Inclusion of Stroke as an Outcome and Risk Equivalent in Risk Scores for Primary and Secondary Prevention of Vascular Disease

Mandip S. Dhamoon, MD, MPH; Mitchell S.V. Elkind, MD, MS

The goal of this review is to summarize the evidence related to the following 2 questions: (1) Among stroke patients, is the risk of MI/coronary death high enough to justify calling stroke itself a risk equivalent? (2) Should stroke be included along with CHD in the vascular disease outcome cluster for purposes of absolute estimation of risk in primary and secondary prevention? In other words, should we speak of “coronary and stroke risk equivalents” rather than just “CHD risk equivalents”?

The answers to these questions have important clinical implications because current guidelines may underestimate risk, leaving untreated patients who might be eligible for primary and secondary preventive therapies. These issues may be especially important for race/ethnic groups for whom stroke risk is as great as or exceeds coronary risk.4,5

Methods

We first reviewed the ATP III guidelines for the definition of a CHD risk equivalent and the discussion supporting the inclusion of diabetes mellitus, PAD, AAA, and carotid artery disease as risk equivalents.6

To address the first question, we reasoned that the most appropriate data would be derived from prospective studies that examine risk or event rates of MI and vascular or coronary death among patients who have had a stroke. A structured, stepwise database search involving PubMed, the Cochrane Database of Systematic Reviews, and the ISI Web of Knowledge was performed under the limits of English language, human subjects, age ≥19 years, and publication date between January 1, 1980, and January 1, 2010, with search terms mapped to medical subject heading (MeSH) as well as queried as text words. Search terms included stroke, risk, cardiac, myocardial infarction, and coronary death. All citation summaries were reviewed for relevance, and studies were selected if they met the following criteria: original, prospective data or meta-analysis of prospective data was reported; follow-up period was ≥3 months; patients had a first stroke or transient ischemic attack (TIA) as a qualifying event; and risk or event rates of MI and vascular or coronary death were reported.

To address the second question, we reasoned that the most appropriate data would be derived from prospective studies examining stroke-free populations followed over time for the outcomes of MI, vascular or coronary death, and nonfatal and fatal stroke. Comparing the 10-year risk of CHD in such studies with the 10-year risk of CHD plus stroke would reveal the effect of including stroke on current guideline recommendations that assign “high” risk on the basis of a particular level of absolute risk. A second search was...
performed as described above, with the use of the same databases and limits. Search terms included myocardial infarction, vascular, coronary death, and stroke. All citation summaries were reviewed for relevance, and studies were selected if the following criteria were met: original, prospective data or meta-analysis of prospective data was reported; follow-up period was ≥3 months; patients were free of CVD at entry; and MI, vascular or coronary death, and nonfatal and fatal stroke were reported separately as outcomes.

For both questions, the reference lists of selected studies were reviewed to identify studies that may have been missed in the initial database searches. Experts in the field were also asked to suggest relevant articles. Unpublished data were not sought, nor were authors contacted to provide additional information. In the case of multiple publications from the same study, the data most relevant to the questions of this review were selected.

All studies meeting the inclusion criteria were reviewed in detail, and the following information was abstracted: study design, inclusion and exclusion criteria, sample size, follow-up period, definition of outcomes, and rates or risk of outcome events. Data from relevant studies are presented in summary tables that describe study participants, follow-up period, and risk or rates of outcome events. Studies are grouped by design: meta-analysis, observational studies, and clinical trials. For studies related to the first question, risk or event rate data are presented in 2 groups: cardiac and cardiac plus stroke. For clinical trials, data for the placebo group are presented, and exceptions are noted in the tables. For studies related to the second question, 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 time period. Annualized risks were calculated by dividing total risk by the follow-up period. We present a narrative overview rather than a meta-analysis because, for the first question, a meta-analysis was performed recently (2005), which we review along with studies published since 2005, and for the second question, there were significant differences in methodology among studies.

Results

CHD Risk Equivalent Definitions

According to ATP III guidelines, persons with established CHD in the United States have a risk of recurrent MI and CHD death of ≥20% over 10 years. Hence, a CHD risk equivalent is defined as a condition conferring a risk of MI or coronary death equivalent to that among those with established CHD (ie, ≥20% over 10 years). These guidelines define 4 diseases as CHD risk equivalents: PAD, carotid artery disease, AAA, and diabetes mellitus (Table 1). Five studies are cited to support PAD as a risk equivalent, with sample sizes ranging from 567 to 1592 and follow-up ranging from 3 to 10 years. Seven studies are cited to support carotid artery disease as a risk equivalent, with sample sizes ranging from 158 to 3024 and follow-up ranging from 2.5 to 8 years. Only 1 study was cited to support including AAA as a risk equivalent, including 343 participants with 6 to 11 years of follow-up. Three studies are cited to illustrate the risk of CHD among those with diabetes mellitus, with sample sizes ranging from 1059 to 4075 with 2 to 11 years of follow-up. Further evidence is cited to illustrate an increased case fatality rate for MI among diabetics and worse prognosis for survival among diabetics who develop CHD compared with nondiabetics. The CHD risk for each of the traditional risk equivalents is ~2% per year (Table 1).

<table>
<thead>
<tr>
<th>Table 1. Risk of CHD With Traditional CHD Risk Equivalents and Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>Traditional risk equivalents*</td>
</tr>
<tr>
<td>PAD</td>
</tr>
<tr>
<td>Symptomatic CAD</td>
</tr>
<tr>
<td>Asymptomatic CAD</td>
</tr>
<tr>
<td>AAA</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Stroke†</td>
</tr>
</tbody>
</table>

NA indicates not available.

*These findings were used to justify designation of each condition as a traditional risk equivalent in the National Cholesterol Education Panel ATP III report. Ranges of outcome events are presented; some studies report only CHD mortality and some total CHD risk, and therefore ranges are reported separately.

†The studies pertaining to stroke are discussed in this review.

Stroke as a CHD Risk Equivalent

A total of 1844 articles were identified through database queries, and 1311 met language, age, and date range criteria. Of these, 41 met inclusion criteria, and 3 more studies were identified through bibliographic review and suggestions from experts. Because a recent meta-analysis7 (2005) summarized results of 39 of these studies, we present data from this meta-analysis and 4 other studies, 3 of which have been published since 2005 (Table 2).

In a recent publication, Touze et al7 performed a systematic review and a meta-analysis of the absolute risk of MI and vascular death after stroke or TIA in 39 studies. Inclusion criteria included prospective cohort study or randomized controlled trial design, published after 1979, reporting on long-term follow-up of ≥100 patients, with follow-up ≥1 year with <5% loss to follow-up, written in English, 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.” Overall, there were 25 randomized controlled trials, 8 population-based cohorts, and 6 single-center hospital-based cohorts, including a total of 65996 patients with a mean follow-up of 3.5 years. Overall, meta-regression showed annual risks of total MI of 2.2% (95% confidence interval [CI], 1.7% to 2.7%; 22 studies), nonfatal MI of 0.9% (95% CI, 0.7% to 1.2%; 16 studies), and fatal MI of 1.1% (95% CI, 0.8% to 1.5%; 19 studies).

In the Northern Manhattan Study (NOMAS), a population-based cohort of first ischemic stroke patients aged ≥40 years was prospectively followed 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% to 20.6%). In the lowest-risk group, those aged ≤70 years without coronary artery disease (CAD), 5-year risk of MI or vascular death was 9.7%. The 5-year risk of MI, recurrent stroke, or vascular death was 29.0% (95% CI, 25.2% to 32.7%). In another observational study of administrative databases with
In the placebo group of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial of lipid-lowering therapy among patients with stroke or TIA, the risk of major coronary events (including death from cardiac causes, nonfatal MI, and resuscitation after cardiac arrest) was 5.1% over the median of 4.9 years, which is less than the 2% per year cutoff for a CHD risk equivalent, likely because patients without coronary disease were enrolled. However, in the composite outcome of major coronary event plus stroke, the risk was 17.2% over 5 years, which is well over the 10% cutoff over 5 years for a risk equivalent. In the placebo group of the Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) study, a secondary stroke prevention trial, a composite of major cardiovascular events (death from cardiovascular causes, recurrent stroke, MI, or new or worsening heart failure) occurred in 1463 patients (14.4%) over a mean of 2.5 years.

**Summary**

The studies reviewed here, which examine recurrent stroke and cardiac events after stroke, show that the risk of cardiac events after stroke is 2% per year, and a large meta-analysis suggests that the risk may even be 2% annually. When recurrent stroke is added to the outcomes for absolute risk estimates, the risk of vascular events after stroke is increased further.

### Table 2. Studies That Report Risk of MI or Cardiac Death After Stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>n</th>
<th>Follow-Up Period</th>
<th>Total Risk, %</th>
<th>Annual Risk, %</th>
<th>Total Risk, %</th>
<th>Annual Risk, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Touze et al (2005)</td>
<td>Meta-analysis With stroke or TIA; from 25 RCTs, 8 population-based cohorts, 6 hospital-based cohorts</td>
<td>65 996</td>
<td>Mean 3.5 y</td>
<td>NR</td>
<td>Total MI: 2.2; nonfatal MI: 0.9; fatal MI: 1.1; nonstroke vascular death: 2.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOMAS (2007)</td>
<td>Observational Incident ischemic stroke; aged ≥40 y</td>
<td>655</td>
<td>Median 4 y</td>
<td>5-y risk of MI or vascular death: 17.4</td>
<td>3.5*</td>
<td>5-y risk of MI, recurrent stroke, or vascular death: 29.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vickrey et al (2002)</td>
<td>Observational With ischemic stroke; administrative databases; aged ≥40 y</td>
<td>1631 in commercial database (mean age 62 y); 1518 in Medicare database (mean age 80 y)</td>
<td>1.2 to 1.3 y</td>
<td>In commercial database: rate of MI at 3 y: 3.03; in Medicare database: rate of MI at 3 y: 5.05</td>
<td>1.0*</td>
<td>In commercial database: rate of stroke at 3 y: 12.17; calculated rate of MI + stroke: 17.22</td>
<td>3.5*</td>
<td>5.8*</td>
</tr>
<tr>
<td>SPARCL (2008)</td>
<td>Clinical trial With ischemic or hemorrhagic stroke or TIA; aged ≥18 y</td>
<td>2365 (placebo group)</td>
<td>Median 4.9 y</td>
<td>Risk of major coronary event: 5.1</td>
<td>1.0*</td>
<td>Risk of major coronary event + stroke: 17.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROFESS (2008)</td>
<td>Clinical trial With recent ischemic stroke; aged ≥55 y</td>
<td>10186 (placebo group)</td>
<td>Mean 2.5 y</td>
<td>Rate of MI: 1.7; rate of death from CV causes: 2.6</td>
<td>Rate of MI: 0.7; rate of death from CV causes: 1.0*</td>
<td>Rate of death from CV causes, recurrent stroke, MI, or heart failure: 14.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NR indicates not reported; RCT, randomized controlled trial; and CV, cardiovascular.

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

Inclusion of Stroke in the Vascular Outcome Cluster

A total of 722 articles were identified through database queries, and 449 met language, age, and date range criteria. Of these, 10 met inclusion criteria, and 3 more studies were identified through bibliographic review and suggestions from experts; we review the resulting 13 studies here (Tables 3 and 4).

**Observational Studies**

In 2008, the Framingham Heart Study published a general cardiovascular risk profile scoring system (Table 3). Participants were free of CVD and aged 30 to 74 years. CVD was defined as a composite of CHD (coronary death, MI, coronary insufficiency, and angina), cerebrovascular events (ischemic stroke, hemorrhagic stroke, and TIA), PAD, and heart failure. Maximum follow-up was 12 years. The authors compared risk of individual components with the composite outcomes. For women in the fifth decile of risk, the mean 10-year risk of CVD was 4%, corresponding to a risk of CHD of 2.4%, a risk of stroke of 0.95%, and a combined risk of CHD or stroke of 3.4%. For men in the fifth decile of risk, the mean 10-year risk of CVD was 12%, corresponding to a risk of CHD of 7.3%, a risk of stroke of 2.9%, and a combined risk of CHD or stroke of 10.2%.

In the Riskard 2005 study, 9 population-based studies in Italy comprising 12,045 men and 51,08 women aged 35 to 74 years were analyzed. Follow-up ranged from 5 to 15 years,
Table 3. Observational Studies That Report Cardiac and Cerebrovascular Event Rates in Stroke-Free Populations

<table>
<thead>
<tr>
<th>Study</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>Framingham (2008)¹²</td>
<td>Free of CVD, aged 30–74 y</td>
<td>8491</td>
<td>Up to 12 y</td>
<td>10-y risk of CHD: men in decile 5 of risk: 7; 3; women in decile 5 of risk: 2 4</td>
<td>Men in decile 5 of risk: 0.7; women in decile 5 of risk: 0.2</td>
<td>Men in decile 5 of risk: 0.3; women in decile 5 of risk: 0.1</td>
</tr>
<tr>
<td>Riskard (2005)¹³</td>
<td>Aged 35–74 y</td>
<td>17 153</td>
<td>5–15 y</td>
<td>10-y risk of first major coronary event: men aged 60 y: 0.6; women aged 60 y: 0.3</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>REACH (2007)¹⁴</td>
<td>Free of CVD, with multiple risk factors; aged ≥ 45 y</td>
<td>11 766</td>
<td>1 y</td>
<td>Rate of nonfatal MI + CV death: 1.51</td>
<td>NA</td>
<td>0.30</td>
</tr>
</tbody>
</table>

NA indicates not applicable; CV, cardiovascular.

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

and outcomes assessed included mortality, causes of death, and nonfatal cardiovascular events. 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 comprising fatal and nonfatal aortic aneurysms, fatal lower limb artery disease, surgery of aorta or lower limb arteries). We estimated from the Figure in the Riskard report depicting risk of these 3 outcomes by sex, age, and follow-up time that the 10-year risk of first major coronary events was ≈6% in men and ≈3% in women aged 60 years, whereas the 10-year risk of first major cardiovascular events was ≈11% in men and ≈4% in women.

In the Reduction of Atherothrombosis for Continued Health (REACH) study, participants were enrolled with either (1) a history of CAD, cerebrovascular disease, or PAD or (2) at least 3 atherothrombotic risk factors. Participants were enrolled from multiple international outpatient sites and followed 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 plus nonfatal MI was 1.51%, whereas the rate of stroke was 0.80%. The 1-year event rate of the combined outcome of cardiovascular death, MI, or stroke was 2.15%.

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 the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial, the rate of MI was 4%, the rate of stroke was 6%, and the rate of the combined outcome of cardiovascular mortality, stroke, or MI was 12% (Table 4). Although there was a significant reduction in risk with losartan treatment, the results from both treatment groups are pooled here to reflect antihypertensive treatment in the community, which may not be in accordance with the stipulations of a clinical trial. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, in the standard therapy group, the rate of nonfatal MI and cardiovascular death was 6.4%, the rate of nonfatal and fatal stroke was 1.4%, and the rate of nonfatal MI or nonfatal stroke or cardiovascular death was 7.2%. In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, in the standard therapy group, 9.1% of participants had a history of stroke at study entry. In the standard therapy group, the rate of nonfatal MI and cardiovascular death was 8.0%, the rate of all cerebrovascular events was 5.9%, and the rate of nonfatal MI, nonfatal stroke, and cardiovascular death was 10.6%. In the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial, in the placebo plus aspirin group, the rate of nonfatal MI and cardiovascular death was 4.9%, the rate of nonfatal stroke was 2.4%, and the rate of nonfatal MI, nonfatal stroke, or cardiovascular death was 7.3%. In the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET), in the combination therapy group, 20.9% had a history of stroke or TIA. In the combination therapy group, the rate of fatal and nonfatal MI and cardiovascular death was 12.5%, the rate of fatal and nonfatal stroke was 4.4%, and the rate of death from cardiovascular causes, MI, or stroke was 14.1%. Table 4 summarizes 5 additional trials that show similar increases in combined risk compared with cardiac risk or stroke risk alone.

In summary, observational studies and clinical trial data show that adding risk of stroke to risk of cardiac events significantly elevates risk and, in most cases, results in crossing the threshold of absolute risk of 20% over 10 years that defines “high” risk.

International Guidelines That Address Risk Estimation of CVD
Guidelines from other international groups already include stroke in the outcome cluster for risk calculation. In the
European guidelines on CVD prevention in clinical practice (Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice),26 the stated rationale for changing the focus from CHD to CVD prevention was a similar pathogenesis for MI, ischemic stroke, and PAD, as well as treatments that are effective for all of these forms of vascular disease.

The Joint British Societies’ guidelines on prevention of CVD27 present a risk prediction chart to estimate risk of developing CVD over 10 years. In the latest version of the

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### Table 4. Clinical Trials That Report Cardiac and Cerebrovascular Event Rates in Stroke-Free Populations

<table>
<thead>
<tr>
<th>Study</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>LIFE (2002)15</td>
<td>With hypertension and LVH on ECG; aged 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>2.5</td>
</tr>
<tr>
<td>ACCORD (2008)16</td>
<td>With type 2 DM, HbA1c ≥7.5%, aged 40–79 y with CVD, or 55–79 y with CV risk factors</td>
<td>5123 (standard therapy group)</td>
<td>Mean 3.5 y</td>
<td>Rate of nonfatal MI+CV death: 6.4</td>
<td>Rate of nonfatal and fatal stroke: 1.4</td>
<td>2.1</td>
</tr>
<tr>
<td>ADVANCE (2008)17</td>
<td>Age ≥55 y, with type 2 DM, major macrovascular or microvascular disease, or ≥1 other CV risk factors; 9.1% had history of stroke</td>
<td>5569 (standard therapy group)</td>
<td>Median 5 y</td>
<td>Rate of nonfatal MI+CV death: 8.0</td>
<td>Rate of all cerebrovascular events: 5.9</td>
<td>2.1</td>
</tr>
<tr>
<td>CHARISMA (2006)18</td>
<td>Age ≥45 y, with CV disease 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 CV death: 4.9</td>
<td>Rate of nonfatal stroke: 2.4</td>
<td>3.2</td>
</tr>
<tr>
<td>ONTARGET (2008)19</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 CV death: 12.5</td>
<td>Rate of fatal and nonfatal stroke: 4.4</td>
<td>3.0</td>
</tr>
<tr>
<td>HOPE (2009)20</td>
<td>Age ≥55 y, with CAD, stroke, PVD, or DM and 1 other CV 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>3.6</td>
</tr>
<tr>
<td>PROactive (2007)21</td>
<td>Age 35–75 y with type 2 DM; 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>5.1</td>
</tr>
<tr>
<td>EUROPA (2003)22</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 CV death: 9.8</td>
<td>Rate of stroke: 1.7</td>
<td>3.0</td>
</tr>
<tr>
<td>PROSPECT (2002)23</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>5.1</td>
</tr>
<tr>
<td>POPADAD (2008)24</td>
<td>Age ≥40 y with DM and asymptomatic PVD</td>
<td>318 (placebo+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>3.3</td>
</tr>
</tbody>
</table>

LVH indicates left ventricular hypertrophy; CV, cardiovascular; DM, diabetes mellitus; PVD, peripheral vascular disease; HOPE, Heart Outcomes Prevention Evaluation; PROactive, PROspective pioglitAzone Clinical Trial In macroVascular Events 04; EUROPA, European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease; PROSPER, PROspective Study of Pravastatin in the Elderly at Risk; and POPADAD, Prevention of Progression of Arterial Disease and Diabetes.

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

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Joint British Societies’ guidelines, CHD risk was replaced by CVD risk, a combined end point of CHD (fatal and nonfatal MI and new angina) plus stroke (fatal and nonfatal stroke and cerebral hemorrhage) and transient cerebral ischemia.

The latest New Zealand guidelines provide a chart to estimate 5-year risk of “a cardiovascular event … defined as a death related to coronary disease, nonfatal myocardial infarction, new angina, fatal or nonfatal stroke or transient ischemic attack, or the development of congestive heart failure or peripheral vascular disease.”

Discussion
A review of evidence from hospital- and population-based studies supports (1) the designation of stroke as a risk equivalent and (2) the inclusion of stroke in the outcome cluster for purposes of absolute estimation of risk in primary and secondary prevention. Among patients who have had a stroke, the risk of subsequent cardiac events is high enough to designate stroke a CHD risk equivalent according to definitions in current guidelines. Including recurrent stroke in the outcome cluster leads to even higher absolute risk levels after first stroke. Furthermore, in observational studies and clinical trials of stroke-free subjects, including stroke in the calculation of cardiovascular risk often results in a crossing of the 10-year 20% threshold designating elevated risk. The amount and quality of the data supporting these estimations are at least as significant as those of the data that supported the designation of PAD, AAA, CAD, and diabetes mellitus as CHD risk equivalents (Table 1). As a result, many recent, large-scale studies (for example, the Women’s Health Study, QRISK, ASSIGN, and SCORE) and international guidelines for primary and secondary prevention have already included stroke in the risk calculation of CVD. Similarly, many recent clinical trials evaluating treatments for prevention of vascular disease have used primary outcomes that are a combined end point of cardiac events, stroke, and vascular death (for example, CHARISMA, Management of Atherothrombosis With Clopidogrel in High-Risk Patients [MATCH], European/Australasian Stroke Prevention in Reversible Ischaemia Trial [ESPRIT], ADVANCE, ONTARGET, and ACCORD).

Excluding stroke as an outcome in risk calculation could have significant clinical implications because of an underestimation of risk and failure to treat patients who would otherwise qualify for preventive therapy. For example, for an individual whose risk score when only coronary events are used puts him or her just below the threshold for treatment (10% over 10 years for aspirin or 20% over 10 years for statin therapy), inclusion of stroke in the outcome cluster would likely push him or her over the threshold.

Although many of the studies that report cerebrovascular events include both ischemic and hemorrhagic strokes, for which treatment strategies differ, a large population-based study that included only ischemic stroke patients showed that cardiac risk exceeded the threshold designating elevated risk. Furthermore, hemorrhagic strokes form a minority of total strokes, and the aggregation of ischemic and hemorrhagic strokes is unlikely to significantly affect the risk estimations reviewed here. However, the approach to the primary and secondary prevention of hemorrhagic stroke is not addressed by this review.

Ischemic stroke and CAD have clearly different and specific treatment approaches. For example, warfarin for atrial fibrillation is indicated for stroke prevention, carotid endarterectomy for carotid disease, and β-blockers for CAD. However, for many current and possibly future therapies, ischemic stroke and CAD are likely to be treated in a similar manner. It is with a view of this overlap that practitioners are likely to achieve the greatest impact in prevention, provided that accurate risk estimates are used. For example, well-documented modifiable risk factors that are common to both CAD and ischemic stroke are hypertension, cigarette smoking, diabetes mellitus, dyslipidemia, and physical inactivity. Despite debates about the sex-specific effects of aspirin in primary prevention, antiplatelet therapy is currently a mainstay in the prevention of both cardiac and cerebrovascular diseases. Furthermore, trials such as the Heart Protection Study and SPARCL have shown that statins provide effective primary and secondary prevention of cardiac events as well as stroke. Secondary analysis from SPARCL showed that atorvastatin was similarly effective in reducing risk of stroke and cardiovascular outcomes regardless of baseline stroke subtype, lending further support to the inclusion of all-cause stroke in risk calculation.

For providers interested in primary and secondary stroke prevention, there is also a current class of treatments that falls within a gray zone, in which there is little guidance about how to treat stroke patients. For example, the influenza vaccine is recommended by the American Heart Association for patients with “coronary artery disease and other forms of atherosclerotic disease.” These patients presumably include those with symptomatic carotid disease, but this definition leaves out the other 80% to 90% of stroke patients without symptomatic carotid disease, including, for example, those with lacunar or cryptogenic strokes. Including stroke patients in the category of CHD risk equivalents, as suggested in this review, however, would emphasize the importance of treating stroke patients with influenza vaccination, along with those with atherosclerotic heart disease, diabetes mellitus, and chronic kidney disease.

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References
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