Primary Prevention of Ischemic Stroke: A Guideline From the American Heart Association/American Stroke Association Stroke Council: Cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: The American Academy of Neurology affirms the value of this guideline.


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Primary Prevention of Ischemic Stroke

A Guideline From the American Heart Association/American Stroke Association Stroke Council: Cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group

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

Larry B. Goldstein, MD, FAAN, FAHA, Chair; Robert Adams, MS, MD, FAHA; Mark J. Alberts, MD, FAHA; Lawrence J. Appel, MD, MPH, FAHA; Lawrence M. Brass, MD, FAHA†; Cheryl D. Bushnell, MD, MHS, FAHA; Antonio Culebras, MD, FAAN, FAHA; Thomas J. DeGraba, MD, FAHA; Philip B. Gorelick, MD, MPH, FAAN, FAHA; John R. Guyton, MD, FAHA; Robert G. Hart, MD, FAHA; George Howard, DrPH, FAHA; Margaret Kelly-Hayes, RN, EdD, MS, FAHA; J.V. (Ian) Nixon, MD, FAHA; Ralph L. Sacco, MD, MS, FAAN, FAHA

Background and Purpose—This guideline provides an overview of the evidence on various established and potential stroke risk factors and provides recommendations for the reduction of stroke risk.

Methods—Writing group members were nominated by the committee chair on the basis of each writer’s previous work in relevant topic areas and were approved by the American Heart Association Stroke Council’s Scientific Statement Oversight Committee. The writers used systematic literature reviews (covering the time period since the last review published in 2001 up to January 2005), reference to previously published guidelines, personal files, and expert opinion to summarize existing evidence, indicate gaps in current knowledge, and when appropriate, formulate recommendations based on standard American Heart Association criteria. All members of the writing group had numerous opportunities to comment in writing on the recommendations and approved the final version of this document. The guideline underwent extensive peer review before consideration and approval by the AHA Science Advisory and Coordinating Committee.

Results—Schemes for assessing a person’s risk of a first stroke were evaluated. Risk factors or risk markers for a first stroke were classified according to their potential for modification (nonmodifiable, modifiable, or potentially modifiable) and strength of evidence (well documented or less well documented). Nonmodifiable risk factors include age, sex, low birth weight, race/ethnicity, and genetic factors. Well-documented and modifiable risk factors include hypertension, exposure to cigarette smoke, diabetes, atrial fibrillation and certain other cardiac conditions, dyslipidemia, carotid artery stenosis, sickle cell disease, postmenopausal hormone therapy, poor diet, physical inactivity, and obesity and body fat distribution. Less well-documented or potentially modifiable risk factors include migraine headaches, family history of stroke, stress, sleep apnea, hypertension during pregnancy, menses, and other hormonal factors.
Stoke remains a major healthcare problem. Its human and economic toll is staggering. It is estimated that there are >700,000 incident strokes in the United States each year, resulting in >160,000 deaths annually, with 4.8 million stroke survivors alive today. Although there was a 60% decline in stroke mortality over the 29-year period between 1968 and 1996, the rate of decline began to slow in the 1990s and has plateaued in several regions of the country. Despite an overall 3.4% fall in per capita stroke-related mortality between 1991 and 2001, the actual number of stroke deaths rose by 7.7%. Stroke ranks as the country’s third leading cause of death. Stroke incidence may be increasing. From 1988 to 1997, the age-adjusted stroke hospitalization rate grew 18.6% (from 560 to 664 per 100,000), while total stroke hospitalizations increased 38.6% (from 592,811 to 821,760 annually). In 2004, the cost of stroke was estimated at $53.6 billion (direct and indirect costs), with a mean lifetime cost estimated at $140,048.

Stroke is also a leading cause of functional impairments, with 20% of survivors requiring institutional care after 3 months and 15% to 30% being permanently disabled. Stroke is a life-changing event that affects not only the person who may be disabled, but the entire family and other caregivers as well. Utility analyses show that a major stroke is viewed by more than half of those at risk as being worse than death. Despite the advent of treatment of selected patients with acute ischemic stroke with intravenous tissue-type plasminogen activator and the promise of other acute therapies, effective prevention remains the best treatment for reducing the burden of stroke. Primary prevention is particularly important because >70% of strokes are first events. The age-specific incidence of major stroke in Oxfordshire, UK, has fallen by 40% over the past 20 years in association with an increased use of preventive treatments and general reductions in risk factors. As discussed in the sections that follow, high-risk or stroke-prone individuals can now be identified and targeted for specific interventions.

This guideline provides an overview of the evidence on various established and potential stroke risk factors and represents a complete revision of the last statement on this topic (published in 2001). This guideline largely focuses on an individual patient-oriented approach to stroke prevention. This is in contrast to a population-based approach in which “...the entire distribution of risk factors in the population is shifted to lower levels through population-wide interventions,” which is reflected in the AHA Guide for Improving Cardiovascular Health at the Community Level.

The writing group consisted of experts with special interests in primary prevention representing disciplines including several medical specialties, epidemiology, and the neurosciences. Writing group members were nominated by the committee chair on the basis of each individual’s previous work in relevant topic areas and were approved by the American Heart Association Stroke Council’s Scientific Statement Oversight Committee. The writers used systematic literature reviews (covering the time period since the last review published in 2001 up to January 2005), reference to previously published guidelines, personal files, and expert opinion to summarize existing evidence, indicate gaps in current knowledge, and when appropriate, formulate recommendations based on standard American Heart Association criteria (Table 1, Figure). Because of the diverse nature of the topics, it was not possible to provide a systematic, uniform summary of the magnitude of the effect associated with each of the recommendations. Patient preferences need to be considered, as with all recommendations. All members of the writing group had numerous opportunities to comment in writing on the recommendations and approved the final version of this document. The guideline underwent extensive peer review before consideration and approval by the AHA Science Advisory and Coordinating Committee.

As given in Tables 2, 3, and 4, risk factors or risk markers for a first stroke were classified according to their potential for modification (nonmodifiable, modifiable, or potentially modifiable) and strength of evidence (well documented, less well documented). Although this classification system is somewhat subjective, well-documented and modifiable risk factors (Table 3) were considered as those with clear, supportive epidemiological evidence in addition to evidence of risk reduction with modification as documented by randomized trials. Less well-documented or potentially modifiable risk factors (Table 4) were those with either less clear epidemi-
### Applying Classification of Recommendations and Level of Evidence

#### “Size of Treatment Effect”

<table>
<thead>
<tr>
<th>Level</th>
<th>Multiple (3-5) population risk strata evaluated*</th>
<th>Limited (2-3) population risk strata evaluated*</th>
<th>Very limited (1-2) population risk strata evaluated*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I</strong></td>
<td>Benefit &gt;&gt;&gt; Risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure/Treatment SHOULD be performed/administered</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Class IIa</strong></td>
<td>Benefit &gt;&gt; Risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional studies with focused objectives needed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IT IS REASONABLE to perform procedure/administer treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Class IIb</strong></td>
<td>Benefit &gt;= Risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional studies with broad objectives needed; Additional registry data would be helpful</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure/Treatment MAY BE CONSIDERED</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Class III</strong></td>
<td>Risk &lt; Benefit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No additional studies needed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure/Treatment should NOT be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Estimate of Certainty (Precision) of Treatment Effect

- **Level A**
  - Recommendation that procedure or treatment is useful/effective
  - Sufficient evidence from multiple randomized trials or meta-analyses

- **Level B**
  - Recommendation that procedure or treatment is useful/effective
  - Limited evidence from single randomized trial or non-randomized studies

- **Level C**
  - Recommendation that procedure or treatment is useful/effective
  - Only expert opinion, case studies, or standard-of-care

### Suggested phrases for writing recommendations

- **should** is indicated
- **is recommended** is useful/effective/beneficial
- **may/might be considered** useful/effective/beneficial
- **is probably recommended** or indicated
- **may/might be reasonable** usefulness/effectiveness is unknown/not clear/uncertain or not well established
- **is not recommended** is not indicated
- **should not** is not useful/effective/beneficial

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

†In 2003, the ACC/AHA Task Force on Practice Guidelines developed a list of suggested phrases to use when writing recommendations. All recommendations in this guideline have been written in full sentences that express a complete thought, such that a recommendation, even if separated and presented apart from the rest of the document (including headings above sets of recommendations), would still convey the full intent of the recommendation. It is hoped that this will increase readers’ comprehension of the guidelines and will allow queries at the individual recommendation level.
logical evidence or without evidence from randomized trials demonstrating a reduction of stroke risk with modification. The tables give the estimated prevalence, population-attributable risk (ie, the proportion of ischemic stroke in the population that can be attributed to a particular risk factor, given by the formula
\[
100 \times \frac{\text{Prevalence (Relative Risk} \div 1)}{\text{Prevalence (Relative Risk} \div 1 + 1)}
\]
relative risk, and risk reduction with treatment for each factor when known. Gaps in current knowledge are indicated by question marks in the tables. It should also be noted that precise estimates of attributable risk for factors such as hormone replacement therapy are not available because of variation in the estimates of risk and changes in prevalence. Other tables summarize guideline or consensus statement management recommendations as available. Other recommendations are indicated in the text and tables.

Assessing the Risk of a First Stroke
It is helpful for healthcare providers and the public to be able to estimate a person’s risk for a first stroke. As detailed in the sections that follow, numerous factors can contribute to a person’s stroke risk, and many individuals have >1 risk factor. Some of these risk factors are relatively less well documented, and specific or proven treatments may be lacking. Although most risk factors have an independent effect, there may be important interactions between individual factors that need to be considered in predicting overall risk or choosing an appropriate risk modification program. Risk-assessment tools have been used in community stroke screening programs and utilized in some guideline statements to select certain treatments for primary stroke prevention.\textsuperscript{13,14} Some of the goals of such risk-assessment tools are (1) to identify persons at elevated risk who might be unaware of their risk; (2) to assess risk in the presence of >1 condition; (3) to measure an individual’s risk that can be tracked and lowered by appropriate modifications; (4) to estimate a quantitative risk for selecting treatments or stratification in clinical trials; and (5) 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 risk factors stratified by age, gender, race-ethnicity, and geography are incompletely captured by any available global risk-assessment tool. In addition, these tools tend to be focused and generally do not include the full range of possible contributing factors. Some risk-assessment tools are gender 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.\textsuperscript{15} Independent stroke predictors include age, systolic blood pressure, hypertension, diabetes mellitus, current smoking, established cardiovascular disease (any one of myocardial infarction [MI], angina or coronary insufficiency, congestive heart failure, or intermittent claudication), atrial fibrillation, and left ventricular (LV) hypertrophy on ECG. Point values can be calculated that correspond to a gender-specific 10-year cumulative stroke risk. The FSP has been updated to account for the use of antihypertensive therapy and the risk of stroke and stroke or death among individuals with new-onset atrial fibrillation (Table 5).\textsuperscript{16,17} Despite its widespread use, the validity of the FSP among individuals of a different age range or belonging to racial-ethnic groups other than those in the Framingham cohort has not been adequately studied. The FSP has been applied to ethnic minorities in the United Kingdom and found to vary across groups, but the suitability of the scale to predict outcomes has not been well tested.\textsuperscript{18}

**TABLE 2. Nonmodifiable Risk Factors**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Prevalence (per 100 000)</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y\textsuperscript{23}</strong></td>
<td></td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>Black</td>
</tr>
<tr>
<td>45–54</td>
<td>1.4</td>
<td>2.1</td>
</tr>
<tr>
<td>55–64</td>
<td>2.6</td>
<td>4.9</td>
</tr>
<tr>
<td>65–74</td>
<td>6.7</td>
<td>10.4</td>
</tr>
<tr>
<td>75–84</td>
<td>11.8</td>
<td>23.3</td>
</tr>
<tr>
<td>≥85</td>
<td>16.8</td>
<td>24.7</td>
</tr>
<tr>
<td><strong>Race\textsuperscript{24}</strong></td>
<td></td>
<td>...</td>
</tr>
<tr>
<td>Blacks</td>
<td>233</td>
<td></td>
</tr>
<tr>
<td>Hispanics</td>
<td>196</td>
<td></td>
</tr>
<tr>
<td>Whites</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td><strong>Sex\textsuperscript{3}</strong></td>
<td></td>
<td>...</td>
</tr>
<tr>
<td>Men</td>
<td>174</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>122</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>145</td>
<td></td>
</tr>
<tr>
<td><strong>Low birth weight\textsuperscript{29,30}</strong></td>
<td>...</td>
<td>≈2 for birth weights &lt;2500 vs ≥4000 g</td>
</tr>
<tr>
<td><strong>Family history of stroke/TIA\textsuperscript{41}</strong></td>
<td>...</td>
<td>RR paternal history 2.4 (95% CI 0.96–6.03); RR maternal history 1.4 (95% CI 0.60–3.25)</td>
</tr>
</tbody>
</table>

\textsuperscript{e876} Circulation June 20, 2006

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<table>
<thead>
<tr>
<th>Factor</th>
<th>Prevalence, %</th>
<th>Population-Attributable Risk, %*</th>
<th>RR</th>
<th>Risk Reduction With Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>8.4</td>
<td>5.8†</td>
<td>1.73 (1.68–1.78)14</td>
<td>16</td>
</tr>
<tr>
<td>Women</td>
<td>5.6</td>
<td>3.9†</td>
<td>1.55 (1.17–2.07)14</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>2.6</td>
<td>1.4†</td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>Women</td>
<td>2.1</td>
<td>1.1†</td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>4.9</td>
<td>3.0†</td>
<td></td>
<td>16</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 50 y</td>
<td>20</td>
<td>40</td>
<td>4.0</td>
<td>38%; see Table 6 and text.</td>
</tr>
<tr>
<td>Age 60 y</td>
<td>30</td>
<td>35</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Age 70 y</td>
<td>40</td>
<td>30</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Age 80 y</td>
<td>55</td>
<td>20</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Age 90 y</td>
<td>60</td>
<td>0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>25</td>
<td>12–18</td>
<td>1.8</td>
<td>50% within 1 y; baseline after 5 y552</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7.3†</td>
<td>5–27</td>
<td>1.8–6</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic carotid stenosis</td>
<td>2–8228,236,255,553–556</td>
<td>2–7‡ 2.0557</td>
<td></td>
<td>2.057</td>
</tr>
<tr>
<td><strong>Atrial fibrillation (nonvalvular)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 50–59 y</td>
<td>0.5</td>
<td>1.5</td>
<td>4.0</td>
<td>Adjusted-dose warfarin vs control: 62% (CI 48% to 72%); 6 trials, 2900 patients.</td>
</tr>
<tr>
<td>Age 60–69 y</td>
<td>1.8</td>
<td>2.8</td>
<td>2.6</td>
<td>Aspirin vs placebo: 22% (CI 2% to 38%); 6 trials, 3119 patients.</td>
</tr>
<tr>
<td>Age 70–79 y</td>
<td>4.8</td>
<td>9.9</td>
<td>3.3</td>
<td>Adjusted-dose warfarin vs aspirin: 45% (CI 29% to 57%); 6 trials, 4025 patients.</td>
</tr>
<tr>
<td>Age 80–89 y</td>
<td>8.8</td>
<td>23.5</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>0.25 (of African Americans)558</td>
<td>... 200–400265§</td>
<td></td>
<td>27% to 32% with statins in high-risk patients with coronary heart disease, hypertension, or diabetes; 25% reduction with high-dose vs low-dose statins (see text).</td>
</tr>
<tr>
<td><strong>Dyslipidemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High total cholesterol</td>
<td>25227</td>
<td>15</td>
<td>2.0 for men and for women age &lt;55 y 27% to 32% with statins in high-risk patients with coronary heart disease, hypertension, or diabetes; 25% reduction with high-dose vs low-dose statins (see text).</td>
<td></td>
</tr>
<tr>
<td>Low HDL cholesterol</td>
<td>25227</td>
<td>10</td>
<td>1.5–2.5 for men Note: Observational studies show an 8% reduction in stroke mortality from a 3-mm Hg reduction in systolic blood pressure.559 The extent of systolic blood pressure reduction from reduced Na and increased K intake can exceed 3 mm Hg according to baseline intake levels and other factors.</td>
<td></td>
</tr>
<tr>
<td><strong>Dietary factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na intake &gt;2300 mg</td>
<td>75–90</td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>K intake &lt;4700 mg</td>
<td>90–99289</td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>17.9266</td>
<td>12–20‡</td>
<td>1.75–2.3740,325</td>
<td>Unknown</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>25</td>
<td>30</td>
<td>2.7‡</td>
<td>Unknown</td>
</tr>
<tr>
<td>Postmenopausal hormone therapy</td>
<td>2061 (women age 50–74 y)262</td>
<td>7 1.4277</td>
<td>None (and may increase risk).</td>
<td></td>
</tr>
</tbody>
</table>

Data derived from Hart et al143,161 and van Walraven et al.159 Stroke includes both ischemic and hemorrhagic stroke. Cardiovascular disease includes coronary heart disease, heart failure, and peripheral arterial disease.

*Population-attributable risk is the proportion of ischemic stroke in the population that can be attributed to a particular risk factor (see text for formula).
†Calculated on the basis of point estimates of referenced data provided in the table. For peripheral arterial disease, calculation was based on average RR for men and women.
‡Calculated based on referenced data provided in the table or text.
§Relative to stroke risk in children without sickle cell disease.
||For high-risk patients treated with transfusion.
<table>
<thead>
<tr>
<th>Factor</th>
<th>Prevalence, %</th>
<th>Population-Attributable Risk, %</th>
<th>RR or OR</th>
<th>Risk Reduction With Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic syndrome</td>
<td>23.7&lt;sup&gt;446&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol abuse&lt;sup&gt;368,563&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥5 drinks/d</td>
<td>5–7</td>
<td>1–3</td>
<td>1.6†</td>
<td>Unknown</td>
</tr>
<tr>
<td>More than moderate (see text)</td>
<td>60</td>
<td>32</td>
<td>1.8†</td>
<td>Unknown</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 40–59 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>29</td>
<td>26</td>
<td>1.3–2.3&lt;sup&gt;445,446,560&lt;/sup&gt;</td>
<td>Unknown</td>
</tr>
<tr>
<td>Women</td>
<td>21</td>
<td>37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥60 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>43</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>47&lt;sup&gt;456&lt;/sup&gt;</td>
<td>37&lt;sup&gt;445,456&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug abuse</td>
<td>3–14&lt;sup&gt;419&lt;/sup&gt;</td>
<td>Unknown</td>
<td>6.5&lt;sup&gt;368&lt;/sup&gt;</td>
<td>Unknown</td>
</tr>
<tr>
<td>Hypercoagulability</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticardiolipin antibody</td>
<td></td>
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</tr>
<tr>
<td>Men</td>
<td>19.7&lt;sup&gt;492&lt;/sup&gt;</td>
<td>6&lt;sup&gt;492&lt;/sup&gt;</td>
<td>1.3 (0.7–2.3)*</td>
<td>0.99 (0.69–1.41)&lt;sup&gt;479&lt;/sup&gt;‡</td>
</tr>
<tr>
<td>Women overall</td>
<td>17.6&lt;sup&gt;492&lt;/sup&gt;</td>
<td>14&lt;sup&gt;492&lt;/sup&gt;</td>
<td>1.9 (1.1–3.5)*</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Women age 15–44 y</td>
<td>26.9&lt;sup&gt;484&lt;/sup&gt;</td>
<td>11&lt;sup&gt;484&lt;/sup&gt;</td>
<td>1.9 (1.24–2.83)†</td>
<td></td>
</tr>
<tr>
<td>Lupus anticoagulant (women age 15–44 y)</td>
<td>12.8&lt;sup&gt;484&lt;/sup&gt;</td>
<td>9&lt;sup&gt;484&lt;/sup&gt;</td>
<td>1.80 (1.06–3.06)&lt;sup&gt;494&lt;/sup&gt;</td>
<td>0.78 (0.50–1.21)&lt;sup&gt;479&lt;/sup&gt;‡</td>
</tr>
<tr>
<td>Factor V Leiden&lt;sup&gt;519&lt;/sup&gt;</td>
<td>7.7</td>
<td>0</td>
<td>0.92 (0.56–1.53)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Prothrombin 20210 mutation&lt;sup&gt;57&lt;/sup&gt;</td>
<td>3.7</td>
<td>3</td>
<td>1.9 (0.5–6.2)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Protein C deficiency&lt;sup&gt;57&lt;/sup&gt;</td>
<td>2.0</td>
<td>0</td>
<td>0.7 (0.2–3.1)</td>
<td>Unknown</td>
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<tr>
<td>Protein S deficiency&lt;sup&gt;57&lt;/sup&gt;</td>
<td>1.0</td>
<td>0</td>
<td>0.9 (0.1–6.7)</td>
<td>Unknown</td>
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<td>Antithrombin III deficiency&lt;sup&gt;57&lt;/sup&gt;</td>
<td>4.1</td>
<td>1</td>
<td>1.3 (0.5–3.3)</td>
<td>Unknown</td>
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<tr>
<td>Oral contraceptive use (women age 25–44 y)</td>
<td>1&lt;sup&gt;364&lt;/sup&gt;</td>
<td>19</td>
<td>2.8&lt;sup&gt;392&lt;/sup&gt;</td>
<td>None (and may increase risk)</td>
</tr>
<tr>
<td>Inflammatory processes</td>
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<td></td>
<td></td>
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<tr>
<td>Periodontal disease</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Age 25–74 y</td>
<td>16.8&lt;sup&gt;511&lt;/sup&gt;</td>
<td>16</td>
<td>2.11 (1.30–3.42)&lt;sup&gt;511&lt;/sup&gt;</td>
<td>Effects of medical therapy on periodontal disease remain to be studied</td>
</tr>
<tr>
<td>Age 60–64 y</td>
<td>15&lt;sup&gt;515&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥65 y</td>
<td>45&lt;sup&gt;516&lt;/sup&gt;</td>
<td></td>
<td></td>
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<tr>
<td>C pneumoniae</td>
<td></td>
<td></td>
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<tr>
<td>Age ≥65 y</td>
<td>75–100 IgA&lt;sup&gt;597,568&lt;/sup&gt;</td>
<td>72–78</td>
<td>IgA ≥1:16</td>
<td>4.51 (1.44–14.06)&lt;sup&gt;519&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>85–88</td>
<td>IgG ≥1:512 and/or IgA ≥1:64</td>
</tr>
<tr>
<td>Age &lt;5 yr</td>
<td>0–5</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age 5–20 y</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cytomegalovirus</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Adults</td>
<td>69&lt;sup&gt;134&lt;/sup&gt;</td>
<td>82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>62.5</td>
<td></td>
<td>OR 1.04; 95% CI 0.68–1.58&lt;sup&gt;534&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>72.8</td>
<td></td>
<td>OR 7.6; 95% CI 3.21–17.96&lt;sup&gt;533&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>H pylori CagA seropositivity</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Adults with vascular disease: IgG Ab &gt;40 AU</td>
<td>39</td>
<td>Atherothrombotic stroke: OR 1.97; CI 1.33–2.91&lt;sup&gt;536&lt;/sup&gt;</td>
<td>83</td>
<td>Carotid plaque irregularities: OR 8.42; CI 1.58–44.84&lt;sup&gt;537&lt;/sup&gt;</td>
</tr>
<tr>
<td>65.7&lt;sup&gt;234&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Acute infection</td>
<td></td>
<td></td>
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<tr>
<td>Systemic respiratory infection</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Days 1–3</td>
<td>Stroke IR 3.19; CI 2.81–3.62</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days 29–91</td>
<td>Stroke IR 1.27; CI 1.15–1.41</td>
<td></td>
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</tbody>
</table>
Alternative prediction models have been developed using other cohorts and utilizing different sets of stroke risk factors. Retaining most of the Framingham covariates, one alternative stroke risk scoring system omits cigarette smoking and antihypertensive medication but adds “time to walk 15 feet” and serum creatinine.19 Another score is derived from a mixed cohort of stroke and stroke-free patients and includes prior history of stroke, marital status, blood pressure as a categorical variable, high-density lipoprotein (HDL) cholesterol, impaired expiratory flow, physical disability, and a depression score.20 Several studies have generated risk-assessment tools for use in subjects with atrial fibrillation (see below).

Summary and Gaps
It is clear that an ideal stroke risk-assessment tool that is generally applicable, simple, and widely accepted does not exist. Each available tool has its own limitations. The impact of newer risk factors for stroke, not collected in older studies, needs to be considered.21 Risk-assessment tools should be used with care, as they do not include all the factors that contribute to future disease risk.22 The utility of the FSP (Table 5) or other stroke risk-assessment scales as a way of improving the effectiveness of primary stroke prevention programs is not well studied. Research is needed to validate risk-assessment tools across age, gender, and racial-ethnic groups; evaluate whether any of the more recently identified risk factors add to the predictive accuracy of existing scales; and determine whether the use of these scales improves primary stroke prevention programs.

Recommendation
Each patient should have an assessment of his or her stroke risk (Class I, Level of Evidence A). The use of a risk-assessment tool such as the FSP should be considered as these tools can help identify individuals who could benefit from therapeutic interventions and who may not be treated on the basis of any 1 risk factor (Class IIa, Level of Evidence B).

Nonmodifiable Risk Factors
Although these factors are not modifiable, they identify those who are at highest risk of stroke and who may benefit from rigorous prevention or treatment of modifiable risk factors (Table 2).

Age
The cumulative effects of aging on the cardiovascular system and the progressive nature of stroke risk factors over a prolonged period of time substantially increase stroke risk.
The risk of stroke doubles for each successive decade after age 55 years.3,23

**Sex**

Stroke is more prevalent in men than in women.3 Men also generally have higher age-specific stroke incidence rates than do women (based on age-specific rates calculated from strata defined by race/ethnicity).24 Exceptions are in 35- to 44-year-olds and in those >85 years of age—groups in which women have slightly greater age-specific stroke incidence than do men.24 Factors such as oral contraceptive (OC) use and pregnancy contribute to the increased risk of stroke in young women.25–27 and the earlier cardiac-related deaths of men with cardiovascular disease may contribute to the relatively greater risk of stroke in older women. Women accounted for 61.5% of US stroke deaths in 2002 (100 500 deaths among women were attributed to stroke versus 62 662 among men).1 Overall, 1 in 6 women die of stroke as compared with 1 in 25 who die of breast cancer.28 In 2002, age-adjusted stroke mortality rates were 53.4/100 000 among white women and 71.8/100 000 among black women, versus rates of 54.2 and 81.7/100 000 among white and black men, respectively.1

**Low Birth Weight**

Stroke mortality rates among adults in England and Wales are higher among persons who had lower birth weights.29 A similar study compared a group of South Carolina Medicaid beneficiaries <50 years of age who had stroke to population controls.30 The odds of stroke were more than double for those with birth weights <2500 g as compared with those weighing ≥4000 g (with a significant linear trend for intermediate birth weights). Regional differences in birth weight may partially underlie geographic differences in stroke-related mortality. However, the reason for this relationship remains uncertain, and statistical association does not prove causality.

**Race-Ethnicity**

Racial and ethnic effects on disease risk can be difficult to consider separately. African Americans24,31 and some Hispanic Americans32,33 have higher stroke incidence and mortality rates as compared with European Americans. In the Atherosclerosis Risk In Communities (ARIC) Study, blacks had an incidence of stroke 38% higher than that of whites.34 Possible reasons for the higher incidence and mortality rate of strokes in blacks include a higher prevalence of hypertension, obesity, and diabetes within the black population.35,36 However, a higher incidence of these risk factors does not explain all of the excess risk.35 Epidemiological studies have shown an increase in stroke incidence among self-identified Hispanic racial-ethnic populations.24,37,38 Incidence rates are also relatively higher among some Asian groups.39

**Genetic Factors**

Both paternal and maternal history of stroke have been associated with an increased stroke risk.40,41 This increased
risk could be mediated through a variety of mechanisms, including (1) genetic heritability of stroke risk factors, (2) the inheritance of susceptibility to the effects of such risk factors, (3) familial sharing of cultural/environmental and lifestyle factors, and (4) the interaction between genetic and environmental factors.\(^4^2\) Twin studies provide strong data suggesting familial inheritance of stroke risk. Concordance rates for stroke are markedly higher in monozygotic than in dizygotic twins,\(^4^3\) with a nearly 5-fold increase in stroke prevalence among monozygotic as compared with dizygotic twins.\(^4^4\)

Genetic influences on stroke risk can be considered on the basis of individual risk factors, the genetics of common stroke types, and uncommon or rare familial stroke types. Many of the established and emerging risk factors that are described in the sections that follow, such as hypertension, diabetes, and hyperlipidemia, have both genetic and environmental/behavioral components.\(^4^3,^4^5,^4^6\) In some cases, elevations of blood homocysteine are due to 1 or more mutations in the methylene-tetrahydrofolate reductase gene.\(^4^7–^4^9\) Many coagulopathies are inherited as autosomal dominant traits.\(^5^0\) These disorders, including protein C and S deficiencies, factor V Leiden mutations, and various other factor deficiencies, can lead to an increased risk of venous thrombosis.\(^5^1–^5^6\) However, as discussed below, there has not been a strong association between several of these disorders and arterial events, such as MI and stroke.\(^5^2,^5^3,^5^4\) Some apparently acquired coagulopathies, such as the presence of a lupus anticoagulant or anticardiolipin antibody, can be familial in \(\approx\)10% of cases.\(^5^5,^5^6\) Inherited disorders of various clotting factors (ie, factors V, VII, X, XI, and XIII) are autosomal recessive traits and can lead to cerebral hemorrhage in childhood or the neonatal period.\(^5^0\) Arterial dissections, moyamoya syndrome, and fibromuscular dysplasia have a genetic or familial component in 10% to 20% of cases.\(^5^1,^5^2\)

The DeCode genetics group (Iceland) has reported genetic linkage of phosphodiesterase 4D (chromosome 5q12) and 5-lipoxygenase activating protein (chromosome 13q12-13) to common forms of ischemic stroke.\(^6^3,^6^4\) In both cases, there appears to be an association between several specific genetic haplotypes and stroke, although no pathogenic mutations have been identified.

Several rare genetic disorders have been associated with stroke. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is characterized by subcortical infarcts, dementia, and migraine headaches.\(^6^5\) CADASIL can be caused by any of a series of mutations in the Notch3 gene.\(^6^5,^6^6\) Acetazolamide may reduce migraine headaches in patients with CADASIL\(^6^7\) (Class IIb, Level of Evidence C). Marfan syndrome (due to mutations in the fibrillin gene) and neurofibromatosis types I and II are associated with an increased risk of ischemic stroke. Gene transfer therapy has been attempted to correct the genetic defect.\(^6^8\) Fabry disease is a rare inherited disorder that can lead to ischemic stroke. It is caused by lysosomal \(\alpha\)-galactosidase A deficiency, which causes the progressive accumulation of globotriaosylceramide and related glycosphingolipids.\(^6^9\) Deposition affects mostly small vessels in the brain and other organs, although involvement of the larger vessels has been reported. Two prospective randomized studies using human recombinant lysosomal \(\alpha\)-galactosidase A found a significant reduction in microvascular deposits as well as reduced plasma levels of globotriaosylceramide (Class I, Level of Evidence A).\(^7^0–^7^2\) These studies had short follow-up periods, and no effects on stroke rates were found. Enzyme replacement therapy also appears to improve cerebral vessel function.\(^7^3\)

**Summary and Gaps**

Genetic factors could arguably be classified as potentially modifiable, but because specific gene therapy is not presently available, these have been placed in the “nonmodifiable” section. It should be recognized that treatments are available for some of the factors that have a genetic predisposition or cause (such as Fabry disease), and as described in the sections that follow.

**Recommendations**

Referral for genetic counseling may be considered for patients with rare genetic causes of stroke (Class IIb, Level of

### TABLE 5. Continued

<table>
<thead>
<tr>
<th>Points</th>
<th>10-Year Probability, %</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
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<td>30</td>
<td>88</td>
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</table>

The table gives the probability of stroke within 10 y for men and women 55–85 y of age and free of previous stroke in the Framingham Heart Study. Modified from D’Agostino et al.\(^1^6\) History of MI indicates angina pectoris, 55–85 y of age and free of previous stroke in the Framingham Heart Study.
Evidence C). There remain insufficient data to recommend genetic screening for the prevention of a first stroke.

Well-Documented and Modifiable Risk Factors
There are several well-documented risk factors for first ischemic stroke with clear data showing a reduction in stroke risk with treatment. An important risk factor for a first stroke that is not adequately reflected in the organizational scheme used in this guideline is the presence of atherosclerotic vascular disease in another vascular bed. Those with a history of cardiovascular disease (coronary heart disease, cardiac failure, or symptomatic peripheral arterial disease) have a significant increased risk of a first stroke as compared with those without such a history, after adjustment for other risk factors (relative risk \( RR = 1.73 \), 95% confidence interval [CI] 1.68 to 1.78 for men; \( RR = 1.55 \), 95% CI 1.17 to 2.07 for women; adjusted for age, blood pressure, LV hypertrophy, cigarette smoking, atrial fibrillation, and diabetes).16 Treatments used in the management of these other conditions (eg, platelet antiaggregants) may also reduce the risk of stroke. The risk factors for first stroke and the risk factors for cardiovascular disease overlap. The impact of management of these common risk factors is reviewed in the context of their specific impact on stroke throughout this statement but should also be considered in the context of global reduction of vascular disease.

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

Hypertension
Hypertension (Table 3) affects at least 65 million persons in the United States and is a major risk factor for both cerebral infarction and intracerebral hemorrhage.74,75 The relationship between blood pressure and cardiovascular risk is “continuous, consistent, and independent of other risk factors.”76 The higher the blood pressure, the greater the stroke risk.77 Blood pressure, particularly systolic blood pressure, increases with increasing age.78 The Framingham Study found that individuals who are normotensive at 55 years of age have a 90% lifetime risk for developing hypertension.79 More than two thirds of persons >65 years of age are hypertensive.76

There has been compelling evidence for more than 30 years that the control of high blood pressure contributes to the prevention of stroke as well as to the prevention or reduction of other target-organ damage, including congestive heart failure and renal failure.76 A meta-analysis of 18 long-term randomized trials found that both \( \beta \)-blocker therapy (RR = 0.71; 95% CI 0.59 to 0.86) and treatment with diuretics (RR = 0.49; 95% CI 0.39 to 0.62) were effective in preventing stroke.80 Overall, antihypertensive therapy is associated with a 35% to 44% reduction in the incidence of stroke.81 In at least 1 study, there was no significant difference in the rates of stroke among groups of hypertensive persons (mean diastolic blood pressures between 100 and 115 mm Hg) who achieved mean diastolic blood pressures of 85.2, 83.2, or 81.1 mm Hg.82 Recent national guidelines recommend lowering blood pressure to <140/90 mm Hg (with lower targets in some subgroups, such as individuals with diabetes; see section on diabetes), and ongoing trials are exploring optimal lower general targets.76

Several categories of antihypertensive agents, including thiazide diuretics, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), \( \beta \)-adrenergic receptor blockers, and calcium channel blockers, reduce cardiovascular risk, including the risk of stroke, in patients with hypertension.81,83–86 Blood pressure control can be achieved in most patients, but the majority require combination therapy with \( \geq 2 \) antihypertensive agents.87,88 Direct comparisons among the various types of antihypertensives are limited. At least 1 study compared the effects of an angiotensin II type 1 receptor blocker with a \( \beta \)-adrenergic receptor blocker in 9193 persons with essential hypertension (160 to 200/95 to 115 mm Hg) and electrocardiographically determined LV hypertrophy over 4 years.85 Blood pressure reductions were similar for each group. There was a 13% (RR = 0.87; 95% CI 0.77 to 0.98) reduction in MI, stroke, or death among the ARB-treated patients as compared with those given a \( \beta \)-adrenergic receptor blocker, which included a 25% (RR = 0.75; 95% CI 0.63 to 0.89) reduction in fatal or nonfatal stroke. It remains unsettled whether specific classes of antihypertensive agents offer special protection against stroke in addition to their blood pressure–lowering effects in other settings.

Controlling isolated systolic hypertension (systolic blood pressure >160 mm Hg and diastolic blood pressure <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 showed a 42% risk reduction in the actively treated group.89 The Systolic Hypertension in the Elderly Program (SHEP) Trial found a 36% reduction in the incidence of stroke with treatment with a thiazide diuretic with or without a \( \beta \)-blocker.90

Despite the efficacy of antihypertensive therapy and the ease of diagnosis and monitoring, a significant proportion of the population has undiagnosed or inadequately treated hypertension.91 Only 70% of Americans with hypertension are aware that they have the condition; 60% are being treated and 34% are controlled (<140/90 mm Hg).76 Lack of diagnosis and inadequate treatment are particularly evident in minority populations and in the elderly.76,92 Because the risk of stroke increases progressively with increasing blood pressure and because a substantial number of individuals have a blood pressure level below current drug treatment thresholds, non-drug or lifestyle approaches have been recommended as a means to reduce the risk of stroke in nonhypertensive individuals.93

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High
TABLE 6. Classification and Treatment of Blood Pressure (JNC 7)\textsuperscript{76}

<table>
<thead>
<tr>
<th>Classification</th>
<th>Systolic Blood Pressure, mm Hg</th>
<th>Diastolic Blood Pressure, mm Hg</th>
<th>No Compelling Indication*</th>
<th>With Compelling Indication*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
<td>No antihypertensive drug</td>
<td>No antihypertensive drug</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120–139 or 80–90</td>
<td></td>
<td>No antihypertensive drug</td>
<td>Drugs for the compelling indication</td>
</tr>
<tr>
<td>Stage 1 hypertension</td>
<td>140–159 or 90–99</td>
<td></td>
<td>Thiazide-type diuretics for most. May consider ACEIs, ARBs, (\beta)-blockers, calcium channel blockers, or combination.</td>
<td>Drugs for the compelling indication, Other drugs (diuretics, ACEIs, ARBs, (\beta)-blockers, calcium channel blockers) as needed.</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
<td>(\geq 160) or (\geq 100)</td>
<td></td>
<td>Two-drug combination for most† (usually thiazide-type diuretic and ACEI or ARB or (\beta)-blocker or calcium channel blocker).</td>
<td>Drugs for the compelling indication, Other drugs (diuretics, ACEIs, ARBs, (\beta)-blockers, calcium channel blockers) as needed.</td>
</tr>
</tbody>
</table>

*In the absence of interaction for the smoking OC users would be \(\approx 2.7\). \textsuperscript{102} There was also a synergistic impact of smoking and OC use on hemorrhagic stroke risk. With nonsmoking, non-OC-using women used as the reference group, the odds of hemorrhagic stroke were 1.6 times greater (95% CI 1.2 to 2.0) for women who smoked but did not use OC, 1.5 times greater (95% CI 1.1 to 2.1) for nonsmoking OC users, but 3.7 times greater (95% CI 2.4 to 5.7) for OC users who smoked (note that the “expected” odds ratio [OR] in the absence of interaction for the smoking OC users would be \(\approx 2.4\)). \textsuperscript{103}

There is growing acceptance that exposure to environmental tobacco smoke (passive cigarette smoke) is a risk factor for heart disease. \textsuperscript{104} Several studies suggest that environmental tobacco smoke is also a substantial risk factor for stroke, with a risk approaching the doubling found for active smoking. \textsuperscript{105,106} Because the dose of exposure to environmental tobacco smoke is substantially lower than for active smoking, the magnitude of the risk associated with environmental tobacco smoke seems surprising. This lack of an apparent dose–response relationship between the level of exposure and risk may in part be explained by physiological studies suggesting that there is a tobacco smoke exposure “threshold” rather than a linear dose–effect relationship. \textsuperscript{107}

Smoking likely contributes to increased stroke risk through both acute effects on the risk of thrombus generation in narrowed arteries and chronic effects related to an increased burden of atherosclerosis. \textsuperscript{108}

Blood Pressure (JNC 7) provides a comprehensive, evidence-based approach to the classification and treatment of hypertension. \textsuperscript{76} Although somewhat controversial, this recent revision classifies blood pressure into 4 groupings (Table 6). Treatment recommendations are based on this revised classification scheme (Table 6).

Summary and Gaps
The benefit of hypertension treatment for primary prevention of stroke is clear. Choice of a specific regimen must be individualized, but reduction in blood pressure is generally more important than the specific agent used to achieve this goal. Hypertension remains undertreated in the community, and programs to improve treatment compliance need to be developed and supported.

Recommendations
Regular screening for hypertension (at least every 2 years in most adults and more frequently in minority populations and the elderly) and appropriate management (Class I, Level of Evidence A), including dietary changes, lifestyle modification, and pharmacological therapy as summarized in JNC 7, \textsuperscript{78} are recommended (Table 6).

Cigarette Smoke
Virtually every multivariable assessment of stroke risk factors (eg, Framingham, \textsuperscript{15} Cardiovascular Health Study, \textsuperscript{94} and the Honolulu Heart Study\textsuperscript{95}) has identified cigarette smoking as a potent risk factor for ischemic stroke (Table 3), associated with an approximate doubling of ischemic stroke risk (after adjustment for other risk factors). In addition, smoking has been clearly associated with a 2- to 4-fold increased risk for hemorrhagic stroke. \textsuperscript{96,97} A meta-analysis of 32 studies estimated the RR for ischemic stroke to be 1.9 (95% CI 1.7 to 2.2) for smokers versus nonsmokers and the RR for subarachnoid hemorrhage to be 2.9 (95% CI 2.5 to 3.5). \textsuperscript{98} The annual number of stroke deaths attributed to smoking in the United States has been estimated to be between 21 400 (without adjustment for potential confounding factors) and 17 800 (with adjustments), which suggests that smoking contributes to 12% to 14% of all stroke deaths. \textsuperscript{99} In 1989, these and other studies led the US Surgeon General to conclude that a definite relationship exists between smoking and both ischemic and hemorrhagic stroke, particularly at young ages. \textsuperscript{100,101}

Cigarette smoking may also potentiate the effects of other stroke risk factors. For example, a synergistic effect exists between the use of OCs and smoking on the risk of cerebral infarction. With nonsmoking, non–OC-using women used as the reference group, the odds of cerebral infarction were 1.3 times greater (95% CI 0.7 to 2.1) for women who smoked but did not use OC, 2.1 times greater (95% CI 1.0 to 4.5) for nonsmoking OC users, but 7.2 times greater (95% CI 3.2 to 16.1) for OC users who smoked (note that the “expected” odds ratio [OR] in the absence of interaction for the smoking OC users would be \(\approx 2.7\)). \textsuperscript{102} There was also a synergistic impact of smoking and OC use on hemorrhagic stroke risk. With nonsmoking, non–OC-using women used as the reference group, the odds of hemorrhagic stroke were 1.6 times greater (95% CI 1.2 to 2.0) for women who smoked but did not use OC, 1.5 times greater (95% CI 1.1 to 2.1) for nonsmoking OC users, but 3.7 times greater (95% CI 2.4 to 5.7) for OC users who smoked (note that the “expected” OR in the absence of interaction for the smoking OC users would be \(\approx 2.4\)). \textsuperscript{103}

There is growing acceptance that exposure to environmental tobacco smoke (passive cigarette smoke) is a risk factor for heart disease. \textsuperscript{104} Several studies suggest that environmental tobacco smoke is also a substantial risk factor for stroke, with a risk approaching the doubling found for active smoking. \textsuperscript{105,106} Because the dose of exposure to environmental tobacco smoke is substantially lower than for active smoking, the magnitude of the risk associated with environmental tobacco smoke seems surprising. This lack of an apparent dose–response relationship between the level of exposure and risk may in part be explained by physiological studies suggesting that there is a tobacco smoke exposure “threshold” rather than a linear dose–effect relationship. \textsuperscript{107}

Smoking likely contributes to increased stroke risk through both acute effects on the risk of thrombus generation in narrowed arteries and chronic effects related to an increased burden of atherosclerosis. \textsuperscript{108}
cigarette increases heart rate, mean blood pressure, and cardiac index and decreases arterial distensibility. In addition to the immediate effects of smoking, both active and passive cigarette smoke are associated with the development of atherosclerosis. 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 low atherosclerotic burdens and no evidence of cardiac sources of emboli.

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.

Sustained smoking cessation is difficult to achieve. However, effective behavioral and pharmacological treatments for nicotine dependence now exist. A combination of nicotine replacement therapy, social support, and skills training provides an effective approach for quitting. A comprehensive review of the public health impact of smoking is provided in the 2004 Surgeon General’s report.

**Summary and Gaps**

Cigarette smoking is clearly associated with the risk of stroke. Epidemiological studies show a reduction in risk with smoking cessation over time. Although effective programs to facilitate smoking cessation exist, data showing that participation in these programs leads to a reduction in stroke are lacking.

**Recommendations**

Abstention from cigarette smoking and (for current smokers) smoking cessation are recommended (Table 7) (Class I, Level of Evidence B). Data from cohort and epidemiological studies are consistent and overwhelming. Avoidance of environmental tobacco smoke for stroke prevention should also be considered (Class IIa, Level of Evidence C). The use of counseling, nicotine replacement, and oral smoking-cessation medications has been found to be effective for smokers and should be considered (Class IIa, Level of Evidence B). 

**Diabetes**

Persons with type 2 diabetes have both an increased susceptibility to atherosclerosis and an increased prevalence of atherogenic risk factors, notably hypertension, obesity, and abnormal blood lipids. Since 1990, the prevalence of those diagnosed with diabetes rose 61%, with an increase of 8.2% from 2000 to 2001. In 2001, 11.1 million Americans had physician-diagnosed diabetes, and an estimated additional 5.1 million had undiagnosed disease.

Case-control studies of stroke patients and prospective epidemiological studies have confirmed an independent effect of diabetes on ischemic stroke, with an increased RR in persons with diabetes ranging from 1.8-fold to nearly 6-fold (Table 3). Among Hawaiian Japanese men in the Honolulu Heart Program, those with diabetes had twice the risk of thromboembolic stroke as compared with those who did not have diabetes—an increase in risk that was independent of other factors. In the Framingham Heart Study, although the impact of diabetes was greatest on peripheral arterial disease with intermittent claudication, where the RR was increased 4-fold, coronary and cerebral artery territories were also affected. The impact of diabetes was greater in women than in men, reaching significance as an independent contributor in older women. In 2000, 1.1 million persons ≥35 years of age with diabetes reported being diagnosed with a stroke.

Stroke risk can be reduced in patients with diabetes. A small randomized trial of multifactorial intensive interventions in patients with type 2 diabetes and microalbuminuria targeted hyperglycemia, hypertension, dyslipidemia, and microalbuminuria with interventions including behavioral risk factor modification and the use of a statin, ACEI, ARB, or an antiplatelet drug as appropriate. After a mean of 7.8 years, the risk of cardiovascular events was reduced by nearly 50% (adjusted hazard ratio [HR] = 0.47; 95% CI 0.22 to 0.74; P = 0.01) with intensive treatment versus conventional therapy. First events included 3 nonfatal strokes, 4 nonfatal MIs, and 3 cardiovascular deaths in the 80 patients in the intensive arm versus 11 nonfatal strokes, 8 nonfatal MIs, and 1 cardiovascular death in the 80 patients in the control arm.

The combination of hyperglycemia and hypertension has long been believed to increase the frequency of diabetic complications, including stroke. Several trials have compared the effect on stroke and other cardiovascular outcomes of tight control of blood glucose and blood pressure in type 2 diabetic patients versus less stringent management. For example, the UK Prospective Diabetes Study Group found that for combined fatal and nonfatal stroke, tight blood pressure control (mean blood pressure achieved 144/82 mm Hg) resulted in a 44% RR reduction as compared with more liberal control (mean blood pressure achieved 154/87 mm Hg). There was also a ≥20% risk reduction with antihypertensive treatment in diabetic subjects in the Systolic Hypertension in the Elderly Program. Although tight control of hypertension in diabetic individuals significantly reduces stroke incidence, improved glycemic control did not produce a significant reduction in stroke over 9 years of follow-up (although the use of oral hypoglycemic drugs, potentially working through other mechanisms, may reduce stroke risk). Nevertheless, intensive therapy to achieve tight control of hyperglycemia in patients with recent-onset insulin-dependent (type 1) diabetes mellitus was shown to reduce microvascular complications of the disease, such as nephropathy, retinopathy, and peripheral neuropathy.

The Heart Outcomes Prevention Evaluation (HOPE) Study compared the addition of an ACEI to the current medical regimen of high-risk patients. The substudy of 3577 diabetic patients (of a total population of 9541 participants in the HOPE Study) showed a reduction of the primary combined outcome of MI, stroke, and cardiovascular death by 25% (95% CI 12 to 36; P = 0.0004) and stroke by 33% (95% CI 10 to 50; P = 0.0074) among diabetic patients with a previous cardiovascular event or an additional cardiovascular risk factor. Whether these benefits were a specific effect of the ACEI or were an effect of blood pressure lowering has been the subject of debate. Diabetic complications (overt nephropathy, dialysis, or need for laser therapy) were also reduced.
The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Study compared the effects of an angiotensin II type 1 receptor blocker with a β-adrenergic receptor blocker in 9193 persons with essential hypertension (160 to 200/95 to 115 mm Hg) and electrocardiographically determined LV hypertrophy over 4 years. Blood pressure reductions were similar for each group. The 2 regimens were compared among the subgroup of 1195 persons who also had diabetes in a prespecified analysis. There was a 24% reduction (RR 0.76; 95% CI 0.58 to 0.98) in major vascular events and a nonsignificant 21% reduction (RR 0.79; 95% CI 0.55 to 1.14) in stroke among those treated with the ARB. Although secondary subgroup analyses of some studies did not find a benefit of statins in diabetic subjects, 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 6% to 39%; P = 0.01) in strokes occurred among 5963 diabetic individuals treated with the statin in addition to best medical care. The Collaborative Atorvastatin Diabetes Study (CARDS) reported that in type 2 diabetic subjects with at least 1 additional risk factor (retinopathy, albuminuria, current smoking, or hypertension) and a low-density lipoprotein (LDL) cholesterol level <160 mg/dL but without a prior history of cardiovascular disease, treatment with a statin resulted in a 48% reduction (95% CI 11% to 69%) in stroke.

### Summary and Gaps

A comprehensive program that includes tight control of hypertension with ACEI or ARB treatment reduces the risk of stroke in persons with diabetes. Glycemic control reduces microvascular complications, but evidence showing a reduction in stroke risk with tight glycemic control is lacking. Adequately powered studies show that treatment of diabetic patients with a statin decreases their risk of a first stroke.

### Recommendations

It is recommended that hypertension be tightly controlled in patients with either type 1 or type 2 diabetes (the JNC 7...
Atrial Fibrillation

With or without atrial fibrillation, all patients with mechanical heart valves require anticoagulation, with the target level of anticoagulation varying according to the type and position of the valve and the presence of other risk factors (Class I). The rate of thromboembolism in patients with mechanical heart valves is 4.4 per 100 patient-years without antithrombotic therapy, 2.2 per 100 patient-years with antiplatelet drugs, and 1 per 100 patient-years with warfarin. Patients with paroxysmal or persistent atrial fibrillation and valvular heart disease such as mitral stenosis are at the highest risk for future embolic events and should also be anticoagulated (Class I).

Atrial fibrillation alone is associated with a 3- to 4-fold increased risk of stroke after adjustment for other vascular risk factors (Table 3). For those without prior transient ischemic attack (TIA) or stroke, 2% to 4% per year have an ischemic stroke. About 60,000 strokes occur annually among the estimated 2.3 million Americans with this cardiac dysrhythmia, with the number of atrial fibrillation–related strokes anticipated to more than double in coming decades.

The prevalence of atrial fibrillation increases with age. Atrial fibrillation affects ≈5% of those ≧70 years of age, and the mean age of atrial fibrillation patients is 75 years. Estimates of attributable risk reveal that about one quarter of strokes in the very elderly (≧80 years old) are due to atrial fibrillation. Atrial fibrillation is also associated with increased mortality after adjustment for other vascular risk factors. Strokes associated with atrial fibrillation are especially large and disabling. Importantly, rhythm control does not appear to reduce stroke rates, and as discussed below, antithrombotic therapies remain the mainstay for stroke prevention.

Randomized clinical trials have firmly established the value of antithrombotic therapies for reducing the risk of stroke in patients with atrial fibrillation (Table 3). Risk is reduced by ≈60% with adjusted-dose warfarin and by ≈20% with aspirin. Adjusted-dose warfarin reduces stroke by ≈45% as compared with aspirin. Randomized trials have also been conducted comparing a direct thrombin inhibitor to high-quality adjusted-dose warfarin in persons with atrial fibrillation, but the US Food and Drug Administration has not approved its use.

The absolute risk of stroke varies 20-fold among atrial fibrillation patients, according to age and associated vascular diseases. Several stroke risk–stratification schemes have been developed and validated. The 2001 American College of Cardiology (ACC)/AHA/European Society of Cardiology (ESC) guideline recommends anticoagulation for patients with atrial fibrillation who are >60 years of age and have a history of hypertension, diabetes, coronary artery disease (CAD), impaired LV systolic function, heart failure, or prior thromboembolism, and for all those with atrial fibrillation who are >75 years of age. However, this stratification scheme had not been prospectively validated (although the individual factors had been validated). Since publication of the 2001 ACC/AHA/ESC guideline, the so-called CHADS2 stratification scheme has been proposed and validated. CHADS2 is an acronym for congestive heart failure, hypertension, age >75 years, diabetes mellitus, and prior stroke or TIA. The CHADS2 score was derived from independent predictors of stroke risk in patients with nonvalvular atrial fibrillation (Table 8). The score gives 1 point each for congestive heart failure, hypertension, age >75 years, and diabetes mellitus and 2 points for prior stroke or TIA. The score was validated in a large cohort study and in clinical trials. Atrial fibrillation patients with low (≦1%/year, typically less than 1.5%/year), moderate (1.5%/year to 2.5%/year), and high risk (≧2.5%/year) can be appropriately managed with aspirin (75–325 mg/d) or warfarin (INR 2–3). Larger studies are required to confirm that CHADS2 is a useful clinical tool.
CHADS2 score = 0 to 1, about half of patients), moderate (2.5%/year, CHADS2 score = 2, ≈25% of patients), and high (>5%/year, CHADS2 score ≥ 3, ≈25% of patients) stroke risk were reliably predicted.138 An apparent limitation of the CHADS2 scheme that applies to secondary prevention involves patients with prior stroke or TIA and no other risk factors. These rare patients score 2 on the CHADS2 scale (moderate risk), but in the validation study of the CHADS2 score, patients with prior stroke or TIA averaged 10.8 strokes per 100 patient-years.147 In the Stroke Prevention in Atrial Fibrillation (SPAF) 2012 aspirin analysis, the few patients with prior stroke or TIA without other risk factors (which included the CHADS2 risk factors except heart failure) had a stroke rate of 5.9%/year (95% CI 2 to 18).150 Therefore, patients with prior stroke or TIA in the setting of atrial fibrillation without additional risk factors should be considered at high risk for recurrence and should be treated with warfarin unless contraindicated. For patients with echocardiographic data, the SPAF III scheme has also been validated.147,148

The threshold of absolute stroke risk warranting anticoagulation is importantly influenced by the estimated bleeding risk if anticoagulated, patient preferences, and access to high-quality anticoagulation monitoring. Risk stratification is the first step in the decision process (Table 8). Most patients with atrial fibrillation who are <75 years of age without prior stroke or TIA have a relatively low risk of stroke (1% to 2% per year) if given aspirin, and they do not benefit sufficiently from anticoagulation to warrant its use for primary stroke prevention.138,151,152 It is generally agreed that atrial fibrillation patients whose estimated stroke risk exceeds 4% per year should be anticoagulated in the absence of contraindications.153

Several studies have found that only about half of patients with atrial fibrillation who are candidates for anticoagulation receive warfarin.154–156 Anticoagulation is particularly underused in elderly patients with atrial fibrillation.157 Although the attributable risk of stroke associated with atrial fibrillation increases with age,135 elderly (ie, ≥75 years of age) atrial fibrillation patients have about twice the risk of serious bleeding complications during anticoagulation as compared with younger patients.158 Nevertheless, anticoagulation is still warranted if their risk of ischemic stroke without warfarin is greater than their risk of bleeding.139 In addition to age, poorly controlled hypertension and concomitant aspirin or nonsteroidal antiinflammatory drug use confer higher bleeding risk during anticoagulation. Therefore, age per se is not a contraindication to the anticoagulation of high-risk atrial fibrillation patients.

The optimal target international normalized ratio (INR) for primary prevention of stroke in patients with nonvalvular atrial fibrillation appears to be 2.0 to 2.5.159 This range is too narrow for practical management, and a range of 2 to 3 is generally recommended for most atrial fibrillation patients.153,160 For primary prevention in the very elderly (for whom the lowest efficacious intensity of anticoagulation is particularly important to minimize bleeding), a target INR of 2 (target range 1.6 to 2.5) is recommended by some experts,153,159,161 although others favor a target range of 2 to 3 for atrial fibrillation patients of all ages.162

The importance of treatment of hypertension is discussed in a previous section. Hypertension is also an independent risk factor for stroke in atrial fibrillation patients (particularly those with systolic blood pressure >160 mm Hg). It is unclear whether sustained control of hypertension in atrial fibrillation patients reduces cardiogenic embolism. However, intracerebral bleeding, the most devastating complication of anticoagulation in the elderly, is exquisitely sensitive to blood pressure control.163 Control of hypertension in atrial fibrillation patients is therefore critically important, reducing both the risk of ischemic stroke and the risk of intracerebral hemorrhage complicating antithrombotic therapy.164

Summary and Gaps

Atrial fibrillation is an important, treatable stroke risk factor. Validated stroke risk–stratification schemes identify those at particularly low risk (<2% per year) who can be treated with aspirin. It should be noted that guideline statements from different groups may vary in their recommendations about risk stratification. Long-term anticoagulation importantly reduces stroke risk in those at higher risk and without contraindications to this treatment. The development of safer, easier-to-use oral anticoagulants might improve the risk-benefit ratio. Controversy remains about the optimal target level of anticoagulation in those at risk of increased bleeding. Many patients with atrial fibrillation, particularly those >75 years of age, who would benefit from anticoagulation do not receive this treatment.165

Recommendations

Anticoagulation of patients with atrial fibrillation who have valvular heart disease (particularly those with mechanical heart valves) is recommended (Class I, Level of Evidence A). Antithrombotic therapy (warfarin or aspirin) is recommended to prevent stroke in patients with nonvalvular atrial fibrillation according to assessment of their absolute stroke risk, estimated bleeding risk, patient preferences, and access to high-quality anticoagulation monitoring (Table 8) (Class I, Level of Evidence A). Warfarin (INR 2.0 to 3.0) is recommended for high-risk (>4% annual risk of stroke) patients (and most moderate-risk patients according to an assessment of bleeding risk) with atrial fibrillation who have no clinically significant contraindications to oral anticoagulants (Class I, Level of Evidence A).

Other Cardiac Conditions

Other types of cardiac disease that can contribute to the risk of thromboembolic stroke include dilated cardiomyopathy, valvular heart disease (eg, mitral valve prolapse, endocarditis, prosthetic cardiac valves), and intracardiac congenital defects (eg, patent foramen ovale [PFO], atrial septal defect, atrial septal aneurysm). Potential cardiac sources of emboli are associated with up to 40% of cryptogenic strokes in some series involving the younger population.166 The presence of cerebrovascular disease is strongly associated with the presence of symptomatic167,169 and asymptomatic170–174 cardiac disease. In addition, MI is associated with the development of atrial fibrillation and is a source of cardiogenic emboli.141 Because of shared risk factors, patients with MI represent a group that is also at increased risk of stroke. Acute coronary
syndromes are infrequently associated with stroke in the acute setting, occurring in 0.8% of patients.175–177 The majority of these strokes (0.6%) are ischemic.176

Although a detailed review of the management of cardiac conditions is beyond the scope of this guideline, several points will be highlighted. The incidence of stroke is inversely proportional to cardiac ejection fraction. Patients with MI who have an ejection fraction <29% have a RR of stroke of 1.86, as compared with patients who have an ejection fraction of >35% (P=0.01; an 18% increase in stroke risk for every 5% decline in ejection fraction).178 The use of warfarin for cardioembolic prophylaxis in patients with reduced LV ejection fraction in the setting of idiopathic cardiomyopathy remains controversial, and trials are in progress comparing warfarin with antiplatelet treatment.

Perioperative stroke occurs in 1% to 7% of patients undergoing cardiac surgical procedures (predominantly coronary artery bypass procedures and open heart surgery). A history of prior neurological events, increasing age, diabetes, and atrial fibrillation have been identified as risk factors for early and delayed stroke after cardiac surgery.179–190 Other factors associated with perioperative stroke include duration of cardiopulmonary bypass and the presence of aortic atherosclerosis.191,192 Studies proving the benefits of specific prophylactic procedures are lacking.

Summary and Gaps
In addition to atrial fibrillation, a variety of cardiac conditions have been associated with an increased risk of stroke. Data on the relative benefits and risks of specific prophylactic interventions are beyond the scope of this document.

Recommendations
Various AHA/ACC practice guidelines recommend strategies to reduce the risk of stroke in patients with a variety of cardiac conditions. These include the management of patients with valvular heart disease,136 unstable angina,193 chronic stable angina,194 and acute MI.195 Strategies to prevent postoperative neurological injury and stroke in patients undergoing surgical revascularization for atherosclerotic heart disease are discussed in detail in the recently published coronary artery bypass graft surgery guidelines.196 It is reasonable to prescribe warfarin to post–ST-segment–elevation MI patients with LV dysfunction with extensive regional wall-motion abnormalities (Class IIa, Level of Evidence A), and warfarin may be considered in patients with severe LV dysfunction, with or without congestive heart failure (Class IIb, Level of Evidence C).197

Dyslipidemia
Epidemiological studies initially found no consistent association between cholesterol levels and overall stroke rates but were likely confounded by the inclusion of hemorrhagic as well as ischemic stroke.198–203 Three prospective studies in men subsequently showed increases in ischemic stroke rates at higher levels of total cholesterol, particularly for levels above 240 to 270 mg/dL.199,200,202 The Asia Pacific Cohort Studies Collaboration, which included 352 033 individuals, found a 25% increase in ischemic stroke rates for every 1-mmol/L (38.7-mg/dL) increase in total cholesterol.203 The Eurostroke project (22 183 subjects, 34% female) found only a trend toward increased risk with 6% more cases of cerebral infarction for every 1-mmol/L increase in total cholesterol.204 The US Women’s Pooling Project (24 343 women at risk) found a 25% increased risk of fatal ischemic stroke for each 1-mmol/L increase in total cholesterol in women 30 to 54 years of age.205 Therefore, there does appear to be a clear relationship between dyslipidemia and the risk of ischemic stroke in both men and women (Table 3).

Only a few studies have analyzed the relationship between LDL cholesterol (the major component of total cholesterol) and ischemic stroke. No consistent association has been found, although the total number of subjects at risk in these studies is limited.206–208

The relationship between HDL cholesterol and ischemic stroke is best determined from prospective studies because tissue inflammation and caloric deficit can reduce HDL levels after stroke. The Copenhagen City Heart Study, including both sexes, found a 47% reduction of ischemic stroke events for every 1-mmol/L increase in HDL cholesterol.209 In 3 prospective population-based studies, men had significantly increased rates of ischemic stroke at low HDL cholesterol levels, especially levels <30 to 35 mg/dL.202,210,211 The Eurostroke project found fewer ischemic strokes in men with low HDL (nonsignificant trend) but more ischemic strokes in women with low HDL (marginally significant).204 Studies in Japan and the United States found trends toward higher ischemic stroke rates in women with low HDL.208,211 Thus, it appears that low HDL is a risk factor for ischemic stroke in men, but more data are needed to verify its effect in women.

Triglyceride levels vary considerably, making elevated levels difficult to evaluate as a risk factor for stroke. Elevated triglycerides are a component of the metabolic syndrome. Trends toward higher triglyceride levels in patients who subsequently experience ischemic stroke have been reported.206,209 In a study of 11 117 subjects with CAD, ischemic cerebrovascular events were significantly associated with high triglyceride and low HDL cholesterol levels.207

Carotid intima-media thickness, measured by B-mode ultrasound, is an atherosclerotic disease marker. Lipoprotein levels have been correlated with carotid intima-media thickness.212 In clinical trials, colesteipol-niacin combination therapy, statin monotherapy, and statin-niacin combination therapy each retarded the progression of asymptomatic carotid atherosclerosis assessed by carotid intima-media thickness.213–217

HMG-CoA reductase inhibitors (statins) have received regulatory approval for the prevention of ischemic stroke in patients with CAD; the approval was based on consistent benefits in large randomized trials using these agents.27,83,214,218 Additional studies include the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), which enrolled high-risk hypertensive subjects, and the Heart Protection Study, which enrolled high-risk subjects mostly with previous coronary events.129,219 In these studies, stroke rates were reduced 27% to 32% among subjects assigned to the statin as compared with placebo. Another statin trial including elderly people (≥70 years of age) found no effect on total stroke rate but did find a 25% reduction in TIAs. However, confidence intervals in this study were wide, so a beneficial effect on stroke cannot be excluded.220 Among a comparable
number of elderly people in the Heart Protection Study, statin therapy reduced the rate of first strokes by 29%.219 In a combined analysis of 9 trials, statin treatment was estimated to prevent 9 strokes per 1000 coronary heart disease or high-risk patients treated for 5 years.221 The Treating to New Targets (TNT) Trial randomized 10,001 persons with stable coronary heart disease and an LDL cholesterol level <130 mg/dL to high- and low-dose statins, achieving mean LDL cholesterol levels of 101 and 77 mg/dL, respectively.222 Those in the high-dose group had fewer major vascular events (10.9% versus 8.7%; HR = 0.78; 95% CI 0.69 to 0.89; P < 0.0001), including fewer fatal and nonfatal strokes (3.1% versus 2.3%; HR = 0.75; 95% CI 0.59 to 0.96; P = 0.02).

Nonstatin lipid-modifying therapies may also offer stroke protection, although the supporting data are less certain. Niacin treatment was associated with a 24% reduction in known or suspected cerebrovascular events (including TIs) in the Coronary Drug Project.223 The effect of niacin on stroke rate was similar but not significant.223 The Veterans Administration HDL Intervention Trial (VA-HIT) evaluated the effect of gemfibrozil in men with coronary heart disease and low levels of HDL cholesterol (≤40 mg/dL).224 There was a trend toward a reduction in strokes in the treated group (6.0% versus 4.6%; HR = 0.75; 95% CI 0.53 to 1.06; P = 0.10). HDL cholesterol can be increased by 25% to 40% when multiple modalities are used, especially when niacin is included.225,226

Summary and Gaps
Plasma lipids and lipoproteins (total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, and lipoprotein[a]) affect the risk of ischemic stroke, but the exact relationships are still being clarified. In general, increasing levels of total cholesterol are associated with higher rates of ischemic stroke. Low HDL is a risk factor for ischemic stroke in men, but more data are needed to determine its effect in women. Lipid-modifying medications can substantially reduce the risk of stroke in patients with coronary heart disease. Additional studies are needed to clarify the risk associated with lipoproteins in women and the effect of treatment in older persons (>70 to 75 years of age).

Recommendations
National Cholesterol Education Program III guidelines for the management of patients who have not had a cerebrovascular event and who have elevated total cholesterol or elevated non–HDL cholesterol in the presence of hypertriglyceridemia are endorsed (Table 9).227,228 It is recommended that patients with known CAD and high-risk hypertensive patients even with normal LDL cholesterol levels be treated with lifestyle measures and a statin (Class I, Level of Evidence A). The use of lipid-lowering therapy in diabetic patients is specifically addressed in that section of this guideline. Suggested treatments for patients with known CAD and low HDL cholesterol include weight loss, increased physical activity, smoking cessation, and possibly niacin or gemfibrozil (Class IIa, Level of Evidence B).

Asymptomatic Carotid Stenosis
In the Cardiovascular Health Study, a carotid stenosis >50% was detected in 7% of the men and 5% of the women >65 years of age, with 1.2% and 1.1% having a 75% to 99% stenosis, respectively.229 Similarly, stenoses of ≥50% were detected in 9% of men and 7% of women in the Framingham cohort 66 to 93 years of age; 2% of men and 0.7% of women had stenoses in the 81% to 100% range.230 The Berlin Aging Study, a population-based study of functionally healthy volunteers 70 to 100 years of age, found a 4% prevalence of ≥75% carotid stenoses among both men and women.231 Therefore, it seems likely that between 5% and 10% of men and women >65 years of age have carotid stenoses >50%, with ≥1% having stenoses >80%.

Natural history studies reflect an annual stroke risk between 1% and 3.4% among persons with an asymptomatic carotid artery stenosis between 50% and 99%.232–237 Most of these studies focused on short-term follow-up (ie, 2 to 3 years). However, at least 1 cohort study found similar rates of ipsilateral stroke over 10 years (9.3%; 95% CI 1% to 18%; 0.9%/year) and 15 years (16.6%; 95% CI 1% to 32%; 1.1%/year).238

Several studies have attempted to identify subgroups of patients with asymptomatic carotid artery stenosis who may be at particularly elevated stroke risk. The Toronto Asymptomatic Cervical Bruit Study followed a cohort of 500 patients for a mean of 23 months.234 Overall, cerebral ischemic events (TIA or stroke) were more frequent in patients with severe (narrowed >75%) carotid artery stenosis, progressing carotid artery stenosis, or heart disease, and in men. A total of 8 patients (1.6%) had an unheralded stroke; however, only 2 (0.4%) were ipsilateral to a high-grade extracranial carotid artery stenosis as demonstrated by Doppler ultrasonography. In another study, 38 asymptomatic patients with >90% stenosis of the internal carotid artery were followed up for a mean period of 48 months.235 Each year, 1.7% of the patients had an unheralded ipsilateral stroke. The North American Symptomatic Carotid Endarterectomy Trial investigators retrospectively reviewed their data on the risk of stroke in the territory of an asymptomatic carotid artery stenosis contralateral to the side of a symptomatic vessel.239,240 The annual risk of stroke was 3.2% (over 5 years) in patients with a 60% to 99% asymptomatic stenosis. The average annual risk of ipsilateral stroke increased from 3.0% for those with 60% to 74% stenosis to 3.7% for those with 75% to 94% stenosis and decreased to 2.9% for those with 95% to 99% stenosis, with a rate of 1.9% for those with complete occlusion. Overall, 45% of ipsilateral strokes in patients with asymptomatic stenosis contralateral to a symptomatic stenosis could be attributable to lacunes or cardioemboli, underscoring the need to fully evaluate patients with asymptomatic carotid stenosis for other treatable causes of stroke.

Taken together, these and other observational studies suggest that the rate of unheralded stroke ipsilateral to a hemodynamically significant extracranial carotid artery stenosis is ±1% to 2% annually, with some data suggesting that the rate of stroke may be higher in those persons with progressing stenosis and in those with more severe stenosis (Table 3). However, it should be noted that most of these studies were carried out before the widespread use of HMG-CoA reductase inhibitors (ie, statins), which may be associated with a stabilization or reduction in carotid atherosclerotic
### TABLE 9. Dyslipidemia: Guideline Management Recommendations*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Goal</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C227,228</td>
<td>LDL-C &lt;160 mg/dL</td>
<td>Diet, weight management, physical activity. Drug therapy recommended if LDL-C remains ≥190 mg/dL. Drug therapy optional for LDL-C 160–189 mg/dL.</td>
</tr>
<tr>
<td>≥0–1 CHD risk factor*</td>
<td>LDL-C &lt;130 mg/dL</td>
<td>Diet, weight management, physical activity. Drug therapy recommended if LDL-C remains ≥160 mg/dL.</td>
</tr>
<tr>
<td>≥2 CHD risk factors and 10-y CHD risk &lt;20%</td>
<td>LDL-C &lt;130 mg/dL, or optionally LDL-C &lt;100 mg/dL</td>
<td>Diet, weight management, physical activity. Drug therapy recommended if LDL-C remains ≥130 mg/dL (optionally ≥100 mg/dL).</td>
</tr>
<tr>
<td>≥2 CHD risk factors and 10-y CHD risk 10% to 20%</td>
<td>LDL-C &lt;100 mg/dL, or optionally LDL-C &lt;70 mg/dL</td>
<td>Diet, weight management, physical activity. Drug therapy recommended if LDL-C is ≥130 mg/dL. Drug therapy optional for LDL-C 70–129 mg/dL.</td>
</tr>
<tr>
<td>CHD or CHD risk equivalent† (10-y risk &gt;20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non–HDL-C in persons with triglycerides ≥200 mg/dL227</td>
<td>Goals are 30 mg/dL higher than LDL-C goal.</td>
<td>Same as LDL-C with goals 30 mg/dL higher.</td>
</tr>
<tr>
<td>Low HDL-C227</td>
<td>No consensus goal</td>
<td>Weight management, physical activity. Consider niacin (nicotinic acid) or a fibrate in high-risk individuals with HDL-C &lt;40 mg/dL.</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>No consensus goal</td>
<td>Treat other atherosclerotic risk factors in subjects with high Lp(a). Consider niacin (immediate- or extended-release formulation) up to 2000 mg/d469 for reduction of Lp(a) levels, optimally in conjunction with glycemic control468 and LDL control.484</td>
</tr>
</tbody>
</table>

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

*To screen for dyslipidemia, a fasting lipoprotein profile (cholesterol, triglycerides, HDL-C, and LDL-C) should be obtained every 5 years in adults. It should be obtained more often if ≥2 CHD risk factors are present (risk factors include cigarette smoking, hypertension, LDL-C <40 mg/dL, CHD in a male first-degree relative <55 y of age or in a female first-degree relative <65 y of age, or age ≥45 y for men or ≥65 y for women) or if LDL-C levels are borderline or high. Screening for Lp(a) is not recommended for primary prevention unless (1) unexplained early cardiovascular events have occurred in first-degree relatives or (2) high Lp(a) is known to be present in first-degree relatives.227

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

and the rigor of adherence to other preventive strategies as reviewed in this guideline is not known. As with asymptomatic carotid bruit, an asymptomatic stenosis of the carotid artery is an important indicator of concomitant ischemic cardiac disease.234,235,237,238

There have been 2 underpowered and 3 larger published randomized controlled trials designed to assess the benefit of carotid endarterectomy in patients with asymptomatic carotid artery stenosis. The Mayo Clinic Asymptomatic Carotid Endarterectomy (MACE) Study included 71 randomized and 87 nonrandomized patients.244 Surgically treated patients were not given aspirin. There were no major strokes or deaths in either group. However, the study was stopped because MI occurred in 26% of those in the surgical arm (no aspirin) as compared with 9% of those in the aspirin-treated medical arm (P=0.002), reflecting the high incidence of concomitant CAD in patients with an asymptomatic carotid artery stenosis.

Of the larger trials, the VA Cooperative Study of carotid endarterectomy for patients with asymptomatic carotid artery stenosis included 444 men followed up for a mean of 48 months.245 Two hundred eleven patients received best medical therapy plus carotid endarterectomy, and 233 received medical therapy alone (including 650 mg of aspirin twice daily). Patients had >50% stenosis of the extracranial carotid artery demonstrated by angiography. Combined perioperative and angiographic risk was 4.7%. There was a 38% risk reduction for the combined end points of ipsilateral TIA, transient monocular blindness, and stroke over 2 years (P<0.001). Although the rate of fatal and nonfatal stroke was reduced in the surgical group (4.7% versus 9.4%, or 1.2%/year versus 2.4%/year), the difference was not significant (P=0.08). However, the study was not powered to detect differences in outcome subgroups.

The Asymptomatic Carotid Atherosclerosis Study (ACAS) was a randomized trial investigating the efficacy of carotid endarterectomy in patients with asymptomatic high-grade (>60% diameter reduction) carotid artery stenosis.246 Patients (n=1662) were randomized to surgery plus medical therapy (n=828) or to medical therapy without carotid endarterectomy (n=834). There was a 1.2% risk of angiography-related complications among the 414 patients undergoing postrandomization angiograms and a 1.5% 30-day risk of stroke or death among those having endarterectomy (overall 2.7% rate of perioperative stroke or death). The study was halted after a median follow-up of 2.7 years (4465 patient-years) because a significant benefit of surgery was
found. The aggregate rate of ipsilateral stroke, any perioperative stroke, or death in surgically treated patients was estimated at 5% over 5 years; in medically treated patients, the corresponding rate was 11% (53% risk reduction, approximate 2%/year event rate reduced to 1%/year; \( P = 0.004 \)). The benefit began to accrue after 1 to 2 years. As with the VA Trial, the study was not powered to detect differences among patient subgroups. However, there was no relationship between benefit and the degree of carotid artery stenosis, and women appeared to benefit less than men (17% nonsignificant risk reduction in women, 95% CI −4% to 65%, versus a 66% risk reduction in men, 95% CI 36% to 82%), a difference at least partially ascribed to a higher rate of perioperative complications in women (3.6% versus 1.7%). Despite the differences in point estimates, a definite difference between men and women cannot be concluded because of the wide confidence intervals and the post hoc nature of analysis. Although a large population-based study did not find a significant overall difference in endarterectomy complication rates in women as compared with men, asymptomatic patients were not analyzed separately.\(^{247}\) Consistent with the ACAS observation, a retrospective study also noted an increased risk of perioperative complications after endarterectomy in asymptomatic women as compared with men.\(^{248}\)

Begun before the completion of ACAS, the Medical Research Council Asymptomatic Surgery Trial (ACST) is the largest randomized trial comparing a strategy of immediate versus deferred carotid endarterectomy in persons with asymptomatic stenosis.\(^{249}\) Between 1993 and 2003, ACST enrolled 3120 patients without relevant symptoms in the prior 6 months who had at least a 60% diameter reduction carotid stenosis according to ultrasound (few had cerebral angiograms). There was a 3.1% (95% CI 2.3% to 4.1%) risk of stroke or death within 30 days of the operation. It should be noted that although the overall periprocedural complication rate was similar to that in ACAS, the point estimate of the ACST surgical complication rate was approximately twice that of ACAS (ACAS: 1.2% arteriography + 1.5% surgical = 2.7%; ACST: 3.1% surgical). The overall 5-year risk of any stroke or perioperative death was 11.8% with deferred surgery versus 6.4% with immediate endarterectomy (\( P < 0.0001 \); 2.4%/year reduced to 1.3%/year). For fatal or disabling strokes, the respective rates were 6.1% versus 3.5% (\( P = 0.004 \); 1.2%/year reduced to 0.7%/year). The benefit began to accrue after 2 years. Although subgroup analyses again need to be interpreted with caution, as in ACAS, there did not appear to be any difference in benefit based on the degree of carotid stenosis (70% versus 80% or 90% stenosis).

Although not significantly different, women benefited somewhat less than men after successful endarterectomy (4.1% [95% CI 0.7% to 7.4%] absolute 5-year benefit in women versus 8.2% [95% CI 5.6 to 10.8%] in men) but had a somewhat higher rate (albeit nonsignificant) of perioperative complications (3.8% versus 2.7%). Calculated from data provided in ACAS and ACST, surgical benefit (any stroke or perioperative death) is greater in men than in women (men: pooled interaction \( P = 0.01 \), OR 0.49, 95% CI 0.36 to 0.60; women: OR 0.96, 95% CI 0.63 to 1.45). Therefore, it remains uncertain whether there is a benefit in women.\(^{250}\)

Data presented in the ACST publication also permit calculation of the comparative rates of any stroke or death and of any major stroke or death. Similar to ACAS, the overall rate of any stroke or death was 31.2% for deferred endarterectomy versus 28.9% for immediate endarterectomy (RR reduction [RRR] = 7%, 95% CI −3% to 17%; \( P = 0.172 \)). For any major stroke or death, the respective ACST rates were 25.5% versus 25.3% (RRR = 7%; 95% CI −5% to 18%; \( P = 0.242 \)). These sobering data must be taken into account when the procedure is considered.

It should be noted that the benefit of endarterectomy in the setting of asymptomatic carotid artery stenosis is highly dependent on surgical risk, with the benefit being obviated by perioperative complication rates in excess of the 2.7% to 3.1% rates observed in ACAS and ACST. Even after community-wide performance measurement and feedback, the overall risk for stroke or death after endarterectomy performed for asymptomatic stenosis in 10 US states was 3.8% (including 1% mortality).\(^{251}\) Nevertheless, most physicians are not aware of the complication rates of the surgeon to whom they refer patients for the operation.\(^{252,253}\)

It is also important to recognize that surgery is only one of several potential treatments that can be used to reduce the risk of stroke in patients with asymptomatic carotid artery stenosis. Medical therapy was different at the time ACAS was performed as compared with current practice. Carried out later than ACAS, the ACST report indicates that at randomization there was “widespread use of antiplatelet and antihypertensive drugs” (~80% and 60% to 75%, respectively) and increasing use of lipid-lowering drugs (17% among those randomized in the period 1993 to 1996, 58% in the period 2002 to 2003), with >90% on antiplatelet therapy, 81% on antihypertensives, and 70% on lipid-lowering therapy at the last follow-up visit.

Although highly selected patients may benefit, screening of general populations for asymptomatic carotid stenosis is unlikely to be cost-effective.\(^{254–256}\) The cost-effectiveness of even a one-time screening approach would be highly dependent on the ability to identify a group of persons with a high pretest likelihood of having high-grade asymptomatic disease, the availability of a screening test with a very high sensitivity and specificity when used on a wide-scale basis, and very low perioperative complication rates.

Carotid angioplasty with stenting has been available for several years, but clinical studies showing that it is equivalent or superior to carotid endarterectomy have been limited. The Stenting & Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) Trial found that this procedure was not inferior (within 3%, \( P = 0.004 \)) to carotid endarterectomy (based on a composite of stroke, death, or MI within 30 days, or death from neurological causes or ipsilateral stroke between 31 days and 1 year) in a cohort of patients considered at high risk for the operation.\(^{257}\) Approximately 70% of the enrolled patients had asymptomatic stenoses, with rates of stroke, MI, or death of 5.4% for stenting versus 10.2% for endarterectomy at 30 days (\( P = 0.20 \)) and 9.9% versus 21.5% at 1 year, respectively (\( P = 0.02 \)). Because these rates include MI (including those defined by cardiac enzyme elevations in the absence of electrocardiographic changes),
the results are not directly comparable to ACAS or ACST. However, even in the stenting arm, the cumulative 1-year end point rate of 9.9% is high as compared with the stroke risk associated with asymptomatic carotid artery stenosis (1% to 2%/year). There was no evidence in any subgroup that carotid stenting was superior to endarterectomy for the prevention of stroke as an end point. Because the study did not include medically treated controls, we cannot be certain how these asymptomatic, high-surgical-risk patients would have fared without either procedure.

**Summary and Gaps**
The results of ACST substantially support those of ACAS. Combining data from ACAS and ACST, the total 5-year risk of stroke or procedural morbidity was calculated at 11.5% for deferred endarterectomy versus 6.0% for immediate endarterectomy (5.5% absolute difference, number needed to treat = 18 to prevent 1 event over 5 years). Perioperative risk is not balanced by benefit for ~2 years. These types of results can only be achieved with periprocedural complication rates as low as those reported in these trials (ie, <3%). Although limited by post hoc and nonprespecified analyses, it is clear that careful patient selection is critical, with substantially less benefit or no benefit if all-cause mortality is considered as a part of the end points. The advent of carotid angioplasty–stenting offers another potential intervention. Given the low likelihood of ipsilateral stroke among patients with asymptomatic stenosis, complication rates will need to be in a similar range, and careful patient selection is imperative.

**Recommendations**
It is recommended that patients with asymptomatic carotid artery stenosis be screened for other treatable causes of stroke and that intensive therapy of all identified stroke risk factors be pursued (Class I, Level of Evidence C). The use of aspirin is recommended unless contraindicated because aspirin was used in all of the cited trials as an antiplatelet drug except in the surgical arm of 1 study, in which there was a higher rate of MI in those who were not given aspirin (Class I, Level of Evidence B). Prophylactic carotid endarterectomy is recommended in highly selected patients with high-grade asymptomatic carotid stenosis performed by surgeons with <3% morbidity/mortality rates (Table 7) (Class I, Level of Evidence A). Patient selection should be guided by an assessment of comorbid conditions and life expectancy, as well as other individual factors, should be balanced by an understanding of the overall impact of the procedure if all-cause mortality is considered as one of the end points, and should include a thorough discussion of the risks and benefits of the procedure with an understanding of patient preferences. Carotid angioplasty–stenting might be a reasonable alternative to endarterectomy in asymptomatic patients at high risk for the surgical procedure (Class IIb, Level of Evidence B); however, given the reported perioperative and overall 1-year event rates, it remains uncertain whether this group of patients should have either procedure.

**Sickle Cell Disease**
Sickle cell disease (SCD) is inherited as an autosomal recessive disorder in which the abnormal gene product is an altered hemoglobin β-chain. Although the clinical manifestations are highly variable, SCD typically manifests early in life as a severe hemolytic anemia with painful episodes involving the extremities and bones ("vaso-occlusive crises"), bacterial infections, and organ infarctions, including stroke. Other systemic effects include impaired growth and possible cognitive developmental retardation.

Stroke prevention is most important for patients with homozygous SCD disease because most of the strokes associated with SCD occur in these patients. The prevalence of stroke by 20 years of age is at least 11%, with a substantial number having "silent" strokes on brain magnetic resonance imaging (MRI) (Table 3). The highest stroke rates occur in early childhood. Transcranial Doppler ultrasound (TCD) has made identification of those at highest risk of stroke possible, allowing rational decisions about treatment for primary stroke prevention. The risk of stroke during childhood in those with SCD is 1% per year, but patients with TCD evidence of high cerebral blood flow velocities (time-averaged mean velocity >200 cm/s) have a stroke rate in excess of 10% per year. A randomized trial (Stroke Prevention Trial in Sickle Cell Anemia (STOP)) compared periodic blood transfusion with standard care in 130 children with SCD ranging in age from 2 to 16 years (mean 8 years). Blood transfusions were given an average of 14 times per year for >2 years in the treatment group, with a target reduction of hemoglobin S from a baseline of >90% to <30%. The risk of stroke was reduced from 10% per year to <1%.

The frequency of screening needed to detect most cases at risk has not been determined. Although the STOP study used time-averaged means of the maximum velocity, peak systolic velocity may also be used, with a threshold for prophylactic transfusion placed at 250 cm/s. In general, younger children and those with relatively high cerebral blood flow velocities should be monitored more frequently because of a higher risk of conversion to abnormal in younger patients and in those with TCD velocities closer to the 200-cm/s cutoff. In practice, studies may need to be repeated within days or weeks in cases at or near the threshold for treatment or may be performed annually for cases in which the risk of conversion to abnormal is low.

Unless exchange methods in which blood is removed from the patient with each transfusion are used, long-term transfusion is associated with iron toxicity that must be treated with chelation. In the STOP study, there was no evidence of transfusion-related infection, but iron overload and allopurinol remain important transfusion risks. To address these risks, a randomized controlled trial of withdrawal of transfusion was conducted. This trial (STOP II) tested whether chronic transfusions for primary stroke prevention could be safely discontinued after at least 30 months (range 30 to 91 months) in children who had not had an overt stroke and who had reversion to low-risk TCD velocity with chronic transfusion therapy. Low-risk TCD velocity was defined as <170 cm/s time-averaged mean of the maximum. The study end points were the first occurrence of reversion of TCD to abnormal, confirmed by ≥2 TCDs with mean velocities of 200 cm/s or higher, or stroke. The study was stopped after 79 of a planned sample of 100 children were randomized when
an interim analysis showed poorer outcomes in those who had transfusion therapy discontinued. Eight children (≈20%) tolerated removal from chronic transfusion therapy without apparent adverse consequences, but discontinuation of transfusion after 30 months is not recommended on the basis of STOP II because of a high TCD reversion rate and the small risk of overt stroke despite frequent TCD surveillance.267

MRI has also been used to identify children with SCD who are at risk before clinical events. Observational data from the Cooperative Study of Sickle Cell Disease, which preceded the use of TCD-based monitoring, found that 8.1% of children with an asymptomatic MRI lesion versus 0.5% of those with a normal MRI had a stroke during the ensuing 5 years.268 A randomized controlled trial of MRI-guided prophylactic transfusion is in progress (the Silent Infarct Treatment Trial [SITT]).269 The role of therapies other than transfusion, such as bone marrow transplantation or hydroxyurea, which reduce the number of painful crises but have an uncertain effect on organ damage (including stroke), requires further study.270,271

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

Summary and Gaps
TCD can be used to identify children with SCD who are at high risk of stroke and who may benefit from transfusion therapy. The optimal screening interval has not been established. As reviewed above, treatment criteria using peak systolic velocities have now been published. On the basis of STOP II, even those whose risk of stroke decreases with transfusion therapy according to 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 in view of the data indicating the need for ongoing active treatment despite TCD normalization. Predictive methods other than TCD (eg, magnetic resonance–based techniques) should be systematically compared with, and combined with, TCD to further refine the estimation of stroke risk in individuals. Preventive therapies other than transfusion need to be tested. Data on risk and prevention options in adults with SCD are sorely inadequate, and a stroke prevention strategy for adults needs to be developed.

Recommendations
It is recommended that children with SCD be screened with TCD starting at 2 years of age (Table 7) (Class I, Level of Evidence B). It is recommended that transfusion therapy be considered for those at elevated stroke risk (Class I, Level of Evidence B). Although the optimal screening interval has not been established, it is reasonable that younger children and those with TCD velocities in the conditional range should be rescreened more frequently to detect development of high-risk TCD indications for intervention (Class IIa, Level of Evidence B). Pending further studies, it is reasonable to continue transfusion even in those whose TCD velocities revert to normal (Class IIa, Level of Evidence B). MRI and magnetic resonance angiography (MRA) criteria for selection of children for primary stroke prevention using transfusion have not been established, and these tests should not be substituted for TCD (Class III, Level of Evidence B). Adults with SCD should be evaluated for known stroke risk factors and managed according to the general guidelines in this statement (Class I, Level of Evidence A).

Postmenopausal Hormone Therapy
Although laboratory and observational studies of postmenopausal hormone therapy have suggested a beneficial effect for the prevention of cardiovascular disease272 and a reduction of stroke severity,273 randomized trials suggest harm. Previously, these guidelines surmised that the impact of postmenopausal hormone replacement therapy on stroke risk appeared to be neutral, but because of a lack of controlled studies, definitive conclusions could not be reached.10 Since that time, 3 consistent prospective trials have been completed (Table 4).

The Women’s Estrogen for Stroke Trial (WEST) was designed to determine the effects of hormone therapy on the incidence of vascular events after stroke.274 Although more relevant for secondary prevention, hormone therapy with estradiol did not reduce the risk of recurrent stroke or death. Within the first 6 months, the risk of stroke was higher among those randomized to estradiol (RR 2.3; 95% CI 1.1 to 5.0). In addition, those who had a recurrent stroke and were randomized to hormonal therapy were less likely to recover.

The Heart and Estrogen/Progestrone Replacement Study (HERS) Trial examined the role of hormone therapy (equine estrogens and the progestin medroxyprogesterone) for secondary prevention among postmenopausal women who had an MI.275 The overall trial was negative, with no net effect on the risk of stroke.276

A goal of the Women’s Health Initiative (WHI) was to examine the role of hormone therapy for primary prevention of cardiovascular disease among postmenopausal women.277 Stroke was a prespecified end point. The first results from the WHI were for women with an intact uterus in whom a combination therapy (conjugated equine estrogen and me-droxyprogesterone) was used as the active treatment. The trial was stopped because of an increase in vascular events that included an absolute increase of 8 strokes per 10 000 person-years. A parallel trial included women with a previous hysterectomy who were treated with conjugated equine estrogen.278 The risk of stroke was increased with active treatment (RR 1.39; 95% CI 1.10 to 1.77).

Selective estrogen receptor molecules lack the steroidal structure of estrogen but have a tertiary structure that permits binding to estrogen receptors.279 Exploratory analyses from a trial using a selective estrogen receptor molecule for osteoporosis suggest that these drugs may decrease cardiovascular and cerebrovascular events in women at high risk for vascular disease.280

Summary and Gaps
An increased risk of stroke is associated with the tested forms of hormone therapy. Two trials focused on women without a prior history of stroke and are directly relevant to primary stroke prevention. Prospective randomized data for other forms of hormone therapy are lacking.
**Diet and Nutrition**

In observational studies, several aspects of diet are associated with stroke risk. As reviewed by Bazzano et al.\(^{281}\) and as corroborated by more recent publications,\(^{282}-284\) a generally consistent body of evidence from prospective studies has documented that increased fruit and vegetable consumption is associated with a reduced risk of stroke in a dose-response fashion. For example, in analyses of the Nurses’ Health Study and the Health Professionals’ Follow-Up Study,\(^{286}\) the RR of incident stroke was 0.69 (95% CI 0.52 to 0.92) for persons in the highest versus lowest quintile of fruit and vegetable intake. Median intake in the highest quintile was 10.2 servings of fruit and vegetables in men and 9.2 in women. For each 1-serving/day increment in fruit and vegetable intake, the risk of stroke was reduced by 6%. According to national survey data, daily servings of fruits and vegetables for individuals ≥2 years of age have remained low, just 4.9 servings in 1994 to 1996 and 4.7 servings in 1999 to 2000 (National Cancer Institute Web site: http://cancer.gov/cancerinfo/pdq/prevention/).

In ecological\(^{286}\) and some prospective studies,\(^{287,288}\) a higher level of sodium intake is associated with an increased risk of stroke. A higher level of potassium intake is also associated with a reduced risk of stroke in prospective studies.\(^{289,290}\) 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 results in observational studies.

The potential effects of sodium and potassium on stroke risk appear to be at least partially mediated through blood pressure. In clinical trials, particularly dose-response studies, the relationship between sodium intake and blood pressure is direct and progressive without an apparent threshold.\(^{291}-293\) In other trials, an increased intake of potassium has been shown to lower blood pressure\(^{294}\) and blunt the pressor effects of sodium.\(^{295}\) Diets rich in fruits and vegetables, including the Dietary Approaches to Stop Hypertension (DASH) diet (rich in fruit, vegetables, and low-fat dairy products and reduced in saturated and total fat), lower blood pressure.\(^{296,297}\)

However, there is a reasonable biological basis, and some empirical evidence from animal studies, that the effects of sodium and potassium on stroke are also mediated through mechanisms that are independent of blood pressure.\(^{298}\) As documented in a recent review by the Institute of Medicine,\(^{299}\) 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. In Asian countries, a low intake of animal protein, saturated fat, and cholesterol has been associated with an increased risk of stroke,\(^{300}\) but such relationships have been less apparent in Western countries.\(^{301}\)

**Summary and Gaps**

Randomized controlled trials that are focused on diet and specifically target stroke do not exist. According to epidemiological studies, it is likely that diets rich in fruits and vegetables and with reduced sodium and increased potassium intake would reduce stroke risk.

**Recommendations**

A reduced intake of sodium and increased intake of potassium are recommended to lower blood pressure (Class I, Level of Evidence A), which may thereby reduce the risk of stroke. The recommended sodium intake is ≤2.3 g/d (100 mmol/d), and the recommended potassium intake is ≥4.7 g/d (120 mmol/d). The DASH diet, which emphasizes fruit, vegetables, and low-fat dairy products and is reduced in saturated and total fat, also lowers blood pressure and is recommended (Class I, Level of Evidence A). A diet that is rich in fruits and vegetables may lower the risk of stroke and may be considered (Table 7) (Class IIb, Level of Evidence C).

**Physical Inactivity**

Regular physical activity has well-established benefits for reducing the risk of premature death and cardiovascular disease. The beneficial effects of physical activity have also been documented for stroke.\(^{302}-310\) The Framingham Heart Study, Honolulu Heart Program, and Oslo Study have shown the protective effect of physical activity for men.\(^{303}-305\) For women, the Nurses’ Health Study and Copenhagen City Heart Study demonstrated an inverse association between level of physical activity and stroke incidence.\(^{309,310}\) The protective effects of leisure-time physical activity have also been found for blacks and Hispanics in the National Health and Nutrition Examination Survey (NHANES) I Follow-Up Study and the Northern Manhattan Stroke Study.\(^{306,308}\)

Dose-response studies comparing the effects of vigorous and lower levels of physical activity are limited.\(^{304,307,311}\) In the Northern Manhattan Stroke Study, intensive forms of physical activity provided additional benefits as compared with light to moderate activities. Additional protection was observed with increasing duration of exercise; however, the prevalence of such activities in the elderly was quite low.\(^{308}\) The protective effect of physical activity may be partly mediated through its role in reducing blood pressure\(^{310}\) and controlling other risk factors for cardiovascular disease,\(^{312,313}\) diabetes,\(^{310}\) and increased body weight. Other biological mechanisms have also been associated with physical activity, including reductions in plasma fibrinogen and platelet activity and elevations in plasma tissue plasminogen activator activity and HDL concentrations.\(^{314}-316\)

Currently available data support the benefits of physical activity (Table 7). Guidelines endorsed by the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health recommend that Americans should exercise moderately for ≥30 minutes on most, and preferably all, days of the week.\(^{317,318}\) For stroke, the benefits are apparent...
even for light to moderate activities, such as walking, and the data support additional benefit from increasing the level and duration of recreational activity. Physical activity is a modifiable behavior that requires greater emphasis in stroke prevention campaigns (Table 4).

**Summary and Gaps**

A sedentary lifestyle is associated with an increased risk of stroke. Clinical trials documenting a reduction in the risk of a first stroke with regular exercise have not been done; however, exercise has beneficial effects on several other important stroke risk factors and is associated with a reduction in stroke risk in epidemiological studies.

**Recommendations**

Increased physical activity is recommended because it is associated with a reduction in the risk of stroke (Class I, Level of Evidence B). Exercise guidelines as recommended by the CDC and the National Institutes of Health of regular exercise (≥30 minutes of moderate-intensity activity daily) as part of a healthy lifestyle are reasonable (Table 7) (Class IIa, Level of Evidence B).

**Obesity and Body Fat Distribution**

The traditional classification of weight status is defined by body mass index (BMI: weight [in kilograms] divided by the square of height [in meters]). Persons with a BMI of 25 to 29.9 kg/m² are classified as being overweight, and those with a BMI of ≥30 kg/m² are classified as being obese. Abdominal obesity is commonly measured by either the waist-to-hip ratio or waist circumference. Clinically, abdominal obesity is defined by a waist circumference >102 cm (40 in) in men and 88 cm (35 in) in women. The prevalence rates of obesity and overweight have been increasing in the United States and elsewhere, with the epidemic affecting children as well as adults (Table 4). Being overweight is particularly common among black and Hispanic children.

According to national survey data collected in the period 2000 to 2001, the prevalence of overweight and obesity remains extraordinarily high: 65.7% of US adults are either overweight or obese, and 30.4% are obese.

A growing body of evidence from large-scale prospective studies has documented that increased weight is associated with an increased risk of stroke in a dose-response fashion. Among 234,863 middle-aged men enrolled in the Korean Medical Insurance Corporation Study, the adjusted RR of stroke per 1 U BMI was 1.04 (95% CI 1.03 to 1.05) for total stroke, 1.06 (95% CI 1.04 to 1.07) for ischemic stroke, and 1.02 (95% CI 1.00 to 1.05) for hemorrhagic stroke.

Among 21,414 male health professionals, the adjusted RRs in overweight and obese men as compared with nonoverweight men were 1.32 (95% CI 1.14 to 1.54) and 1.91 (95% CI 1.45 to 2.52) for total stroke, 1.35 (95% CI 1.15 to 1.59) and 1.87 (95% CI 1.38 to 2.54) for ischemic stroke, and 1.25 (95% CI 0.84 to 1.88) and 1.92 (95% CI 0.94 to 3.93) for hemorrhagic stroke. In those studies that examined the effects of obesity (typically defined by BMI) and abdominal body fat, abdominal body fat tended to be a stronger predictor of stroke risk. The age-adjusted RR of stroke was 2.33 (95% CI 1.25 to 4.37) in a comparison of the extreme quintiles of waist-to-hip ratios in male health professionals.

In multivariate analyses that control for other cardiovascular risk factors (blood pressure, blood lipids, and diabetes/insulin resistance), the direct relationship of BMI with stroke often persists; however, the strength of the relationship is typically attenuated. This apparent reduction in the strength of the association between BMI and stroke risk may be misleading because overweight is hypothesized to cause stroke via these other factors.

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

**Summary and Gaps**

A growing body of evidence shows that increased weight is associated with an increased risk of stroke in a dose-response fashion. Although no clinical trial has tested the effects of weight reduction on stroke outcomes, weight reduction is associated with a lowering in blood pressure (see section on hypertension) and may thereby contribute to a reduced stroke risk. Randomized trials of weight reduction for reducing stroke risk should be conducted.

**Recommendations**

Epidemiological studies indicate that increased body weight and abdominal fat are directly associated with stroke risk. Weight reduction is recommended because it lowers blood pressure (Class I, Level of Evidence A) and may thereby reduce the risk of stroke.

**Less Well-Documented or Potentially Modifiable Risk Factors**

**Metabolic Syndrome**

The National Cholesterol Education Program (Adult Treatment Panel III [ATP III]) defined metabolic syndrome as the presence of ≥3 of the following: (1) abdominal obesity as determined by waist circumference >102 cm or >40 inches for men and >88 cm or >35 inches for women; (2) triglycerides ≥150 mg/dL; (3) HDL cholesterol <40 mg/dL for men and <50 mg/dL for women; (4) blood pressure ≥130/≥85 mm Hg; and (5) fasting glucose ≥110 mg/dL.

The World Health Organization modified the definition for epidemiological studies with the addition of hyperinsulinemia (fasting insulin levels in the upper quartile of the non-diabetic population). Obesity and sedentary lifestyle coupled with diet and other factors seem to interact to produce the metabolic syndrome.

Obesity, discussed separately in the previous section, is an important component of the metabolic syndrome and is associated with major health risk factors (such as diabetes, hypertension, and hypercholesterolemia), poor health status, and lower life expectancy. The visceral adiposity characteristic of the metabolic syndrome is associated with insulin...
resistance, inflammation, diabetes, and other metabolic and cardiovascular derangements. Visceral adipocytes provoke insulin resistance by promoting extensive lipolysis and release of fatty acids. They also stimulate inflammation by releasing cytokines and may play a role in the pathophysiology of dyslipidemia, hypertension, impaired thrombolysis, and renal damage.

Leptin, nonesterified fatty acids, plasminogen activator inhibitor-1, tumor necrosis factor, and other factors have been implicated in the adipocyte-mediated pathophysiological processes.

Hyperinsulinemia/insulin resistance is an important marker of the metabolic syndrome. A variety of studies support or refute a relationship between glucose intolerance and stroke risk. However, fasting insulin levels are associated with stroke risk in nondiabetic individuals, hyperinsulinemia is associated with risk indicators of carotid atherosclerosis, and high proinsulin levels may predict first-ever stroke in nondiabetic individuals. A review of 5 prospective and 4 case-control studies concluded that insulin resistance may be a prevalent risk factor for stroke and speculated that new drugs can safely reduce insulin resistance and may be effective for stroke prevention. The relationship between other individual components of the metabolic syndrome and stroke risk is reviewed in other sections.

The metabolic syndrome is highly prevalent in the United States (Table 4). It is estimated that 47 million Americans have the metabolic syndrome, with an age-adjusted prevalence of 23.7% (1988–1994). Mexican Americans have the highest age-adjusted prevalence (31.9%), and among African Americans, women have a 57% higher prevalence as compared with men.

The metabolic syndrome is a substantial predictor of coronary heart disease, cardiovascular disease (which includes coronary heart disease and stroke), and all-cause mortality. However, there is a paucity of information about the specific risk of stroke. Most stroke risk estimates are combined with other outcomes (e.g., cardiovascular disease), making it difficult to determine the specific stroke risk component.

Summary and Gaps

Individual components of the metabolic syndrome have been associated with an increased risk of ischemic stroke and should be treated as appropriate. The specific risk of stroke in persons with the metabolic syndrome is uncertain, as is the impact of treatment of the combined syndrome.

Recommendations

Management of individual components of the metabolic syndrome, including lifestyle measures and pharmacotherapy as recommended in the National Cholesterol Education Program ATP III and the JNC 7 as reviewed in other sections of this guideline, are endorsed. Lifestyle management should include exercise, appropriate weight loss, and proper diet. Pharmacotherapy may include medications for blood pressure lowering, lipid lowering, glycemic control, treatment of microalbuminuria or proteinuria, and antiplatelet therapy (e.g., aspirin) according to the individual circumstance and risk. It is not known whether agents that ameliorate aspects of the insulin resistance syndrome are useful for reducing stroke risk.

Alcohol Abuse

Alcohol abuse can lead to multiple medical complications, including stroke. Strong evidence indicates that alcoholism and heavy drinking are risk factors for all stroke subtypes (Table 4). The majority of studies have suggested a J-shaped relationship between alcohol consumption and ischemic stroke risk, with a protective effect in light or moderate drinkers and an elevated risk with heavy alcohol consumption. Light-to-moderate alcohol consumption (for women ≤1 drink/day and for men ≤2 drinks/day) can increase HDL cholesterol, reduce platelet aggregation, and lower plasma fibrinogen concentration. Heavy alcohol consumption can lead to hypertension, hypercoagulability, reduced cerebral blood flow, and a greater likelihood of atrial fibrillation. A meta-analysis of 35 observational studies categorized alcohol consumption as abstention, <1, 1 to 2, >2 to ≤5, or >5 drinks per day (1 drink defined as 12 g of alcohol). As compared with abstainers, those who consumed >5 drinks per day had a 69% increased stroke risk (RR = 1.69; 95% CI 1.34 to 2.15). Consumption of <1 drink per day, but not abstaining, was associated with a reduced risk (RR = 0.80, 95% CI 0.67 to 0.96), as was consumption of 1 to 2 drinks per day (RR = 0.72; 95% CI 0.57 to 0.91).

The amount and possibly type of alcohol consumed influence risk. In the Copenhagen City Heart Study, consumption of 3 to 5 glasses of wine per day, but not beer or spirits, was associated with a reduced risk of stroke-related mortality. Several other studies have found light-to-moderate consumption of wine to reduce the risk of a first stroke. A meta-analysis of 13 studies of beer and wine consumption found light-to-moderate consumption of wine and to a lesser extent beer was associated with reduced vascular risk.

Summary and Gaps

In retrospective cohort studies, light-to-moderate consumption of alcohol in the form of wine has been associated with a reduced risk of stroke, whereas risk is increased with heavier consumption. Prospective trials are lacking. It is well established that alcohol can induce dependence and that alcoholism is a major public health problem.

Recommendations

For a variety of health benefits, reduction of alcohol consumption in heavy drinkers through established screening and counseling methods as outlined in the US Preventive Services Task Force Update 2004 is endorsed (Table 7). For those who consume alcohol, a recommendation of ≤2 drinks per day for men and ≤1 drink per day for nonpregnant women best reflects the state of the science for alcohol and stroke risk (Class IIb, Level of Evidence B).

Drug Abuse

Drug addiction is often a chronic relapsing disorder associated with a number of societal and health-related problems. Drugs of abuse, including cocaine, amphetamines, and heroin, have been associated with an increased risk of stroke.
These drugs can cause abrupt changes in blood pressure, induce vasculitic-type changes, lead to embolization caused by infective endocarditis, and induce hemostatic and hematoletic abnormalities that can result in increased blood viscosity and platelet aggregation. Information about stroke-related drug abuse is mainly limited to epidemiological studies focused on urban populations. An increase in the risk of both ischemic and hemorrhagic stroke has been reported. In 1 study, drug abuse increased the risk of stroke 6.5-fold (95% CI 3.1 to 13.6) across all age groups and with an RR of 11.2 (95% CI 3.2 to 42.5) in persons <35 years of age. Long-term treatment strategies based on medication, psychological support, and outreach programs play an important part in treatment of drug dependency.

Summary and Gaps
Several drugs of abuse have been associated with stroke (Table 4). However, there is a paucity of data on the independent risk of stroke associated with drugs of abuse and no controlled trials demonstrating a reduction in risk with abstinence.

Recommendation
Successful identification and management of drug abuse can be challenging. When a patient is identified as having a drug addiction problem, referral for appropriate counseling may be considered (Table 7) (Class Ib, Level of Evidence C).

Oral Contraceptive Use
Much of the perceived increased stroke risk associated with the use of OCs is based on early studies with high-dose preparations (ie, first-generation OCs containing $\geq 50 \mu g$ of estradiol). The majority of studies of later-generation OCs containing lower doses of estrogens did not find an increased risk of stroke. However, at least 1 study reported an increased risk of stroke in women using first-, second-, or third-generation OCs. Meta-analyses have also been conflicting and the reasons for the discrepancy are not certain. Fewer data are available on the association between OC use and hemorrhagic stroke. The reported risks appear lower than for ischemic stroke except among older women in whom the risk of hemorrhagic stroke is greatest. Few studies have examined the association between the use of OCs and less common stroke mechanisms. One exception is cerebral venous thrombosis, for which there are data to suggest an association, especially among women with congenital thrombophilias such as factor V Leiden or a prothrombin gene mutation.

Some groups of women appear to be at higher risk for stroke associated with OC use. Women who are $>35$ years of age, smoke cigarettes, are hypertensive, are diabetic, have migraines, or have had prior thromboembolic events (especially if while on OCs) may be at increased stroke risk if they use OCs. Some data suggest that the total stroke risk may be more than additive for combinations of smoking, migraine with aura, and age $>35$ years, but the issue remains unsettled for low-dose OCs.

The absolute increase in stroke risk with low-dose OCs, if one exists, is small. Estimates of the incidence of ischemic stroke in young women range from 0.9 to $\approx 10$ per 100 000. Using the highest part of this range, even if the risk of stroke is increased by as much as 30% (ie, 3 per 100 000), the excess number of strokes associated with OC medication remains several-fold lower than the mortality rate for pregnancy in the United States (9 per 100 000 live births).

Summary and Gaps
The risk of stroke associated with OC use is low (Table 4). Certain women, particularly those who have had a prior thrombotic event, may be at higher risk. Estimates are primarily based on epidemiological studies.

Recommendations
The incremental risk of stroke associated with use of low-dose OCs in women without additional risk factors, if one exists, appears low (Class III, Level of Evidence B). It is suggested that OCs be discouraged in women with additional risk factors (eg, cigarette smoking or prior thromboembolic events) (Class III, Level of Evidence C). For those who elect to assume the increased risk, aggressive therapy of stroke risk factors may be useful (Class IIb, Level of Evidence C).

Sleep-Disordered Breathing
Epidemiological studies suggest that habitual snoring is a risk factor for ischemic stroke and is independent of confounding factors such as hypertension, ischemic heart disease, obesity, and age (Table 4). Consistent with these observations, a case-control study of 181 patients found that excessive daytime sleepiness likely due to obstructive sleep apnea was associated with stroke (OR = 3.07, 95% CI 1.65 to 6.08). A 10-year observational study of 1651 men found that severe obstructive sleep apnea-hypopnea (apnea-hypopnea index $>30$/h of sleep) increased the risk of fatal (OR = 2.87, 95% CI 1.17 to 7.51) and nonfatal (OR = 3.17, 95% CI 1.12 to 7.52) cardiovascular events (MI, acute coronary insufficiency requiring coronary artery bypass surgery and/or percutaneous transluminal angioplasty, and stroke) as compared with healthy participants. The outcomes of those who were compliant with continuous positive airway pressure (CPAP) treatment did not differ from outcomes of controls. Those with obstructive sleep apnea who were treated with CPAP did not differ with regard to fatal (OR = 1.05, 95% CI 0.39 to 2.21) or nonfatal (OR = 1.42, 95% CI 0.52 to 3.40) cardiovascular events as compared with healthy participants. However, the outcomes of those who were or were not treated with CPAP did not significantly differ (the 95% CIs overlap). Data on stroke was not reported separately.

Snoring may be a marker for sleep-disordered breathing (SDB), which can secondarily increase stroke risk by leading to or worsening hypertension and heart disease and possibly by causing reductions in cerebral blood flow, altered cerebral autoregulation, impaired endothelial function, accelerated atherogenesis, hypercoagulability, inflammation, and paradoxical embolism in patients with PFO. For example, the community-based Sleep Heart Health Study found a dose-response relationship between SDB and hypertension. Another study found a similar association. Each additional apneic event per hour of sleep increases the odds of...
hypertension by 1%, and each 10% decrease in nocturnal oxygen saturation increases the odds by 13%. The association of SDB with drug-resistant hypertension is particularly high. In patients with advanced SDB, cardiac arrhythmias, atrioventricular block, and atrial fibrillation appear when the oxyhemoglobin saturation falls to <65%. Rapid eye movement sleep–related apnic events with oxygen desaturation can be profound in the setting of abdominal obesity, which may contribute to the observed epidemiological link between abdominal obesity, hypertension, and vascular risk.

Treatment of SDB must be individualized and can include CPAP ventilation, bi-level positive airway pressure, and automatic control of airway pressure delivery with CPAP devices. A variety of surgical interventions and prosthetic oral devices are available. Successful treatment of SDB can lead to a reduction in blood pressure.

**Summary and Gaps**

SDB (sleep apnea) is associated with a variety of other stroke risk factors and adverse cardiovascular events and may independently contribute to stroke risk (Table 4). Successful treatment of sleep apnea can reduce blood pressure. There are no prospective randomized studies showing that treatment of sleep apnea reduces stroke risk.

**Recommendations**

Questioning bed partners and patients, particularly those with abdominal obesity and hypertension, about symptoms of SDB and referral to a sleep specialist for further evaluation as appropriate may be reasonable, especially in the setting of drug-resistant hypertension (Table 7). The risk may be particularly high in young adults.

**Migraine**

Migraine headache has been most consistently associated with stroke in young women. Most studies have not found any association between migraine and stroke in those >60 years of age. The OR for migraine in stroke patients ranges from 1.48 (95% CI 1.0 to 2.2) in a study of working adults to 6.2 (95% CI 2.1 to 18.0) in young women who have migraine with aura. A meta-analysis of 6 case-control studies focusing on migraine and stroke reported a summary OR of 2.08 (95% CI 1.68 to 2.58). On the basis of an OR of 2.0, the population-attributable risk for migraine is estimated to be 17% for women between 20 and 44 years of age. This estimate does not take into consideration additional vascular risk factors that have consistently been associated with an increased stroke risk in young adults with migraine.

Migraine headache characteristics, such as frequency or severity, have not been accounted for in most case-control studies. A Dutch population-based study of migraine patients and matched controls investigated the relationship between silent infarction on MRI and headache characteristics. Although there was no overall difference between the 2 groups, migraine patients had a 7-fold increased odds of silent brain infarction localized to the posterior circulation. This also correlated positively with attack frequency. Risk factors such as hypertension, smoking, and OC use did not modify the effect of migraine on deep white matter lesions in women. Whether this represents a true risk for clinical stroke is uncertain, and there is no evidence that prevention of migraine attacks decreases the risk of silent ischemic damage.

Several of the mechanisms underlying the pathophysiology of migraine with aura have been linked to stroke risk. These include reduced blood flow, blood volume, and oligemia, especially the posterior circulation. Another mechanism that links migraine and stroke in young adults is paradoxical embolism via a PFO. PFOs are more common in both young patients with cryptogenic stroke and those with migraine, particularly migraine with aura. Speculation has suggested a relationship between PFO and migraine whereby microemboli flowing through the PFO cause brain ischemia and thereby trigger migraine, especially migraine with aura. Migraine patients also have increased platelet activation and platelet–leukocyte aggregation, a mechanism that may increase the risk for emboli formation as well as provide a link between migraine and stroke risk at a cellular level. The majority of patients who are diagnosed with a PFO have already had a first ischemic stroke or TIA; therefore, this diagnostic information is most appropriate for secondary rather than primary prevention. However, primary prevention may become an issue if more patients undergo evaluation for PFO because of migraine headaches.

**Summary and Gaps**

Migraine headache has been most consistently associated with stroke in young women. Specific data showing that migraine prophylaxis decreases stroke risk are lacking. No proven primary prevention strategies exist for patients with migraine and/or PFO.

**Recommendations**

There are insufficient data to recommend a specific treatment approach that would reduce the risk of first stroke in women with migraine, including migraine with aura.

**Hyperhomocysteinemia**

Homocysteine is a sulfhydryl-containing amino acid derived from dietary methionine. Numerous studies support an association between elevated homocysteine levels and atherosclerotic disease. The NHANES Epidemiologic Follow-up Study III found that subjects in the highest quartile of homocysteine had an adjusted OR of 19% lower risk of stroke (OR = 0.81; 95% CI 0.69 to 0.95). The Framingham Study also found that baseline total homocysteine levels were an independent risk factor for incident stroke in the elderly. In the Framingham Heart Study, the RR for stroke, in a comparison of the lowest quartile with the highest, was 1.82 (95% CI 1.14 to 2.91). A nested case-control study from the Benznidate Infarction Prevention cohort found that patients with preexisting coronary heart disease and a homocysteine level at the highest quartile (>17.4 μmol/L) had an adjusted OR of 4.6 (95% CI 1.3 to 18.9) for ischemic stroke as compared with those in the...
lowest quartile. There was a linear trend across all quartiles of homocysteine concentrations that was independent of traditional risk factors or inflammatory markers. The risk estimate from NHANES III coupled with prevalence estimates gives a population-attributable risk of 26% for men 40 to 59 years of age, 35% for men ≥60 years of age, 21% for women 40 to 59 years of age, and 37% for women ≥60 years of age. These population-attributable risk estimates must be interpreted with caution because no data are available that would permit the estimation of population-attributable risk after adjustment for other cerebrovascular risk factors that are positively correlated with homocysteine levels.

A single-nucleotide polymorphism in the gene methylene-tetrahydrofolate reductase (MTHFR), in which cytosine (C) is replaced by thymidine (T) at base position 677, reduces activity of the enzyme that metabolizes homocysteine, resulting in an increase in serum homocysteine concentration. The homozygous TT genotype is found in ~10% to 12% of the population and is associated with a 25% higher homocysteine level than in those patients with a wild-type CC genotype. A recent meta-analysis was performed on 72 studies of MTHFR gene prevalence in vascular disease and 20 prospective studies of serum homocysteine in disease risk. A 5-μmol/L increase in serum homocysteine was associated with an increased OR in ischemic heart disease (OR = 1.42; 95% CI 1.11 to 1.89) and an OR for stroke of 1.59 (95% CI 1.2 to 1.96). Furthermore, a 3-μmol/L decrement of homocysteine concentration was associated with decrements in the risk of ischemic coronary disease by 16% and stroke by 24%. Although the definition of hyperhomocysteinemia has not been standardized across epidemiological studies, fasting plasma levels of homocyst(e)ine ≥16 μmol/L are frequently classified as indicating hyperhomocysteinemia (although the risk is likely continuous). In the Framingham Heart Study original cohort (67 to 96 years of age), 19% had homocysteine concentrations >16.4 μmol/L. Homocysteine concentrations increase with age, with men having higher levels than women, especially at younger ages. From NHANES III, the prevalence of high homocyst(e)ine (defined as ≥11.4 μmol/L) for men 40 to 59 years of age and ≥60 years of age are 28.6% and 43.2%, respectively. For women 40 to 59 years of age and ≥60 years of age, the prevalences of high homocysteine (defined as >10.4 μmol/L) are 21.1% and 46.5%, respectively. Age-related reductions in renal function may be partially responsible for this relationship because homocysteine levels increase in persons with kidney disease.

The B vitamins (folic acid, B12, and B6) reduce homocysteine serum levels across the range of baseline homocysteine. This information holds great promise given that B vitamin supplementation has been associated with a reduction in atherosclerotic plaque progression. However, no randomized trials have been conducted showing that lowering elevated homocysteine levels reduces the risk of a first stroke. The Vitamin Intervention for Stroke Prevention (VISP) trial tested whether high doses of B vitamins (25 mg of pyridoxine, 0.4 mg of cobalamin, and 2.5 mg of folic acid) given to reduce total homocysteine levels would reduce the risk of recurrent stroke over 2 years as compared with lower doses (200 μg of pyridoxine, 6 μg of cobalamin, and 20 μg of folic acid). The mean reduction of total homocysteine was only 2 μmol/L greater in the high- versus low-dose groups, with no treatment effect on the risk of recurrent stroke (RR = 1.0, 95% CI 0.8 to 1.3) or on the combined risk of any stroke, coronary heart event, or death (RR = 1.0, 95% CI 0.8 to 1.1). However, as with observational studies, there was a consistent overall relationship between homocysteine levels and vascular risk. The VISP trial was methodologically complex, and a benefit of treatment of elevated homocysteine levels cannot be excluded.

Summary and Gaps

Epidemiological and prospective studies show a positive relationship between blood homocysteine levels and stroke risk (Table 4). Prospective trials designed to determine whether pharmacological lowering of total homocysteine reduces the risk of a first stroke are needed.

**Recommendations**

Recommendations to meet current guidelines for daily intake of folate (400 μg/d), B6 (1.7 mg/d), and B12 (2.4 μg/d) by consumption of vegetables, fruits, legumes, meats, fish, and fortified grains and cereals (for nonpregnant, nonlactating individuals) may be useful in reducing the risk of stroke (Class IIb, Level of Evidence C). There are insufficient data to recommend a specific treatment approach that would reduce the risk of first stroke in patients with elevated homocysteine levels. In the interim, use of folic acid and B vitamins in patients with known elevated homocysteine levels may be useful given their safety and low cost (Class IIb, Level of Evidence C).

**Elevated Lipoprotein(a)**

Lipoprotein(a) [Lp(a)], a lipid-protein complex with proatherogenic and prothrombotic properties, has emerged as a risk factor for coronary heart disease. Lp(a) resembles an LDL particle in which apolipoprotein B-100 is linked by a single interchain disulfide bridge to apolipoprotein(a) [apo(a)]. It enhances arterial cholesterol deposition, thereby promoting atherogenesis. Furthermore, apo(a) has a high sequence homology with plasminogen and is believed to increase the risk of thrombosis through inhibition of plasminogen activation resulting from the interaction with the ternary complex of tissue plasminogen activator, plasminogen, and fibrin. Lp(a) plasma concentration and fibrinolytic activity are reported to be dependent on the apo(a) isoform size. A meta-analysis of 27 prospective studies with a mean follow-up period of 10 years found that patients with baseline Lp(a) levels in the top third of the concentration distribution have an ~60% increased risk of coronary heart disease as compared with those with Lp(a) levels in the bottom third (RR = 1.6; 95% CI 1.4 to 1.8; P = 0.00001). Considerable evidence suggests that high Lp(a) levels promote ischemic stroke, but findings have not been completely consistent (Table 4). Along with other prothrombotic factors, elevated Lp(a) has been associated with the rare occurrence of ischemic stroke in childhood.
stroke patients with intracranial stenosis demonstrated by TCD showed that patients in the highest Lp(a) quartile had an increased likelihood of having ≥3 high-grade intracranial stenotic lesions (OR=3.43; 95% CI 1.04 to 11.33; P=0.04) as compared with those in the lowest quartile. Multiple logistic regression models identified diabetes and high Lp(a) as independent markers for intracranial large-artery occlusive disease.466 A prospective study of 5888 adults >65 years of age enrolled in the Cardiovascular Health Study found that men in the highest quintile had an adjusted RR of stroke of 2.92 (95% CI 1.53 to 5.57; P=0.003). The increase in RR was identified in elderly men, but no increase in risk was seen in elderly women. Elevated levels of Lp(a) can be reduced by ≈25% with niacin.469 Other lipid-lowering medications do not affect Lp(a) levels but may reduce overall lipoprotein-associated risk.

Summary and Gaps
Additional studies are necessary to determine whether reduction of Lp(a) is associated with a reduction in stroke risk.

Recommendations
Although no definitive recommendations about Lp(a) modification can be made because of an absence of outcome studies showing clinical benefit, treatment with niacin (extended-release or immediate-release formulation at a total daily dose of 2000 mg/d as tolerated) can be considered because it reduces Lp(a) levels by ≈25% (Class IIb, Level of Evidence C). Further recommendations must await the results of prospective trials utilizing niacin and statins in subjects stratified for Lp(a) concentration and apo(a) isoform subtypes.469

Elevated Lipoprotein-Associated Phospholipase A2
Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a calcium-independent serine lipase that is associated with LDL in human plasma.470 Elevated plasma levels of Lp-PLA2 are associated with an increased risk of cardiovascular events, independent of other risk factors.471–473 In a population-based study, those in the highest versus the lowest quartile of Lp-PLA2 levels had a 2-fold increased risk of ischemic stroke (HR=1.97, 95% CI 1.03 to 3.79), even after adjustment for age, sex, BMI, systolic blood pressure, non-HDL cholesterol level, HDL cholesterol level, diabetes, smoking, cholesterol-lowering medication, C-reactive protein (CRP), white blood cell count, and alcohol consumption.474 Lp-PLA2 levels can be reduced with statins,475 fenofibrate,476 and β-blockers.477 There are no outcome studies showing whether reducing Lp-PLA2 levels, independent of other risk factors, reduces the risk of ischemic stroke.

Summary and Gaps
Elevated Lp-PLA2 is associated with an increased risk of cardiovascular events, and in 1 population-based study, an increased risk of stroke. Additional studies are required to better define its independent impact on stroke risk and the effects of treatment.

Recommendations
No recommendations about Lp-PLA2 modification can be made because of an absence of outcome studies showing clinical benefit with reduction in blood levels of Lp-PLA2.

Hypercoagulability
Most of the acquired and hereditary hypercoagulable states (thrombophilias) are associated with venous thrombosis but not cerebral infarction (Table 4). Of these, the presence of antiphospholipid antibodies (aPLs) is most likely to be associated with arterial thrombosis. Anticardiolipin antibody (more prevalent but less specific) and lupus anticoagulant (less prevalent but more specific) tests are most frequently used to detect aPL. Although previous retrospective studies suggested an association between anticardiolipin antibodies (ACLs) and ischemic stroke,478 the Antiphospholipid Antibody and Stroke Study (APASS) (using a cutoff of ACL immunoglobulin G titer of >21 μg/dL) did not find an association between aPL and subsequent ischemic stroke (or any vascular occlusive event).479 Similarly, 2 other well-designed longitudinal studies in the elderly found no association between stroke recurrence and elevated ACL titers.480,481 The Framingham Offspring Cohort Study did find an association between ACL titers and ischemic stroke or TIA, but only in women.482 Even if an elevated ACL titer is found in a stroke patient, APASS found no differential response to aspirin versus warfarin in the prevention of recurrent events.479 Overall, although elevated ACL titers may be commonly found in ischemic stroke patients, the strength of the association between elevated ACL titers and stroke etiology or risk is questionable.

The shortcoming of many studies of ACL in stroke patients has been the use of the ACL ELISA, a test with low sensitivity. The assay for anti-β2 glycoprotein 1 antibodies, a cofactor for antiphospholipid binding, is specific for thrombosis, including stroke and MI.483 However, only a few studies have utilized this test.479,483

There are data suggesting that young women with ischemic stroke have a higher prevalence of aPL.484 Therefore, those stroke patients (primarily young women) who have a history of thrombotic events and meet the laboratory criteria for antiphospholipid syndrome485 might benefit from primary prevention strategies, such as moderate-intensity warfarin (INR 2.0 to 3.0)214 or other antithrombotic therapies. This is currently being tested in a primary prevention trial of warfarin therapy (INR 2.0 to 2.5) to decrease thromboembolic events in patients with lupus and aPL.486

The majority of the case-control studies have not found an association between other hereditary hypercoagulable states, such as factor V Leiden or prothrombin 20210 mutations, or deficiencies of protein C, protein S, or antithrombin III, and stroke (Table 4).57,58 However, 1 study has suggested that hypercoagulable states may be more frequent in stroke patients with a PFO as compared with those without a PFO. That study found no difference in the prevalence of either the factor V Leiden or prothrombin 20210 mutation in patients with cryptogenic strokes versus controls. However, the prevalence of prothrombin 20210 mutation alone (OR 10.09; 95% CI 1.09 to 109) was higher in those with cryptogenic stroke and PFO versus those without PFO,487 suggesting a greater thrombotic risk in the setting of a PFO versus either condition alone.
Summary and Gaps
Young women with ischemic stroke have a higher prevalence of aPL. The majority of case-control studies have not found an association between other hereditary hypercoagulable states and stroke. The relationship between the presence of a PFO and thrombophilia deserves further study, as it may impact primary and secondary stroke prevention strategies.

Recommendations
There are insufficient data to support specific recommendations for primary stroke prevention in patients with a hereditary or acquired thrombophilia.

Inflammation
Risk factors and medical conditions that disrupt the integrity of the endothelial lining of the cerebral blood vessels increase the potential for intraluminal thrombosis and stroke. Atherosclerosis, one of the most common causes of stroke, is a chronic inflammatory condition initiated by a host of agents that injure the endothelial surface. CRP is an acute phase reactant and a component of the human innate immunity, which increases in response to inflammatory stimuli and is a known mediator of complement activity, adhesion molecule production, and chemokine and thrombogenic factor release. Numerous cohort studies have shown a strong correlation between elevated CRP levels and cardiovascular/cerebrovascular events and indicate a 2- and 3-fold increase in stroke risk in healthy men and women, respectively. When comparing the highest versus the lowest quartile for CRP, the age-adjusted risk of first ischemic stroke and TIA is 2.0 (P=0.027) for men and 2.7 (P=0.0003) for women (Table 4). The multivariate-adjusted trend in RR of ischemic stroke across CRP quartiles is 1.25 (95% CI 1.01 to 1.54) for men and 1.30 (95% CI 1.07 to 1.55) for women. CRP levels correlate with the 10-year Framingham Coronary Heart Disease Risk Score (FCRS) but not with its individual components. CRP adds to the predictive value of the Framingham Risk Score and to the vascular risk associated with the metabolic syndrome. Population-based studies provide data supporting cutpoints in CRP levels associated with increased risk and the determination of survival curves associated with CRP and LDL cholesterol levels. CRP cutoff levels for cardiovascular events, which include coronary heart disease, ischemic stroke, and cardiovascular death, are RR 1.6 (95% CI 1.1 to 2.4) for CRP levels 1.08 to 2.09 mg/L; RR 2.0 (95% CI 1.3 to 3.0) for CRP levels 2.09 to 4.19; and RR 2.3 (95% CI 1.6 to 3.4) for CRP levels >4.19 mg/L; P<0.001. RR for ischemic stroke is significantly increased in patients with CRP levels >1.08 (RR >2.0), and CRP levels of >4.19 mg/L are associated with RR for ischemic stroke of 3.0 compared with the lowest quintile of CRP level <0.5. CRP levels are dependent on the patient’s ethnic/racial group, which must be taken into consideration when the influence of CRP-associated risk is determined.

Prospective randomized treatment trials with statins show reductions in coronary atherosclerotic plaque progression and cardiovascular events and a strong association between the utilization of statins and a reduction of CRP levels. Patients who have had an acute coronary syndrome and have low CRP levels (<2 mg/L) after statin therapy have better clinical outcomes (ie, reduction of recurrent MI or coronary death) as compared with those with higher CRP levels, regardless of whether the LDL cholesterol level was reduced to <70 mg/dL. Statin dose was not altered to achieve these levels. Another study found a reduction in coronary events in those with relatively low lipid levels but with elevated CRP levels who were treated with a statin, but patients were not randomized according to CRP levels and there was no mention of an effect on stroke. It remains uncertain whether asymptomatic persons at otherwise low cardiovascular risk and without dyslipidemia who have elevated CRP levels have a reduced risk of stroke associated with statins.

The vascular response to injury is characterized by an upregulation of adhesion molecules (such as P-selectin, intracellular adhesion molecule-1, E-selectin, and vascular cell adhesion molecule-1) and prompts the migration of inflammatory cells, monocytes, T lymphocytes, and lipids into the wall of the vessel. Macrophage and T-cell interaction, in part mediated by CD40–CD40L interactions, results in the release of proinflammatory cytokines such as tumor necrosis factor-α and interleukin (IL)-1β, and chemokines such as IL-8 and monocyte chemotactic protein-1, that serve to convert the endothelial surface over the plaque from an anticoagulant to a procoagulant and prothrombotic state.

Intraplaque inflammatory cells mediate the release of matrix metalloproteinases, such as gelatensase-B (MMP-9), stromelysin (MMP-3), and gelatensase-A (MMP-2), that cause instability of the fibrous cap leading to rupture. Symptomatic carotid atherosclerotic plaques have an increase of inflammatory and prothrombotic mediators as compared with plaques from asymptomatic patients. Antigen-driven T-cell activation provides a pathway by which quiescent plaques can be rapidly activated to a symptomatic state.

Numerous inflammatory markers are emerging as identifiable factors associated with atherosclerotic plaque instability. The CD40/CD40 ligand system (CD40/CD40L) plays a role in the activation of inflammatory mediators in atherogenesis as well as representing a biologically active soluble mediator released by platelets that is associated with cardiovascular risk. Elevated CD40L (>5.0 µg/L) had an adjusted HR of 2.71 (95% CI 1.51 to 5.35) for death and nonfatal MI as compared with patients with low levels of the ligand. The risk was significantly reduced by treatment with the glycoprotein IIb/IIIa receptor inhibitor abciximab (HR=0.39; CI 0.20 to 0.68) as compared with those given placebo. This suggests that CD40L expression may identify a subgroup of patients most likely to benefit from antiplatelet therapy. A nested case-control analysis among participants in the Women’s Health Study revealed that women with CD40L concentrations above the 95th percentile of the control distribution (>3.7 ng/mL) had a significantly increased RR of developing MI, stroke, and cardiac death (RR=3.3; 95% CI 1.2 to 8.6). In a study evaluating markers after first acute ischemic cerebrovascular events, soluble CD40L was significantly elevated in patients with noncardioembolic stroke as compared with control subjects with comparable atherosclerotic risk profiles (17.1±7.5 ng/mL versus 3.4±1.6 ng/mL). Levels remain significantly elevated in both stroke and TIA.
patients at 3 months, indicating continuous marker elevation associated with the disease state.

IL-18 is a potent proinflammatory cytokine with proathero-
genic properties. With the use of real-time quantitative polymer-
ase chain reaction, significant expression of IL-18 messenger RNA was found in human carotid atherosclerotic plaque as compared with little or no expression in normal arteries. Fur-
thermore, IL-18 messenger RNA was >3-fold higher in symp-
tomatic (unstable) carotid plaque versus asymptomatic (stable) plaque (P<0.01).

In a nested case-control comparison of 10 600 healthy European men in a prospective epidemiological study of MI, plasma levels of soluble IL-18 were significantly higher in men who developed coronary events (n=335 cases) than in age-matched controls (n=678), 225.1 versus 203.9 pg/mL, P=0.005, with a RR for coronary events of 1.82 (95% CI 1.30 to 2.55).

Polymorphisms of genes that regulate inflammation are being identified as risk factors individually and in combination. A study examining the IL-6 GG, IL-6 GC, monocyte chemotactic protein-1 GG, intracellular adhesion molecule-1 EE, E-select AA, and MMP-3 5A5A genotypes reveals that carrying 1 proinflam-
macrophages, T lymphocytes, human leuko-
cytes, human IgA titer of 1:16 treated with 12 weeks of azithromycin had no reduction in the

To take full advantage of the evolving understanding of the inflammatory profile in atherosclerosis from the standpoint of both predictive value and primary risk reduction, treatment based on reliable biomarkers must be subjected to prospective randomized trials.

Summary and Gaps
Data supporting the importance of inflammation in the patho-
physiology of atherosclerotic vascular disease are mounting; however, prospective studies demonstrating a reduction in risk of stroke due to the treatment of persons with elevated inflam-
amatory markers or due to treatment to achieve a target level of any inflammatory marker (eg, CRP) are currently lacking.

Recommendations
Currently, no evidence supports the use of high-sensitivity CRP (hs-CRP) screening of the entire adult population as a marker of general vascular risk. Aggressive risk factor mod-
ification is recommended for patients at high risk for stroke
given exposure to traditional risk factors regardless of hs-
CRP level. In agreement with AHA/CDC guidelines, hs-CRP can be useful in considering the intensity of risk factor modification in those at moderate general cardiovascular risk on the basis of traditional risk factors (Class IIA, Level of Evidence B).

Infection
Case-control studies have found that recent infections (within 1 week) are associated with acute stroke. This may be in part related to generalized activation of circulating leuko-
cytes that enhance the tendency for thrombosis at the site of atherosclerotic plaque. In addition, numerous pathogens have been associated with the initiation, progression, and develop-
ment of atherosclerotic disease and increased risk for future ischemic vascular events. Among these, Chlamydia pneumonias, an obligate intracellular organism, has been identified in atherosclerotic plaques.

In the population-based Northern Manhattan Stroke Study, elevated C pneumoniae immunoglobulin A titers were associated with the risk of ischemic stroke (adjusted OR 4.51; 95% CI 1.44 to 14.06). An association with stroke risk was identified in both younger and older persons, men and women, and in Hispanics, blacks, and whites. Despite numerous studies finding an association between elevated serum antibody titers for C pneumoniae and cerebrovascular and cardiovascular events, there remains no clear evidence of risk reduction associated with antibiotic therapy.

One study reported a 5-fold decrease in recurrent cardiovascular events in patients with high positive immunoglobulin G titers for C pneumoniae (≥1:64) who were treated with azithromycin (OR=0.2; 95% CI 0.05 to 0.8). Subsequent studies failed to demonstrate benefit of antibiotics in patients who were seropositive for C pneumoniae.

In a randomized placebo-controlled trial, patients with previous MI and a C pneumoniae immunoglobulin G titer of ≥1:16 treated with 12 weeks of azithromycin (n=3879) or placebo (n=3868) had no reduction in the number of vascular end points with antibiotic therapy. A study randomizing 4162 patients with acute coronary syn-

Periodontal disease found to be related to continuous and intermittent seeding of the bloodstream with Gram-negative organisms has been associated with carotid atherosclerosis
and the risk of stroke. NHANES I found an adjusted OR of 2.11 (95% CI 1.3 to 3.42) for ischemic stroke among those with periodontal disease.\textsuperscript{531}

Cytomegalovirus (CMV) is purported to increase the risk of development of vascular disease by increasing inflammatory mediators, facilitating the coagulation cascade, and enhancing adhesion molecule expression on vascular endothelial cells. Seropositivity for CMV was associated with increased risk for combined end points of carotid artery intimal-medial thickness and stenosis for immunoglobulin G titers (adjusted OR 1.7; 95% CI 1.1 to 2.8) and for immunoglobulin A (adjusted OR 2.3; 95% CI 1.1 to 4.9).\textsuperscript{532} Additionally, case-control studies found that CMV-specific immune complexes represent a strong independent stroke risk factor (OR 7.60; 95% CI 3.21 to 17.96).\textsuperscript{533} Subgroup analysis

Infectious burden of 4 to 5 seropositivities was associated with atherosclerotic plaque.\textsuperscript{535} Case-control studies found that the association between H pylori and stroke appears to be dependent on strain. H pylori with cytotoxin-associated gene-A seropositivity was associated with ischemic stroke (OR 1.97; 95% CI 1.33 to 2.91) in contrast to general H pylori seropositivity (OR 1.20; 95% CI 0.82 to 1.76).\textsuperscript{536} CagA-positive H pylori have further been shown to be independently associated with carotid plaque irregularities (adjusted OR 8.42; 95% CI 1.58 to 44.64).\textsuperscript{537} Future studies on H pylori influence on both the development of atherosclerosis and symptomatic disease will require knowledge of strain specificity.\textsuperscript{538}

Aggregates suggest that no single organism is likely to account for atherosclerosis. The evolving concept of “infectious burden” proposes that lifelong exposure to multiple organisms enhances the development and activation of atherosclerotic plaque. In a prospective study evaluating the aggregate burden of 8 pathogens on the progression of carotid atherosclerosis, an increased number of seropositive organisms, including C pneumoniae, H pylori, H influenzae, M pneumoniae, CMV, Epstein-Barr virus, and Herpes simplex virus types I and II, was associated with atherosclerotic plaque progression. Infectious burden of 4 to 5 seropositivities had an OR of 1.8 (95% CI 1.1 to 2.9), and 6 to 8 seropositivities had an OR of 3.8 (95% CI 1.6 to 8.8) for atherosclerotic plaque progression, as compared with 0 to 3 seropositivities.\textsuperscript{539} Under the same paradigm, an increased risk for coronary and peripheral vascular disease, as well as cardiovascular death, was associated with a person’s increasing number of seropositive organisms.\textsuperscript{540} In a study using within-person comparison and case-series methodology in which 50,766 patients with first stroke (median age at stroke 78.3 years) were studied, the presence of a systemic respiratory tract infection imparted an age-adjusted incidence ratio of 3.19 (95% CI 2.8 to 3.62) in the first 3 days, with a persistently increased, although less robust, incidence ratio of 1.33 (95% CI 1.26 to 1.40) at 91 days for stroke. Urinary tract infections were also associated with an increased incidence ratio for stroke over the first 3 days (incidence ratio 2.72; 95% CI 2.32 to 3.20) that persisted at 91 days (incidence ratio 1.22; 95% CI 1.15 to 1.30). These data support the concept that exposure to multiple organisms can influence stroke incidence in the population.\textsuperscript{541}

Summary and Gaps

Despite numerous studies demonstrating bacterial pathogens in coronary and carotid atherosclerotic plaque, treatment with antibiotics has not been proven to lower the risk of ischemic stroke, and no specific recommendation can be made about the usefulness of this approach for primary stroke prevention. The concept of infectious burden implies that no single antiinfectious regimen is likely to be effective. Further studies are required to test this hypothesis.

Recommendations

Data are insufficient to recommend antibiotic therapy for stroke prevention on the basis of seropositivity for 1 or a combination of putative pathogenic organisms. Future studies on stroke risk reduction based on treatment of infectious diseases will require careful stratification and identification of patients at risk for organism exposure.

Aspirin for Primary Stroke Prevention

The US Preventive Services Task Force recommends aspirin at a dosage of 75 mg/d for cardiac prophylaxis for persons whose 5-year coronary heart disease risk is ≥3%.\textsuperscript{542} The 2002 update of the AHA Guidelines for the primary prevention of cardiovascular disease and stroke agrees with the US Preventive Services Task Force Report on the use of aspirin in persons at high coronary risk but use a ≥10% risk per 10 years, rather than >3% risk over 5 years, to improve the likelihood of a positive balance of coronary risk reduction over bleeding and hemorrhagic stroke caused by aspirin.\textsuperscript{543} The benefit of platelet antiaggregants for secondary stroke prevention in patients with a prior history of stroke or TIA is also well established.\textsuperscript{544–546} There is no evidence that this class of drugs reduces the risk of stroke in the general population of persons at low risk.\textsuperscript{542,547,548}

There were relatively few women 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 Women’s Health Study randomized 39,876 initially asymptomatic women ≥45 years of age to receive 100 mg of aspirin or placebo on alternate days and followed them for 10 years for a first major vascular event (nonfatal MI, nonfatal stroke, or cardiovascular death).\textsuperscript{549} Unlike data from prior studies that included mainly men, this study found a nonsignificant 9% reduction (RR = 0.91; 95% CI 0.80 to 1.03; P = 0.13) for the combined primary end point among women but a 17% reduction in the risk of stroke (RR = 0.83; 95% CI 0.69 to 0.99; P = 0.04). This was based on a 24% reduction in the risk of ischemic stroke (RR = 0.76; 95% CI 0.63 to 0.93; P = 0.009) and a nonsignificant increase in the risk of hemorrhagic stroke (RR = 1.24; 95% CI 0.82 to 1.87; P = 0.31). The overall average stroke rates were 0.11% per year in aspirin-treated patients and 0.13% per year in placebo-treated patients (absolute risk reduction = 0.02% per year, number needed to treat [NNT] = 5000). Gastrointestinal hemorrhage requiring transfusion was more frequent in the aspirin group.
(RR = 1.40; 95% CI 1.07 to 1.83; P = 0.02). The average gastrointestinal hemorrhage rates were 0.06%/year for aspirin and 0.05%/year for placebo (absolute risk increase = 0.01% per year, number needed to harm = 10,000). The most consistent benefit for aspirin was in women ≥65 years of age at study entry, among whom the risk of major cardiovascular events was reduced by 26% (RR = 0.74; 95% CI 0.59 to 0.92; P = 0.008), including a 30% reduction in the risk of ischemic stroke (RR = 0.70; 95% CI 0.49 to 1.00; P = 0.05); however, there was only a trend in the reduction of the overall (ischemic + hemorrhagic) risk of stroke (RR = 0.78; 95% CI 0.57 to 1.08; P = 0.13), likely related to an increase in the risk of brain hemorrhages. Subgroup analyses showed a reduction in stroke for those women with a history of hypertension (RR = 0.76; 95% CI 0.59 to 0.98; P = 0.04), hyperlipidemia (RR = 0.62; 95% CI 0.47 to 0.83; P = 0.001), or diabetes (RR = 0.46; 95% CI 0.25 to 0.85; P = 0.01) or a 10-year cardiovascular risk ≥10% (RR = 0.54; 95% CI 0.30 to 0.98; P = 0.04).

Summary and Gaps
Previous guideline statements endorse the use of aspirin (dose as low as 75 mg/d as reflected in the US Preventive Services Task Force recommendation) for cardiovascular prophylaxis among men whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment (a 10-year risk of 6% to 10%). These recommendations are based on a reduction of cardiovascular events, not stroke. The Women’s Health Study shows a reduction in the risk of stroke in women, but not cardiac events or death from cardiovascular causes with aspirin. The overall benefit of aspirin is most consistent among women >65 years of age; however, there was not an overall reduction of stroke in this group. The reasons for the differences between men and women remain uncertain.

Recommendations
Aspirin is not recommended for the prevention of a first stroke in men (Class III, Level of Evidence A). Previous guideline statements have recommended the use of aspirin for cardiovascular (including but not specific to stroke) prophylaxis among persons whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment (a 10-year risk of cardiovascular events of 6% to 10%), and this panel agrees (Class I, Level of Evidence A). Aspirin can be useful for prevention of a first stroke among women whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment (Class IIa, Level of Evidence B). The use of aspirin for other specific situations (eg, atrial fibrillation, carotid artery stenosis) is discussed in the relevant sections of this statement.

Summary of Recommendations
Assessing the Risk of a First Stroke
Each individual patient should have an assessment of his or her stroke risk (Class I, Level of Evidence A). The use of a risk-assessment tool such as the Framingham Stroke Profile should be considered as these tools can help identify individuals who could benefit from therapeutic interventions and who may not be treated based on any 1 risk factor (Class IIa, Level of Evidence B).

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

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

Hypertension
Regular screening for hypertension (at least every 2 years in adults and more frequently in minority populations and the elderly) and appropriate management (Class I, Level of Evidence A), including dietary changes, lifestyle modification, and pharmacological therapy as summarized in the JNC 7, are recommended.

Cigarette Smoking
Abstention from cigarette smoking and smoking cessation for current smokers are recommended (Table 7) (Class I, Level of Evidence B). Data from cohort and epidemiological studies are consistent and overwhelming. Avoidance of environmental tobacco smoke for stroke prevention should also be considered (Class IIa, Level of Evidence C). The use of counseling, nicotine products, and oral smoking-cessation medications has been found to be effective for smokers and should be considered (Class IIa, Level of Evidence B).

Diabetes
It is recommended that hypertension be tightly controlled in patients with either type 1 or type 2 diabetes (the JNC 7 recommendation of <130/80 mm Hg in diabetic patients is endorsed) as part of a comprehensive risk-reduction program (Class I, Level of Evidence A). Treatment of adults with diabetes, especially those with additional risk factors, with a statin to lower the risk of a first stroke is recommended (Class I, Level of Evidence A). Recommendations to consider treatment of diabetic patients with an ACEI or ARB are endorsed.

Atrial Fibrillation
Anticoagulation of patients with atrial fibrillation who have valvular heart disease (particularly those with mechanical heart valves) is recommended (Class I, Level of Evidence A). Antithrombotic therapy (warfarin or aspirin) is recommended to prevent stroke in patients with nonvalvular atrial fibrillation based on assessment of their absolute stroke risk and estimated bleeding risk while considering patient preferences and access to high-quality anticoagulation monitoring (Class I, Level of Evidence A). Warfarin (INR 2.0 to 3.0) is recommended for high-risk (>4% annual risk of stroke) patients (and for most moderate-risk patients according to patient preferences) with atrial fibrillation who have no clinically significant contraindications to oral anticoagulants (Class I, Level of Evidence A).
Other Cardiac Conditions

Various AHA/ACC practice guidelines recommend strategies to reduce the risk of stroke in patients with a variety of cardiac conditions. These include the management of patients with valvular heart disease, unstable angina, chronic stable angina, and acute MI. Strategies to prevent postoperative neurological injury and stroke in patients undergoing surgical revascularization for atherosclerotic heart disease are discussed in detail in the recently published coronary artery bypass graft surgery guidelines. It is reasonable to prescribe warfarin for post–ST-segment–elevation patients with MI and LV dysfunction with extensive regional wall-motion abnormalities (Class IIa, Level of Evidence A), and warfarin may be considered in patients with severe LV dysfunction with or without congestive heart failure (Class IIb, Level of Evidence C).

Dyslipidemia

National Cholesterol Education Program III guidelines for the management of patients who have not had a cerebrovascular event with elevated total cholesterol, or with elevated non–HDL cholesterol in the presence of hypertriglyceridemia, are endorsed. It is recommended that patients with known coronary heart disease (CHD) and high-risk hypertensive patients even with normal LDL cholesterol levels be treated with lifestyle measures and a statin (Class I, Level of Evidence A). The use of lipid-lowering therapy in diabetic patients is specifically addressed in the diabetes section of this guideline. Suggested treatments for patients with known CHD and low HDL cholesterol include weight loss, increased physical activity, smoking cessation, and possibly niacin or gemfibrozil (Class IIa, Level of Evidence B).

Asymptomatic Carotid Stenosis

It is recommended that patients with asymptomatic carotid artery stenosis be screened for other treatable causes of stroke and that intensive therapy of all identified stroke risk factors be pursued (Class I, Level of Evidence C). The use of aspirin is recommended unless contraindicated because aspirin was used in all of the cited trials as an antiplatelet drug except in the surgical arm of 1 study, in which there was a higher rate of MI in those who were not given aspirin (Class I, Level of Evidence B). Prophylactic carotid endarterectomy is recommended in highly selected patients with high-grade asymptomatic carotid stenosis performed by surgeons with <3% morbidity/mortality rates (Class I, Level of Evidence A). Patient selection should be guided by an assessment of comorbid conditions and life expectancy, as well as other individual factors, and be balanced by an understanding of the overall impact of the procedure if all-cause mortality is considered as one of the end points, and it should include a thorough discussion of the risks and benefits of the procedure with an understanding of patient preferences. Carotid angioplasty–stenting might be a reasonable alternative to endarterectomy in asymptomatic patients at high risk for the surgical procedure (Class IIb, Level of Evidence B); however, given the reported peri-procedural and overall 1-year event rates, it remains uncertain whether this group of patients should have either procedure.

Sickle Cell Disease

It is recommended that children with SCD be screened with TCD ultrasound starting at 2 years of age (Class I, Level of Evidence B). It is recommended that transfusion therapy be considered for those at elevated stroke risk (Class I, Level of Evidence B). Although the optimal screening interval has not been established, it is reasonable that younger children and those with TCD velocities in the conditional range should be re-screened more frequently to detect development of high-risk TCD indications for intervention (Class IIa, Level of Evidence B). Pending further studies, it is reasonable to continue transfusion even in those whose TCD velocities revert to normal (Class IIa, Level of Evidence B). MRI and MRA criteria for selection of children for primary stroke prevention using transfusion have not been established, and these tests should not be substituted for TCD (Class III, Level of Evidence B). Adults with SCD should be evaluated for known stroke risk factors and managed according to the general guidelines in this statement (Class I, Level of Evidence A).

Postmenopausal Hormone Therapy

It is recommended that postmenopausal hormone therapy (with estrogen with or without a progestin) not be used for primary prevention of stroke (Class III, Level of Evidence A). The use of hormone replacement therapy for other indications should be informed by the risk estimate for vascular outcomes provided by the reviewed clinical trials. There are not sufficient data to provide recommendations about the use of other forms of therapy such as selective estrogen receptor modulators.

Diet and Nutrition

A reduced intake of sodium and increased intake of potassium is recommended to lower blood pressure in persons with hypertension (Class I, Level of Evidence A), which may thereby reduce the risk of stroke. The recommended sodium intake is ≤2.3 g/d (100 mmol/d), and the recommended potassium intake is ≥4.7 g/d (120 mmol/d). The DASH diet, which emphasizes fruit, vegetables, and low-fat dairy products and is reduced in saturated and total fat, also lowers blood pressure and is recommended (Class I, Level of Evidence A). A diet that is rich in fruits and vegetables may lower the risk of stroke and may be considered (Class IIb, Level of Evidence C).

Physical Inactivity

Increased physical activity is recommended because it is associated with a reduction in the risk of stroke (Class I, Level of Evidence B). Exercise guidelines as recommended by the CDC and the National Institutes of Health (≥30 minutes of moderate-intensity activity daily) as part of a healthy lifestyle are reasonable (Class IIa, Level of Evidence B).

Obesity and Body Fat Distribution

Epidemiological studies indicate that increased body weight and abdominal fat are directly associated with stroke risk. Weight reduction is recommended because it lowers blood pressure (Class I, Level of Evidence A) and may thereby reduce the risk of stroke.

Metabolic Syndrome

Management of individual components of the metabolic syndrome, including lifestyle measures and pharmacotherapy as recommended in the National Cholesterol Educa-
tion Program ATP III and the JNC 7 as reviewed in other sections of this guideline, are endorsed. Lifestyle management should include exercise, appropriate weight loss, and proper diet. Pharmacotherapy may include medications for blood pressure lowering, lipid lowering, glycemic control, treatment of microalbuminuria or proteinuria, and antiplatelet therapy (eg, aspirin) according to the individual circumstance and risk. It is not known whether agents that ameliorate aspects of the insulin resistance syndrome are useful for reducing stroke risk.

**Alcohol Abuse**
Reduction of alcohol consumption in heavy drinkers through established screening and counseling methods as outlined in the US Preventive Services Task Force Update 2004 is endorsed. For those who consume alcohol, a recommendation of ≤2 drinks per day for men and ≤1 drink per day for nonpregnant women best reflects the state of the science for alcohol and stroke risk (Class IIb, Level of Evidence C).

**Drug Abuse**
Successful identification and management of drug abuse can be challenging. When a patient is identified as having a drug addiction problem, referral for appropriate counseling may be considered (Class IIb, Level of Evidence C).

**Oral Contraceptives**
The incremental risk of stroke associated with use of low-dose OCs in women without additional risk factors appears low, if it exists (Class III, Level of Evidence B). It is suggested that OCs be discouraged in women with additional risk factors (eg, cigarette smoking or prior thromboembolic events [Class III, Level of Evidence C]). For those who elect to assume the increased risk, aggressive therapy of stroke risk factors may be useful (Class IIb, Level of Evidence C).

**Sleep-Disordered Breathing**
SDB is associated with stroke risk. Questioning bed partners and patients, particularly those with abdominal obesity and hypertension, about symptoms of SDB and referral to a sleep specialist for further evaluation as appropriate may be useful, especially in the setting of drug-resistant hypertension (Class IIb, Level of Evidence C).

**Migraine**
There are insufficient data to recommend a specific treatment approach that would reduce the risk of first stroke in women with migraine, including migraine with aura.

**Hyperhomocysteinemia**
Recommendations to meet current guidelines for daily intake of folate (400 µg/d), B$_6$ (1.7 mg/d), and B$_12$ (2.4 µg/d) by consumption of vegetables, fruits, legumes, meats, fish, and fortified grains and cereals (for nonpregnant, nonlactating individuals) may be useful in reducing the risk of stroke (Class IIb, Level of Evidence C). There are insufficient data to recommend a specific treatment approach that would reduce the risk of first stroke in patients with elevated homocysteine levels. In the interim, use of folic acid and B vitamins in patients with known elevated homocysteine levels may be useful given their safety and low cost (Class III, Level of Evidence B).

**Elevated Lipoprotein(a)**
Although no definitive recommendations about Lp(a) modification can be made because of an absence of outcome studies showing clinical benefit, treatment with niacin (extended-release or immediate-release formulation at a total daily dose of 2000 mg/d as tolerated) can be considered because it reduces Lp(a) levels by ≈25% (Class IIb, Level of Evidence C). Further recommendations must await the results of prospective trials utilizing niacin and statins in subjects stratified for Lp(a) concentration and apo(a) isoform subtypes.

**Elevated Lipoprotein-Associated Phospholipase A$_2$**
No recommendations about Lp-PLA$_2$ modification can be made because of an absence of outcome studies showing clinical benefit with reduction in its blood levels.

**Hypercoagulability**
There are insufficient data to support specific recommendations for primary stroke prevention in patients with a hereditary or acquired thrombophilia.

**Inflammation**
Currently, no evidence supports the use of hs-CRP screening of the entire adult population as a marker of general vascular risk. Aggressive risk factor modification is recommended for patients at high risk for stroke given exposure to traditional risk factors regardless of hs-CRP level. In agreement with AHA/CDC guidelines, hs-CRP can be useful in considering the intensity of risk factor modification in those at moderate general cardiovascular risk on the basis of traditional risk factors (Class IIa, Level of Evidence B).

**Infection**
Data are insufficient to recommend antibiotic therapy for stroke prevention on the basis of seropositivity for 1 or a combination of putative pathogenic organisms. Future studies on stroke risk reduction based on treatment of infectious diseases will require careful stratification and identification of patients at risk for organism exposure.

**Aspirin**
Aspirin is not recommended for the prevention of a first stroke in men (Class III, Level of Evidence A). The use of aspirin is recommended for cardiovascular (including but not specific to stroke) prophylaxis among persons whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment (a 10-year risk of cardiovascular events of 6% to 10%) (Class I, Level of Evidence A). Aspirin can be useful for prevention of a first stroke among women whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment (Class IIa, Level of Evidence B). The use of aspirin for other specific situations (eg, atrial fibrillation, carotid artery stenosis) is discussed in the relevant sections of this statement.
### TABLE 10. Writing Group Disclosures

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<th>Writing Group Member Name</th>
<th>Employment</th>
<th>Research Grant</th>
<th>Speakers Bureau/Honoraria</th>
<th>Stock Ownership</th>
<th>Consultant/Advisory Board</th>
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<tbody>
<tr>
<td>Larry B. Goldstein</td>
<td>Duke Center for Cerebrovascular Disease, Duke University Medical Center; Durham Veterans Administration Medical Center</td>
<td>Grants: NIH, Veterans Administration, CDC/University of North Carolina–Chapel Hill, Pfizer/Parke-Davis (SPARCL Steering Committee)</td>
<td>Speaking honoraria: Bayer, Pfizer/Parke Davis, Speakers bureau: None</td>
<td>None</td>
<td>AstraZeneca, Bristol-Myers Squibb/Sanofi, CuraGen Corp, DPharm, GlaxoSmithKline, Johnson &amp; Johnson, Merck Research Laboratories, Pfizer/Parke Davis</td>
<td>None</td>
</tr>
<tr>
<td>Robert Adams</td>
<td>Medical College of Georgia</td>
<td>None</td>
<td>None</td>
<td>Boehringer Ingelheim, BMS, Wyeth, Sanofi-Synthelabo, Novartis</td>
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<tr>
<td>Mark J. Alberts</td>
<td>Northwestern University Medical School</td>
<td>None</td>
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<tr>
<td>Lawrence J. Appel</td>
<td>Johns Hopkins</td>
<td>None</td>
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<tr>
<td>Lawrence M. Brass</td>
<td>Yale University</td>
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<tr>
<td>Cheryl D. Bushnell</td>
<td>Duke Center for Cerebrovascular Disease, Duke University Medical Center</td>
<td>None</td>
<td>None</td>
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</tr>
<tr>
<td>Antonio Culebras</td>
<td>Upstate Medical University</td>
<td>None</td>
<td>None</td>
<td>Boehringer Ingelheim</td>
<td>None</td>
<td>None</td>
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<tr>
<td>Thomas J. DeGraba</td>
<td>National Naval Medical Center</td>
<td>None</td>
<td>None</td>
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<tr>
<td>Philip B. Gorelick</td>
<td>University of Illinois at Chicago</td>
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<td>Robert G. Hart</td>
<td>University of Texas Health Science Center</td>
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<tr>
<td>George Howard</td>
<td>University of Alabama at Birmingham</td>
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<td>Margaret Kelly-Hayes</td>
<td>University School of Medicine</td>
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<td>J. V. (Ian) Nixon</td>
<td>Medical College of Virginia</td>
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<td>Ralph L. Sacco</td>
<td>Columbia University</td>
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### TABLE 11. Reviewers' Disclosures

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<th>Reviewer</th>
<th>Employment</th>
<th>Research Grant</th>
<th>Other Research Support</th>
<th>Speakers Bureau/Honoraria</th>
<th>Ownership Interest</th>
<th>Consultant/Advisory Board</th>
<th>Other</th>
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<tr>
<td>Tamilyn Bakas</td>
<td>Indiana University School of Nursing</td>
<td>None</td>
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<td>Vito M. Campese</td>
<td>University of Southern California</td>
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<td>Christopher Cannon</td>
<td>Brigham &amp; Women's Hospital/Harvard Medical School</td>
<td>None</td>
<td>None</td>
<td>AstraZeneca, Bristol-Myers Squibb, Merck, Sanofi-Aventis, AstraZeneca</td>
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<td>J. Donald Easton</td>
<td>Rhode Island Hospital–Brown Medical School</td>
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<td>S. Claiborne Johnston</td>
<td>University of California, San Francisco</td>
<td>NIH/NINDS, Centocor/Johnson &amp; Johnson, St Jude Medical, Boston Scientific</td>
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<tr>
<td>David A. Morrow</td>
<td>Brigham &amp; Women’s Hospital/Harvard Medical School</td>
<td>Merck &amp; Co, Bayer, Biosite, Bristol-Myers Squibb, Beckman Coulter, Roche Diagnostics</td>
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This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit.

### References


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Goldstein et al.  

Primary Prevention of Ischemic Stroke  
e915


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449. Brantstrom L, Wilson DE, Ohvik J, Brudin L. Common methylene-tetrahydrofolate reductase gene mutation leads to hyperhomocys-


In the AHA/ASA Guideline, “Primary Prevention of Ischemic Stroke: A Guideline From the American Heart Association/American Stroke Association Stroke Council,” which appeared in the June 2006 issue of *Stroke* (Stroke. 2006;37:1583–1633) and was later published online only in the June 20, 2006, issue of *Circulation* (Circulation. 2006;113:e873–e923), the following items require correction:

1. On page 1602 of the *Stroke* version (page e892 of the *Circulation* version), in the first sentence under “Sickle Cell Disease,” the word “dominant” should be replaced by “recessive,” to read: “Sickle cell disease (SCD) is inherited as an autosomal recessive disorder in which the abnormal gene product is an altered hemoglobin β-chain.”

2. On page 1612 of the *Stroke* version (page e902 of the *Circulation* version), the reference cited at the end of the Recommendations section (reference 263) is incorrect and should be replaced by reference 263a, which should be added to the Reference list:


These errors have been corrected in the current online version of the article in both journals.

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