate dehydrogenase concentrations and baseline reticulocyte counts to be predictive of stroke[573,574] and elevated plasma glial fibrillary acidic protein concentrations to be predictive of cognitive impairment, suggesting subclinical injury.[575] Markers of systemic inflammation such as interleukin-1β also have been associated with stroke risk.[576] A future process that integrates blood biomarkers and TCD blood flow findings may identify children at greatest risk.

Other genetic factors also affect stroke risk in patients with SCD. A study evaluated 108 SNPs in 39 candidate genes in 1398 individuals with SCD using bayesian networks and found that 31 SNPs in 12 genes interact with fetal hemoglobin to modulate the risk of stroke.[577] 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.[577] STOP data were used to confirm previous findings of associations between the tumor necrosis factor (−308) G/A, IL4R 503 S/P, and ADRB2 27 Q/E polymorphisms and risk of large-vessel stroke in SCD.[578] Consistent with prior findings, the tumor necrosis factor (−308) GG genotype increased the risk of large-vessel disease by >3-fold (OR, 3.27; 95% CI, 1.6–6.9; *P*=0.006). Unadjusted analyses also showed a previously unidentified association between the leukotriene C4-synthase (−444) A/C variant and risk of large-vessel stroke.[578] The Stroke With Transfusions Changing to Hydroxyurea (SWiTCH) study found that of the 38 candidate SNPs in 22 genes studied, 5 polymorphisms had significant influence on stroke risk; SNPs in the *ANXA2*, *TGFBR3*, and *TEK* genes were associated with increased stroke risk, and α-thalassemia and an SNP in the *ADCY9* gene were linked to decreased stroke risk.[579] The SIT Trial found that 2 variations in the *G6PD* gene that are linked to reduced enzymatic function, rs1050828 and rs1050829, were associated with vasculopathy in male participants with SCD (OR, 2.78; 95% CI, 1.04–7.42; *P*=0.04).[580] Further validation of these findings is required before these genetic variations can be used for stroke risk prediction.

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Periodic red cell transfusion is the only intervention proven in randomized trials to prevent stroke in patients with SCD. STOP randomized children with SCD who had abnormal high-risk TCD profiles to either standard care, which included episodic transfusion as needed for pain, or periodic red 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%/y to <1%/y.[552] Unless exchange methods in which blood is removed from the patient with each transfusion are used, long-term transfusion results in iron toxicity that requires treatment with chelation.[581] In STOP, there was no evidence of transfusion-related infection, but iron overload and alloimmunization remain important transfusion risks.[582] 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, 30–91 months) in children who had not had an overt stroke and who had reversion to low-risk TCD velocities (time-averaged mean velocity in middle cerebral or internal carotid artery, <170 cm/s) with long-term transfusion therapy. The study end point was the first occurrence of reversion of TCD to abnormal confirmed by ≥2 TCDs with mean velocities of ≥200 cm/s or stroke. The study was terminated earlier than planned when an interim analysis showed worse outcomes with discontinuation of transfusion therapy. Eight children (≈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.[583,584] Further analyses from STOP II also demonstrated increased rates of silent infarcts on MRI in the discontinuation group (27.5% versus 8.1%; P=0.03).[585] Primary stroke prevention for children with SCD remains centered on red cell transfusions.

Therapies other than transfusion such as hydroxyurea or bone marrow transplantation that reduce the number of painful crises have an uncertain effect on organ damage, including stroke. Of the 127 children with SCD enrolled in the Belgian Hydroxyurea SCD registry, 72 patients were evaluated by TCD. Of these 72, 34 were found at risk of stroke, and only 1 had a cerebrovascular event after a follow-up of 96 patient-years, suggesting a benefit of hydroxyurea in stroke prevention.[586] A study of 291 children with SCD included clinical and imaging follow-up of 35 children with abnormal TCDs who were placed on transfusion therapy (median follow-up, 4.4 years). Of 13 patients with normalized velocities on transfusion, 10 had normal MRAs, and transfusion therapy was replaced with hydroxyurea. Four of these 10 patients redeveloped high velocities, so only 6 remained transfusion free.[569] In another study, the adjusted mean change in TCD velocities was −13.0 cm/s (95% CI, −20.19 to −5.92) in a hydroxyurea-treated group and 4.72 cm/s (95% CI, −3.24 to 12.69) in control subjects (P<0.001).[587] In a study of 59 initiating hydroxyurea therapy for severe vaso-occlusive complications who had pretreatment baseline TCD measurements, 37 had increased time-averaged maximum velocities ≥140 cm/s and were enrolled in a trial with TCD velocities measured at maximum tolerated dose and 1 year later.[588] At the hydroxyurea maximum tolerated dose (mean±SD=27.9 ± 2.7 mg/kg per day), decreases were observed in bilateral middle cerebral artery velocities. The magnitude of the TCD velocity decline correlated with the maximal baseline TCD value.[588] Most recently, the phase III Pediatric Hydroxyurea Clinical Trial (BABY HUG) demonstrated significantly lower increases in TCD velocities in the hydroxyurea group, but neurocognitive testing of the infants was not statistically different between groups.[589] The SWiTCH study, a phase III noninferiority trial comparing standard treatment (transfusions/chelation) with alternative treatment (hydroxyurea/phlebotomy) for children with SCA, stroke, and iron overload,[579] was stopped for safety reasons when adjudication documented no strokes in patients on transfusions/chelation but a 10% stroke rate in patients on hydroxyurea/phlebotomy. Hydroxyurea therapy for stroke prevention is promising for primary stroke prevention but requires additional study. Results from the ongoing Transcranial Doppler With Transfusions Changing to Hydroxyurea (TWiTCH) trial may provide greater insight into the benefit of hydroxyurea in stroke prevention.

Bone marrow transplantation is usually entertained after stroke, but TCD and other indexes 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.[590] In a study of 55 children who underwent bone marrow transplantation for severe SCD, 16 patients without prior stroke and unremarkable MRI before bone marrow transplantation had no clinical or silent stroke on follow-up, and the 10 patients with prior silent ischemia had no further events.[591] Bone marrow transplantation is promising for primary stroke prevention but requires additional study.

No trial has been done on the primary prevention of stroke in adults with SCD. Improvements in care have increased life expectancy in people with SCD, and it is anticipated that stroke prophylaxis in older patients with SCD will pose an increasing challenge in the future.

SCD: Summary and Gaps

Significant progress has been achieved in the primary prevention of stroke in children with SCD. TCD can be used to identify children who are at high risk of stroke and who benefit from transfusion therapy. Although the optimal screening interval has not been established, TCD remains the most extensively validated method for risk assessment. Improvements in prediction may come from incorporating additional predictors such as anterior cerebral artery velocity, blood biomarkers, variations in several genes, and nocturnal oxygen saturation. On the basis of STOP II, even those whose risk of stroke decreases with transfusion therapy on the basis of TCD criteria have an ≈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 because studies show the need for ongoing active treatment despite TCD normalization and the risk of iron toxicity with repeated transfusions. Predictive methods other than TCD (eg, MRI techniques) need to be systematically compared and combined with TCD to further refine the estimation of stroke risk in individuals. Hydroxyurea may be beneficial when red cell transfusions are

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not feasible but should not be considered as a substitute for transfusion. 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. Future stroke prevention trials are needed for adults with SCD.

SCD: Recommendations

1. **TCD screening for children with SCD is indicated starting at 2 years of age and continuing annually to 16 years of age (*Class I; Level of Evidence B*).**
2. **Transfusion therapy (target reduction of hemoglobin S, <30%) is effective for reducing stroke risk in those children at elevated risk (*Class I; Level of Evidence B*).**
3. **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 the development of high-risk TCD indications for intervention (*Class IIa; Level of Evidence B*).**
4. **Pending further studies, continued transfusion, even in those whose TCD velocities 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 periodic red cell transfusion, it might be reasonable to consider hydroxyurea or bone marrow transplantation (*Class IIb; Level of Evidence B*).**
6. **MRI and MRA criteria for selection of children for primary stroke prevention with transfusion have not been established, and these tests are not recommended in place of TCD for this purpose (*Class III; 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.[592] A meta-analysis of 21 studies (13 case-control and 8 cohort) reported an overall pooled RR of 2.04 (95% CI, 1.72–2.43).[593] The risk was greater in migraine with aura (pooled adjusted OR for 7 studies, 2.51; 95% CI, 1.52–4.14) compared with the association of ischemic stroke and migraine without aura (pooled adjusted OR for 6 studies, 1.29; 95% CI, 0.81–2.06).[593] A second meta-analysis of 9 studies (6 case-control and 3 cohort) reported a pooled RR of 1.73 (95% CI, 1.31–2.29) between any migraine and ischemic stroke.[594] This study also found a significantly higher risk of stroke among individuals with migraine with aura (RR, 2.16; 95% CI, 1.53–3.03) compared with individuals with migraine without aura (RR, 1.23; 95% CI, 0.90–1.69; meta-regression for aura status, P=0.02).[594] Furthermore, there was a significant risk among women (RR, 2.08, 95% CI, 1.13–3.84) but not among men (RR, 1.37; 95% CI, 0.89–2.11). Age <45 years, especially in women (RR, 3.65; 95% CI, 2.21–6.04), smoking (RR, 9.03; 95% CI, 4.22–19.34), and OC use (RR, 7.02; 95% CI, 1.51–32.68) further increased the risk.[594] Both meta-analyses are in general agreement with prior studies.[595] Counseling on possible alternative forms of birth control other than OCs in women with migraine may lower the risk of stroke, but this recommendation should be placed in the context of overall health implications of such a change.

The WHS, a primary prevention trial of women ≥45 years of age and free of CVD at enrollment, continues to inform the association between women with migraine and stroke. After a mean follow-up of 11.9 years, multivariable-adjusted analysis found that high migraine frequency (more than weekly) had an increased association with ischemic stroke (HR, 2.77; 95% CI, 1.03–7.46) but not in lower frequencies.[596] When migraine aura status was taken into account, a significant association of migraine frequency was found only in the migraine with aura group (HR, 4.25; 95% CI, 1.36–13.29).[596] From this analysis, increased frequency of attacks in migraine with aura appears to increase the risk for ischemic stroke. However, caution in overly interpreting these results is needed because the incident numbers for these subgroup analyses were small. In a separate analysis of the WHS, the association of migraine with aura and ischemic stroke was found to be more pronounced in the absence (HR, 3.27; 95% CI, 1.93–5.51) than in the presence (HR, 0.91; 95% CI, 0.43–1.93) of nausea/vomiting.[597] Overall, the WHS found that increased frequency in patients with migraine with aura increases ischemic stroke risk and that this increased risk is more pronounced in the absence of typical migraine features.

The WHS also investigated the association between migraines and ICH. Although there was no increased risk of ICH in those who reported any history of migraine compared with those without a history of migraine (HR, 0.98; 95% CI, 0.56–1.71), there was an increased risk for ICH in women with active migraine with aura (HR, 2.25; 95% CI, 1.11–4.54).[598] The age-adjusted increased risk was stronger for ICH (HR, 2.78; 95% CI, 1.09–7.07) and for fatal events (HR, 3.56; 95% CI, 1.23–10.31).[598] From this study, it is estimated that 4 additional ICH events are attributable to migraine with aura per 10 000 women per year.[598] Women who reported active migraine without aura had no increased risk for ICH. This increase in risk for ICH for women with migraine with aura, but not for women with migraine without aura, was similar to the increased risk found with ischemic strokes.

The association of migraine in middle-aged to late-life infarct-like lesions on imaging was studied in a Reykjavik, Iceland, population-based cohort.[599] After multivariable adjustment, midlife migraine with aura had an increased risk of late-life infarct-like lesions (OR, 1.4; 95% CI, 1.1–1.8).[599] This was particularly reflected by an association with cerebellar lesions in women (OR, 1.9; 95% CI, 1.4–2.6), but not in men, with migraine with aura (OR, 1.0; 95% CI, 0.6–1.8).[599] Migraine without aura and nonmigraine headache were not associated with an increased risk.[599] Therefore, similar to the risk for ischemic stroke found in women with migraine with aura in the WHS, in this Icelandic population, women with migraine with aura had an increased risk for late-life ischemic lesions as seen on brain MRI; however, this association was not appreciated in men or in those with migraine without aura or nonmigraine headaches. Overall, the Icelandic study is in agreement with the previous studies, including the Cerebral Abnormalities in Migraine, an Epidemiological Risk

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Analysis (MRI CAMERA) study, which found that, on the basis of MRI, migraineurs with aura had higher prevalence of subclinical infarcts in the posterior circulation (OR, 13.7; 95% CI, 1.7–112), with female migraineurs at an independent increased risk of white matter lesions (OR, 2.1; 95% CI, 1.0–4.1).[600,601] The mechanism and relevance of the migraine–brain lesion association are unclear. In 1 cohort study based on MRA, there was a significant association between anatomical variants of the circle of Willis and both migraines without aura (OR, 2.4; 95% CI, 1.5–3.9) and migraines with aura (OR, 3.2; 95% CI, 1.6–4.1).[602] Unilateral posterior variants with basilar hypoplasia were statistically associated only with migraines with aura (OR, 9.2; 95% CI, 2.3–37.2).[602] However, there was no statistical association between the presence of circle of Willis variants and ischemic lesions on MRI (OR, 1.5; 95% CI, 0.68–1.94), or with infratentorial lacunar lesions (OR, 1.58; 95% CI, 0.48–5.24).[602] The relationship between these vascular anatomical variants in migraineurs to ischemic strokes is unclear.

Once considered a disease of cerebral blood vessels, recent experimental and clinical data have indicated that migraine results from a complex interaction of several converging pathogenic factors. These include disturbance of cortical excitability, cortical spreading depression, meningeal inflammation, and activation of the trigeminovascular system.[603] However, factors contributing to the increased risk of stroke with migraine remain elusive. Clinical-epidemiological studies have suggested several mechanisms. In 1 prospective study of patients <55 years of age, hypercoagulable states were more frequent in the migraine than the nonmigraine group (38.6% versus 16.4%; $P<0.01$).[604] Multivariate analysis showed that migraine without aura was associated with a 2.88-fold increased risk for hypercoagulable diagnosis (95% CI, 1.14–7.28), but in the group with brain infarcts who were <50 years of age, only migraine with aura was independently associated with hypercoagulable states (OR, 6.81; 95% CI, 1.01–45.79).[604] The Stoke Prevention in Young Women Study (SPYW) reported a 50% increased risk of ischemic stroke in those with probable migraine and visual aura (OR, 1.5; 95% CI, 1.1–2.0).[605] Interrelationships among the ACE deletion/insertion (D/I) polymorphism (rs1799752), migraine, and CVD, including ischemic stroke, were investigated in the WHS cohort.[606] The increased risk for CVD among migraineurs with aura was apparent only for carriers of the DD (RR, 2.10; 95% CI, 1.22–3.59; $P=0.007$) and DI (RR, 2.31; 95% CI, 1.52–3.51) genotypes, suggesting that the DD/DI genotype may play a role in, or at least be a marker for, this complex association.[606] However, because of the small numbers, further studies are warranted.

Perhaps the most heavily investigated potential mechanistic link between migraine and stroke is the association of migraine and PFO. Initial studies found that PFOs are more common in young patients with cryptogenic stroke and those with migraine,[481,486,607] particularly migraine with aura.[608] The speculated relationship between PFO and migraine includes microemboli that flow through the PFO, causing brain ischemia and thereby triggering migraine.[609] 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; $P=0.51$).[610] There is much controversy concerning the results of this trial,[611] and it was not designed to evaluate the primary prevention of stroke in patients with migraines with aura. Furthermore, recent studies have found a lack of association between migraine and PFO in a large population-based study among elderly individuals,[612] in a hospital-based case-control study,[613] and in a recent meta-analysis,[614] placing some doubt on whether PFO has a causal role in migraines.

In terms of primary prevention of stroke in patients with migraine, aspirin reduced risk of ischemic stroke (RR, 0.76; 95% CI, 0.63–0.93) but not other clinical atherothrombotic end points in the WHS group.[615] In subgroup analyses, the protective effect of aspirin on ischemic stroke was similar among women with or without migraines.[615] However, women with migraine with aura on aspirin had an increased risk of MI (RR, 3.72; 95% CI, 1.39–9.95), primarily women with history of smoking or hypertension.[615] The clinical significance of this increased risk for this subgroup is unclear because of small numbers.

Migraine: Summary and Gaps

Migraine headache, particularly migraine with aura, appears to be associated with stroke in women <55 years of age, but the mechanisms linking these 2 conditions remain unclear. The stroke risk of migraine in men appears to be less established. Randomized trial evidence that migraine prophylaxis decreases stroke risk is lacking. The significance of deep white matter lesions and other infarct-like lesions seen on MRI in patients with migraine remains unclear. No proven primary prevention strategy exists for patients with migraine. Closure of PFO for treatment of migraine and for primary or secondary stroke prevention remains controversial, with no data from well-controlled studies showing benefit.

Migraine: Recommendations

1. **Smoking cessation should be strongly recommended in women with migraine headaches with aura (*Class I; Level of Evidence B*).**
2. **Alternatives to OCs, especially those containing estrogen, might be considered in women with active migraine headaches with aura (*Class IIb; Level of Evidence B*).**
3. **Treatments to reduce migraine frequency might be reasonable to reduce the risk of stroke (*Class IIb; Level of Evidence C*).**
4. **Closure of PFO is not indicated for preventing stroke in patients with migraine (*Class III; Level of Evidence B*).**

Metabolic Syndrome

The National Cholesterol Education Program (Adult Treatment Panel III) originally defined metabolic syndrome as the presence of ≥3 of the following: (1) abdominal obesity as determined by waist circumference >102 cm (>40 in) for men and >88 cm (>35 in) for women; (2) triglycerides ≥150 mg/dL;

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(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.[616] A modified criterion for fasting glucose was published in 2004.[617] The International Diabetes Foundation (IDF) then modified the definition by requiring inclusion of a waist circumference >88 cm for men and >80 cm in women plus 2 of the other National Cholesterol Education Program–Adult Treatment Panel III criteria.[618] In 2009, a harmonized definition was proposed wherein an identical set of thresholds was used for all components except waist circumference, an area in which further evidence for the relationship to CVD events was felt to be required.[619] In the interim, the Harmonized Definition Work Group suggested that national or regional cut points for waist circumference should be used. Thus, because the waist circumference and risk for CVD and diabetes mellitus vary around the world, the National Cholesterol Education Program–Adult Treatment Panel III, IDF, and harmonized definitions all make a provision for an ethnic/racial/geographic modification of waist circumference.[620] Obesity and sedentary lifestyle, in addition to other genetic or acquired factors, seem to interact to produce the metabolic syndrome.[621] Screening for the syndrome requires no more than a routine physical examination and routine blood tests.[622]

Obesity, discussed separately, is an important component of the metabolic syndrome and is associated with major health risk factors (such as diabetes mellitus, hypertension, and dyslipidemia), poor health status, and, when extreme, lower life expectancy.[623–625] The visceral adiposity characteristic of the metabolic syndrome is associated with insulin resistance, inflammation, diabetes mellitus, and other metabolic and cardiovascular derangements.[626] Visceral adipocytes provoke insulin resistance by promoting extensive lipolysis and release of fatty acids into the splanchnic circulation. Leptin, plasminogen activator inhibitor-1, tumor necrosis factor-α, and other proinflammatory cytokines, in addition to reduced production and release of adiponectin by adipocytes, have all been implicated in this pathophysiological process.[626]

The metabolic syndrome is highly prevalent in the United States.[626] Applying the harmonized definition of the metabolic syndrome to data from the National Health and Nutrition Examination (2003 through 2006) in up to 3461 participants ≥20 years of age with a waist circumference threshold of ≥102 cm for men and ≥88 cm for women, the age-adjusted prevalence of metabolic syndrome was 34.3% among all adults, 36.1% among men, and 32.4% among women.[627] With the use of race- or ethnicity-specific IDF criteria for waist circumference, the age-adjusted prevalence was 38.5% for all participants, 41.9% for men, and 35.0% for women. Prevalence increased with age, with the highest prevalence in subjects between 60 to 69 years of age. Prevalence was lower among black men than white or Mexican American men and lower among white women than among black or Mexican American 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.

Hyperinsulinemia/insulin resistance is an important marker of the metabolic syndrome; however, results concerning a relationship between glucose intolerance and stroke risk are conflicting.[628–639] In 18 990 men and women who were screened for entry into the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial from 21 different countries, 8000 subjects were normoglycemic, 8427 had impaired fasting glucose or impaired glucose tolerance, and 2563 had newly diagnosed type 2 diabetes mellitus.[640] Among all subjects, an 18-mg/dL increase in fasting plasma glucose or a 45-mg/dL increase in the 2-hour glucose after an oral glucose tolerance test was associated with an increase in cardiovascular events, including stroke or death (HR, 1.17; 95% CI, 1.13–1.22). The relationships between other individual components of the metabolic syndrome and stroke risk, including elevated BP, are reviewed in other sections of this guideline.

The metabolic syndrome is a predictor of CVD and vascular death; however, this risk does not appear to be any larger than the sum of the components of the syndrome.[626,641] A similar lack of greater predictability is true for the metabolic syndrome and stroke.[642] This lack of relationship may be because of sample size or a small number of stroke events. The National Health and Nutrition Examination Survey, among 10 357 subjects,[643] the prevalence of metabolic syndrome was higher in people with self-reported history of stroke (43.5%) than in those with no history of stroke or myocardial infarct (22.8%; $P \leq 0.001$). The metabolic syndrome was independently associated with stroke history in all ethnic groups and in both sexes (OR, 2.16; 95% CI, 0.48–3.16). The association between metabolic syndrome and stroke has been confirmed in other populations, including those enriched with elderly subjects, and the frequency of the metabolic syndrome was notably higher in patients with a history of nonhemorrhagic stroke[269,643–646] but also in Korean patients with spontaneous ICH.[645] The adjusted RRs for ischemic stroke associated with the metabolic syndrome in prospective studies has ranged between 2.10 and 2.47, and an HR as high as 5.15 has been reported.[647–653] This predictive capacity does not appear to be influenced by the definition used for the metabolic syndrome and showed no significant variation across sex, age, or ethnic groups. Yet, in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, the 642 subjects with the metabolic syndrome and a previous stroke or TIA did not experience an increased risk of stroke.[654] Although many studies have used >1 definition of the metabolic syndrome to assess the risk for stroke, the harmonized definition may prove to be superior in establishing the relationship.[655,656]

There are essentially no trial data that have addressed the effects of treatment on cardiovascular morbidity and mortality in patients with the metabolic syndrome. In the JUPITER Trial, 17 802 healthy men and women with LDL cholesterol levels <130 mg/dL and hs-CRP levels ≥2.0 mg/L were randomized to receive rosuvastatin 20 mg daily or placebo and followed up for the occurrence of the combined primary end point of MI, stroke, arterial revascularization, hospitalization for unstable angina, or death resulting from cardiovascular causes.[657] The rates were reduced by a hazard ratio of 0.56 (95% CI, 0.46–0.69) for the primary end point, 0.46 (95% CI, 0.30–0.70) for MI, and 0.52 (95% CI, 0.34–0.79) for stroke. Patients with or without the metabolic syndrome had similar reductions in CVD events. The TNT study included 10 001 patients with clinically evident coronary heart disease.[658] Treating to an LDL cholesterol substantially <100 mg/dL

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with a high dose of a high-potency statin reduced both stroke and cardiovascular 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.[659] As expected, the higher dose led to greater reductions in LDL cholesterol (73 versus 99 mg/dL at 3 months). Regardless 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, 1.26–1.64; $P<0.0001$). At a median follow-up of 4.9 years, major cardiovascular events occurred in 13% patients receiving the low-dose statin compared with 9.5% receiving the higher dose (HR, 0.71; 95% CI, 0.61–0.84; $P<0.0001$), and cardiovascular events were reduced by 26% (HR, 0.74; 95% CI, 0.59–0.93; $P=0.011$).

Metabolic Syndrome: Summary and Gaps

Individual components of the metabolic syndrome are associated with an increased risk of ischemic stroke and should be treated as appropriate. The specific risk of stroke in people with the metabolic syndrome appears to be higher but remains uncertain, as is the effect of treatment of the syndrome.

Metabolic 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 BP lowering, lipid lowering, glycemic control, and antiplatelet therapy), as endorsed in other sections of this guideline. (Refer to relevant sections for Class and Levels of Evidence for each recommendation.)**

Alcohol Consumption

The National Institute on Alcohol Abuse and Alcoholism defines heavy drinking for a man as >4 drinks in any single day or >14 drinks per week and defines heavy drinking for a woman as >3 drinks any single day and >7 drinks per week.[660] A standard drink is defined as 12 fl oz of regular beer, 5 fl oz of table wine, or a 1.5–fl oz shot of 80-proof spirits. Heavy alcohol consumption can lead to multiple medical complications, including stroke. Heavy alcohol consumption is a risk factor for all types of stroke.[661–665] Most studies suggest a J-shaped association between alcohol consumption and the risk of total and ischemic stroke, with a protective effect in light (<151 g/wk) or moderate (151 to 300 g/wk) drinkers and an elevated risk with heavy (>300 g/wk) alcohol consumption.[661,662,666–676] In contrast, a linear association exists between alcohol consumption and the risk of ICH.[330,334,677,678] In a prospective cohort study of 540 patients with spontaneous ICH,[679] heavy alcohol intake was associated with ICH at a young age (median age, 60 versus 74 years in nonabusers; $P<0.001$).

Light-to-moderate alcohol consumption is associated with higher levels of HDL cholesterol,[680,681] reduced platelet aggregation,[682,683] lower fibrinogen concentrations,[684] and increased insulin sensitivity and glucose metabolism.[685,686] Heavy alcohol consumption can result in hypertension,[687–693] hypercoagulability, reduced cerebral blood flow,[694] and an increased risk of AF.[662,668,695–698] Studies show an increased risk for stroke in hypertensive patients who consume alcohol, as well as poor BP control in heavy drinkers with hypertension.

A study of 43 685 men from the Health Professionals Follow-Up Study and 71 243 women from the Nurses' Health Study showed that alcohol intake had a J-shaped association for risk of stroke.[667] A lower risk for stroke was found in women who were light drinkers, but women who drank ≥ 30 g alcohol per day had a 40% increased risk for stroke (RR, 1.41; 95% CI, 1.07–1.88 for ischemic stroke; RR, 1.40; 95% CI, 0.86–2.28 for ICH). There was a similar but nonsignificant pattern for men. In the WHS,[699] alcohol consumption was not associated with risk for stroke, even for ≥10.5 drinks per week. However, a recent meta-analysis showed a higher mortality risk for women compared with men who drank >3 drinks per day.[700]

A prospective study of Chinese men[701] supports the association between heavy alcohol and risk for stroke. A 22% increase in stroke occurred for those consuming at least 21 drinks per week, whereas consumption of 1 to 6 drinks per week was associated with the lowest risk. In a meta-analysis of 35 observational studies,[678] consumption of 60 g alcohol per day was associated with a 64% increased risk for all stroke (RR, 1.64; 95% CI, 1.39–1.93), a 69% increase for ischemic stroke (RR, 1.69; 95% CI, 1.34–2.15), and more than doubling for hemorrhagic stroke (RR, 2.18; 95% CI, 1.48–3.20). Consumption of <12 g/d was associated with a reduced risk of total (RR, 0.83; 95% CI, 0.75–0.91) and ischemic (RR, 0.80; 95% CI, 0.67–0.96) stroke, with consumption of 12 to 24 g/d associated with a lower risk of ischemic stroke (RR, 0.72; 95% CI, 0.57–0.91). A systematic review of triggers of ischemic stroke showed a significant association between ischemic stroke and alcohol abuse of >40 to 60 g within the preceding 24 hours (OR, 2.66; 95% CI, 1.54–4.61) or >150 g within the previous week (OR, 2.47; 95% CI, 1.52–4.02).[702]

Alcohol Consumption: Summary and Gaps

In observational studies, light to moderate alcohol consumption is associated with reduced risk of total and ischemic stroke, whereas heavier alcohol consumption increases stroke risk. Prospective, randomized, clinical trials showing that reduction of heavy alcohol consumption reduces risk or that light alcohol consumption is beneficial are lacking and are ethically untenable because it is well established that alcohol dependence is a major health problem.

Alcohol Consumption: Recommendations

1. **Reduction or elimination of alcohol consumption in heavy drinkers through established screening and counseling strategies as described in the 2004 US Preventive Services Task Force update is recommended[703] (*Class I; Level of Evidence A*).**
2. **For individuals who choose to drink alcohol, consumption of ≤2 drinks per day for men and ≤1 drink per day for nonpregnant women might be reasonable[704,705] (*Class IIb; Level of Evidence B*).**

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Drug Abuse

Drug addiction is often a chronic, relapsing condition associated with societal and health-related problems.[706] Drugs of abuse, including khat, cocaine, amphetamines, 3,4-methylenedioxy-N-methylamphetamine (also known as MDMA or ecstasy), and heroin, are associated with an increased risk of stroke.[707–709] Use of these drugs can produce acute severe BP elevations, cerebral vasospasm, vasculitis, embolization resulting from infective endocarditis, endothelial dysfunction, hemostatic and hematological abnormalities resulting in increased blood viscosity and platelet aggregation, and ICH.[710–716] In a recent Middle Eastern cohort study of patients with acute coronary syndrome,[717] khat chewing was prevalent and was associated with an increased risk of stroke and death. Cathinone, the major ingredient of the khat plant, has sympathomimetic and central nervous system–stimulating effects. The literature also includes case series of stroke associated with cannabis use; however, the mechanism remains unclear.[718,719] In a prospective study of 48 young patients with ischemic stroke, 21% had multifocal intracranial stenosis associated with cannabis use.[720]

Information about stroke-related drug abuse is limited mainly to epidemiological studies of urban populations. There is an increase in the risk of both ischemic and hemorrhagic stroke.[721–726] In a cross-sectional study of hospitalized patients,[726] amphetamine abuse was associated with ICH (adjusted OR, 4.95; 95% CI, 3.24–7.55) but not with ischemic stroke; cocaine abuse was associated with ICH (OR, 2.33; 95% CI, 1.74–3.11) and ischemic stroke (OR, 2.03; 95% CI, 1.48–2.79). Amphetamine abuse was associated with a higher risk of fatal ICH (OR, 2.63; 95% CI, 1.07–6.50). In a retrospective analysis of patients with ICH, patients with cocaine-associated ICH had worse functional outcomes and an almost 3-fold greater risk of death during the acute hospitalization than patients with cocaine-negative ICH.[727]

Long-term treatment strategies, including medication, psychological counseling, and community-based programs, are effective in the management of drug dependency.[706,728] According to the US Preventive Services Task Force, there is insufficient evidence to assess the balance of benefits and harms of screening adolescents, adults, and pregnant women for illicit drug use. Although standardized questionnaires to screen individuals for drug use/misuse have been shown to be valid and reliable, there is insufficient evidence to assess the clinical utility of these instruments when applied widely in primary care settings.[729]

Drug Abuse: Summary and Gaps

Several drugs of abuse are associated with ischemic and hemorrhagic stroke. There are no controlled trials demonstrating a reduction in stroke risk with abstinence.

Drug Abuse: Recommendation

1. **Referral to an appropriate therapeutic program is reasonable for patients who abuse drugs that have been associated with stroke, including cocaine, khat, and amphetamines (*Class IIa; Level of Evidence C*).**

Sleep-Disordered Breathing

Approximately 4% of adults in the United States have sleep apnea.[730,731] The diagnosis of sleep apnea is based on the apnea-hypopnea index (AHI), which describes the number of respiratory events (cessations or reductions in air flow) observed during sleep. Sleep apnea is defined as present if the AHI is ≥5 events per hour, and an increasing AHI indicates increasing severity.[730]

Several longitudinal studies have identified sleep apnea as an independent risk factor for stroke. The first prospective data demonstrating an association between sleep apnea and stroke risk came from the Wisconsin Sleep Cohort Study.[732] This cohort included 1189 subjects followed up for 4 years. There was a 3-fold increase in the risk of stroke (OR, 3.09; 95% CI, 0.74–12.81) for subjects with an AHI ≥20 events per hour. The Sleep Heart Health Study followed up 5422 adults who were ≥40 years of age without a history of stroke but with untreated sleep apnea for a median of 8.7 years.[733] The unadjusted stroke risk associated with sleep apnea was somewhat higher in men than in women; the OR for ischemic stroke per 10 years was 2.26 (95% CI, 1.45–3.52) for men and 1.65 (95% CI, 1.45–3.52) for women. After adjustment for age, BMI, race, smoking, SBP, antihypertensive medications, and diabetes mellitus, sleep apnea was associated with stroke risk in men but not women. Among men, there was a progressive increase in ischemic stroke risk with increasing sleep apnea severity: AHI 9.5 to 19.1 events per hour, adjusted OR, 1.86 (95% CI, 0.70–4.95); AHI >19.1 events per hour, adjusted OR, 2.86 (95% CI, 1.10–7.39). A meta-analysis of 5 prospective studies that included 8435 participants identified an OR for incident stroke risk of 2.24 (95% CI, 1.57–3.19).[734] This meta-analysis also found that increased stroke risk is associated with increasing sleep apnea severity with an OR of 1.35 (95% CI, 1.25–1.45) for every 10-unit increase in AHI. A study of 50 men with sleep apnea and 15 obese male control subjects found that silent brain infarctions on MRI were more common among patients with moderate to severe sleep apnea than among control subjects or patients with mild sleep apnea (25% versus 7.7% versus 6.7%, respectively; $P<0.05$).[735]

Although alternative therapeutic strategies exist, the mainstay of sleep apnea treatment is continuous positive airway pressure (CPAP), which improves a variety of clinical outcomes (eg, daytime sleepiness).[730,736] No randomized trial has evaluated the effectiveness of CPAP on primary stroke prevention. The existing longitudinal cohort data indicate that CPAP treatment is associated with a reduction in cardiovascular risk among patients with sleep apnea compared with patients who are not treated with CPAP even after adjustment for vascular risk factors and that this finding is most robust for patients with the most severe sleep apnea.[737–739] For example, a study of 264 healthy subjects, 403 untreated patients with sleep apnea, and 372 patients with CPAP treatment for 10 years[739] had a combined vascular event end point that included fatal or nonfatal stroke or MI or acute coronary syndrome requiring cardiac intervention. In this cohort, severe untreated sleep apnea was associated with a 3-fold increased risk of vascular events (adjusted OR, 2.87; 95% CI, 1.17–7.51 for cardiovascular death; OR, 3.17; 95% CI, 1.12–7.52 for nonfatal cardiovascular events), but patients with treated sleep apnea had vascular

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event risks that were similar to those of patients with mild untreated sleep apnea and healthy subjects. A cardiovascular end-point benefit was observed with CPAP treatment among 364 patients receiving CPAP compared with 85 untreated patients.[738] The adjusted HR was 0.34 (95% CI, 0.20–0.58) for CPAP treatment.

Although no randomized, controlled trials have been published on primary prevention, several randomized, controlled trials and cohort studies have evaluated the effectiveness of CPAP among patients with stroke and TIA (These data are reviewed in detail in the AHA secondary stroke prevention guidelines).[740] Among these secondary prevention studies, the one with the longest follow-up studied 189 patients after stroke with sleep apnea for 7 years, finding that patients who did not use CPAP had a much higher recurrent stroke rate than patients who used CPAP (32% versus 14%; P=0.021) and a higher adjusted incidence of nonfatal vascular events (HR, 2.87; 95% CI, 1.11–7.71).[741] The number needed to treat to prevent 1 new vascular event was 4.9 patients (95% CI, 2–19).

Adherence to CPAP can be measured directly by CPAP machines in hours per night used and proportion of nights used. The reported CPAP adherence has varied considerably across studies and across populations, with mixed data about differences in adherence related to differences in CPAP mode (eg, autotitrating versus fixed pressure) or humidification use.[742–746] Cognitive-behavioral interventions appear to improve CPAP adherence.[747] Several studies have sought to identify predictors of CPAP adherence, and results have varied across studies. In general, however, patients who are most symptomatic (eg, excessive daytime sleepiness) are most likely to adhere to treatment in the long term.[745] A CPAP use study among 1155 patients with sleep apnea found that 68% were continuing to use the CPAP after 5 years of follow-up.[748]

Patients with sleep apnea often have concomitant stroke risk factors, including hypertension, AF, diabetes mellitus, obesity, and hyperlipidemia, and several studies have demonstrated the importance of adjusting for these factors when examining the relationship between sleep apnea and risk of stroke.[733,734] Given the robust relationship between sleep apnea and hypertension,[749–751] numerous studies have specifically examined the degree to which CPAP treatment is associated with improvements in BP. Several meta-analyses suggest that the difference in SBP that can be expected with CPAP ranges from a decrease of 1.4 to 7.2 mm Hg,[736,752–754] with most of the estimates closer to the lower end of this range.

Despite being highly prevalent, as many as 70% to 80% of patients with sleep apnea are neither diagnosed nor treated.[755] The American Academy of Sleep Medicine[730] advocates screening high-risk patients for symptoms of sleep apnea. High-risk populations include those with risk factors for stroke (eg, AF, refractory hypertension) and patients with stroke. The recommended screening includes a sleep history (eg, snoring, witnessed apneas, daytime sleepiness), an evaluation of conditions that may occur as a consequence of sleep apnea (eg, motor vehicle accidents, stroke), and physical examination (eg, BMI ≥35 kg/m^2, neck circumference >17 in for men or 16 in for women). The Epworth Sleepiness Scale[756] and Berlin Questionnaire[757] are tools for screening for sleep apnea. However, most clinical screening tests miss a significant proportion of patients.[758] Patients who are considered to be high risk on the basis of this screening should be referred for polysomnography.[730]

Sleep-Disordered Breathing: Summary and Gaps

Sleep apnea independently contributes to risk of stroke, and increasing sleep apnea severity is associated with increasing risk. No prospective, randomized trial has evaluated the effectiveness of sleep apnea treatment for primary stroke prevention.

Sleep-Disordered Breathing: Recommendations

1. **Because of its association with stroke risk, screening for sleep apnea through a detailed history, including structured questionnaires such as the Epworth Sleepiness Scale and Berlin Questionnaire, physical examination, and, if indicated, polysomnography may be considered (*Class IIb; Level of Evidence C*).**
2. **Treatment of sleep apnea to reduce the risk of stroke may be reasonable, although its effectiveness for primary prevention of stroke is unknown (*Class IIb; Level of Evidence C*).**

Hyperhomocysteinemia

Homocysteine is an amino acid derived from the metabolism of the essential amino acid methionine. Increased plasma levels of homocysteine are often a consequence of reduced enzymatic activity in its metabolic pathways. This may be caused by genetic defects in the enzymes involved in homocysteine metabolism such as deficiencies of cystathionine β-synthase and methylenetetrahydrofolate reductase (MTHFR), involved in the transsulfuration and remethylation pathways, respectively, or by a thermolabile variant of MTHFR that results from a point mutation in which cytosine is replaced by thymidine at position 677 (*MTHFR* C677T).[759] Hyperhomocysteinemia also is 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.[760] Decreased renal clearance of homocysteine in patients with chronic renal failure may contribute to hyperhomocysteinemia.

Elevated levels of plasma homocysteine are associated with 2- to 3-fold increased risk for atherosclerotic vascular disease, including stroke.[761–767] Carotid IMT and carotid artery stenosis are increased in people with elevated homocysteine levels.[768–770] 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.[771] 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.[772,773] One meta-analysis of epidemiological studies found a 19% (95% CI, 5–31) reduction in odds of stroke per 25% lower homocysteine concentration after adjustment for smoking, SBP, and cholesterol.[774] Another meta-analysis found that for each 5-μmol/L increase in homocysteine, the odds of stroke

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increased by 59% (95% CI, 29–96), and for each 3-μmol/L decrease in homocysteine, the odds of stroke decreased by 24% (95% CI, 15–33).[775] A further line of evidence supporting a causal role for homocysteine in a stroke is a meta-analysis of 29 studies comparing the MTHFR C677T genotype between 4454 stroke patients and 7586 control subjects. This "mendelian randomization" approach found increased stroke in those with the TT genotype (OR for stroke, 1.26; 95% CI, 1.11–1.43) without significant between-study heterogeneity or evidence of publication bias.[776]

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.[777–780] In a clinical trial of healthy adults without diabetes mellitus 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.[781] A meta-analysis of 10 randomized trials of folic acid similarly found that treatment decreased IMT but with substantial heterogeneity resulting from larger effects at higher baseline IMTs or with greater reductions in homocysteine.[782] A substudy of the Vitamins to Prevent Stroke (VITATOPS) trial, however, reported that B complex vitamins did not slow the progression of carotid IMT.[783]

Most trials 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 vitamin B_6, vitamin 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, 1 trial of patients with MI and the other of patients with coronary artery disease or aortic stenosis, B complex vitamins did not reduce mortality or cardiovascular events, including stroke.[784,785] Similarly, in the Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS), these B complex vitamins did not alter the risk of stroke in women with established CVD or ≥3 risk factors.[786] Most recently, the VITATOPS trial,[787] in which 8164 subjects with recent stroke or TIA were randomized to vitamin B_6, vitamin B_{12}, and folic acid versus placebo and followed up for a median of 3.4 years, found no effect of B vitamin supplementation on risk of stroke (HR, 0.92; 95% CI, 0.81–1.06). Interestingly, a post hoc analysis restricted to the 1463 subjects in VITATOPS not taking antiplatelet medication[788] found a reduced risk of stroke in the B vitamin group (HR, 0.6; 95% CI, 0.50–0.95) and a significant interaction between antiplatelet use and assignment to B vitamins. It remains unclear whether the effectiveness of B vitamin treatment within the no-antiplatelet subgroup represents biological modification of the effects of homocysteine by antiplatelet drugs, intergroup differences between patients on and off antiplatelet therapy (such as the greater proportion of patients with hemorrhagic or cardioembolic strokes among those not taking antiplatelets), or a spurious result of secondary analysis. A meta-analysis of folic acid supplementation in 26 randomized, controlled trials enrolling 58 804 participants[789] found no effect on the risk of CVD (RR, 0.98; 95% CI, 0.95–1.02) but a trend toward reduced stroke risk (RR, 0.93; 95% CI, 0.86–1.00). A somewhat stronger reduction in stroke (RR, 0.89; 95% CI, 0.79–0.99) was noted in a different subgroup analysis[790] restricted to 35325 participants who did not have stroke as a qualifying event for inclusion in the trial.

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.[791–793] In the Atherosclerosis and Folic Acid Supplementation Trial, 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 (RR reduction, 0.55; 95% CI, 0.01–0.80).[793,794] Similarly, in the HOPE 2 study of patients with established vascular disease or diabetes mellitus, combination therapy with vitamin B_6, vitamin B_{12}, and folic acid lowered plasma homocysteine levels; did not affect the composite end point of cardiovascular death, MI, or stroke; but did reduce the risk of stroke by 25% (RR, 0.75, 95% CI, 0.59–0.97).[795] A subsequent exploratory analysis found no heterogeneity in the effect on stroke based on whether or not the subjects had a prior history of stroke or TIA (*P* for interaction=0.88).[796]

Hyperhomocysteinemia: Summary and Gaps

Hyperhomocysteinemia is associated with an increased risk of stroke. Trials that have examined the effect of homocysteine-lowering therapy with B complex vitamins on the 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 where patients were recruited did not fortify diet with folate, and the 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 the risk of stroke in patients with elevated homocysteine levels.

Hyperhomocysteinemia: Recommendation

1. **The use of the B complex vitamins, cobalamin (B_{12}), pyridoxine (B_6), and folic acid might be considered for the prevention of ischemic stroke in patients with hyperhomocysteinemia, but its effectiveness is not well established (*Class IIb; Level of Evidence B*).**

Elevated Lp(a)

Lp(a) is an LDL 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 those of LDL. Lp(a) contributes to atherogenesis in experimental models[797] and is associated with an increased risk for coronary artery disease.[798,799] 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.[797,800]

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Some, but not all, population-based epidemiological studies have found that Lp(a) is associated with an increased risk of stroke.[801–803] In the Physicians' Health Study, which comprised primarily healthy, white, middle-aged men, there was no association between baseline plasma concentration of Lp(a) and future risk of stroke.[804] In the CHS, the risk of stroke was increased 3-fold (RR, 3.00; 95% CI, 1.59–5.65) in older men whose Lp(a) levels were in the highest quintile compared with men with levels in the lowest quintile but not older women.[801] In the ARIC study, the incidence of ischemic stroke was significantly increased in individuals with higher Lp(a) levels after adjustment for age, sex, and CVD risk factors, and this association was stronger in blacks than in whites. Compared with those with Lp(a) <10 mg/dL, the incidence of ischemic stroke was 2.12-fold greater (RR, 2.12; 95% CI, 1.48–3.03) in blacks with Lp(a) >30 mg/dL. In whites, it was 1.65-fold greater (RR 1.65; 95% CI, 1.04–2.61).[805] Several studies have found Lp(a) level to be associated with the severity of carotid artery stenosis and occlusion.[806,807] One study found that Lp(a) levels were higher in patients with strokes related to large-vessel atherothrombotic disease than in patients with lacunar strokes.[808] 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, 1.04–1.43) more frequent in patients in the highest compared with the lowest tertile of Lp(a).[809]

A recent study assessing the value of emerging circulating lipid markers such as Lp(a) for the prediction of first cardiovascular events showed that the addition of information on Lp(a) to that on conventional risk factors such as total and HDL cholesterol slightly improved the prediction of cardiovascular events and would reclassify ≈4% of individuals to a ≥20% predicted risk of having a cardiovascular event within 10 years and therefore needing statin treatment according to Adult Treatment Panel III guidelines.[810]

A meta-analysis of observational studies reported an association of elevated Lp(a) with first childhood arterial ischemic stroke (OR, 6.53; 95% CI, 4.46–9.55).[811] More recently, elevated Lp(a) was also associated with recurrent arterial ischemic stroke in children.[812]

Niacin decreases Lp(a) levels.[813] In a meta-analysis of secondary prevention trials including a total of 9959 subjects, niacin treatment yielded relative odds reductions of 34% of any CVD event (P=0.007).[173] However, no significant effect of niacin on stroke was observed.

Lp(a): Summary and Gaps

Elevated Lp(a) is associated with a higher risk of stroke. Although niacin lowers Lp(a), randomized trials have not showed that niacin supplementation lowers the risk of stroke.

Elevated Lp(a): Recommendations

1. **The use of niacin, which lowers Lp(a), might be reasonable for the prevention of ischemic stroke in patients with high Lp(a), but its effectiveness is not well established (*Class IIb; Level of Evidence B*).**
2. **The clinical benefit of using Lp(a) in stroke risk prediction 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 based largely on case series or case-control studies. Of these, the presence of aPLs, generally an acquired condition, is most strongly associated with arterial thrombosis. 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 ischemic stroke.[814,815] From limited, often uncontrolled data that include predominantly patients with SLE and potentially other vascular risk factors that are poorly detailed, asymptomatic patients with aPL are estimated to have a 0% to 3.8% annual thrombosis risk.[816]

Acquired Hypercoagulable State: Relationship to Ischemic Stroke

Case-control studies of aPL in young stroke patients have uniformly demonstrated an association, as have most studies of unselected stroke populations. However, this is not the case for case-control studies among older adults with ischemic stroke. The Sneddon syndrome was formerly thought to be a manifestation of aPL syndrome, but it may be present in patients with or without aPLs,[817] and the risk of ischemic stroke is increased only in those patients with increased aPLs.

Several prospective cohort studies have assessed the relationship between aPL and ischemic stroke. 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 adult men.[818] This was a nested, case-control study in a prospective cohort with 60.2 months of follow-up. At entry into the study, 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 or pulmonary embolus. The aCL titers were higher in cases with deep vein thrombosis or pulmonary embolus than in matched controls (P=0.01). People with aCL titers above the 95th percentile had an RR for developing deep vein thrombosis or pulmonary embolus of 5.3 (95% CI, 1.55–18.3; P=0.01). Although an aCL level above the 95th percentile was an important risk factor for deep vein thrombosis or pulmonary embolus, there was no effect on stroke (an RR of 2 for ischemic stroke could not, however, be excluded because of low power).

The Honolulu Heart Study was a nested case-control study examining aCL as a risk factor for ischemic stroke and MI.[819] The study used stored frozen sera obtained from subjects in the Honolulu Heart Program who were followed for up to 20 years. aCL (β_2 glycoprotein-I [β_2GPI] 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 both conditions. aCL was significantly associated with both incident ischemic stroke and MI. Men with a positive aCL had higher risk of stroke relative to men with negative aCL (OR, 2.2 [95% CI, 1.5–3.4] at 15 years and OR, 1.5 [95% CI, 1.0–2.3] at 20 years). These data suggest that aCL is an important predictor of future stroke and MI in men.

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The Framingham Offspring Cohort Study, a longitudinal observational study, used an ELISA to measure aCL from stored frozen sera. This study found an association between aCL titers and ischemic stroke or TIA, but only in women.[820] Overall, although elevated aCL titers may be commonly found in ischemic stroke patients, the strength of the association between elevated aCL titers and stroke origin or risk is uncertain.

The shortcoming of many studies evaluating aCL in stroke patients such as the Framingham Offspring Cohort study has been the use of the aCL ELISA, a test with low sensitivity. The assay for anti-β_2GPI antibodies, a cofactor for antiphospholipid binding, may be more specific for thrombosis, including stroke and MI.[819,821] Only a few studies have investigated β_2GPI in the absence of SLE. [819,821,822] 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.[821] A prospective, observational study was performed to establish the incidence of first-time thromboembolic events in subjects with a high-risk aPL profile (positive lupus anticoagulant, positive aCL, and positive β_2GPI).[823] The incidence of first thromboembolus was 5.3% annually compared with an annual rate of 1.9% in a study from the same group looking at subjects with only a single positive aPL test.[824] Forty percent of thromboembolic events were stroke or TIA, and aspirin did not affect the incidence.

Acquired Hypercoagulable State: Treatment for Primary Prevention of Stroke

Adequately powered, controlled studies evaluating treatment of elevated aCL to prevent a first stroke are not available. In a subgroup analysis of the Physicians' Health Study,[818] 325 mg aspirin every other day did not protect against venous thromboembolism in 40- to 84-year-old men with moderate to high aCL titers. There is an ongoing primary prevention trial of warfarin therapy (INR, 2.0–2.5) to decrease thromboembolic events in patients with lupus and aPL.[825]

The Antiphospholipid Antibody Acetylsalicylic Acid (APLASA) study was a small, multicenter, double-blind, placebo-controlled trial for the primary prevention of thrombosis in asymptomatic patients who were persistently aPL positive that compared low-dose aspirin (81 mg/d; n=48) with placebo (n=50) over an average follow-up of 2.30±0.95 years.[816] The rates of acute thrombosis were 2.75 per 100 patient-years for the aspirin-treated subjects and 0 per 100 patient-years for placebo-treated subjects (HR, 1.04; 95% CI, 0.69–1.56; *P*=0.83). The sample size was relatively small; thus, the study insufficiently powered. A parallel and separate observational study published within the APLASA study[816] found no reduction in the rate of first thrombotic events with low-dose (81 mg/d) aspirin over placebo in persistently aPL-positive asymptomatic individuals. These individuals 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.

Inherited Hypercoagulable State: Relationship to Ischemic Stroke

Inherited hypercoagulable states that have been associated with stroke include fibrinogen level, the β-chain–455 G/A fibrinogen, factor VIII levels, factor XIII Val34Leu, von Willebrand factor small polymorphism in intron 2, tissue-type plasminogen activator −7351 C/T, thrombotic thrombocytopenic purpura, and heparin-induced thrombocytopenia.[826] The majority of case-control studies have not found an association between arterial stroke and other hereditary hypercoagulable states such as factor V Leiden or prothrombin 20210 mutations or deficiencies of protein C, protein S, or antithrombin III.[98,99] 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 mutation or the prothrombin 20210 mutation in patients with cryptogenic strokes compared with control subjects. The prevalence of the prothrombin 20210 mutation alone (OR, 10.09; 95% CI, 1.09–109) was higher in those with cryptogenic stroke and PFO versus those without PFO,[827] suggesting a greater thrombotic risk in the setting of PFO than in either condition alone. The presumed stroke mechanism is paradoxical embolism related to venous rather than arterial thrombosis. Similarly, a familial cohort study found that the prothrombin 20210 mutation was a mild risk factor for venous thromboembolism but was not found to increase the risk of arterial thromboembolic events.[828]

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.[829] 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.

The 2 most common genetic causes of thrombophilia are the factor V Leiden mutation and the G20210A mutation of prothrombin.[830] Although their association with adult stroke is unclear, there is evidence of an association with ischemic stroke in children and young adults. A combination of multiple case-control studies demonstrated an 4.3-fold increased incidence of factor V Leiden in children with acute ischemic stroke.[829] A meta-analysis of the association of factor V Leiden with ischemic stroke in adults ≤50 years of age showed a fixed-effect OR of 2.00 for the mutation. This association was even stronger (OR, 2.73; 95% CI, 1.98–3.75) in those patients with cryptogenic stroke in whom there is an increased suspicion of hypercoagulability; however, the estimated effect carries the risk of inflation by case selection bias.[831]

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 homocysteinemia.[832] 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: women using oral estrogen preparations, women during pregnancy, and patients undergoing major orthopedic surgery.[833] This is relevant for the primary prevention of cerebral venous thrombosis and ischemic stroke from 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

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thrombophilia compared with no screening were evaluated. Selective screening based on prior venous thromboembolism history was more cost-effective than universal screening.

Inherited Hypercoagulable State: Treatment for Primary Prevention of Stroke

There is very little evidence to guide the management of asymptomatic people with thrombophilia. A systematic review of prospective observational studies indicated that most venous thromboembolic events occurred during periods of high risk such as surgery, trauma, or pregnancy.[834] These studies and expert opinion suggest that antithrombotic prophylaxis during these periods would be likely to be effective.[829,834] However, the effect of prophylaxis on the incidence of stroke or TIA in these subjects is not known.

Hypercoagulability: Summary and Gaps

Inherited and acquired hypercoagulable states are associated with venous thrombosis, but their association with arterial cerebral infarction is uncertain. Young women with ischemic stroke have a higher prevalence of aPL. The majority of case-control studies have not found an association between acquired or hereditary hypercoagulable states and stroke in other patient populations. 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 to establish the associations of thrombophilias with venous thromboembolism and first ischemic stroke. Although the pathogenic role of prothrombotic abnormalities in childhood and young adult ischemic stroke is increasingly becoming evident, the lack of any clinical trial data precludes definitive recommendations for screening or treatment.

Hypercoagulability: Recommendations

1. **The usefulness of genetic screening to detect inherited hypercoagulable states for the 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 a 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 individuals who are persistently aPL positive (*Class III; Level of Evidence B*).**

Inflammation and Infection

Inflammation affects the initiation, growth, and stability of atherosclerotic lesions.[835] Furthermore, inflammation has prothrombotic effects and plays a role in major stroke risk factors such as AF, which could increase the risk of stroke.[836] Nevertheless, the value of assessing inflammation in assessing risk to optimize the primary prevention of stroke remains controversial. A number of serum markers of inflammation, including fibrinogen, serum amyloid A, lipoprotein-associated phospholipase A2, and interleukin-6, have been proposed as risk markers. Several studies suggest a relationship between hs-CRP and lipoprotein-associated phospholipase A2 and stroke risk.[837-840] 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, [841] the WHS,[842] and the Framingham Heart Study.[843] The RRs 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. However, hs-CRP is also associated with similar increases in mortality from several cancers and lung diseases,[844] indicating that its association with cardiovascular risk is not specific. On the basis of multiple prospective studies, hs-CRP was recommended for measurement limited to people 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.[835] Recent evidence indicates that elevated plasma levels of YKL-40, a product of lipid-laden macrophages, are associated with an increased risk of ischemic stroke independently of hs-CRP levels.[845] The JUPITER study, a randomized trial of a statin versus placebo, was performed in people free of CVD with otherwise normal LDL cholesterol levels (≤130 mg/dL) but with hs-CRP levels >2 mg/dL. The trial found a reduction in cardiovascular end points, including stroke (RR, 0.52; 95% CI, 0.34–0.79), in the statin-treated patients.[160] The study design did not include similarly treated subjects with lower levels of hs-CRP. No data are 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 whether 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 people 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 people with RA, with ORs consistently in the range of 1.4 to 2.0 compared with people without RA.[846–850] At least 50% of premature deaths in patients with RA have been attributed to CVDs.[851] Excess risk was especially apparent in 35- to 55-year-old women with RA.[846] This association remained after adjustment for other cardiovascular risk factors. Furthermore, data from the Danish Nationwide Cohort Study indicate that RA increases the rates of both AF (incidence rate ratio, 1.42) and stroke (1.32),[852] but a causal relationship between AF and stroke in RA has not been established. Patients with SLE had very elevated RRs for CVD in the 2- to 52-fold range.[853] Although stroke rates were not assessed, several studies have identified higher prevalence rates of atherosclerotic plaques in the carotid arteries in RA or SLE patients compared with control subjects.[854–856] Patients with RA and SLE might be considered a subgroup at high risk for CVD worthy of enhanced risk factor measurement and control.[857]

Chronic infections such as periodontitis, chronic bronchitis, and infection with *Helicobacter pylori*, *Chlamydia pneumoniae*, or cytomegalovirus might promote atherosclerosis and increase the risk of stroke.[858] There is evidence that the cumulative effect

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of multiple infections, or infectious burden, rather than single organisms, may be associated with risk of stroke and carotid atherosclerosis.[859,860] Unfortunately, several randomized trials of antibiotic therapy have failed to find any benefit in the prevention of cardiovascular end points, including stroke.[861,862]

A final issue in the role of infection and inflammation in stroke relates to acute infectious diseases (such as influenza). Possible mechanisms include the induction of procoagulant acute-phase reactants (such as fibrinogen) or destabilization of atherosclerotic plaques. Hospitalization for infection appears to be a short-term risk factor for stroke,[863] although it is unclear what, if any, management implications this has for patients. An increase in cardiovascular deaths has long been observed in association with influenza.[864,865] 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, 0.62–0.82) in the risk of stroke or TIA over the ensuing 6 months.[866] One case-control study[867] and 1 cohort study[868] of influenza vaccination demonstrate a reduced risk of stroke associated with vaccination. A prospective study in Taiwan found that influenza vaccination of people >65 years of age was associated with lower all-cause mortality, including a 65% reduction in stroke (HR, 0.35; 95% CI, 0.27–0.45).[869] However, because of the risk of bias, randomized trials have been advocated.[870] Although all people at increased risk of complications from influenza should receive influenza vaccinations on the basis of evidence including randomized trials, influenza vaccination is recommended by the AHA/ACC for the secondary prevention of CVD. There have been no recommendations for influenza vaccination in the primary prevention of stroke. No studies have identified any increase in the risk of stroke after influenza vaccinations.[871]

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Inflammation and Infection: Recommendations

1. **Patients with chronic inflammatory disease such as RA or SLE should be considered at increased risk of stroke (*Class I; Level of Evidence B*).**
2. **Annual influenza vaccination can be useful in lowering stroke risk in patients at risk of stroke (*Class IIa; Level of Evidence B*).**
3. **Measurement of inflammatory markers such as hs-CRP or lipoprotein-associated phospholipase A2 in patients without CVD may be considered to identify patients who may be at increased risk of stroke, although their usefulness in routine clinical practice is not well established (*Class IIb; Level of Evidence B*).**
4. **Treatment of patients with hs-CRP >2.0 mg/dL with a statin to decrease stroke risk might be considered (*Class IIb; Level of Evidence B*).**
5. **Treatment with antibiotics for chronic infections as a means to prevent stroke is not recommended (*Class III; Level of Evidence A*).**

Antiplatelet Agents for Primary Prevention of Stroke

Aspirin use is associated with an increased risk of gastrointestinal bleeding. For example, 1 observational study found that the overall hemorrhagic event incidence was 5.58 (95% CI, 5.39–5.77) per 1000 person-years for aspirin users compared with 3.60 (95% CI, 3.48–3.72) per 1000 person-years for nonusers (incidence rate ratio, 1.55; 95% CI, 1.48–1.63).[872] A meta-analysis of 9 clinical trials including 50 868 subjects found no overall benefit of aspirin for the primary prevention of stroke (OR, 0.919; 95% CI, 0.828–1.021; *P*=0.116), with no heterogeneity among trials.[873] Similarly, a second meta-analysis of 9 trials with 100 076 subjects found that aspirin reduced the risk of ischemic stroke (RR, 0.86; 95% CI, 0.75–0.98), but this benefit was offset by an increase in hemorrhagic stroke (RR, 1.36; 95% CI, 1.01–1.82), again with no heterogeneity among trials.[874] A third meta-analysis had similar results (risk of stroke, 0.20%/y versus 0.21%/y, *P*=0.4; hemorrhagic stroke, 0.04%/y versus 0.03%/y, *P*=0.05; other stroke, 0.16%/y versus 0.18%/y, *P*=0.08, aspirin versus control, respectively).[875] Taken together, these results reflect risk but no benefit of aspirin for the prevention of a first stroke in the general population. The US Preventive Services Task Force recommends aspirin at a dose of 75 mg/d to prevent MI (but not stroke) in men 45 to 79 years of age and to prevent stroke in women 55 to 79 years of age on the basis of their vascular risk and the chances of serious gastrointestinal hemorrhage.[876] The US Preventive Services Task Force further notes that the 10-year level of cardiovascular risk for which the benefit exceeds bleeding risk varies from 3% to 11%, depending on age and sex. The most recent AHA guideline for the primary prevention of CVD and stroke also recommends aspirin for primary cardiovascular prevention in those with a 10-year coronary heart risk ≥10%.[877] There is no evidence that antiplatelet medications reduce the risk of stroke in the general population at low risk.[878–880] Although stroke was not analyzed as a separate end point, lack of aspirin use was independently associated with a 16% higher risk of cardiovascular events (HR, 1.16; 95% CI, 1.03–1.31) among healthy male physicians ≥65 years of age.[881] The benefit of aspirin for primary prevention of stroke is therefore limited to selected subgroups of patients. Several relevant trials further inform the use of aspirin and other antiplatelet agents for the prevention of a first stroke.

The Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial randomized 2539 patients with type 2 diabetes mellitus but without a history of atherosclerotic disease (including stroke) to either low-dose aspirin (81 or 100 mg/d) or no aspirin.[321] 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 primary end point (HR, 0.80; 95% CI, 0.58–1.10; *P*=0.16) and no effect on cerebrovascular events (2.2% with aspirin versus 2.5% with no aspirin; HR, 0.84; 95% CI, 0.53–1.32; *P*=0.44). There was no difference in the combined rates of hemorrhagic stroke and severe gastrointestinal bleeding. A subgroup analysis of the JPAD trial noted that aspirin therapy lowered the rate of cerebrovascular events in patients with diabetes mellitus with uncontrolled hypertension (SBP ≥140 mm Hg and/or DBP ≥90 mm Hg) compared with those with controlled BP (HR, 1.64; 95% CI, 0.83–3.29), although the 95% CI includes the possibility of no benefit.[882]

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 2 diabetes mellitus and an ankle-brachial index of ≤0.99 but no symptomatic CVD who were randomized in a 2-by-2 factorial design to 100 mg aspirin or placebo plus antioxidants or placebo daily.[883] The study had 2 primary end points: (1) death resulting from coronary heart disease or stroke, nonfatal MI or stroke, or amputation above the ankle for critical limb ischemia and (2) death resulting from coronary heart disease or stroke. There was no interaction between aspirin and antioxidant. There was no effect of aspirin on the composite primary end points (HR, 0.98; 95% CI, 0.76–1.26; *P*=0.86) or on death resulting from coronary heart disease or stroke (HR, 1.23; 95% CI, 0.79–1.93; *P*=0.36). There was no effect of aspirin on fatal stroke (HR, 0.89; 95% CI, 0.34–2.30; *P*=0.80) or nonfatal stroke (HR, 0.71; 95% CI, 0.44–1.14; *P*=0.15). There was no difference in the risk of gastrointestinal hemorrhage (HR, 0.90; 95% CI, 0.53–1.52; *P*=0.69). The lack of increased bleeding risk with aspirin in those with diabetes mellitus was also found in the observational study cited above (incidence rate ratio for aspirin users versus nonusers, 1.09; 95% CI, 0.97–1.22).[872] Diabetes mellitus was independently associated with an increased risk of major bleeding regardless of aspirin use (RR, 1.36; 95% CI, 1.28–1.44). A meta-analysis of 7 trials (11 618 subjects) of the effects of aspirin in patients with diabetes mellitus found a treatment-associated 9% reduction in major cardiovascular events (RR, 0.91; 95% CI, 0.82–1.00) but found no significant reduction in stroke (RR, 0.84; 95% CI, 0.64–1.11).[323] Four additional meta-analyses also found no reduction in stroke with aspirin in subjects with diabetes mellitus.[884–887]

A focused, multisociety position paper on the primary prevention of cardiovascular events in people with diabetes mellitus considered these and other studies and recommended low-dose aspirin for adults with diabetes mellitus who have a 10-year cardiovascular risk >10% (men >50 years of age and women >60 years of age who have at least 1 additional major risk factor such as smoking, hypertension, dyslipidemia, a family history of premature CVD, or albuminuria) and who are not at high risk of aspirin-related bleeding complications.[888] It was further recommended that aspirin not be used for cardiovascular prevention among those with diabetes mellitus at low risk and that aspirin might be considered for those at intermediate (10-year risk in the 5%–10% range) risk.

Relatively few women were enrolled in the primary prevention trials that showed a benefit of aspirin in the prevention of coronary heart events but no reduction in stroke. The WHS randomized 39 876 initially asymptomatic women ≥45 years of age to receive 100 mg aspirin on alternate days or placebo and followed them up for 10 years for a first major vascular event (nonfatal MI, nonfatal stroke, or cardiovascular death).[889] Unlike data from earlier studies that included mainly men, this study found a nonsignificant 9% reduction (RR, 0.91; 95% CI, 0.80–1.03; *P*=0.13) for the combined primary end point among women but a 17% reduction in the risk of stroke (RR, 0.83; 95% CI 0.69–0.99; *P*=0.04). This was based on a 24% reduction in the risk of ischemic stroke (RR, 0.76; 95% CI, 0.63–0.93; *P*=0.009) and a nonsignificant increase in the risk of hemorrhagic stroke (RR, 1.24; 95% CI, 0.82–1.87; *P*=0.31). The overall average stroke rates were 0.11%/y in aspirin-treated women and 0.13%/y in placebo-treated women (RR, 0.02%/y; number needed to treat, 5000). Gastrointestinal hemorrhage requiring transfusion was more frequent in the aspirin group (RR, 1.40; 95% CI, 1.07–1.83; *P*=0.02). The average gastrointestinal hemorrhage rates were 0.06%/y for aspirin and 0.05%/y for placebo (absolute risk increase, 0.01%/y; 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, 0.59–0.92; *P*=0.008), including a 30% reduction in the risk of ischemic stroke (RR, 0.70; 95% CI, 0.49–1.00; *P*=0.05); however, there was only a trend in the reduction of the overall risk of all types of stroke (RR, 0.78; 95% CI, 0.57–1.08; *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, 0.59–0.98; *P*=0.04), hyperlipidemia (RR, 0.62; 95% CI, 0.47–0.83; *P*=0.001), or diabetes mellitus (RR, 0.46; 95% CI, 0.25–0.85; *P*=0.01) or having a 10-year cardiovascular risk ≥10% (RR, 0.54; 95% CI, 0.30–0.98; *P*=0.04). A further post hoc subgroup WHS analysis found that the overall effect of aspirin was not modified in women with migraine (with or without aura), but aspirin use was associated with an increased risk of MI in those with migraine with aura (RR, 3.72; 95% CI, 1.39–9.95), an unexpected finding that may have been attributable to chance.[615] The AHA evidence-based guidelines for CVD prevention in women also endorse the use of aspirin in high-risk women, unless contraindicated, in women ≥65 years of age if BP is controlled and benefit for ischemic stroke and MI prevention outweighs the risk of gastrointestinal bleeding and hemorrhagic stroke, as well as in women <65 years of age when benefit for ischemic stroke prevention is likely to outweigh complications.[890]

There are several other subpopulations for whom aspirin might be helpful in reducing risk of stroke. Patients with a reduced ankle-brachial index are at higher risk of vascular events. One trial evaluated the benefit of aspirin in a screened general population cohort with a low ankle-brachial index.[891] There was no benefit of aspirin in reducing the rate of fatal or nonfatal coronary events, stroke, or revascularization procedures (HR, 1.03; 95% CI, 0.84–1.27). One meta-analysis evaluated cilostazol versus placebo in 3782, 1187, and 705 patients with peripheral artery disease, cerebrovascular disease, and coronary stenting, respectively.[892] The incidence of vascular events was lower in the cilostazol group compared with the placebo group (RR, 0.86; 95% CI, 0.74–0.99; *P*=0.038), including a lower incidence of cerebrovascular events (RR, 0.58; 95% CI, 0.43–0.78; *P*<0.001), with no increase in serious bleeding complications (RR, 1.00; 95% CI, 0.66–1.51; *P*=0.996). The primary and secondary prevention populations were not analyzed separately; however, there was no statistical heterogeneity among the trials.

In a subgroup analysis of the Hypertension Optimal Treatment (HOT) trial, subjects with renal failure (estimated glomerular filtration rate <45 mL/min/1.73 m^2) had a reduction in stroke risk with aspirin (HR, 0.21; 95% CI, 0.06–0.75).[893] In addition, total mortality was reduced by half (HR, 0.51; 95% CI, 0.27–0.94) and cardiovascular mortality by 64% (HR, 0.36; 95% CI, 0.14–0.90). These results, however, were based on a post hoc analysis. Given the small number of participants with

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stage 4 or 5 chronic kidney disease (estimated glomerular filtration rate <30 mL/min/1.73 m^2) in the HOT trial, the RRs and benefits of aspirin in this population are not known.

Antiplatelet Agents and Aspirin: Summary and Gaps

Previous guideline statements endorse the use of aspirin for cardiac but not stroke prophylaxis among asymptomatic men whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment.[876] These recommendations were based on a reduction of coronary events in men and reduction of stroke in women.

There remains little evidence (aside from cilostazol in those with peripheral artery disease) supporting the use of antiplatelet therapy other than aspirin and cilostazol for primary stroke prevention because of the lack of relevant trials.

Antiplatelet Agents and Aspirin: Recommendations:

1. **The use of aspirin for cardiovascular (including but not specific to stroke) prophylaxis is reasonable for people whose risk is sufficiently high (10-year risk >10%) for the benefits to outweigh the risks associated with treatment. A cardiovascular risk calculator to assist in estimating 10-year risk can be found online at http://my.americanheart.org/cvriskcalculator (*Class IIa; Level of Evidence A*).**
2. **Aspirin (81 mg daily or 100 mg every other day) can be useful for the prevention of a first stroke among women, including those with diabetes mellitus, whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment (*Class IIa; Level of Evidence B*).**
3. **Aspirin might be considered for the prevention of a first stroke in people with chronic kidney disease (ie, estimated glomerular filtration rate <45 mL/min/1.73 m^2) (*Class IIb; Level of Evidence C*). This recommendation does not apply to severe kidney disease (stage 4 or 5; estimated glomerular filtration rate <30 mL/min/1.73 m^2).**
4. **Cilostazol may be reasonable for the prevention of a first stroke in people with peripheral arterial disease (*Class IIb; Level of Evidence B*).**
5. **Aspirin is not useful for preventing a first stroke in low-risk individuals (*Class III; Level of Evidence A*).**
6. **Aspirin is not useful for preventing a first stroke in people with diabetes mellitus in the absence of other high-risk conditions (*Class III; Level of Evidence A*).**
7. **Aspirin is not useful for preventing a first stroke in people with diabetes mellitus and asymptomatic peripheral artery disease (defined as asymptomatic in the presence of an ankle brachial index ≤0.99) (*Class III; Level of Evidence B*).**
8. **The use of aspirin for other specific situations (eg, AF, carotid artery stenosis) is discussed in the relevant sections of this statement.**
9. **As a result of a lack of relevant clinical trials, antiplatelet regimens other than aspirin and cilostazol are not recommended for the prevention of a first stroke (*Class III; Level of Evidence C*).**

Primary Prevention in the Emergency Department

Emergency departments (EDs) in the United States are the default safety net for millions of Americans,[894] yet at a time when more and more Americans use EDs for emergency and primary care, the number of EDs across the United States continues to decline.[895] By definition, EDs provide immediate access to healthcare providers trained in emergency care and allow access to advanced technologies and medical specialists for patients with diverse medical conditions. EDs are equipped to evaluate and manage acute life-threatening illness yet are increasingly called on to provide services typically associated with primary care. For many patients who use the ED for the majority of their healthcare services, the ED may serve as an important location to provide health promotion and disease prevention services, including stroke.

In addition to addressing the primary reason for the ED visit, the ED encounter may serve to reinforce healthy living, to perform primary disease identification and prevention, to provide early disease detection (secondary prevention), to encourage and facilitate compliance with disease management, and to refer patients to primary care providers for continued management of existing disease (tertiary prevention).[896,897] With the growing numbers of Americans using the ED for primary care, especially socioeconomically at-risk populations, the ED may present a unique opportunity to reduce cerebrovascular disease and CVD.[898]

Enthusiasm to use the ED as a site for initiating primary and secondary preventative services, however, must be tempered by the higher cost of providing care in this setting and performance pressures on the ED personnel to decrease length of stay, rates of patients who leave without treatment, overall wait times, and resource use.[896,899] Although the list of potentially modifiable stroke risk factors as reviewed in this guideline is extensive, not all are amenable to assessment and initiation of preventive strategies in the ED.[896] Aside from resource availability, to effectively initiate primary preventive strategies, ED personnel must know the risk factors for various diseases, in this case stroke; must understand the appropriate diagnostic evaluations and definitions for the risk factors; must be aware of recommendations for appropriate interventions; and must be able to arrange primary care follow-up to assess the effect of initiated preventive interventions. Adding delivery of primary care and primary prevention to the growing list of mandated interventions delivered in the ED setting will require engaging and enabling already largely receptive ED professionals.[900]

ED visits serve as opportunities 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.[901] Although patients are asymptomatic, many have target-organ injury; an ED cohort of blacks with elevated BP in the ED found that 90% had subclinical hypertensive heart disease.[902] In ED patients with newly identified hypertension or chronically untreated hypertension, performing screening tests in the ED for target-organ damage and tests for identifiable causes of hypertension in selected patents is appropriate. Most asymptomatic patients will not require acute BP reduction or long-term antihypertensive medication initiation in the ED. For most newly diagnosed hypertensive patients, the ED encounter can serve as a means of arranging appropriate referral

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to outpatient primary care, coupled with counseling on lifestyle modifications, although this is inconsistently performed.[221,903] ED personnel can identify patients with a history of hypertension but nonadherence to their medication regimen who need to resume their previous medications. ED screening for hypertension is feasible and cost-effective. Once hypertensive patients are identified, ED personnel can educate on and encourage healthy lifestyles to address their hypertension and the importance of outpatient follow-up, in accordance with the current Joint National Committee 8 outpatient guidelines.[219,896,904]

The incidence of diabetes mellitus has more than doubled over the last 2 decades, and millions with the condition remain undiagnosed. On the basis of screening hemoglobin A_{1c} and fasting plasma glucose, the National Health and Nutrition Examination Survey estimated the prevalence of undiagnosed diabetes mellitus in the US population to be 2.8%.[905] Similar to hypertension, there is an even higher prevalence of undiagnosed diabetes mellitus in the ED patient population.[905] Although point-of-care glucose and hemoglobin A_{1c} testing of ED patients may be feasible, it remains to be determined whether such screening is cost-effective.[906] Unselected screening by capillary blood glucose or hemoglobin A_{1c} measurement is not currently recommended by emergency medicine societies or other healthcare agencies, but emergency physicians support improved recognition and referral for hyperglycemia.[896,905,907,908] Patients with known diabetes mellitus commonly use EDs for acute care of complications related to diabetes mellitus, and many present with poor glycemic control. These encounters provide another opportunity to encourage medication compliance, dietary management, lifestyle modification, and outpatient follow-up.

Despite decades of public health interventions, cigarette smoking remains a leading cause of preventable deaths in the United States, accounting for 1 of every 5 deaths each year.[909] Recognizing this continuing problem, the American College of Emergency Physicians recommends ED interventions aimed at smoking cessation.[910] Numerous studies have demonstrated that the ED represents a promising site for smoking cessation interventions through self-service kiosks and culturally appropriate literature, brief interventions, and referrals to outpatient treatment.[911,912] With the high prevalence of smoking-related illnesses leading to ED visits, these episodes provide outstanding "teachable moments" to encourage cessation.

The use of oral antithrombotic agents for the prevention of stroke in patients with nonvalvular AF remains a cornerstone of stroke prevention.[390,913] The US National Hospital Ambulatory Medical Care Survey revealed an 88% increase in US ED visits for AF, and visits for AF are likely to increase.[914] Despite ample evidence supporting anticoagulation in selected patients with AF, ≈12% to 34% of patients with AF presenting in the ED are eligible for warfarin but are either undertreated or untreated.[915,916] The ED represents an important location to identify patients with new-onset AF, to initiate anticoagulation depending on comorbidities, and to plan for the initial management. Similar to patients with known hypertension and diabetes mellitus, for patients with known AF, their ED encounters provide opportunities to promote behaviors to improve compliance with medication and to ensure access to outpatient care.[917]

Alcohol consumption is a major contributor to many ED visits. In response to the epidemic of alcohol-related injuries and illnesses, numerous ED-based interventions have been investigated.[918,919] The American College of Emergency Physicians developed a brief alcohol use intervention brochure that does not require significant resources to produce or distribute but, by itself, was found to be only marginally effective in the absence of referral for cessation counseling.[920] More interactive ED interventions require more resources but are more likely to produce enduring benefits.[921] Integrating health promotion into the curriculum of emergency medicine training programs will help overcome existing nihilism of many practicing emergency physicians related to the benefit of alcohol interventions.[922]

Nutrition, physical activity, and drug abuse are potential lifestyle targets for behavioral interventions aimed at primary stroke prevention. Of these issues, only the feasibility and efficacy of substance abuse screening and intervention have been studied in the adult ED setting, although an obesity screening study in a pediatric ED was recently reported, with more than half of the children being overweight or obese.[923] Obesity contributes to medical conditions frequently seen in the ED and may complicate medical interventions. Many physicians are reluctant to discuss issues related to a patient's weight, and patients are not always receptive to the discussion.[924] No study has 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 effect of ED health promotion.[924]

Aside from education on individual risk factors and overall healthy lifestyle promotion, the ED can serve as an effective location to educate patients about stroke signs and symptoms and the need to seek immediate medical attention. A pilot study of stroke education using educational videos was performed using printed stroke education materials and one-on-one counseling.[925] Compared with a control group that did not receive any intervention, the intervention group demonstrated better stroke awareness immediately after the program, but by 3 months after intervention, although statistically still more knowledgeable than the control group, test scores had declined, highlighting the need for reinforcement. The intervention did not affect rates of smoking or positive changes in diet and physical activity. The ED can be part of a broader system to educate and reinforce these key messages.

Health care, in particular emergency care, is undergoing dramatic changes. The increasing demands for emergent and primary care will strain the capacity of many EDs to provide even basic emergency care to acutely ill patients. To effectively incorporate preventive services into routine ED practice, a careful review of feasibility and cost-effectiveness is required of each intervention, again assuming that sufficient resources are available.[896] Effective primary, secondary, and tertiary stroke prevention can occur in EDs, but significant healthcare organizational changes are required.[926] These changes must address current limitations of health promotion training for healthcare providers, program funding, resource availability, and opportunities for timely referral for longitudinal care.

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Primary Prevention in the ED: 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 to begin primary prevention requires further study into resource use, efficacy, effectiveness, and cost.

Primary Prevention in the ED: Recommendations

1. **ED-based smoking cessation programs and interventions are recommended (*Class I; Level of Evidence B*).**
2. **Identification of AF and evaluation for anticoagulation in the ED are 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 mellitus and lifestyle stroke risk factors (obesity, alcohol/substance abuse, sedentary lifestyle) in the ED setting is not established (*Class IIb; Level of Evidence C*).**

Strategies to Improve Preventive Vascular Health Services

Evidence-based guidelines are useful only if the recommendations translate into clinical practice. Primary vascular prevention approaches are underused in general practice.[1,927] For example, in the United States, ≈6% of adults have undiagnosed hypertension, and although the number of patients with BP treated to recommended targets has improved from 27% (in 1988 through 1994) to 50% (in 2007 through 2008), substantial gaps in quality remain.[224,928] Opportunities to improve preventive services exist across the range of vascular risk factors.[1] In the United States, vascular health varies substantially across the 50 states, but overall, only 3% of the adult population has ideal vascular health defined across 7 domains: hypertension, hyperlipidemia, smoking, BMI, diabetes mellitus, physical activity, and consumption of fruits and vegetables.[929]

Although preventive vascular services are a core activity of primary care physicians, specialists also have the opportunity and responsibility to identify stroke risk factors, to ensure that patients receive recommended treatments, and to encourage adherence to therapeutic interventions.[930] Strategies to help clinicians implement guideline recommendations are often aimed at changing physician behavior related to risk factor prevention.[931–933] A combination of techniques is usually necessary to improve stroke preventive care, including physician education, audit and feedback of quality data, and use of checklists.[931–939] Some strategies to improve stroke prevention care, although relatively costly, are more consistently effective, including electronic medical records; computer-based clinical reminder systems; and tailored, multifaceted programs.[940–944] Other strategies focus on changing the organization or context in which the care is delivered, including delegation of preventive services to nonphysician staff (eg, nurses or pharmacists), the use of group visits, or the implementation of clinics devoted to screening and preventive services.[943,945–948] Quality improvement efforts that include activities that focus on the system, the provider, and the patient, as well as the coordination of services across these domains, are often the most effective.[949] Studies examining the effectiveness of stroke education programs have generally identified a modest effect on patient knowledge, risk perception, or health beliefs.[944–947] However, studies have demonstrated the effectiveness of tailored patient self-management programs to improve vascular risk factor control.[950,951] Integrated healthcare systems that have focused on improving the quality of vascular prevention have demonstrated improvements in a variety of stroke risk factors at the facility or system level.[952,953] Achieving sustained improvements in the quality of vascular prevention care at the system level may require multidimensional interventions, including implementation of electronic medical record systems, ongoing performance measurement, change in the culture, and alignment of economic incentives.[953,954] Stroke prevention services are most cost-effective for populations at increased risk (eg, patients >50 years of age).[955]

Preventive Health Services: Summary and Gaps

Although stroke risk factor quality of care is improving, substantial gaps in primary stroke prevention care exist. The existing literature includes prospective trials and observational cohorts that demonstrate the effectiveness of a variety of approaches to delivering vascular prevention services. These studies have been designed to evaluate the effect of primary prevention services on the control of risk factors such as hypertension, not on incident stroke rates. Quality improvement strategies that are multifaceted and tailored appear to be the most effective. Future research should identify the implementation strategies that are associated with the greatest sustained improvements in preventing stroke.

Preventive Health Services: Recommendation

1. **It is reasonable to implement programs to systematically identify and treat risk factors in all patients at risk for stroke (*Class IIa; Level of Evidence A*).**

Summary/Conclusions

In this latest iteration of the guidelines, physicians and scientists should take pride in the advances that continue to be made in preventing stroke. Medications to control BP and lipids, anticoagulants for at-risk individuals with AF, revascularization, cigarette smoking cessation, diet, and exercise are among the interventions broadly applicable to the general public. With so many interventions, optimization of stroke prevention for individuals requires systems of care that identify risk factors as they emerge and that gain control of emerging risk factors safely, expeditiously, and cost-effectively. Access to care is necessary but not sufficient to guarantee optimal stroke prevention. Integration of inpatient and outpatient services and incentivizing efforts directed at preventing stroke must also be considered. New recommendations and important revisions are summarized in Table 5.

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Table 5. New and Revised Recommendations for 2014*

Section	2014 Recommendation	Description of Change from 2011
Assessing the risk of first stroke	The use of a risk assessment tool such as the AHA/ACC CV Risk Calculator (http://my.americanheart.org/cvriskcalculator) is reasonable because these tools can help identify individuals who could benefit from therapeutic interventions and who may not be treated on the basis of any single risk factor. These calculators are useful to alert clinicians and patients of possible risk, but basing treatment decisions on the results needs to be considered in the context of the overall risk profile of the patient (*Class IIa; Level of Evidence B*).	Reworded to add AHA/ACC CV Risk Calculator and link
Genetic factors	Treatment of Fabry disease with enzyme replacement therapy might be considered but has not been shown to reduce the risk of stroke, and its effectiveness is unknown (*Class IIb; Level of Evidence C*).	Slightly reworded; no change in class or level of evidence
	Screening for intracranial aneurysms in every carrier of autosomal-dominant polycystic kidney disease or Ehlers-Danlos type 4 mutations is not recommended (*Class III; Level of Evidence C*).	Previous statement was worded with less specificity, referring to "mendelian disorders associated with aneurysms"
	Pharmacogenetic dosing of vitamin K antagonists may be considered when therapy is initiated (*Class IIb; Level of Evidence C*).	Changed from Class III (is not recommended) to Class IIb (may be considered)
Physical inactivity	Healthy adults should perform at least moderate- to vigorous-intensity aerobic physical activity at least 40 min a day 3 to 4 d/wk (*Class I; Level of Evidence B*).	Changed wording to match new AHA lifestyle guideline
Dyslipidemia	In addition to therapeutic lifestyle changes, treatment with an HMG coenzyme-A reductase inhibitor (statin) medication is recommended for primary prevention of ischemic stroke in patients estimated to have a high 10-y risk for cardiovascular events as recommended in the 2013 "ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults" (*Class I; Level of Evidence A*).	Reworded to incorporate ACC/AHA guidelines (instead of NCEP); no change in class/LOE. Focusing on estimated cardiovascular risk as the determinant for initiating therapy is new.
	Niacin may be considered for patients with low high-density lipoprotein cholesterol or elevated lipoprotein(a), but its efficacy in preventing ischemic stroke in patients with these conditions is not established. Caution should be used with niacin because it increases the risk of myopathy (*Class IIb; Level of Evidence B*).	Changed from LOE C to LOE B; the risk of myopathy is highlighted
	Treatment with nonstatin lipid-lowering therapies such as fibric acid derivatives, bile acid sequestrants, niacin, and ezetimibe may be considered in patients who cannot tolerate statins, but their efficacy in preventing stroke is not established (*Class IIb; Level of Evidence C*).	Reworded from "other" to "nonstatin" (no change in class or LOE). Reference is no longer made to an low-density lipoprotein target for statin therapy because the decision to use moderate or intensive statin therapy depends on estimated risk of future cardiovascular events.
Diet and nutrition	A Mediterranean diet supplemented with nuts may be considered in lowering the risk of stroke (*Class IIb; Level of Evidence B*).	New recommendation
Hypertension	Regular blood pressure screening and appropriate treatment of patients with hypertension, including lifestyle modification and pharmacological therapy, are recommended (*Class I; Level of Evidence A*). Annual blood pressure screening for high blood pressure and health-promoting lifestyle modification are recommended for patients with prehypertension (systolic blood pressure of 120–139 mm Hg or diastolic blood pressure of 80–89 mm Hg) (*Class I; Level of Evidence A*).	New recommendations
	Successful reduction of blood pressure is more important in reducing stroke risk than the choice of a specific agent, and treatment should be individualized on the basis of other patient characteristics and medication tolerance (*Class I; Level of Evidence A*).	New recommendation
	Self-measured blood pressure monitoring is recommended to improve blood pressure control (*Class I; Level of Evidence A*)	New recommendation
Obesity and body fat distribution	Among overweight (body mass index=25 to 29 kg/m^2) and obese (body mass index >30 kg/m^2) individuals, weight reduction is recommended for lowering blood pressure (*Class I; Level of Evidence A*).	Overweight and obesity have now been defined on the basis of body mass index

(*Continued*)

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Table 5. Continued

Section	2014 Recommendation	Description of Change from 2011
Obesity and body fat distribution cont'd	Among overweight (body mass index=25 to 29 kg/m^2) and obese (body mass index >30 kg/m^2) individuals, weight reduction is recommended for reducing the risk of stroke (*Class I; Level of Evidence B*).	Overweight and obesity have now been defined on the basis of body mass index, and the recommendation has been upgraded from IIa to I
Diabetes mellitus	Control of blood pressure in accordance with an AHA/ACC/CDC advisory to a target of <140/90 mm Hg is recommended in patients with type 1 or type 2 diabetes mellitus (*Class I; Level of Evidence A*).	Reworded to reference AHA/ACC/CDC advisory
	The usefulness of aspirin for primary stroke prevention for patients with diabetes mellitus but low 10-y risk of cardiovascular disease is unclear (*Class IIb; Level of Evidence B*).	Deleted the phrase "however, administering aspirin may be reasonable"
Cigarette smoking	Counseling in combination with drug therapy using nicotine replacement, bupropion, or varenicline is recommended for active smokers to assist in quitting smoking (*Class I; Level of Evidence A*).	Reworded and LOE changed from B to A
	Community-wide or statewide bans on smoking in public spaces are reasonable for reducing the risk of stroke and myocardial infarction (*Class IIa; Level of Evidence B*).	New recommendation
Atrial fibrillation	For patients with valvular atrial fibrillation at high risk for stroke, defined as a CHA_2DS_2-VASc score of ≥2, and acceptably low risk for hemorrhagic complications, chronic oral anticoagulant therapy with warfarin at a target INR of 2.0 to 3.0 is recommended (*Class I; Level of Evidence A*).	New recommendation
	For patients with nonvalvular atrial fibrillation, a CHA_2DS_2-VASc score of ≥2, and acceptably low risk for hemorrhagic complications, oral anticoagulants are recommended (*Class I*). Options include warfarin (INR, 2.0 to 3.0) (*Level of Evidence A*), dabigatran (*Level of Evidence B*), apixaban (*Level of Evidence B*), and rivaroxaban (*Level of Evidence B*). The selection of antithrombotic agent should be individualized on the basis of patient risk factors (particularly risk for intracranial hemorrhage), cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including time INR is in therapeutic range for patients taking warfarin.	New recommendation
	For patients with nonvalvular atrial fibrillation and CHA_2DS_2-VASc score of 0, it is reasonable to omit antithrombotic therapy (*Class IIa; Level of Evidence B*).	New recommendation
	For patients with nonvalvular atrial fibrillation, a CHA_2DS_2-VASc score of 1, and acceptably low risk for hemorrhagic complication, no antithrombotic therapy, anticoagulant therapy, or aspirin therapy may be considered (*Class IIb; Level of Evidence C*). The selection of antithrombotic agent should be individualized on the basis of patient risk factors (particularly risk for intracranial hemorrhage), cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including time INR is in therapeutic range for patients taking warfarin.	New recommendation
	Closure of the left atrial appendage may be considered for high-risk patients with atrial fibrillation who are deemed unsuitable for anticoagulation if performed at a center with low rates of periprocedural complications and the patient can tolerate the risk of at least 45 d of postprocedural anticoagulation (*Class IIb; Level of Evidence B*).	New recommendation
Other cardiac conditions	Anticoagulation is indicated in patients with mitral stenosis and a prior embolic event, even in sinus rhythm (*Class I; Level of Evidence B*).	New recommendation
	Anticoagulation is indicated in patients with mitral stenosis and left atrial thrombus (*Class I; Level of Evidence B*).	New recommendation
	Warfarin (target INR, 2.0–3.0) and low-dose aspirin are indicated after aortic valve replacement with bileaflet mechanical or current-generation, single-tilting-disk prostheses in patients with no risk factors* (*Class I; Level of Evidence B*); warfarin (target INR, 2.5–3.5) and low-dose aspirin are indicated in patients with mechanical aortic valve replacement and risk factors* (*Class I; Level of Evidence B*); and warfarin (target INR, 2.5–3.5) and low-dose aspirin are indicated after mitral valve replacement with any mechanical valve (*Class I; Level of Evidence B*).	New recommendations
	Surgical excision is recommended for treatment of atrial myxomas (*Class I; Level of Evidence C*).	New recommendation

(*Continued*)

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Table 5. Continued

Section	2014 Recommendation	Description of Change from 2011
Other cardiac conditions cont'd	Surgical intervention is recommended for symptomatic fibroelastomas and for fibroelastomas that are >1 cm or appear mobile, even if asymptomatic (*Class I; Level of Evidence C*)	New recommendation
	Aspirin is reasonable after aortic or mitral valve replacement with a bioprosthesis (*Class IIa; Level of Evidence C*).	New recommendation
	It is reasonable to give warfarin to achieve an INR of 2.0–3.0 during the first 3 mo after aortic or mitral valve replacement with a bioprosthesis (*Class IIa; Level of Evidence C*).	New recommendation
	Anticoagulants or antiplatelet agents are reasonable for patients with heart failure who do not have atrial fibrillation or a previous thromboembolic event (*Class IIa; Level of Evidence A*).	New recommendation
	Vitamin K antagonist therapy is reasonable for patients with ST-segment–elevation myocardial infarction and asymptomatic left ventricular mural thrombi (*Class IIa; Level of Evidence C*).	The level of evidence has been downgraded from A to C, but the recommendation grade is the same
	Anticoagulation may be considered for asymptomatic patients with severe mitral stenosis and left atrial dimension ≥55 mm by echocardiography (*Class IIb; Level of Evidence B*).	New recommendation
	Anticoagulation may be considered for patients with severe mitral stenosis, an enlarged left atrium, and spontaneous contrast on echocardiography (*Class IIb; Level of Evidence C*).	New recommendation
	Anticoagulant therapy may be considered for patients with ST-segment–elevation myocardial infarction and anterior apical akinesis or dyskinesis (*Class IIb; Level of Evidence C*).	New recommendation
	Antithrombotic treatment and catheter-based closure are not recommended in patients with patent foramen ovale for primary prevention of stroke (*Class III; Level of Evidence C*).	New recommendation
Asymptomatic carotid stenosis	Patients with asymptomatic carotid stenosis should be prescribed daily aspirin and a statin. Patients should also be screened for other treatable risk factors for stroke, and appropriate medical therapies and lifestyle changes should be instituted (*Class I; Level of Evidence C*).	New recommendation. The use of aspirin and statin therapy was implied but not explicitly stated except in the perioperative and postoperative context in the prior guidelines.
	It is reasonable to consider performing carotid endarterectomy in asymptomatic patients who have >70% stenosis of the internal carotid artery if the risk of perioperative stroke, myocardial infarction, and death is low (<3%). However, its effectiveness compared with contemporary best medical management alone is not well established (*Class IIa; Level of Evidence A*).	New recommendation
	It is reasonable to repeat duplex ultrasonography annually by a qualified technologist in a certified laboratory to assess the progression or regression of disease and response to therapeutic interventions in patients with atherosclerotic stenosis >50% (*Class IIa; Level of Evidence C*).	New recommendation
	Prophylactic carotid angioplasty and stenting might be considered in highly selected patients with asymptomatic carotid stenosis (minimum, 60% by angiography, 70% by validated Doppler ultrasound), but its effectiveness compared with medical therapy alone in this situation is not well established (*Class IIb; Level of Evidence B*).	New recommendation
	In asymptomatic patients at high risk of complications for carotid revascularization by either carotid endarterectomy or carotid angioplasty and stenting, the effectiveness of revascularization versus medical therapy alone is not well established (*Class IIb; Level of Evidence B).*	New recommendation
Sickle cell disease	Transcranial Doppler screening for children with sickle cell disease is indicated starting at 2 y of age and continuing annually to 16 y of age (*Class I; Level of Evidence B*).	Slightly reworded to include up to 16 y (no change in class or LOE)
	In children at high risk for stroke who are unable or unwilling to be treated with periodic red cell transfusion, it might be reasonable to consider hydroxyurea or bone marrow transplantation (*Class IIb; Level of Evidence B*).	Changed from LOE C to LOE B
Migraine	Smoking cessation should be strongly recommended in women with migraine headaches with aura (*Class I; Level of Evidence B*).	New recommendation
	Alternatives to oral contraceptives, especially those containing estrogen, might be considered in women with active migraine headaches with aura (*Class IIb; Level of Evidence B*).	New recommendation

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Table 5. Continued

Section	2014 Recommendation	Description of Change from 2011
Migraine cont'd	Closure of patent foramen ovale is not indicated for preventing stroke in patients with migraine (*Class III; Level of Evidence B*).	New recommendation
Drug abuse	Referral to an appropriate therapeutic program is reasonable for patients who abuse drugs that have been associated with stroke, including cocaine, khat, and amphetamines (*Class IIa; Level of Evidence C*).	Wording slightly revised to specifically list drugs associated with stroke
Sleep-disordered breathing	Because of its association with stroke risk, screening for sleep apnea through a detailed history, including structured questionnaires such as the Epworth Sleepiness Scale and Berlin Questionnaire, physical examination, and, if indicated, polysomnography may be considered (*Class IIb; Level of Evidence C*).	Wording slightly revised to include polysomnography and use of specific questionnaires. Recommendation class and LOE have been downgraded.
Elevated lipoprotein(a)	The clinical benefit of using lipoprotein(a) in stroke risk prediction is not well established (*Class IIb; Level of Evidence B*).	New recommendation
Inflammation and infection	Treatment of patients with high-sensitivity C-reactive protein >2.0 mg/dL with a statin to decrease stroke risk might be considered (*Class IIb; Level of Evidence B*).	The revised recommendation now defines elevated high-sensitivity C-reactive protein as >2.0 mg/dL in the context of considering statin initiation
Antiplatelet agents and aspirin	The use of aspirin for cardiovascular (including but not specific to stroke) prophylaxis is reasonable for people whose risk is sufficiently high (10-y risk >10%) for the benefits to outweigh the risks associated with treatment. A cardiovascular risk calculator to assist in estimating 10-y risk can be found online at http://my.americanheart.org/cvriskcalculator (*Class IIa; Level of Evidence A*).	Reworded to include cardiovascular risk calculator and link; changed from Class I to IIa
	Aspirin might be considered for the prevention of a first stroke in people with chronic kidney disease (ie, estimated glomerular filtration rate <45 mL·min^{-1}·1.73 m^{-2}) (*Class IIb; Level of Evidence C*). This recommendation does not apply to severe kidney disease (stage 4 or 5; estimated glomerular filtration rate <30 mL·min^{-1}·1.73 m^{-2}).	New recommendation
	Cilostazol may be reasonable for the prevention of a first stroke in people with peripheral arterial disease (*Class IIb; Level of Evidence B*).	New recommendation
	As a result of a lack of relevant clinical trials, antiplatelet regimens other than aspirin and cilostazol are not recommended for the prevention of a first stroke (*Class III; Level of Evidence C*).	New recommendation

ACC indicates American College of Cardiology; AHA, American Heart Association; CDC, Centers for Disease Control and Prevention; CV, cardiovascular; INR, international normalized ratio; LOE, level of evidence; and NCEP, National Cholesterol Education Program.

*This table does not include recommendations that have been removed.

As health professionals, we must ensure that progress in preventing stroke does not lead to complacency. We must acknowledge that several recommendations remain vague because of suboptimal clinical trial evidence or, even more concerning, may be out of date and therefore irrelevant. Diet and exercise are notoriously challenging to study with the same rigor as drugs or devices. It is easier to convince a patient to take a pill than to radically change his or her lifestyle. Nonetheless, we must expect the same standards of evidence for lifestyle interventions. Devices such as stents for carotid stenosis and occluders for PFO should be required to demonstrate favorable effects on patient-centered outcomes such as preventing stroke and not merely demonstrate favorable effects on surrogates such as expanding lumens or closing holes. The control groups of old that showed the benefits of CEA for asymptomatic stenosis would be seen as grossly undertreated medically by contemporary standards. It would be important to see if revascularization remains relevant in a modern context.

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*Modest.

†Significant.

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David M Greer	Yale University	None	None	None	None	None	None	None
Millie Hepburn-Smith	NYU Langone Medical Center	None	None	None	None	None	American Association of NeuroScience Nurses (member of the Board of Directors)*; National Aphasia Association (Board of Directors)*	None
Steven J. Kittner	University of Maryland	1U01NS069208 The Stroke Genetics Network (SiGN) Study is an NINDS-funded international consortium to study the genetics of ischemic stroke and ischemic stroke subtypes†; R01NS069763 Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) is an NINDS-funded study of the risk factors for intracerebral hemorrhage occurrence and outcome*	None	None	None	None	None	None
Tatjana Rundek	University of Miami	None	None	None	None	None	None	None

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*Modest.

†Significant.

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