Inclusion of Stroke in Cardiovascular Risk Prediction Instruments

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

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

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Background and Purpose—Current US guideline statements regarding primary and secondary cardiovascular risk prediction and prevention use absolute risk estimates to identify patients who are at high risk for vascular disease events and who may benefit from specific preventive interventions. These guidelines do not explicitly include patients with stroke, however. This statement provides an overview of evidence and arguments supporting (1) the inclusion of patients with stroke, and atherosclerotic stroke in particular, among those considered to be at high absolute risk of cardiovascular disease and (2) the inclusion of stroke as part of the outcome cluster in risk prediction instruments for vascular disease.

Methods and Results—Writing group members were nominated by the committee co-chairs on the basis of their previous work in relevant topic areas and were approved by the American Heart Association (AHA) Stroke Council’s Scientific Statements Oversight Committee and the AHA Manuscript Oversight Committee. The writers used systematic literature reviews (covering the period from January 1980 to March 2010), reference to previously published guidelines, personal files, and expert opinion to summarize existing evidence, indicate gaps in current knowledge, and, when appropriate, formulate recommendations using standard AHA criteria. All members of the writing group had the opportunity to comment on the recommendations and approved the final version of this document. The guideline underwent extensive AHA internal peer review, Stroke Council leadership review, and Scientific Statements Oversight Committee review.

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest. This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on March 8, 2012. A copy of the document is available at http://my.americanheart.org/statements by selecting either the “By Topic” link or the “By Publication Date” link. To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.


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before consideration and approval by the AHA Science Advisory and Coordinating Committee. There are several reasons to consider stroke patients, and particularly patients with atherosclerotic stroke, among the groups of patients at high absolute risk of coronary and cardiovascular disease. First, evidence suggests that patients with ischemic stroke are at high absolute risk of fatal or nonfatal myocardial infarction or sudden death, approximating the ≥20% absolute risk over 10 years that has been used in some guidelines to define coronary risk equivalents. Second, inclusion of atherosclerotic stroke would be consistent with the reasons for inclusion of diabetes mellitus, peripheral vascular disease, chronic kidney disease, and other atherosclerotic disorders despite an absence of uniformity of evidence of elevated risks across all populations or patients. Third, the large-vessel atherosclerotic subtype of ischemic stroke shares pathophysiological mechanisms with these other disorders. Inclusion of stroke as a high-risk condition could result in an expansion of ≈10% in the number of patients considered to be at high risk. However, because of the heterogeneity of stroke, it is uncertain whether other stroke subtypes, including hemorrhagic and nonatherosclerotic ischemic stroke subtypes, should be considered to be at the same high levels of risk, and further research is needed. Inclusion of stroke with myocardial infarction and sudden death among the outcome cluster of cardiovascular events in risk prediction instruments, moreover, is appropriate because of the impact of stroke on morbidity and mortality, the similarity of many approaches to prevention of stroke and these other forms of vascular disease, and the importance of stroke relative to coronary disease in some subpopulations. Non-US guidelines often include stroke patients among others at high cardiovascular risk and include stroke as a relevant outcome along with cardiac end points.

Conclusions—Patients with atherosclerotic stroke should be included among those deemed to be at high risk (≥20% over 10 years) of further atherosclerotic coronary events. Inclusion of nonatherosclerotic stroke subtypes remains less certain. For the purposes of primary prevention, ischemic stroke should be included among cardiovascular disease outcomes in absolute risk assessment algorithms. The inclusion of atherosclerotic ischemic stroke as a high-risk condition and the inclusion of ischemic stroke more broadly as an outcome will likely have important implications for prevention of cardiovascular disease, because the number of patients considered to be at high risk would grow substantially. (Stroke. 2012;43:1998-2027.)

Key Words: American Heart Association (AHA) primary prevention guidelines state that those with ≥10% risk of MI or CHD death over 10 years should be considered for aspirin therapy.6 For women, aspirin has been recommended as a consideration even among those at low risk.7 These approaches emphasize the importance of overall CHD risk rather than the presence or absence of specific risk factors. The use of risk prediction instruments may change over time because of secular trends in risk factors and treatments.

The first part of the present statement will address whether stroke patients should be considered among those people at high absolute risk of subsequent CVD, in particular CHD. In some instances, organizations have sought to identify groups of people who can be considered as being at levels of absolute risk of ischemic heart disease similar to those of people who have already developed ischemic heart disease. According to the NCEP, for example, patients considered to be at high risk of CHD (ie, absolute 10-year risk of ≥20%) have been termed “CHD risk equivalents.”9 This category of patients includes those who already have ischemic heart disease, as well as patients deemed to be at the same elevated risk as patients with ischemic heart disease. Patients deemed CHD risk equivalents include patients with diabetes mellitus (DM), those whose Framingham Heart Score calculates to a risk of ≥20% over 10 years, and patients with “other forms of symptomatic atherosclerotic disease.” The latter group includes those with peripheral arterial disease (PAD), abdominal aortic aneurysm (AAA), and symptomatic carotid artery disease.
notably absent from this list of risk equivalents in the NCEP ATP III guidelines. Although symptomatic carotid atherosclerosis is included, this probably accounts for no more than 10% of patients with ischemic stroke. The vast majority of ischemic stroke patients are not considered risk equivalents, although patients with atherosclerosis that produces PAD and aortic arch disease are included. Thus, the present scientific statement will address the inclusion among high-risk groups of patients with atherosclerotic stroke apart from carotid artery disease, as well as the inclusion of ischemic stroke patients more generally.

The second part of the statement will address the inclusion of stroke as a relevant outcome in the cluster recommended for use in risk prediction instruments. Early risk prediction instruments focused only on CHD, with stroke added to the outcomes for the Framingham Risk Score in 2008. More recently, stroke has specifically been proposed as a part of the outcome cluster in absolute risk prediction instruments relevant to treatment decisions, although this has not been generally accepted. Reasons for including stroke as an outcome in risk prediction instruments include the social and economic burden of stroke, the significance of stroke relative to CHD in subpopulations of the United States, similarities in approaches to preventive treatment in stroke as CHD, and the inclusion of stroke as an outcome in international guidelines.

Although the limitations of the concept of risk equivalents have been addressed previously and will be reviewed here briefly, the writing group wishes to emphasize the surprising absence of stroke both among the conditions considered as posing a high absolute risk of subsequent heart disease and among the conditions considered important cardiovascular outcomes. Moreover, the present scientific statement does not specifically endorse the concept of risk equivalents or any particular threshold of risk deemed appropriate for therapy but rather addresses only the relevance of the inclusion of stroke, either in total or specific subtypes, as a predictor and outcome in risk prediction instruments. Specifically, the statement will address the concepts of risk stratification and use of absolute thresholds of risk, reasons for inclusion of certain groups of patients, data on the effects of inclusion of stroke among risk equivalents, and data on the inclusion of stroke as an outcome. These data and their interpretation will have important clinical implications, because current guidelines may underestimate the risk of clinically important cardiovascular events, leaving untreated patients who might be eligible for primary and secondary prevention therapies. These issues may be especially important for high-risk racial/ethnic groups for whom stroke risk is as great as or exceeds CHD risk.

Methods
An international group of experts in CVD, representing a broad spectrum of specialists with interest in clinical CVD and epidemiology, was assembled to address these questions. Expertise among group members included cardiovascular and clinical epidemiology, public health, cardiology, vascular neurology, peripheral vascular disease, vascular surgery, neurosurgery, cerebrovascular nursing, interventional vascular neurosurgery, physical therapy, and cardiovascular rehabilitation. The committee chairs decided on topics and assigned writing groups of 2 authors for each section.

After orientation to the approach, authors chose the appropriate methods for their own sections. Although a single coordinated systematic literature search was not performed for this work group, authors independently performed literature searches and systematic reviews. The writers used systematic literature reviews (covering the period from January 1980 to March 2010), reference to previously published guidelines, personal files, and expert opinion to summarize existing evidence, indicate gaps in current knowledge, and, when appropriate, formulate recommendations using standard AHA criteria (Tables 1 and 2).

Submissions for individual sections were reviewed by the writing committee chairs and AHA scientific statement editorial staff and compiled into a single edited document. This draft was then shared with writing committee members and recirculated to the group. Conference calls were held as needed to discuss the document. The final document was the result of an iterative editing process that addressed the following topic areas:

1. The role of absolute event rates and risk thresholds in primary and secondary prevention
2. Categories of CHD risk equivalents
3. Importance of stroke subtypes/special situations
4. Inclusion of atherosclerotic stroke among the categories of risk equivalents
5. Inclusion of stroke in the vascular outcome cluster
6. Issues common to inclusion of stroke as a high-risk condition and as part of the outcome cluster in risk prediction instruments
7. Recommendations and conclusions

Role of Absolute Event Rates and Risk Thresholds in Primary and Secondary Prevention

Importance of Absolute Event Rates and Risk Thresholds
Estimation of the absolute risk of CVD allows physicians to target preventive measures to those at high risk. Current practice in the United States typically uses risk prediction instruments such as the Framingham score to determine the absolute probability for a person to develop CHD over 10 years. These instruments have variously considered 3 (low, moderately high, and high), or even 5 (including very high-risk patients) different risk category levels. These risk categories have been determined from numerous prospective observational studies in which multiple risk factors were related to the number of CHD events during follow-up and summed to obtain estimates of global risk over 10 years. In initial formulations, the definition of low risk was based on the absence of coronary risk factors. Subsequent formulations used estimates of absolute risk. For example, a risk of $\leq 5\%$ over 10 years was considered low; $6\%$ to $20\%$, medium; and $\geq 20\%$, high.

Absolute risk thresholds have been invoked to justify a more intensive approach to primary prevention of CHD in people who, relative to non-CHD conditions, have a high risk
The concept of CHD risk equivalents may be considered one specific instance of the use of absolute risk thresholds for this purpose. Potential interventions include lifestyle modification but also drug therapy, including treatment of hyperlipidemia, use of aspirin, and treatment of hypertension. An underlying concept is that because the absolute risk of future vascular disease is greater, assuming a relatively constant relative risk reduction, absolute risk reduction and effectiveness of treatment will be maximized. Treatment of DM is always recommended, regardless of overall risk of vascular disease.

US guidelines on lipid management for primary and secondary prevention, including those of the NCEP, expand the use of absolute risk levels by including categories of CHD risk equivalents.5 Those considered to have coronary risk equivalents include those with established CHD, as well as those with DM, PAD, and symptomatic carotid artery disease. Risk stratification can also be performed with the Framingham risk prediction instruments, and patients can be divided into those with low (<10%), moderate (10–20%), or high (>20%) 10-year risks. Those at high risk are also then included in the coronary risk equivalent category.

The use of absolute risk levels in determining prevention strategies, however, is not limited to the NCEP guidelines. The 2007 update to the AHA guidelines for CVD prevention in women defined women at high risk as those with established
Table 2. Definition of Classes and Levels of Evidence Used in AHA Stroke Council Recommendations

<table>
<thead>
<tr>
<th>Class</th>
<th>Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class II</td>
<td>Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.</td>
</tr>
<tr>
<td>Class IIa</td>
<td>The weight of evidence or opinion is in favor of the procedure or treatment.</td>
</tr>
<tr>
<td>Class IIb</td>
<td>Usefulness/efficacy is less well established by evidence or opinion.</td>
</tr>
<tr>
<td>Class III</td>
<td>Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful.</td>
</tr>
</tbody>
</table>

Therapeutic recommendations

- **Level of Evidence A**: Data derived from multiple randomized clinical trials or meta-analyses.
- **Level of Evidence B**: Data derived from a single randomized trial or nonrandomized studies.
- **Level of Evidence C**: Consensus opinion of experts, case studies, or standard of care.

Diagnostic recommendations

- **Level of Evidence A**: Data derived from multiple prospective cohort studies using a reference standard applied by a masked evaluator.
- **Level of Evidence B**: Data derived from a single grade A study, or ≥1 case-control studies, or studies using a reference standard applied by an unmasked evaluator.
- **Level of Evidence C**: Consensus opinion of experts.

CHD, cerebrovascular disease, peripheral arterial disease, abdominal aortic aneurysm, end-stage or chronic renal disease, DM, and 10-year Framingham risk >20%. The 2011 guidelines for women have continued this approach and recommended the use of specific risk prediction instruments that include cerebrovascular disease as part of global risk assessment. Recent European guidelines also use risk of death because of CVD (heart and stroke) as the salient end point, with >5% absolute risk of death because of CVD considered high risk.

### Uses of Absolute Risk Categories

#### Hyperlipidemia

The NCEP ATP III recommended a more intensive approach to treatment of hyperlipidemia in the presence of CHD or CHD risk equivalents. Much of the rationale for an aggressive approach to lipid lowering comes from the West of Scotland Coronary Prevention Study (WOSCOPS), a placebo-controlled study of statin therapy for primary prevention of CVD. In WOSCOPS, the 10-year risk of CHD was ~15% in patients taking placebo. The study convincingly showed reduction of CHD risk in the original 5 years of randomization and during longer-term follow-up. The statin intervention in the higher-risk profile WOSCOPS patients was associated with a greater absolute CHD risk reduction and a lower number needed to treat. The NCEP ATP III guidelines set the LDL-C goal in patients with CHD or CHD risk equivalents at <100 mg/dL and suggested the possibility of a “very high-risk” group (established CHD plus risk factors or acute coronary syndromes) who might qualify for the even lower LDL-C target of <70 mg/dL.

#### Aspirin

The 2009 report of the US Preventive Services Task Force recommended use of aspirin for primary prevention in men >45 years of age and women >55 years of age in whom the risk of MI or stroke, respectively, can be reduced in excess of the risk of a significant hemorrhagic complication. The recommendations suggest that many people with a 10-year risk of CHD of <20% should also begin empirical aspirin therapy for primary prevention.

The Joint British Societies’ guidelines recommend aspirin at 75 mg/d for their high-risk (fatal and nonfatal MI and stroke >20% at 10 years) group, including some patients with DM. The 2007 European guidelines on prevention of CVD recommend aspirin for “virtually all patients with established CVD (including people with DM),” as well as patients without a history of CVD for whom the 10-year risk of CVD mortality is “markedly increased” (>10%) after hypertension has been controlled. The 2011 AHA guidelines for prevention of CVD in women recommend considering aspirin (75–325 mg/d) in women who are at high risk regardless of age or for women >65 years of age who are at risk or healthy, depending on risk of hemorrhage and consideration of risk for ischemic stroke.

#### Hypertension Treatment

In the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), hypertension treatment is not based on a specific level of future risk but on a target blood pressure of <140/90 mm Hg. One exception is “compelling indications,” which represent specific higher-risk conditions, but these address specific classes of antihypertensive therapy to be used as opposed to serving as an indication for blood pressure treatment.

The British Hypertension Society guidelines for management of hypertension also use absolute risk to recommend specific blood pressure medications. High-risk groups include patients with evidence or history of target organ damage related to hypertension, including established CVD, renal disease, DM, or a global CVD risk assessment of ≥20% over 10 years. The blood pressure goal for those considered at high risk (≥20% 10-year overall CVD risk) is <140/85 mm Hg, but the goal for those with established CVD, including stroke, or DM is <130/80 mm Hg.

#### Influenza Vaccination

Another recommendation based on the presence of CHD or other atherosclerotic vascular disease (PAD, atherosclerotic aortic disease, and CAD) is an annual influenza vaccination.
Section Summary
In summary, a history of high absolute risk of vascular disease has been invoked in many CVD guidelines as an indication for more intensive preventive interventions. Stroke has been inconsistently included in these high-risk categories. Interventions that have been based on high risk in at least some guidelines include lipid management, antihypertensive therapy, and antiplatelet use. The varying definitions of the high-risk groups confound a simple and universal recommendation and support the need for an international alignment.

Categories of CHD Risk Equivalents
Existing CHD
Although the development of categories of CHD risk equivalents by the NCEP is only one example of the use of absolute risk to determine approaches to treatment, it provides an instructive example for deciding what disorders to consider under the umbrella of high vascular risk conditions. Patients with existing CHD may logically be considered to have a CHD risk equivalent because they already have the disease of interest. It is reasonable, then, to consider the absolute event rates of these patients as a standard level with which other patient groups may be compared.

Patients with existing CHD may be considered to have absolute event rates of further CHD events of at least 20% per decade. The placebo groups in 2 long-term secondary prevention trials (Cholesterol And Recurrent Events [CARE] and Long-term Intervention with Pravastatin in Ischemic Disease [LIPID]) among people with “average” cholesterol levels had an absolute risk of CHD of ≈26% per decade (Table 3). The risk of CHD in other clinical trials is summarized in Table 3.32–39

It is notable that many of the data used in the NCEP statement were based on trials that followed patients for 5 to 6 years rather than for the 10 years on which risk equivalent status is based. Given that clinical trial participants are likely to have event rates lower than those of similar people in the general population (because of the healthy volunteer effect) and that the event rates likely will increase as participants age beyond typical 5- to 6-year trial periods, an event rate of 20% per decade in people with CHD probably represents a minimum estimate of the absolute annual risk associated with existing CHD. Although event rates have decreased somewhat over time,46 probably because of increased penetrance of statins and other secondary preventive strategies, there is still evidence that patients with existing coronary disease have event rates of ≈2% annually.

DM as a CHD Risk Equivalent
In the 2002 NCEP ATP III recommendations, DM was considered a “CHD risk equivalent”; in other words, the risk of CHD in people with DM was considered as great as the risk of recurrent CHD in those with recent CHD events.5 Three lines of evidence were presented to support this designation for patients with type 2 DM, with a short statement saying that there was insufficient evidence for designating type 1 DM as a CHD risk equivalent.

The first line of evidence came from cohort studies and randomized trials that demonstrated elevated risks of coronary outcomes among patients with DM and no heart disease similar to those in patients with heart disease alone. A Finnish population-based study published in 1998 reported an 18.8% recurrent risk of MI in people without DM with a history of MI versus a 20.2% risk of MI in people with DM without a prior CHD history.47 The Organization to Assess Strategies for Ischemic Syndromes (OASIS) study showed that over 2 years, the rate of new MI was 10.7% in people with DM without CHD and 10.2% in those with a history of CHD but no DM.48 The Heart Outcomes Prevention Evaluation (HOPE) trial demonstrated an estimated 2.5% annual rate of CHD in people with DM with vascular risk factors. Broader outcomes showed rates of combined MI, stroke, and vascular death over 5 years of 19.8% in people with DM and 18.7% in those with a history of CVD (some of whom had DM).49 CHD rates of 15% to 20% over 10 years in the UK Prospective Diabetes Study were also broadly supportive of considering DM as a CHD risk equivalent.50

The second line of evidence supporting DM as a CHD risk equivalent in ATP III was the finding that an initial MI is more severe in people with DM, with greater rates of complications, including acute congestive heart failure and greater case-fatality rates after MI, which justifies a more intensive preventive approach. One study of patients presenting with symptoms of possible MI showed a 1-year mortality rate of 25% for those with DM versus 10% for those without DM.51 The Corpus Christi Heart Project (CCHP) showed greater rates of in-hospital congestive heart failure, longer lengths of stay, and greater rates of 28-day and long-term mortality among patients with DM, with 28-day case-fatality rates of 10.1% among people with DM compared with 5.0% among those without DM.52 Another study showed MI fatality rates out of hospital, at 28 days, and at 1 year to be consistently higher in those with DM than in those without DM.53

The third line of evidence was that long-term mortality after MI is higher in people with DM. In CCHP, 44-month post-MI mortality rates were 37.4% among people with DM compared with 23.3% among those without DM.52 The Finnish study mentioned above showed death attributable to cardiovascular causes occurred at a rate of 2.6% annually in people without DM after MI versus 7.3% annually in people with DM without MI.57 In a Framingham, MA, cohort, after initial survival, 2-year mortality rates were 14% in people with DM versus 6% to 8% in people without DM.54 In a follow-up study to the Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT), 10-year mortality after MI was increased in both men and women with DM (versus those without DM) and even more so for those requiring insulin treatment (versus oral medications).55

There are limitations to the arguments presented in ATP III to include people with DM as risk equivalents. Not all cohort studies provide evidence that event rates are higher in people with DM, and patients with DM are not a homogeneous group. In an older cohort of patients from the Australian Dubbo Study,56 risk of subsequent CHD was significantly lower in patients with DM but no history of CHD versus those with prior CHD. In the Physicians’ Health Study, risk of CHD was higher among people without DM with baseline...
CHD than among people with DM without CHD. Cross-sectional and cohort analyses from a Tayside, Scotland, study and the Atherosclerosis Risk In Communities (ARIC) study showed higher rates of overall mortality, cardiovascular death, and hospital admission for MI in patients with recent MI than in people with DM without a history of CHD. Finally, a systematic review and meta-analysis using data from 13 studies and 45,108 patients found a significant summative odds ratio of 0.56 for risk of CHD events in people with DM without history of MI versus MI patients without DM. Circling back, even if the risk of CHD in people with DM is less than the risk in people without DM after MI, the higher post-MI mortality rates observed in people with DM despite these lower event rates may again essentially equalize CHD deaths, a counterargument some have used for continuing to consider DM as a CHD risk equivalent for practical purposes.

Several studies, moreover, have demonstrated that there is heterogeneity in risk levels among patients with DM. A report from the Prospective Cardiovascular Munster Study assessed rates of coronary events over 10 years in a subcohort of 406 people with DM drawn from among 5389 participants.

CHD indicates coronary heart disease; PAD, peripheral artery disease; 4S, Scandinavian Simvastatin Survival Study; CARE, Cholesterol And Recurrent Events; MI, myocardial infarction; LIPID, Long-Term Intervention with Pravastatin in Ischaemic Disease; VA-HIT, Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial; HDL-C, high-density lipoprotein cholesterol; HERS, Heart and Estrogen/progestin Replacement Study; WHI, Women's Health Initiative; PEACE, Prevention of Events with Angiotensin Converting Enzyme inhibitor therapy trial; ACCORD, Action to Control Cardiovascular Risk in Diabetes trial; DM, diabetes mellitus; CVD, cardiovascular disease; ABI, ankle-brachial index; and CAD, coronary artery disease.

Table 3. Studies Providing Absolute Cardiac Risks Among Patients With CHD and PAD

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Study Design</th>
<th>Participants</th>
<th>n</th>
<th>Follow-Up Period</th>
<th>Outcome</th>
<th>Risk of Outcome, % Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Existing CHD</td>
<td>Clinical trial</td>
<td>Persons with high cholesterol levels</td>
<td>2223 (Placebo group)</td>
<td>10 y</td>
<td>Risk of CHD</td>
<td>26</td>
</tr>
<tr>
<td>CARE33 (1996)</td>
<td>Clinical trial</td>
<td>Persons with average cholesterol levels</td>
<td>2078 (Placebo group)</td>
<td>Median 5 y</td>
<td>Nonfatal MI or cardiovascular death</td>
<td>13</td>
</tr>
<tr>
<td>LIPID34 (1998)</td>
<td>Clinical trial</td>
<td>Persons with average cholesterol levels</td>
<td>4502 (Placebo group)</td>
<td>Median 6 y</td>
<td>Fatal CHD or nonfatal MI</td>
<td>16</td>
</tr>
<tr>
<td>VA-HIT35 (1999)</td>
<td>Clinical trial</td>
<td>Persons with low HDL-C levels</td>
<td>1267 (Placebo group)</td>
<td>10 y</td>
<td>Risk of CHD</td>
<td>43</td>
</tr>
<tr>
<td>HERS36 (2002)</td>
<td>Clinical trial</td>
<td>Women</td>
<td>1383 (Placebo group)</td>
<td>6.8 y</td>
<td>Annual rate of CHD</td>
<td>3.7</td>
</tr>
<tr>
<td>WHI37 (2003)</td>
<td>Clinical trial</td>
<td>Women with preexisting CHD</td>
<td>8102 (Placebo group)</td>
<td>Mean 5.2 y</td>
<td>Annual nonfatal MI or fatal CHD event rate</td>
<td>1.65</td>
</tr>
<tr>
<td>PEACE38 (2004)</td>
<td>Clinical trial</td>
<td>Stable CHD and normal or mildly reduced ejection fraction</td>
<td>4132 (Placebo group)</td>
<td>4.8 y</td>
<td>Nonfatal MI, fatal CHD, or cardiac arrest</td>
<td>8.6</td>
</tr>
<tr>
<td>ACCORD39 (2008)</td>
<td>Clinical trial</td>
<td>With DM and CVD</td>
<td>5051 (Standard care group)</td>
<td>Mean 3.5 y</td>
<td>Annual risk of nonfatal MI or CHD death</td>
<td>2</td>
</tr>
</tbody>
</table>

PAD

Lipid Research Council, San Diego cohort40 (1985) Cohort study With peripheral vascular disease 159 4 y Annual coronary mortality 2 Over 10 y (n = 67), annual mortality was 2.5% per year for men but only 0.4% for women41

McKenna et al42 (1991) Cohort study ABI =<0.85 744 . . . Annual CHD mortality 6 40% of patients had known CHD

Poulias et al43 (1992) Cohort study Age 35–87 y undergoing aortofemoral bypass 1000 (941 men) Range 1 mo to 20 y Annual mortality 2.4

Multicenter Study of Osteoporotic Fractures44 (1993) Prospective cohort study Women without CHD 1027 Mean 4.3 y Annual total CHD mortality rate among those with ABI =<0.9 2.9

Edinburgh Artery Study45 (1996) Cohort study Men and women age 55–74 y 1592 5 y Annual major coronary event rate among those with ABI =<0.9 2.4–3.8 614 (39%) had preexisting CAD, and results were not presented differentially for those with and without heart disease.

2004 Stroke July 2012

CHD indicates coronary heart disease; PAD, peripheral artery disease; 4S, Scandinavian Simvastatin Survival Study; CARE, Cholesterol And Recurrent Events; MI, myocardial infarction; LIPID, Long-Term Intervention with Pravastatin in Ischaemic Disease; VA-HIT, Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial; HDL-C, high-density lipoprotein cholesterol; HERS, Heart and Estrogen/progestin Replacement Study; WHI, Women’s Health Initiative; PEACE, Prevention of Events with Angiotensin Converting Enzyme inhibitor therapy trial; ACCORD, Action to Control Cardiovascular Risk in Diabetes trial; DM, diabetes mellitus; CVD, cardiovascular disease; ABI, ankle-brachial index; and CAD, coronary artery disease.
Among their main findings: that 13.3% of participants experienced a coronary event over 10 years of follow-up and that only 27% of the subcohort with DM were estimated to have a 10-year CHD risk ≥20%, the purported cutoff for a CHD risk equivalent. They concluded that DM should not be considered a CHD risk equivalent. Another cohort showed that people with DM without prior CHD had a lower rate of vascular events over 4 years (9%) than people without DM with CHD (25%), who in turn had lower rates than people with DM with CHD (43%). The conclusion was that it is the combination of very high-risk and lower-risk patients with DM that makes DM overall appear to be a CHD risk equivalent in some previous epidemiological studies.

Some guideline statements reflect this uncertainty with regard to the inclusion of all people with DM among those at high absolute risk. In 2010, an American Diabetes Association/AHA/American College of Cardiology Foundation scientific statement discussed the use of aspirin for primary prevention in patients with DM and made the following recommendation:

Low-dose (75–162 mg/d) aspirin use for prevention is reasonable for adults with and no previous history of vascular disease who are at increased CVD risk (10-year risk of CVD events over 10%) and who are not at increased risk for bleeding (based on a history of previous gastrointestinal bleeding or peptic ulcer disease or concurrent use of other medications that increase bleeding risk, such as nonsteroidal anti-inflammatory drugs [NSAIDS] or warfarin). Those adults with DM at increased CVD risk include most men over age 50 years and women over age 60 years having one or more of the following additional major risk factors: smoking, hypertension, dyslipidemia, family history of premature CVD, and albuminuria. (ACCF/AHA Class IIa, Level of Evidence: B) (ADA Level of Evidence: C).

This statement specifically does not recommend the use of aspirin for primary prevention in a lower-risk subgroup of people with DM. A similar recommendation for aspirin in only the higher-risk subset of people with DM is found in the 2010 American Diabetes Association standards of medical care in DM.

The evidence reviewed above calls into question the blanket assertion of DM as a CHD risk equivalent. What is clear is that some of the inconsistency in the literature is related to differences in study design and specifically in the types of patients included (eg, high- versus low-risk people with DM) and the way the outcome events of interest are defined (eg, CHD mortality versus CHD events versus all cardiovascular events). What is also clear is that patients with DM, who vary greatly in age and associated comorbid vascular risk factors, represent a spectrum of risk for future atherosclerotic vascular events. It is also clear that when a person with DM has a CHD event, the short- and long-term outcomes are much worse for people with DM, a finding that enhances the importance of preventing that initial event. Thus, those most likely to benefit from more intensive preventive interventions are those with DM who are at highest risk for an initial event, and the most recent guidelines appropriately focus on these higher-risk groups.

There is therefore residual controversy about whether patients with DM should be considered risk equivalents. Early attempts to define CHD risk equivalents focused on data indicating that people with DM were at increased risk of CHD and that prognosis after an event was worse among people with DM. More recently, it has been appreciated that some patients with DM may be at higher risk than others, and preventive strategies, such as aspirin, may reasonably be directed to those patients at higher risk.

**Others (Chronic Kidney Disease, Symptomatic Atherosclerotic Disease, Symptomatic Carotid Disease, Aortic Disease)**

In addition to DM, the NCEP ATP III guidelines define certain other conditions as CHD risk equivalents: clinical atherosclerotic disease and multiple risk factors. Other forms of clinical atherosclerotic disease include PAD, carotid artery disease, and AAA. The basis for including these 3 diseases is that they represent other manifestations of atherosclerotic disease and thus are associated with a high rate of CHD events. Chronic kidney disease (CKD) was subsequently considered by the AHA and other organizations to be a risk equivalent as well, on the basis of rather limited data providing evidence of an increased risk of coronary disease among such patients. This section briefly reviews the rationale for including these other atherosclerotic diseases as risk equivalents and compares this rationale with the inclusion of atherosclerotic stroke.

**Peripheral Arterial Disease**

The NCEP statement refers specifically to PAD as a risk equivalent. Although usually directly responsible for claudication rather than life-threatening events, PAD is widely recognized to be associated with an increased risk of subsequent stroke and MI. Five studies are cited in the NCEP ATP III report to support PAD as a risk equivalent, with sample sizes ranging from 567 to 1592 and follow-up ranging from 3 to 10 years. These are summarized in Table 3.

**Carotid Artery Disease**

Symptomatic carotid artery disease is symptomatic by virtue of leading to stroke or transient ischemic attack (TIA), including retinal events. Thus, symptomatic carotid disease is the one variety of cerebrovascular disease that is already explicitly included among risk equivalents. As noted previously, however, symptomatic carotid disease only accounts for ~10% of cerebral infarctions.

Seven studies are cited to support carotid disease as a risk equivalent, with sample sizes ranging from 158 to 3024 and follow-up ranging from 2.5 to 8.0 years. For example, in the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the coronary mortality rate was 19% over 10 years; the inclusion of nonfatal events, it was argued, would increase the event rate well into the range of a risk equivalent.
In the European Carotid Surgery Trial, among 3024 patients, the 10-year nonstroke vascular mortality rate was estimated at 30%. Just under a quarter of patients had preexisting coronary disease. It is likely that even in patients with carotid disease, the absolute risks of MI and vascular death vary, depending on the severity and extent of disease.

In 1 study, among asymptomatic patients followed up for 0.5 to 8.0 years, coronary event rates were 2.7% per year for those with stenosis <50% and increased to 8.3% for patients with stenosis ≥75%. Notably, this study was not a population-based study but a referral population. In the Asymptomatic Carotid Atherosclerosis Study (ACAS), coronary mortality was 19% over 10 years. The prevalence of vascular diseases was high in this cohort: 69% had CHD, 28% were smokers, and 255 had DM. In the Veterans Affairs Cooperative Study Group (n=444 men with ≥50% stenosis monitored for 4 years), the estimated 10-year coronary mortality rate was 51%, or ≈5% annually. Again, there was a high burden of vascular disease among these patients: 27% had a history of MI, 50% were smokers, and 30% had DM. In the Mayo Asymptomatic Carotid Endarterectomy Study (n=158), the 10-year coronary event rate was 30%. In the Carotid Artery Stenosis with Asymmetric Narrowing: Operation Versus Aspirin (CASANOVA) trial (n=410), the 10-year coronary mortality rate was 35%. The burden of vascular risk factors was again high. The absence of a large population-based study of patients with asymptomatic stenosis is a limitation of the available data.

**Abdominal Aortic Aneurysm**

Only 1 study was cited in the NCEP statement to support the inclusion of AAA as a risk equivalent. This was a follow-up study of a cohort of patients who underwent surgery for AAA and were monitored for an end point of fatal MI after recovery from surgery. The study included 343 participants (300 men) 45 to 89 years of age who were studied for 6 to 11 years; there were 286 operative survivors. Among those without a history of coronary disease and a normal ECG before surgery (31% of the population), the annual CHD mortality rate was 1.9%. The rate was higher among those with an abnormal ECG or a history of coronary disease (2.0%–3.9%). Given that nonfatal events were not included, it was considered likely that their inclusion would further push the rates up above those considered to represent those of a risk equivalent.

**Chronic Kidney Disease**

Although CKD was not originally considered a CHD risk equivalent in the ATP III guidelines, subsequent recommendations from major national organizations recommended its inclusion. In 2003, the National Kidney Foundation Task Force on Cardiovascular Disease in Chronic Renal Disease considered patients with CKD to be in the group at highest risk for CHD and recommended that they receive the same targets for risk factor control as those for patients with established CHD. This recommendation was also supported by the AHA. However, although patients with CKD do have an elevated risk of CVD compared with patients without kidney disease, population-based studies do not consistently demonstrate absolute risk levels as high as those for CHD patients or at the level of 20% over 10 years.

Therefore, the data are limited on inclusion of CKD as a risk equivalent, despite the inclusion of patients with CKD in several guideline statements. There are several outstanding questions, moreover. These include the different thresholds of estimated glomerular filtration rate used to define kidney disease; the use of microalbuminuria, which is also associated with increased vascular risk, to define kidney disease; and the fact that kidney function may fluctuate and exists along a continuum, unlike event-defined CVD, which once present, remains present. CKD directly causes and exacerbates hypertension, an atherosclerotic risk factor. In addition, as with DM, it is likely that not all kidney disease is the same in terms of effect on risk for vascular events. Finally, the effectiveness of some CHD-related preventive interventions among patients with CKD remains uncertain.

**Rationale for Inclusion of Other Disease Categories as Risk Equivalents**

Although the evidence for inclusion of these different categories of disease supports the argument that they are CHD risk equivalents, a few general points should be considered. First, although 3 of these conditions (PAD, carotid disease, and AAA) may be considered atherosclerotic, renal disease is not necessarily atherosclerotic. CKD is considered a risk equivalent on the basis of a high risk of CHD events independent of its pathogenesis. Thus, the presence of atherosclerosis is not necessarily required for the definition of a risk equivalent. Second, the inclusion of these conditions is not based uniformly on studies designed to answer the question regarding associated CHD event rates but rather on studies designed to address other questions. Third, the determination of event rates generally relied on overall absolute event rates among a particular category of patient rather than routine incorporation of Framingham risk scores into the analyses. It thus remains unclear whether, for example, PAD, carotid disease, and AAA are risk equivalents in all patients independent of patients’ Framingham risk scores. Fourth, not all studies in each disease category unequivocally demonstrate an increase in absolute event rates >20% over a 10-year threshold. Several studies among patients with renal disease, for example, suggest rates somewhat lower than those for patients with primary CHD.

Grundy, in addressing the inclusion of DM among risk equivalents, considers several reasons why conditions may be considered risk equivalents other than simple consideration of absolute event rates. Some of these reasons are primarily pragmatic. First, even when there is variability in risk among patients with a condition, based on concomitant risk factors, there is an advantage to considering the entire class of patients as risk equivalents. The simplicity of such an approach will yield a net benefit beyond that of considering each individual patient separately. Second, patients with CKD or DM could have a higher case-fatality rate when they experience cardiac events, which would justify more intensive treatment. More data are needed to confirm this in all situations, however. Similar criteria could reasonably be
applied in determining whether stroke patients should be considered risk equivalents.

**Use and Limitations of Risk Prediction Instruments and Absolute Risks**

Risk prediction instruments have been used to identify people at high risk who have not yet developed clear-cut clinical manifestations but whose combination of nonmodifiable risk markers (age and sex) and potentially modifiable risk factors put them at increased risk. It is useful to be able to assess absolute cardiovascular risk among the general population without overt disease.

The Framingham Heart Study algorithm has been the major example of this, although other risk prediction instruments have been used. Multiyear estimates, typically 10 years, are determined on the basis of age, blood pressure, cholesterol levels, smoking status, and DM. The advantages of instruments such as the Framingham score are ready availability, including the ability to calculate risk using an online tool; familiarity; ability to provide quantitative absolute risk over the decade; ability to include interactions for age and sex in the model; and incorporation of graded severity of risk factors, such as lipid levels. Potential disadvantages to using the Framingham algorithm include limits in accounting for variability of risk factor levels across visits; difficulty accounting for purely historical risk factors; absence of several more recently appreciated risk factors such as alcohol consumption, obesity (body mass index or waist circumference), family history, high-sensitivity C-reactive protein, and physical activity; need for slightly more calculation or time to access the algorithm online; and limited applicability to certain minority populations. The major predictor from the Framingham risk score is age, which is not a parameter that can be treated clinically. In addition, and pertinent to the present scientific statement, the widely used Framingham scoring system was developed to estimate risk of coronary end points rather than cerebrovascular disease. However, a separate stroke risk profile has been developed using the Framingham risk models. There is some evidence that the global CVD function and other risk estimation algorithms incorporating other risk factors may provide more informative data about overall cardiovascular health.

**Section Summary**

Multiple different forms of CVD and related conditions, including DM, CKD, and PAD, have been considered as CHD risk equivalents according to existing statements. Risk prediction instruments have also been used to determine absolute risk levels. Regardless of the specific instrument used, it is generally accepted that levels of short-term (≤10 years) absolute risk can be determined by use of easily accessible quantitative scores. In the NCEP guidelines and many others, those with absolute risk levels calculated to be above a certain threshold, typically ≥20% 10-year risk of CHD, have then been considered to have risk equivalents.

Many reasons have been given for inclusion of these different categories of disease, including data from large prospective observational studies demonstrating actual absolute risks, similarity of underlying pathology, severity of outcomes among patients with the condition when they experience a cardiovascular event, and the simplicity and pragmatism of an inclusive approach. In this context, it is notable that cerebrovascular disease has not been included among the group of risk equivalents.

**Importance of Stroke Subtypes/Special Situations**

**Stroke Heterogeneity**

As opposed to acute coronary syndrome, which is usually attributable to large-vessel atherosclerosis, stroke has a far more heterogeneous pathogenesis. Ischemic stroke, the principal stroke type, results mainly from large-vessel atherosclerosis, emboli originating from the heart, or cerebral small-vessel occlusive disease (lacunar infarcts), presumed to result from the occlusion of a single small perforating artery. An abundant variety of other causes are well established, but these are overall much less common. The large-vessel atherosclerotic subtype is generally understood to refer to ischemic stroke caused by atherosclerotic disease that affects the major blood vessels supplying the brain, such as carotid, vertebral, and basilar arteries, or the vessels of the circle of Willis. Classification of ischemic stroke subtype is complex and depends on the intensity and timing of diagnostic investigations. Diagnostic uncertainty about the subtype and misclassification are not uncommon. Additionally, even after comprehensive evaluation, in a considerable proportion of stroke patients the definite cause of stroke remains elusive or >1 potential cause is found. Prevention of stroke sometimes requires specific treatment approaches such as anticoagulation for atrial fibrillation or carotid revascularization for carotid artery disease. Cerebrovascular disease and CAD, however, often coexist. Both share risk factors, pathogenic processes, and numerous preventive strategies.

Overall, long-term cardiovascular risk is high after ischemic stroke, although variation exists in risk of early stroke recurrence according to subtype. Cardioembolic stroke may be expected to have a higher likelihood of CHD events, perhaps related to the underlying presence of cardiac disease. The European Atrial Fibrillation Trial (EAFT) provides some evidence on this point, although the study did not report results for MI alone as an outcome. Median follow-up was only 1.6 years, but investigators presented results for major vascular events (including MI, among other outcomes), as well as for stroke as an independent outcome. Risk factors for major vascular events were derived from multivariate models in which the following emerged as independent predictors: ischemic heart disease, history of thromboembolism, duration of atrial fibrillation, and elevated systolic blood pressure. With these limitations, it is of interest that the major vascular event rate among patients taking aspirin (n = 401) ≤75 years of age with no risk factors was 6.5% (95% confidence interval [CI], 1.8% to 17%) annually, and among patients taking warfarin (n = 225), it was 2.6% (95% CI, 0.1% to 14%) annually. The event rates increased further for those with at least 1 other risk factor, with the lower bounds of the CIs >2% annually (patients ≤75 years of age with 1–2 risk factors, taking aspirin, 13.0% [95% CI, 9.2%–17%] annually;
taking warfarin, 4.4% [95% CI, 2.1%–8.1%] annually). More than 90% of patients had at least 1 other risk factor. Thus, EAFT provides some evidence that the vast majority of patients with atrial fibrillation and stroke will have major vascular event rates of >2% annually.

Lacunar infarcts in particular are known to carry better short-term prognosis. In a systematic review, early mortality and stroke recurrence rates were indeed lower after lacunar versus nonlacunar infarction, whereas long-term vascular risk appeared similar.101 Data on the long-term risk of subsequent MI are limited. In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, the lacunar infarct subgroup had absolute rates of recurrent stroke and major cardiovascular events as high as the large-vessel atherothrombotic subgroup.100 Other studies, however, suggest lower risks of MI after lacunar infarcts,102,106–108 yet even then, the subsequent risk of MI and vascular death approaches 2% annually of a coronary risk equivalent.109 Intracranial stenosis appears to have a relatively high risk of recurrence. In 1 trial, risk of stroke, MI, or vascular death was 23% at 2 years.104

Among young adults, ischemic stroke is rare and the causes are more heterogeneous than among older patients, with a high proportion of cryptogenic stroke.110–115 Even among relatively young people, the incidence of ischemic stroke and atherosclerotic burden rises sharply with increasing age.116 In the Iowa registry, in which patients with ischemic stroke between the ages of 15 and 44 years were followed up for a mean of 6 years, the mortality rate from vascular causes was 1.7% per year, and the incidence of vascular death, nonfatal MI, or recurrent stroke was 2.6% per year.110 In the Helsinki, Finland, registry of consecutive patients 15 to 49 years of age with first-ever ischemic stroke, the cumulative 5-year mortality rate was 10.7%, with more than half of these deaths attributable to vascular causes.111 Patients with large-artery atherosclerosis and cardioembolism underlying the index stroke were at substantially higher risk than those with index strokes of other pathogenetic subtypes.

In a heterogeneous condition such as stroke, there are evidently specific situations that may require particular clinical discretion. Spontaneous cervical artery dissection is an important cause of stroke in younger people. It is considered a paradigm of nonatherosclerotic vasculopathy. There is no apparent association between spontaneous cervical artery dissection and major vascular risk factors, apart from hypertension.117 After dissection of a cervical artery, recurrent stroke risk is restricted mainly to the first weeks and the vascular distribution of the affected artery.118 Beyond that, the risk appears to be quite low for most patients, and redissection is rare.117,119–124 Therefore, it seems prudent not to regard a young patient with stroke caused by dissection as having a risk equivalent. Patent foramen ovale, a remnant of the fetal circulation, is particularly common and present in one quarter of the general population. The risk of recurrence for most young patients with patent foramen ovale and unexplained stroke is usually low,125–128 and atherosclerotic burden is much lower in these patients.128,129 In a systematic review and meta-analysis of observational studies, the risk of recurrent stroke among those with cryptogenic stroke or TIA was similar in those with versus those without a patent foramen ovale.130 In the individual stroke patient, it can be challenging to determine whether a patent foramen ovale is indeed the underlying cause of the stroke. Often, it may be an innocent bystander.131

Intracerebral hemorrhage (ICH) accounts for 10% to 15% of all strokes. Most cases occur in patients who have hypertension, which is the major modifiable risk factor for the occurrence of ICH. Prevalence of other vascular risk factors and comorbidity in those patients is relatively high but not as high as in patients with ischemic stroke.132 There are particular situations in which ICH may be secondary to other specific causes, such as vascular malformations, coagulopathies, or anticoagulation, for which patient-tailored clinical discretion is advised. Recurrent stroke among survivors of primary ICH occurs at a rate of ~2% to 4% per year and is as or more likely to be hemorrhagic than ischemic.133–138 In the population-based South London Stroke Register, the cumulative risk of stroke recurrence over 10 years was 24.5%, with no significant differences noted between ischemic stroke and primary ICH.139 Data on subsequent MI after ICH are particularly scarce, however. In a study based on a state hospital discharge database from South Carolina (n=10 399), hospitalized patients with hemorrhagic stroke were 22% less likely to have subsequent MI but 84% more likely to have stroke, MI, or vascular death as patients with ischemic stroke.140 In a hospital-based study from The Netherlands, the annual rate of any subsequent vascular event after a primary ICH was 5.9% per year.138 Consideration of the stroke type is essential because some risk factors, notably hypertension, pose increased risk for both ICH and ischemic stroke, whereas others, such as high blood cholesterol, may have differing effects. Likewise, some preventive therapies, such as antihypertensive medications, are clearly effective in preventing both ICH and ischemic stroke, whereas others, such as antithrombotic medications or statins, may have opposing effects.

There is some evidence from clinical trials, moreover, that some preventive therapies are likely to be of broad benefit across multiple different stroke subtypes. In a secondary analysis of the SPARCL trial, for example, the benefits of atorvastatin therapy, which might be hypothesized to have a benefit limited to those with large-vessel atherosclerotic disease, were seen among all ischemic stroke subtypes. Although the point estimate of efficacy was greatest for those with large-vessel disease, there was no evidence of statistical heterogeneity in the benefits across different ischemic stroke subtypes. For the primary outcome, for example, comparing atorvastatin with placebo, for those with large-artery disease, the hazard ratio (HR) was 0.70 (95% CI, 0.49 to 1.02); for TIA, the HR was 0.81 (95% CI, 0.57 to 1.17); for small-vessel disease, the HR was 0.85 (95% CI, 0.64 to 1.12); and for those with stroke of unknown cause, the HR was 0.87 (95% CI, 0.61 to 1.24; for heterogeneity, P=0.421).100

Section Summary

Stroke is more heterogeneous than CHD, a situation that argues to some extent against the simple generalization that all stroke patients are at equal risk of future coronary events.
Strokes include both ischemic and hemorrhagic types. Large-vessel atherosclerotic stroke, which can affect not only the extracranial carotid arteries but the intracranial vessels as well, may be the most similar to CAD in terms of risk factors and CHD risk. Patients with cardioembolic stroke also appear to be at increased risk of CHD, but additional study is needed. Other common ischemic stroke subtypes, notably lacunar stroke, appear to convey a lower risk of CHD than others. Similarly, younger patients and those with unusual causes of stroke, such as dissection, other nonatherosclerotic arteriopathies, and paradoxical embolism, may be at lower risk of coronary events. More data are needed about subsequent risks among patients with ischemic stroke caused by nonatherosclerotic arteriopathies (dissection, fibromuscular dysplasia, vasculitis) and hypercoagulable states. Nonetheless, most patients with ischemic stroke fall into higher-risk groups (cardioembolic, atherosclerotic, older age) that have higher CHD event rates, and there is some evidence that the long-term event rates are elevated even among patients with lacunar stroke and patients with hemorrhagic stroke. Evidence from trials such as SPARCL, moreover, supports the notion that treatments hypothesized to benefit primarily those with large-vessel atherosclerotic stroke may provide similar benefits to patients with large-artery, small-vessel disease, and cryptogenic ischemic stroke subtypes.

**Inclusion of Atherosclerotic Stroke Among the Categories of Risk Equivalents**

**Rationale**

The omission of ischemic stroke, in particular atherosclerotic ischemic stroke, from the list of conditions and diseases that are considered to pose an elevated absolute risk of CHD outcomes is glaring. There are many reasons why atherosclerotic stroke should be considered among disorders associated with an increased risk of heart disease and other cardiovascular outcomes. First, data from observational studies and clinical trials demonstrate that patients with ischemic stroke are at approximately the same high levels of risk as those patients with other forms of established CVD. Second, the types of data that have been used to justify the inclusion of DM and these other conditions (AAA, renal failure) as being at these high absolute risk levels are as limited as or even more limited than the data for stroke. It is thus unreasonable to expect a different level of evidence (ie, formal improvement of risk classification) for incorporating stroke compared with the rationale for inclusion of these other entities. Third, inclusion of atherosclerotic stroke among the categories of risk equivalents is consistent with our understanding of the pathophysiology of atherosclerosis, which is recognized to be a diffuse and multifocal disease. Fourth, there is a public health benefit to inclusion of stroke among conditions with high absolute risk, because it would lead to these patients receiving the same intensive prevention therapies used to prevent cardiovascular events among those with heart disease, DM, and other manifestations of atherosclerotic disease. Such an approach would be simple and pragmatic and on a population level would likely yield a net benefit greater than considering each person separately.

**Risk Stratification After Stroke**

Risk stratification after ischemic stroke remains rather primitive compared with the use of risk stratification after MI. No risk stratification systems have been generally recommended for use after stroke in existing guidelines for secondary prevention.

Preliminary attempts to create and validate appropriate risk stratification schemes after ischemic stroke and TIA have been undertaken. In a comparison of several of these long-term risk prediction instruments involving a cohort of 1897 patients with >6 months of follow-up from 10 German centers, each instrument performed equally well and similarly. For the Stroke Prognostic Instrument II (SPI-II), the annual risk of recurrent stroke was 3.2% for those in the low-risk group, 5.5% for the medium-risk group, and 9.1% for the high-risk group.

There are several limitations to the existing data. First, the different prediction instruments analyze risk according to different outcomes. For example, the SPI-II originally considered death and recurrent stroke; the Essen Stroke Risk Score considered risk of recurrent stroke alone. Some predictive models include coronary events, but validated instruments for prediction of risk of MI after stroke are not available. There is an absence of consensus at present about the most important outcome events to be included. Second, each of the studies designed to analyze these risk scores used a different duration of follow-up, ranging from 1 to 10 years. Third, although the schemes may be able to stratify patients into different risk groups, it is not clear how clinically meaningful these groups are, particularly with regard to absolute event rates. Two-year rates of stroke or death in low-risk groups defined by the SPI-II ranged from 9% to 16%. and in the subsequent German analysis that considered the risk of stroke alone as an outcome, annual risk was 3.2% for those in the low-risk SPI-II group. The Essen Stroke Risk Score risk of stroke approached 4% annually for those in the low-risk group. Thus, the approximate risk of clinically significant recurrent events is well above the 2% per year threshold for risk equivalents, even in the lowest-risk groups, and it may be that the vast majority of stroke patients are at levels of risk high enough to justify the most intensive levels of treatment. Fourth, these risk stratification schemes ignore clinically important outcome events other than stroke or death, including functional decline, disability, and dementia.

Finally, because of heterogeneity among stroke patients, risk prediction instruments designed for use after stroke should be created and tested independently of instruments used for primary prevention of stroke or after MI. One limitation to this approach is the paucity of data on risk of vascular events among patients with different stroke subtypes.

**Studies With Data on Absolute Event Rates of MI/Sudden Death Among Stroke Patients**

**Observational Studies**

Touzet et al performed a systematic review and meta-analysis of 39 studies focusing on the absolute risk of MI and vascular death after stroke or TIA. Inclusion criteria included...
prospective cohort study or randomized controlled trial design, with publication date after 1979, reporting on long-term follow-up of ≥100 patients, with follow-up of ≥1 year with <5% loss to follow-up, written in English language publications, with outcome data for MI or vascular death. Exclusion criteria included reporting hemorrhagic strokes only, having a highly selected population (eg, single sex, young subjects, or specific race), or patients with a “specific unusual cause of stroke.” There were 25 randomized controlled trials, 8 population-based cohorts, and 6 single-center hospital-based cohorts, including a total of 65,996 patients with a mean follow-up of 3.5 years. Overall, meta-regression showed annual risks of total MI of 2.2% (95% CI, 1.7%–2.7%; 22 studies); nonfatal MI, 0.9% (95% CI, 0.7%–1.2%; 16 studies); and fatal MI, 1.1% (95% CI, 0.8%–1.5%; 19 studies).

In the population-based Northern Manhattan Stroke (NOMAS),109 a cohort of patients with first ischemic stroke who were ≥40 years of age was prospectively followed up annually for recurrent stroke, MI, and cause-specific mortality. The 5-year risk of MI or vascular death was 17.4% (95% CI, 14.2%–20.6%). In the lowest-risk group, those ≥70 years of age without CHD, 5-year risk of MI or vascular death was 9.7%. Five-year risk of MI, recurrent stroke, or vascular death was 29.0% (95% CI, 25.2%–32.7%). The results of other studies are summarized in Table 4.152–155

Clinical Trials
Clinical trials (Table 5) provide information about cardiovascular event rates in patients with ischemic stroke. Some trials include a placebo group providing baseline risk information. In others, all patients received one or another preventive treatment, giving event rates in patients undergoing standard stroke prevention therapies. Because patients are selected for participation, however, there is always concern for a healthy volunteer bias that can lead to an underestimation of risks in the general population. Moreover, the trials enrolled different populations of patients. Some trials, such as the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), enrolled patients with most stroke subtypes, including hemorrhage but excluding subarachnoid hemorrhage. Other trials, such as SPARCL, excluded patients with atrial fibrillation and other cardiac sources of embolism, patients with subarachnoid hemorrhage, and patients with ICH without an investigator-identified specific indication of higher atherosclerotic risk. For this analysis, the studies were divided into (1) risk factor reduction strategies, (2) antithrombotic therapies, and (3) carotid revascularization trials. Only trials with TIA or stroke as the inclusion events were considered.

Risk Factor Reduction Trials
PROGRESS randomly assigned 6105 people with a history of TIA or stroke within the previous 5 years to either a flexible regimen of perindopril with or without indapamide or placebo56 in addition to standard blood pressure treatment. After a mean follow-up of 3.9 years, active therapy was associated with a statistically significant reduction in MI, which occurred in 1.9% of those on active therapy and 3.1% of those receiving placebo. SPARCL enrolled patients with TIA or stroke within 1 to 6 months, LDL-C of 100 to 190 mg/dL, and no known coronary disease.155 Patients were randomly assigned to either atorvastatin 80 mg/d or placebo.
Median follow-up was 4.9 years. Nonfatal MI occurred in 1.8% of patients receiving atorvastatin and 3.5% of those receiving placebo ($P<0.001$). Major coronary events (death attributed to cardiac causes, nonfatal MI, or resuscitation after cardiac arrest) were seen in 3.4% of the atorvastatin group and 5.1% of the placebo group ($P=0.003$). Both of these trials randomized a variety of stroke subtypes, including some ICH cases that may need to be considered when assessing outcome risks.

**Antithrombotic Therapy Trials**

Secondary stroke prevention trials of antithrombotic agents provide a rich source of outcome information about risk of vascular events, mostly among ischemic stroke patients...
or 1300 mg of aspirin daily. In the Warfarin and Aspirin for Symptomatic Intracranial Arterial Disease (WASID) study, 569 patients with 50% to 99% intracranial stenosis and either TIA or stroke within 90 days were randomly assigned to adjusted-dose warfarin (International normalized ratio 2–3) or 1300 mg of aspirin daily. Rates of MI were 4.2% with warfarin and 2.5% with aspirin.

**Carotid Intervention Trials**

Another source for cardiovascular outcomes in stroke patients is trials comparing carotid stenting with endarterectomy. However, only 2 trials reported longer-term rates of MI in addition to stroke and death. The Endarterectomy versus stenting in patients with Symptomatic Severe Stenosis (EVA 3S) study randomized 527 patients with TIA or nondisabling stroke within 120 days and ≥60% carotid stenosis to either carotid endarterectomy (CEA) or stenting (CAS). In the 30 days after the procedure, MI was observed in 0.4% of the CAS group and 0.8% of the CEA group; the mortality rate was 0.8% in the CAS group and 1.2% in the CEA group. In the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), 1321 patients with TIA or nondisabling stroke within 180 days were randomly assigned to either CAS or CEA. MI occurred in 1.0% of those undergoing CAS and 2.3% of patients with CEA. The overall rates for stroke, MI, and death were 6.7% for the CAS group and 5.4% for the CEA group. These lower event rates could represent more intensive therapy in this clinical trial population.

**Summary and Limitations of Observational and Clinical Trial Data**

Observational studies provide evidence that stroke patients, as a group, have absolute risks of MI and combined end points including MI and vascular death that are equal to or greater than the 2% annual threshold that defines high-risk groups. Definitions of vascular death and methods of ascertainment vary among individual studies, however. There is also evidence that risks among stroke patients differ (as discussed above), as they do among patients with DM and kidney disease.

Most clinical trials among patients presenting with stroke and TIA also provide evidence that the rates of MI and vascular death after stroke are elevated. There are limitations to the available data from stroke trials, however. First, there is little definitive evidence that rates of hard CHD end points alone (MI and sudden cardiac death) reach 2% annually, mostly because of a lack of reported data. Second, only a few trials monitored patients for as long as 4 years, and in most trials, mean follow-up was <2 years. Some studies provide evidence that vascular event rates change over time during 10 years, moreover, and therefore extrapolation of event rates should be considered speculative. Recent analyses provide evidence that recurrent vascular event rates in clinical trials have been declining over the past 50 years. Additional follow-up is planned for the CREST trial and may provide more long-term outcome information in the future. Third, trials used different definitions of outcomes and assessed different outcomes. Few assessed all hard coronary end points. Fourth, most did not allow a breakdown of stroke subtypes by category. Finally, patients with a prior history of MI/CHD were not excluded from most of the studies discussed above. In fact, only SPARCL included patients without a history of CHD, and in that trial, the absolute risk of MI was <2% per year.

**Other Arguments for Including Atherosclerotic Stroke as a Risk Equivalent**

Evidence of annual absolute event rates of ≥2% is only one reason for a condition to be considered a risk equivalent. As discussed above, there is heterogeneity in the absolute risk data for other disorders that have been included among risk equivalents, such as DM and CKD. For others, like AAA, data are very limited. Formal improvement of risk classification by inclusion of these conditions has generally not been demonstrated. Because they are nonetheless considered among risk equivalents in many guidelines, as noted above, it is worth considering what additional arguments similarly justify the inclusion of atherosclerotic stroke or other stroke subtypes.

First, inclusion of atherosclerotic stroke among the categories of risk equivalents is consistent with our understanding of the pathophysiology of atherosclerosis, which is recognized to be a diffuse and multifocal disease. Second, there may also be a public health benefit to inclusion of stroke among conditions with high absolute risk, because it would lead to these patients receiving the same intensive prevention therapies used to prevent cardiovascular events among those with heart disease, DM, and other manifestations of atherosclerotic disease. Many patients enter the healthcare system with a first event of stroke rather than MI, and they are therefore better served by being included among patients with high-risk conditions. On a population level, moreover, there are pragmatic reasons to approach all cardiovascular patients in a uniform, simpler way. Third, and consistent with this pragmatic approach, many international guidelines include atherosclerotic stroke and stroke in general among high-risk conditions. Finally, if, as discussed in the next section, stroke is included in the outcome cluster for determination of absolute risks, then it appears reasonable to also include it among the conditions at high risk, especially because stroke patients are generally at even higher risk of recurrent stroke than of MI.

**Magnitude of Effect of Including Stroke as a High-Risk Condition or Risk Equivalent**

Although some stroke patients are already classified as having coronary risk equivalents because of comorbid conditions such as CAD or DM, many stroke patients do not have these risk factors and will, if included in high-risk groups, incrementally contribute to estimates of those at risk of CVD. It is possible to estimate the effect of inclusion of stroke as a risk equivalent on the number of people in the United States considered as having risk equivalents. The prevalence of CHD in the United States among those >20 years of age is ≈17.6 million (8% of the US population), and the preva-
lence of diagnosed DM is \( \approx 17.9 \) million (8% of the US population).\(^{169}\) Between 16% and 58% of people with DM, depending on the population and study design, have CAD.\(^{170–172}\) Assuming that approximately one third of people with DM already have coronary disease (\( n = 6.0 \) million), the approximate number of those already considered to have risk equivalents would be 29.5 million. The prevalence of stroke in the United States is 6.4 million.\(^{168}\) Of those with stroke, \( \approx 30\% \) have coexisting CHD\(^{173}\) and another 10% have DM; therefore, \( \approx 3,800,000 \) people with stroke (60% of the total number of stroke patients) would be added to those considered to have risk equivalents. The addition of stroke would thus lead to an increase of \( \approx 13\% \) in the US population classified as having coronary risk equivalents and in need of more intensive preventive treatments.

There is little in the way of published data to confirm these estimates of the proportion of people with only a stroke among those with CAD, DM, or stroke. Unpublished data from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study\(^{174}\) provide some prevalence rates for stroke alone (Figure). Among 27,438 participants in the REGARDS study for whom data are available on prevalent stroke, CAD, and DM, 10,387 (38%) have \( \geq 1 \) of these conditions. The Figure shows by age strata the proportion of people who are positive because of either DM or CAD but are stroke free, the percentage of people who are positive and have had a stroke but would have been identified already by CAD or DM, and finally the percentage of people who have stroke only and hence would be newly identified. In all age strata, \(< 20\% \) of risk equivalent-positive patients have a stroke. Of those who have had a stroke, approximately half already have a risk equivalent because of coexisting CAD or DM. Thus, regardless of the age strata, these data confirm that inclusion of stroke as a risk equivalent would result in an expansion of \( \approx 10\% \) in the number of patients considered as having risk equivalents. Although these are not national estimates of prevalent stroke, these data are based on a national sample, and weighting can be used to generate national estimates.

Declaring this new 10% of stroke-only people as risk equivalents may require a higher vigilance for the management of some, but not all, of the risk factors in these people. Stroke treatment currently encompasses many of the traditional Framingham CVD risk factors, including management of hypertension, DM, left ventricular hypertrophy, atrial fibrillation, and efforts for smoking cessation.\(^{2,85,87,175}\) Recently, the SPARCL study has indicated use of statins for secondary stroke prevention.\(^{176}\) Thus, the addition of stroke as a CVD risk equivalent may have only a moderate impact on treatment usage, because secondary stroke prevention should already imply management of many of the same comorbid conditions.

TIAs were not included in these calculations, and the number would further increase by adding 200,000 to 500,000 TIAs annually.\(^{177}\) It should be recognized, however, that according to current definitions, it is likely that many TIAs can actually be reclassified as strokes.\(^{177}\) Nonetheless, TIAs as a category of cerebrovascular disease are not included in the risk equivalent consideration because the evidence from studies is less conclusive. Additional future studies of TIAs may identify their appropriate inclusion in categories of atherosclerotic stroke.

**Section Summary**

Few studies have examined risk of cardiac disease after stroke, and well-validated risk prediction instruments for use after stroke are not yet readily available or used. In particular, there is a paucity of data on outcomes after specific stroke subtypes. Those studies that have been conducted, however, suggest that the risk of CHD events is high in most stroke patients. Observational and clinical trial data provide evidence that patients with ischemic stroke are at elevated levels of risk similar to those of patients with other forms of established CVD. A review of the data used to justify inclusion of DM, CKD, and other conditions among those at high absolute risk levels demonstrates that the data for these conditions are limited and conflicting. Justification for inclusion of these conditions is based not only on statistical evidence of formal improvement of risk classification but on other arguments as well, such as increased mortality associated with cardiac events in those conditions, a common pathophysiologial mechanism, simplicity, and pragmatism.
Inclusion of atherosclerotic stroke among the categories of risk equivalents therefore is consistent with our understanding of the pathophysiology of atherosclerosis, which is recognized to be a diffuse and multifocal disease. Moreover, there is a public health benefit to inclusion of stroke among conditions with high absolute risk, because it would lead to these patients receiving the same intensive prevention therapies used to prevent cardiovascular events among those with heart disease, DM, and other manifestations of atherosclerotic disease.

Inclusion of stroke as a high-risk condition could have a substantial impact on risk estimation used in the planning of prevention programs. There could be an increase of 10% in the number of people considered to be risk equivalents and therefore eligible for more intensive preventive interventions.

**Inclusion of Stroke in the Vascular Outcome Cluster**

**Rationale**

The second critical issue addressed by the present scientific statement is the inclusion of stroke among the outcome cluster in cardiovascular risk prediction instruments. The limited focus on cardiac disease alone in estimating absolute risk of outcome events is problematic for several reasons. First, stroke is an important health outcome in terms of morbidity, disability, mortality, and social and economic costs. Failure to include it as an outcome therefore ignores a major preventable cardiovascular outcome. Second, it is conceptually inappropriate to omit stroke, because many of the same risk factors and mechanisms that cause heart disease also cause stroke. Third, excluding stroke perpetuates disparities because it fails to capture an outcome (stroke) that is even more important for minorities than for nonminority populations. Fourth, stroke is often included as an outcome in clinical trials as a major cardiovascular end point. Fifth, as will also be discussed in the following section, primary prevention guidelines from Europe and elsewhere endorse the inclusion of stroke as an outcome of equal importance, putting the US guidelines out of touch with international efforts.

**Importance of Stroke as an Outcome**

Stroke is a major public health issue and will become an increasingly global problem over time as chronic diseases continue to emerge in middle- to lower-income nations. Reducing mortality from stroke (both ischemic and hemorrhagic) and cardiac diseases is an essential part of the AHA 2020 Impact Goal and is being addressed in the United Nations approach to noncommunicable diseases. Most risk factors for stroke overlap with risk factors for CHD, and thus successful interventions aimed at preventing either will often lead to reductions in both. Both CHD and stroke are associated with huge burdens and costs.

**Stroke Incidence**

There are ≈800,000 new or recurrent strokes annually in the United States. Most of these (≈600,000) are first strokes, and the remainder (≈200,000) are recurrent strokes. Of these, ≈87% are ischemic, 10% are primary hemorrhages, and 3% are subarachnoid hemorrhages. Incidence increases rapidly with age, doubling for each decade after age 55. Among adults 35 to 44 years of age, incidence of stroke is 30 to 120 per 100,000 people per year, and for those 65 to 74 years of age, incidence is 670 to 970 per 100,000 per year.

**Stroke Mortality**

Stroke is the second-leading cause of death in the world but has dropped to fourth in the United States, behind CHD, cancer, and chronic respiratory disease. The World Health Organization suggests 5.5 million deaths of stroke in 2002 (≈1 every 6 seconds). These deaths were more likely to be in women (≈3 million versus 2.5 million). The 3 nations with the greatest numbers of stroke deaths were China, India, and the Russian Federation. More than 85% of all strokes occur in low- and middle-income countries.

There were 134,148 stroke deaths (≈1 every 4 minutes) in 2008. US stroke death numbers were higher in women than in men, and stroke death rates were also higher in blacks than whites; other minority groups did not clearly have higher rates. Data from 2002 reveal a younger average age at death because of stroke in virtually all minority races and those of Hispanic ethnicity. Median survival after first stroke is strongly age dependent and is ≈6 to 7 years for people 60 to 69 years of age, 5 to 6 years for people 70 to 79 years of age, and 2 to 3 years for people >80 years of age.

**Effect of Stroke on Disability**

An estimated 15 million strokes occur each year worldwide. Among the survivors, 5 million are left permanently disabled. The burden of stroke and other chronic diseases can be measured and compared, with some limitations, using disability adjusted life years (DALY), a measure that allows simultaneous consideration of both mortality and disability. DALYs allow the weighting of years of life by a factor that represents the level of disability that occurs with that condition. By using DALYs to estimate the burden of stroke, it is projected that global DALY loss caused by stroke will grow from 38 million in 1990 to 61 million in 2020; the corresponding numbers for CHD are 47 million in 1990 to 82 million in 2020. The relative stroke burden may thus be estimated at ≈74% of CHD in 2020.

In the United States, stroke is the largest single cause of long-term disability in adults. Among ischemic stroke survivors at 6 months, 43% had moderate to severe residual neurological deficits. These deficits were more prevalent in women, but only because of their greater age at the time of stroke.

**Relative Importance of Stroke Versus Heart Disease in Different Populations**

On a global scale, cardiac disease and stroke are among the leading 3 and 4 causes of disease burden in men and women, respectively. In men, stroke is responsible for 5.0% of all DALYs lost versus 6.8% for CHD; in women, the burden is nearly identical, with stroke responsible for 5.2% of all DALYs lost versus 5.3% for CHD.

In the United States, mortality rates are relatively increased in blacks versus whites for both stroke and CHD. Also consistent between conditions, point estimates for mortality for both stroke and CHD were lower among whites than
among American Indian and Alaskan Native and Asian and Pacific Islander races and people of Hispanic ethnicity. A unique ethnic difference in stroke patients relates to the relative frequency of ICH and subarachnoid hemorrhage. ICH mortality is increased in the Asian or Pacific Islander races versus whites (in contrast to overall stroke), and subarachnoid hemorrhage is increased in all racial minorities and Hispanics compared with whites.168

Estimated direct and indirect costs for stroke in the United States for 2010 were $73.7 billion versus $177.1 billion for CHD.168 Over the period from 2005 to 2050 in the United States, total costs for ischemic stroke alone are estimated to be $1.5 trillion, $379 billion, and $313 billion for white, black, and Hispanic populations, respectively. The per capita cost is highest in blacks, then Hispanics, then whites, with loss of earnings being the greatest cost for all groups.181,185

Studies With Data on Absolute Event Rates for MI/Sudden Death Versus MI/Sudden Death/Stroke Observational Studies Dhamoon and Elkind10 reviewed studies with data available on absolute risks of both hard cardiac end points (MI and sudden death) and the combination of hard cardiac end points and stroke. The Framingham Heart Study general cardiovascular risk profile scoring system,9 developed among those 30 to 74 years of age and free of heart disease or stroke, was used to compare risk of composite outcomes with risk of individual end points.9 Among women in the fifth decile of risk, mean 10-year risk of global CVD was \( \approx 4\% \), with a risk of hard CHD of \( \approx 2.4\% \); risk of stroke, 0.95%; and combined risk of CHD or stroke, \( \approx 3.4\% \). Among men in the fifth decile of risk, the mean 10-year risk of CVD was \( \approx 12\% \), corresponding to a risk of CHD of \( \approx 7.3\% \); risk of stroke, \( \approx 2.9\% \); and combined risk of CHD or stroke, \( \approx 10.2\% \). Among 9 population-based studies in Italy composed of 12 045 men and 5108 women 35 to 74 years of age with follow-up from 5 to 15 years, outcomes included mortality, causes of death, and nonfatal cardiovascular events.186 Three categories of outcomes were considered: major coronary events (sudden coronary death, nonfatal coronary death, definite nonfatal MI, fatal MI, definite fatal chronic ischemic heart disease, surgery of coronary arteries), major cerebrovascular events (definite fatal and nonfatal hemorrhagic and thrombotic stroke, surgery of carotid arteries), and major cardiovascular events (major coronary and cerebrovascular events as defined above, plus major peripheral artery events, including fatal and nonfatal aortic aneurysms, fatal lower limb artery disease, surgery of aorta or lower limb arteries). The 10-year risk of first major coronary events was \( \approx 6\% \) in men and \( \approx 3\% \) in women 60 years of age, whereas the 10-year risk of first major cardiovascular events was \( \approx 11\% \) in men and \( \approx 4\% \) in women. In the Reduction of Atherothrombosis for Continued Health (REACH) study, participants were enrolled with either (1) a history of CHD, cerebrovascular disease, or PAD or (2) at least 3 atherothrombotic risk factors.187 Participants were derived from multiple international outpatient sites and followed up at 1 year for cardiovascular outcomes. Among the 11 766 participants without a history of CVD but with multiple risk factors, the 1-year event rate of cardiovascular death and nonfatal MI was 1.5% and the rate of stroke was 0.8%. The 1-year event rate of the combined outcome of cardiovascular death, MI, or stroke was 2.15%.

Among 2613 community participants in the Northern Manhattan Study without preexisting heart disease or stroke (53% Hispanic, 25% non-Hispanic black, and 20% non-Hispanic white), 867 were classified as being at intermediate risk based on an estimated 10% to 20% predicted 10-year Framingham risk score.188 The observed 10-year risk of MI or CHD death in this group was 14.20%, which increased to 21.98% (absolute risk difference, 7.78; 95% CI, 5.86–9.75) when stroke was added to the outcome cluster. Thus, in a multiethnic urban population, the addition of stroke to the risk stratification outcome cluster resulted in a 55% increase in total estimated risk and crossing of the high-risk threshold (>20% over 10 years).

The absolute number and proportion of patients who may be classified as risk equivalents is likely to differ across racial/ethnic groups because the relative proportion of cardiac and stroke events may differ among these groups. In the Northern Manhattan Study cited above, for example, the absolute risk difference for the inclusion of stroke in the outcome cluster among blacks was significantly larger than among whites \( (P=0.01) \).188 Thus, the effect of adding stroke as a risk equivalent is likely to have a greater impact in minority populations.

Despite the heterogeneity among these study populations and designs, inclusion of stroke among the outcome cluster leads to a notable increase in global cardiovascular risk. Although this is not unexpected (because more outcomes are being considered), it is notable that the absolute event rate in several studies crosses the 20% over 10 years (or 2% annual) absolute risk threshold of a risk equivalent when stroke is included. It is worth noting that actual risks may change over time and that the 2% annual risk remains an approximation.

Clinical Trials Clinical trial data are limited by selection bias and short-term follow-up but can provide stratified risk of strictly defined outcome events. In Table 6, risk or event rate data are presented in 3 groups: cardiac, stroke related, and combined. Because outcome definitions and follow-up times vary among studies, the outcome definition used in each study is specified, along with the time period. Approximate annualized risks were calculated by dividing total risk by the follow-up period for the individual studies.189 It is worth noting that stroke is a significant outcome after coronary artery bypass grafting as well.198

Several clinical trials among patients with and without CVD therefore provide evidence that the annual absolute risks of cardiovascular events are substantially increased when cerebrovascular events are included among the relevant clinical outcome event cluster. Though many trials and studies did not distinguish stroke subtype, it is important to consider atherosclerotic stroke in particular as a relevant outcome.

Section Summary Stroke is an important cardiovascular health outcome in terms of morbidity, disability, mortality, and social and economic costs. Many of the same risk factors and mechanisms that cause
Table 6. Clinical Trials That Report Both Cardiac and Cerebrovascular Event Rates in Stroke-Free Populations

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Participants</th>
<th>n</th>
<th>Follow-Up Period</th>
<th>Cardiac Risk</th>
<th>Stroke Risk</th>
<th>Combined Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOPE (2000)</td>
<td>Age ≥55 y, with CAD, stroke, PVD, or DM and 1 other cardiovascular risk factor; 11% had history of stroke or TIA in placebo group</td>
<td>4652 (Placebo group)</td>
<td>Mean 5 y</td>
<td>Rate of MI: 8.1%</td>
<td>Rate of stroke: 4.9%</td>
<td>Rate of cardiovascular death, MI, and stroke: 17.8%</td>
</tr>
<tr>
<td>LIFE (2002)</td>
<td>With hypertension and LVH on ECG, age 55–80 y, 8% had history of cerebrovascular disease</td>
<td>9193</td>
<td>Mean 4.8 y</td>
<td>Rate of MI: 4%</td>
<td>Rate of stroke: 6%</td>
<td>Rate of cardiovascular mortality, stroke, or MI: 12%</td>
</tr>
<tr>
<td>PROSPER (2002)</td>
<td>Age 70–82 y with vascular disease or smoking, DM, or hypertension; 11.0% had previous stroke or TIA</td>
<td>2913 (Placebo group)</td>
<td>Mean 3.2 y</td>
<td>Risk of nonfatal MI or CHD death: 12.2%</td>
<td>Risk of nonfatal or fatal stroke: 4.5%</td>
<td>Risk of CHD death, nonfatal MI, or fatal or nonfatal stroke: 16.2%</td>
</tr>
<tr>
<td>EUROPA (2003)</td>
<td>Age ≥18 y with CHD; 3.3% had previous stroke</td>
<td>6108 (Placebo group)</td>
<td>Mean 4.2 y</td>
<td>Rate of MI and cardiovascular death: 9.8%</td>
<td>Rate of stroke: 1.7%</td>
<td>Rate of cardiovascular death, MI, and stroke: 12.6%</td>
</tr>
<tr>
<td>CHARISMA (2006)</td>
<td>Age ≥45 y, with CVD or multiple risk factors; 24.3% had history of stroke, 11.9% had history of TIA</td>
<td>7801 (Placebo + aspirin group)</td>
<td>Median 2.3 y</td>
<td>Rate of nonfatal MI and cardiovascular death: 4.9%</td>
<td>Rate of nonfatal stroke: 2.4%</td>
<td>Rate of nonfatal MI, nonfatal stroke, or cardiovascular death: 7.3%</td>
</tr>
<tr>
<td>PRActive (2007)</td>
<td>Age 35–75 y with DM2; 18.8% had previous stroke</td>
<td>2633 (Placebo group)</td>
<td>Mean 2.9 y</td>
<td>Rate of nonfatal MI and cardiac death: 9.3%</td>
<td>Rate of stroke: 4.1%</td>
<td>Rate of cardiovascular death, MI, and stroke: 14.8%</td>
</tr>
<tr>
<td>ACCORD (2008)</td>
<td>With DM2, HbA1c ≥7.5%, age 40–79 y with CVD or 55–79 y with cardiovascular risk factors</td>
<td>5123 (Standard therapy group)</td>
<td>Mean 3.5 y</td>
<td>Rate of nonfatal MI plus cardiovascular death: 6.4%</td>
<td>Rate of nonfatal MI plus fatal stroke: 1.4%</td>
<td>Risk of nonfatal MI, nonfatal stroke, or cardiovascular death: 7.2%</td>
</tr>
<tr>
<td>ADVANCE (2008)</td>
<td>Age ≥55 y, with DM2, major macrovascular or microvascular disease, or ≥1 other cardiovascular risk factor; 9.1% had history of stroke</td>
<td>5568 (Standard therapy group)</td>
<td>Median 5 y</td>
<td>Rate of nonfatal MI plus cardiovascular death: 8.0%</td>
<td>Rate of all cerebrovascular events: 5.9%</td>
<td>Rate of nonfatal MI, nonfatal stroke, and cardiovascular death: 10.6%</td>
</tr>
<tr>
<td>ONTARGET (2008)</td>
<td>With CHD, PVD, cerebrovascular disease, or DM with end-organ damage; 20.9% had history of stroke or TIA in combination therapy group</td>
<td>8502 (Combination therapy)</td>
<td>Median 4.7 y</td>
<td>Rate of fatal and nonfatal MI and cardiovascular death: 12.5%</td>
<td>Rate of fatal and nonfatal stroke: 4.4%</td>
<td>Risk of death of cardiovascular causes, MI, or stroke: 14.1%</td>
</tr>
<tr>
<td>POPADAD (2008)</td>
<td>Age ≥40 y with DM and asymptomatic PVD</td>
<td>318 (Placebo plus placebo group)</td>
<td>Median 6.7 y</td>
<td>Rate of nonfatal MI and CHD death: 13%</td>
<td>Rate of nonfatal and fatal stroke: 9%</td>
<td>Rate of nonfatal MI, CHD death, and nonfatal and fatal stroke: 22%</td>
</tr>
</tbody>
</table>

HOPE indicates Heart Outcomes Prevention Evaluation Study; CAD, coronary artery disease; PVD, peripheral vascular disease; DM, diabetes mellitus; TIA, transient ischemic attack; MI, myocardial infarction; LIFE, Losartan Intervention For End point reduction in hypertension study; LVH, left ventricular hypertrophy; PROSPER, Pravastatin in Elderly individuals at risk of vascular disease; CHD, coronary heart disease; EUROPA, European Trial on Reduction in Cardiac Events With Perindopril in Stable Coronary Artery Disease; CHARISMA, Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization Management and Avoidance; CVD, cardiovascular disease; PRActive, PROspective pioglitAzone Clinical Trial In Macrovascular Events; DM2, type 2 diabetes mellitus; ACCORD, Action in Controlling Cardiovascular Risk in Diabetes trial; HbA1c, hemoglobin A1c; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; ONTARGET, Ongoing Telmisartan Alone and in Combination with Ramipril Global End point Trial; and POPADAD, Prevention of Progression of Arterial Disease and Diabetes.

*Calculated by dividing total risk by follow-up period.

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heart disease also cause stroke, and many treatments (antihyper-
tensive treatments, statins) that reduce risk of heart disease also 
reduce risk of stroke. Inclusion of stroke as an outcome could 
lead to an increase in the absolute risks of vascular events of 5% 
to 10%. In some minority populations, the contribution of stroke 
to the total burden of CVD may be larger. Inclusion of stroke as 
an outcome measure in risk prediction instruments may there-
fore better capture the overall risk of CVD in these populations 
than when it is left out. For these reasons, primary prevention 
guidelines from Europe and elsewhere endorse the inclusion of 
stroke as an outcome in absolute risk prediction, as discussed in 
the following section.

Inclusion of Stroke in International Guidelines

Table 7. List of Scores for Assessment of Vascular Risk Used in International Guidelines

<table>
<thead>
<tr>
<th>Score/Profile</th>
<th>Original Population</th>
<th>Vascular Events Included as Discrete End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CHD Fatal</td>
</tr>
<tr>
<td>Framingham CHD score²</td>
<td>United States</td>
<td>+</td>
</tr>
<tr>
<td>Framingham stroke score²⁷</td>
<td>United States</td>
<td>+</td>
</tr>
<tr>
<td>Framingham CVD (global) risk score¹⁹⁵</td>
<td>United States</td>
<td>+</td>
</tr>
<tr>
<td>Framingham general cardiovascular risk profile⁹</td>
<td>United States</td>
<td>+</td>
</tr>
<tr>
<td>SCORE charts²⁰⁰</td>
<td>Europe</td>
<td>+</td>
</tr>
<tr>
<td>JBS-2 charts²⁴</td>
<td>United Kingdom, derived from Framingham equations</td>
<td>+</td>
</tr>
<tr>
<td>ASSIGN score²⁰¹</td>
<td>United Kingdom (Scotland)</td>
<td>+</td>
</tr>
<tr>
<td>WHO/ISH²⁰²,²⁰³</td>
<td>Derived from Framingham equations</td>
<td>+</td>
</tr>
<tr>
<td>Modified Sheffield table²⁰⁴</td>
<td>United Kingdom</td>
<td>+</td>
</tr>
<tr>
<td>New Zealand prediction guide²⁰⁵,²⁰⁶</td>
<td>New Zealand</td>
<td>+</td>
</tr>
<tr>
<td>UKPDS risk engine²⁰⁷,²⁰⁸</td>
<td>United Kingdom</td>
<td>+</td>
</tr>
<tr>
<td>Australian CVD risk charts²⁰⁹</td>
<td>Australia</td>
<td>+</td>
</tr>
<tr>
<td>PROCAM⁸³</td>
<td>Germany</td>
<td>+</td>
</tr>
<tr>
<td>QRISK score²⁰⁴</td>
<td>United Kingdom</td>
<td>+</td>
</tr>
<tr>
<td>DECODE²¹⁰</td>
<td>Europe</td>
<td>+</td>
</tr>
</tbody>
</table>

CHD indicates coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction; TIA, transient ischemic attack; PAD, peripheral artery disease; SCORE, Systematic Coronary Risk Evaluation; JBS-2, Joint British Societies; ASSIGN, Assessing cardiovascular risk using SIGN guidelines to ASSIGN preventive treatment; WHO/ISH, World Health Organization/International Society for Hypertension; UKPDS, UK Prospective Diabetes Study; PROCAM, Prospective Cardiovascular Münster Study; and DECODE, Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe.

*Refers to any death that can be related to a vascular disease.

Inclusion of Stroke Among High-Risk Conditions in Estimating Absolute Risk

Table 7.9,24,38,43,84,87,199–210 and the online-only Data Supplement Table 6.23,24,199,206,209,211–232 provide a summary of the 
inclusion of various vascular diseases and end points in 
international CVD guideline statements. Some guidelines 
identified symptomatic carotid disease as a CHD equiva-
 lent²¹⁴,²²¹ or stroke as a high CVD risk equivalent,²⁴,²²⁰,²²² 
although the underlying evidence is not described in the 
publications. Among guidelines for secondary prevention in 
patients who had an ischemic stroke or a TIA that were 
published in the United States,¹⁴²,²³³–²⁵⁵ Canada,²³⁶,²³⁷ Eu-
rope,²³⁸–²⁴⁰ New Zealand,²³⁵ and Australia,²⁰⁹ none specifi-
cally address the question of whether stroke/TIA should 
be considered as a CHD equivalent. Most report, however, that 
measures that aim at preventing recurrent cerebrovascular 
events also decrease the risk of all vascular outcomes. For 
instance, the AHA/American Stroke Association guidelines 
for prevention of stroke in patients with ischemic stroke or 
TIA are focused on prevention of recurrent cerebrovascular 
events but also state that many of the grades for the 
recommendations were chosen to reflect the existing evi-
dence on reduction of all vascular outcomes after stroke, 
including stroke, MI, and vascular death.¹⁴²
Inclusion of Stroke Among Outcomes in Estimating Absolute Risk

Depending on the specific guideline statement, target population, specialists who establish guidelines, and methods used to estimate CVD risk, vascular outcome events refer either to CHD, stroke, both, or even all vascular events, including also heart failure, aortic aneurysm, and PAD. Some also include TIA and new angina. Although many recent guidelines for primary prevention tend to take stroke into account for estimation of global vascular risk, none provide an estimate of the extent to which inclusion of stroke as an outcome contributes to global CVD risk.

Moreover, no guideline considers heterogeneity of stroke (ie, hemorrhagic versus ischemic and/or ischemic stroke subtypes). Yet some risk factors, such as high blood cholesterol, may have a different impact on hemorrhagic and ischemic stroke. There are also problems in estimating risk for some people of nonwhite origins who have a higher risk of stroke but a lower risk of ischemic heart disease. Some methods for vascular risk assessment used in guidelines consider fatal events only. JNC 7 points out that for every 20 mm Hg increase in systolic blood pressure or 10 mm Hg increase in diastolic blood pressure, there is a doubling of mortality caused by both ischemic heart disease and stroke and that antihypertensive therapies reduce the risk of stroke to a greater extent than that of CHD.\(^{218}\)

When referring to estimation of CVD risk, many investigators recommend use of the Framingham CHD risk score. Interestingly, the 2009 Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia now recommend the use of the most recent Framingham risk scores for total CVD,\(^9,217\) whereas the previous versions recommended the Framingham CHD risk score.\(^{241,242}\) Some guidelines provide a more or less comprehensive list of risk scores that can be used to identify high-risk patients but do not always recommend which one should be used in clinical practice, leaving that for the clinician to decide. As expected, North American guidelines tend to recommend the Framingham CHD risk score, whereas European guidelines recommend the Systematic Coronary Risk Evaluation (SCORE) charts, which consider fatal events only for total CVD risk. There are also some discrepancies between guidelines in a single country or within a single national institute, depending on which specialists were involved and the topic. Such variations in methods used to identify high-risk patients likely result in variable proportions of patients eligible for intervention.

Section Summary

There is heterogeneity among published guidelines with regard to inclusion of cerebrovascular disease among conditions at high absolute risk or risk equivalents, although atherosclerotic diseases are often included. Most that do exclude nonatherosclerotic stroke do not explicitly provide any rationale for its exclusion. Guidelines from different countries and different organizations representing different specialists also differ in whether they include only fatal or both fatal and nonfatal events in risk estimation and in their use of different risk prediction instruments. Some more recent guidelines have begun to emphasize the importance of estimating global vascular risk, however, including cerebrovascular disease. Future efforts to harmonize the outcomes considered in these risk prediction instruments may be worthwhile, both to better estimate the burden of CVD internationally and across regions and to provide optimal clinical care.

Recommendations and Conclusions

1. Large-vessel atherosclerotic ischemic stroke should be considered as a CHD risk equivalent similar to other atherosclerotic conditions in risk prediction instruments and guidelines that use CHD risk equivalents (Class I; Level of Evidence B).
2. Ischemic stroke can reasonably be considered a relevant outcome along with CHD outcomes in CVD risk prediction instruments used in primary and secondary prevention, including trials of general preventive strategies not focused on particular blood vessels (Class IIa; Level of Evidence B).
3. Ischemic stroke subtypes other than large-vessel atherosclerosis, including small-vessel disease, may be considered CHD risk equivalents, although further research is needed (Class IIa; Level of Evidence B). The heterogeneity of stroke compared with CHD and the lack of detailed data about cardiovascular outcomes among patients with all ischemic stroke subtypes considered individually make it difficult to generalize about all stroke subtypes. Patients with specific less common causes of ischemic stroke, such as dissection and patent foramen ovale, may be excluded from the category of risk equivalents pending further data. Such patients are expected to be the minority of patients, however.
4. Hemorrhagic strokes and strokes of undetermined subtypes may be included among outcomes in general CVD risk prediction instruments used in primary and secondary prevention (Class IIb; Level of Evidence B).
5. Ischemic stroke can reasonably be considered a relevant outcome in clinical 10-year cardiovascular risk prediction instruments for patients (Class IIa; Level of Evidence B).
6. Further clinical epidemiological studies are needed to increase the level of evidence to improve precision of the absolute risk estimates for different stroke subtypes in risk prediction instruments.
## Disclosures

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<th>Writing Group Member</th>
<th>Employment</th>
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<th>Other Research Support</th>
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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be “significant” if (1) the person receives $10,000 or more during any 12-month period, or 5% or more of the person’s gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns $10,000 or more of the fair market value of the entity. A relationship is considered to be “modest” if it is less than “significant” under the preceding definition.

*Modest.
†Significant.
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†Significant.

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88. Choi CU, Park CG. Comparing the probability of stroke by the Framingham risk score in hypertensive Korean patients visiting private clinics and tertiary hospitals. BMC Neurol. 2010;10:78.


and diabetes (POPADAD trial): factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ. 2008;337:a1840.


Inclusion of Stroke in Cardiovascular Risk Prediction Instruments: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association


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## Supplementary Table 1. Methods Used in International Guidelines to Assess Vascular Risk

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<td>JBS 2: Joint British Societies’ guidelines on prevention of cardiovascular disease in clinical practice²⁴</td>
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<td>Guideline for Management of Modifiable Risk Factors in Adults at High Risk for Cardiovascular Events²¹³</td>
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<td>Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)(^218)</td>
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