

AHA/ASA Scientific Statement

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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On behalf of the American Heart Association Stroke Council, Council on Epidemiology and Prevention, Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular Nursing, Council on Peripheral Vascular Disease, and Council on Quality of Care and Outcomes Research



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This slide set was adapted from the Scientific Statement “Inclusion of Stroke in Cardiovascular Risk Prediction Instruments”

This statement reflects a consensus of expert opinion following thorough literature review that consisted of a look at clinical trials and other evidence related to stroke as a cardiovascular risk prediction element.

Applying classification of recommendations and levels of evidence

SIZE OF TREATMENT EFFECT →

	CLASS I <i>Benefit >>> Risk</i> Procedure/Treatment SHOULD be performed/administered	CLASS IIa <i>Benefit >> Risk</i> Additional studies with <i>focused objectives</i> needed IT IS REASONABLE to perform procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> Additional studies with <i>broad objectives</i> needed; additional registry data would be helpful Procedure/Treatment MAY BE CONSIDERED	CLASS III <i>Risk ≥ Benefit</i> Procedure/Treatment should NOT be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none"> ■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> ■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> ■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> ■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	<ul style="list-style-type: none"> ■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> ■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> ■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> ■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	<ul style="list-style-type: none"> ■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> ■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> ■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> ■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT

Suggested phrases for writing recommendations†

should
is recommended
is indicated
is useful/effective/beneficial

is reasonable
can be useful/effective/beneficial
is probably recommended
or indicated

may/might be considered
may/might be reasonable
usefulness/effectiveness is unknown/unclear/uncertain
or not well established

is not recommended
is not indicated
should not
is not useful/effective/beneficial
may be harmful

Inclusion of Stroke in Cardiovascular Risk Prediction Instruments

- Introduction
 - Estimation of absolute risk of coronary heart disease is a critical component in primary and secondary prevention of cardiovascular disease and in the management of co-morbid conditions.
 - Several US guideline statements utilize absolute cardiovascular risk estimates to determine diagnostic studies and treatment.

Inclusion of Stroke in Cardiovascular Risk Prediction Instruments

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

Role of Absolute Event Rates and Risk Thresholds

- Importance of Absolute Event Rates and Risk Thresholds
 - Allow physicians to target preventive measures toward those at high risk
 - Prediction instrument: Framingham score
 - Provide global risk over 10 years
 - <5% low risk
 - 6-20% medium risk
 - >20% high risk
 - Justify more intensive prevention strategies

Role of Absolute Event Rates and Risk Thresholds

- Importance of Absolute Event Rates and Risk Thresholds
 - CHD risk equivalents based on absolute risk thresholds
 - Established CHD
 - Diabetes mellitus (DM)
 - Peripheral arterial disease (PAD)
 - Symptomatic carotid artery disease
 - Framingham risk score >20%

Role of Absolute Event Rates and Risk Thresholds

- Importance of Absolute Event Rates and Risk Thresholds
 - 2007 AHA “Guidelines for Cardiovascular Disease Prevention in Women”
 - High-risk women: established CHD, cerebrovascular disease, PAD, abdominal aortic aneurysm, end-stage or chronic renal disease, DM, and Framingham risk >20%
 - 2011 AHA guidelines for women
 - Recommended use of risk prediction instruments that include cerebrovascular disease as part of global risk assessment

Role of Absolute Event Rates and Risk Thresholds

- Uses of Absolute Risk Categories
 - Hyperlipidemia
 - NCEP ATP III recommended a more intensive approach to treatment of hyperlipidemia in the presence of CHD or CHD risk equivalents
 - LDL-C cholesterol goal < 100 mg/dL
 - 2004 ATP III guidelines suggested a “very high risk” group
 - Established CHD plus risk factors or acute coronary syndromes
 - May lower LDL-C target to < 70 mg/dL

Role of Absolute Event Rates and Risk Thresholds

- Uses of Absolute Risk Categories
 - Aspirin
 - 2009 report of the U.S. Preventive Services Task Force
 - Primary prevention: recommended use in men > 45 and women >55 where risk of MI or stroke, respectively, can be reduced in excess of the risk of significant hemorrhagic complication
 - Also those with a 10-year risk of CHD >20%
 - 2011 AHA Guidelines for Cardiovascular Disease Prevention in Women
 - Consider aspirin in high-risk women regardless of age
 - All women greater than 65 years at-risk or healthy

Role of Absolute Event Rates and Risk Thresholds

- Uses of Absolute Risk Categories
 - Hypertension treatment
 - Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)
 - Target blood pressure of <140/90 mmHg
 - The British Hypertension Society Guidelines for management of hypertension (BHS IV) and JNC 7
 - Utilize absolute risk to recommend specific BP medications
 - High-risk groups: established cardiovascular disease, renal disease, diabetes, or global CVD risk of >20% over 10 years

Role of Absolute Event Rates and Risk Thresholds

- Uses of Absolute Risk Categories
 - Annual Influenza Vaccination
 - Recommendation based on presence of CHD or other atherosclerotic vascular disease (PAD, atherosclerotic aortic disease, and CAD)
 - Stroke not specifically included in U.S. Guideline

Role of Absolute Event Rates and Risk Thresholds

- Section Summary
 - High absolute risk has been invoked in guidelines as an indication for more intensive preventive interventions
 - Stroke inconsistently included in these high-risk categories
 - Interventions based on high risk
 - Lipid management
 - Antihypertensive therapy
 - Antiplatelet use

Categories of CHD Risk Equivalents

- Existing CHD
 - Consider absolute event rate as a standard level to compare other patient groups
 - Two long-term secondary prevention trials
 - Cholesterol And Recurrent Events (CARE) and Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID)
 - Absolute risks of CHD of ~26% per decade
 - Other trials summarized in Table 2 of statement
 - Event rate >20% per decade considered CHD risk equivalent

Categories of CHD Risk Equivalents

- Diabetes
 - 2003 NCEP ATP III type 2 diabetes considered a CHD risk equivalent
 - Three lines of evidence
 - Cohort studies and randomized trials
 - Elevated risk of coronary outcomes in diabetics without heart disease as patients with heart disease alone
 - Initial myocardial infarction more severe in diabetics
 - Greater rates of acute congestive heart failure and case-fatality
 - One study 1 year mortality: 25% diabetics vs 10% without
 - Long-term mortality post MI higher in diabetics
 - Multiple studies: 37.4% vs 23.3%; 7.3% vs 2.6%; 14% vs 6-8%

Categories of CHD Risk Equivalents

- Diabetes
 - Limitations to diabetes as a risk equivalent
 - Not all cohort studies provide evidence of higher event rates in diabetics
 - Meta-analysis of 13 studies and 45,108 patients
 - Significant odds ratio of 0.56 for the risk of CHD events in diabetics without history of MI vs MI patients without DM
 - Heterogeneity in risk levels among diabetics
 - High- vs low-risk persons with diabetes
 - Most likely to benefit from intensive prevention interventions are diabetics at highest risk for initial event (reflected in most recent guidelines)

Categories of CHD Risk Equivalents

- Peripheral Arterial Disease (PAD)
 - NCEP ATP III considers PAD as a risk equivalent
 - Associated with increased risk of stroke and MI
- Carotid Artery Disease
 - Symptomatic carotid artery disease has caused a stroke or transient ischemic attack
 - One variety of cerebrovascular disease already considered to be a risk equivalent
 - 10-year coronary mortality rate ranges from 19% to 51%

Categories of CHD Risk Equivalents

- Abdominal Aortic Aneurysm (AAA)
 - NCEP statement cited a single study involving a follow-up of a surgical cohort
 - AAA without coronary disease and normal EKG
 - Coronary mortality rate 1.9%
 - AAA with coronary disease or abnormal EKG
 - Coronary mortality rate 2.0-3.9%

Categories of CHD Risk Equivalents

- Chronic Kidney Disease (CKD)
 - 2003 National Kidney Foundation Task Force considered CKD patients as CHD risk equivalents
 - Population-based studies do not consistently demonstrate absolute risk levels as high as CHD patients or >20% over 10 years
 - Effectiveness of some CHD-related preventive interventions in CKD patients remains uncertain

Categories of CHD Risk Equivalents

- Comments on rationale for including PAD, carotid disease, AAA, and CKD
 - PAD, carotid disease, and AAA are atherosclerotic
 - CKD inclusion is independent of its pathogenesis
 - All studies not designed to detect CHD events
 - Relied on absolute event rates independent of Framingham risk score
 - Not all studies unequivocally demonstrate an increase in absolute event rates above 20% in 10 years

Categories of CHD Risk Equivalents

- Use and Limitations of Risk Prediction Instruments and Absolute Risks
 - Useful to assess cardiovascular risk in general population
 - Framingham Heart Study algorithm
 - Advantages: availability, familiarity, quantitative absolute risk over decade, interactions for age and sex
 - Potential disadvantages: difficult to account for purely historical risk factors, variability of risk factors across visits, absence of behavioral risk factors, limited applicability to certain minority populations

Categories of CHD Risk Equivalents

- Section Summary
 - CHD risk equivalents include
 - Diabetes, CKD, PAD, and carotid artery disease
 - Absolute 10-year CHD risk levels >20% have been considered as “risk equivalents”
 - Reasons for inclusion
 - Absolute risk from observational studies, underlying pathology, severity of outcomes, and the simplicity of an inclusive approach
 - Notable that cerebrovascular disease has not been included among the group of risk equivalents

Importance of Stroke Subtypes/Special Situations

- Heterogeneity in ischemic stroke etiology
 - Large vessel atherosclerosis
 - Emboli originating from the heart
 - Cerebral small vessel occlusive disease
 - Various other less common causes
- Cerebrovascular disease and CHD often co-exist
 - Similar risk factors, pathogenic processes, and preventive strategies
- Long-term cardiovascular risk is high after ischemic stroke

Importance of Stroke Subtypes/Special Situations

- Cardioembolic Stroke
 - Possible higher likelihood of CHD events, related to presence of underlying cardiac disease
 - The European Atrial Fibrillation Trial (EAFT)
 - Risk factors for major vascular events: ischemic heart disease, history of thromboembolism, duration of atrial fibrillation, and elevated systolic blood pressure
 - Provides some evidence that majority of patients with atrial fibrillation and stroke will have major vascular event rates > 2% annually.

Importance of Stroke Subtypes/Special Situations

- Lacunar Infarcts
 - Better short-term prognosis; however, data on long-term risk of subsequent MI are limited
 - In SPARCL, lacunar infarct subgroup had absolute rates of recurrent stroke and major cardiovascular events as high as the large vessel atherothrombotic subgroup
 - subsequent risk of MI and vascular death approaches the 2% annual threshold of a coronary risk equivalent.
- Intracranial stenosis appears to have a high risk of recurrence.
 - In one trial, the risk of stroke, MI or vascular death was 23% at 2 years

Importance of Stroke Subtypes/Special Situations

- Young Adults
 - Iowa Registry: ischemic stroke between the ages of 15-44
 - mortality from vascular causes was 1.7%/year
 - incidence of vascular death, nonfatal MI, or recurrent stroke was 2.6%/year.
 - Helsinki Registry: ischemic stroke between ages 15-49
 - cumulative 5-year mortality rate was 10.7%, with over half of these deaths due to vascular causes
 - Stroke due to large artery atherosclerosis and cardioembolism had higher risk than other etiologies

Importance of Stroke Subtypes/Special Situations

- Young Adults
 - Spontaneous cervical artery dissection: no apparent association between spontaneous cervical artery dissection and major vascular risk factors, apart from hypertension
 - Patent foramen ovale (PFO): recurrent stroke and atherosclerotic burden is lower in these patients

Importance of Stroke Subtypes/Special Situations

- Intracerebral Hemorrhage
 - Accounts for 10% to 15% of all strokes
 - Hypertension is the major modifiable risk factor
 - Prevalence of other vascular risk factors and comorbidity is high, but not as high as in ischemic stroke
 - Recurrent stroke among survivors of primary ICH occurs at a rate of about 2-4% per year, and is as likely or more likely to be hemorrhagic than ischemic.

Importance of Stroke Subtypes/Special Situations

- Intracerebral Hemorrhage
 - Data on subsequent MI after ICH are scarce
 - South Carolina Discharge Database: 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 compared to patients with ischemic stroke.
 - The Netherlands hospital-based study: annual rate of any **subsequent vascular event after a primary ICH was 5.9%/year.**

Importance of Stroke Subtypes/Special Situations

- Section Summary:
 - Heterogeneity of stroke argues against the generalization that all stroke patients are at equal risk of future coronary events.
 - Large vessel atherosclerotic stroke may be most similar to CAD.
 - Cardioembolic stroke patients also appear to be at increased risk of CHD, but additional study is needed.
 - Nonetheless, most ischemic stroke patients fall into the higher risk groups that have higher CHD event rates.
 - Some evidence from clinical trials that some preventive therapies are likely to be of broad benefit across multiple different stroke subtypes

Inclusion of Atherosclerotic Stroke among the categories of Risk Equivalents

- Rationale
 - Clinical data demonstrate that ischemic stroke patients have the same high risk as patients with other forms of established cardiovascular disease.
 - The types of data used to justify the inclusion of diabetes and other conditions (abdominal aortic aneurysm, renal failure) as being at these high absolute risk levels are as limited or even more limited than the data for stroke.
 - Inclusion of atherosclerotic stroke among the categories of risk equivalents is consistent with the pathophysiology of atherosclerosis.

Inclusion of Atherosclerotic Stroke among the Categories of Risk Equivalents

- Risk Stratification after Stroke
 - No systems generally recommended in existing guidelines
 - Stroke Prognostic Instrument (SPI-II) annual risk of recurrent stroke:
 - 3.2%, low risk; 5.5%, medium risk; 9.1%, high risk
 - Limitations to existing data include different outcome measures, non-validated instruments, differing duration of follow-up, unclear clinical relevance of stratification since even the lowest risk patients appear to have a high enough risk to justify intensive prevention.

Selected Observational Studies Reporting risk of MI/Sudden Death after Stroke

- Touze' et al. systematic review and meta-analysis (n=65,996)
 - annual risks of total MI of 2.2% (95% CI, 1.7 to 2.7, 22 studies)
- Northern Manhattan Study (NOMAS)
 - 5-year risk of MI or vascular death was 17.4% (95% CI, 14.2% to 20.6%)

Clinical Trials with Data on Event Rates of MI, Sudden Death, and Stroke among Stroke Patients

Risk Factor Reduction Trials

- PROGRESS
 - 6105 patients with hx of TIA/Stroke randomized to perindopril +/- indapamide or placebo
 - active therapy associated with a significant reduction in MI, which occurred in 1.9% of those on active therapy and 3.1% receiving placebo
- SPARCL
 - TIA/Stroke patients, LDL-C of 100-190 mg/dL and no known CAD, randomized to either atorvastatin 80 mg per day or placebo
 - Nonfatal MI occurred in 1.8% of patients receiving atorvastatin and 3.5% with placebo ($P<0.001$).

Clinical Trials with Data on Event Rates of MI, Sudden Death, and Stroke among Stroke Patients

Trials of Antithrombotic Therapy

- Warfarin and Aspirin for Symptomatic Intracranial Arterial Disease (WASID) study
 - 569 patients with 50-99% intracranial stenosis and TIA/stroke randomized to warfarin (INR 2-3) or 1300 mg daily aspirin
 - Rates for **MI were 4.2% with warfarin and 2.5% with aspirin.**

Clinical Trials with Data on Event Rates of MI, Sudden Death, and Stroke among Stroke Patients

Carotid Intervention Trials

- EVA 3S study
 - TIA/non-disabling stroke and $\geq 60\%$ carotid stenosis randomized to either carotid endarterectomy (CEA) or stenting (CAS)
 - 30 days following the procedure, MI observed in 0.4% in the CAS group and 0.8% in the CEA group; mortality was 0.8% CAS and 1.2% CEA
- CREST
 - TIA/non-disabling stroke randomized to either CAS or CEA
 - MI occurred in 1.0% of patients with CAS and 2.3% of patients with CEA; overall rates for stroke, MI, and death were 6.7% for CAS and 5.4% for CEA
- Lower event rates could represent more intensive therapy in this clinical trial population.

Summary and Limitations of Observational and Clinical Trial Data

- Provide evidence that stroke patients have absolute risks of MI and combined endpoints that are $\geq 2\%$ annual threshold that defines high-risk groups
- Limitations to interpretation:
 - different outcome measures, risks among stroke patients may differ, different follow-up time, declining event rates over time, lack of reporting of hard coronary endpoints, inclusion of patients with history of MI/CHD

Other Arguments for Including Atherosclerotic Stroke as a Risk Equivalent

- Inclusion of atherosclerotic stroke among the categories of risk equivalents is consistent with the pathophysiology of atherosclerosis, a diffuse and multifocal disease.
- Possible public health benefit leading to the same intensive prevention therapies used to prevent cardiovascular events among those with heart disease, diabetes, and other manifestations of atherosclerotic disease

Other Arguments for Including Atherosclerotic Stroke as a Risk Equivalent

- Estimation of the effect of inclusion of stroke as a risk equivalent on the number of persons in the US considered as having risk equivalents
 - The addition of stroke would lead to an approximate 10-13% increase in the US population classified as having coronary risk equivalents and **in need of more intensive preventive treatments.**

Section Summary

- Existing literature suggests the risk of CHD events is high in most stroke patients.
- Well-validated risk prediction instruments for use after stroke are not yet readily available.
- Justification for inclusion of other conditions (e.g., DM II, CKD) among those at high absolute risk levels is based not only on statistical evidence of formal improvement of risk classification, but on other arguments as well.
 - Thus, inclusion of atherosclerotic stroke is consistent with the pathophysiology of atherosclerosis.
- Inclusion of stroke as a high-risk condition could have a substantial impact on risk estimation used in the planning of prevention programs

Inclusion of Stroke in the Vascular Outcome Cluster

- Rationale for inclusion
 - Important health outcome
 - Multiple common risk factors with CHD
 - Even more important for minority populations
 - Often included as a major cardiovascular endpoint in clinical trials
 - US guidelines differ from international efforts in this regard

Inclusion of Stroke in the Vascular Risk Factor Cluster

- Importance of stroke as an outcome
 - 800,000 new or recurrent strokes per year in the United States
 - Fourth leading cause of death in the US
 - Single largest cause of adult disability in the US
 - Using Disability Adjusted Life Years (DALY), stroke is responsible for the following:
 - Men: 5.0% of all DALYs lost (vs 6.8% for CHD)
 - Women: 5.2% of all DALYs lost (vs 5.3% for CHD)

Studies with Data on Absolute Event Rates (MI/Sudden Death vs MI/Sudden Death/Stroke)

- Observational Studies
 - Framingham Heart Study
 - Patients without history of CVD but multiple vascular risk factors had 1-year risk rates of:
 - 1.5% cardiovascular death and nonfatal MI
 - 2.15% cardiovascular death, nonfatal MI, or stroke
 - Northern Manhattan Study
 - Patients with intermediate risk (estimated 10-20% predicted 10-year Framingham Risk Score) had 10-year event rates of
 - 14.20% MI or CHD death
 - 21.98% MI, CHD death, or stroke

Studies with Data on Absolute Event Rates

(MI/Sudden Death vs MI/Sudden Death/Stroke)

- Conclusions based on observational trials
 - Inclusion of stroke in the outcome cluster can result in classification of patients in higher risk groups
 - Effect is likely to differ across race-ethnic groups.
 - For example, in the Northern Manhattan Study, the absolute risk difference was significantly larger among blacks than among whites.
 - Inclusion of stroke in the outcome cluster results in a notable increase in global cardiovascular risk.

Studies with Data on Absolute Event Rates

(MI/Sudden Death vs MI/Sudden Death/Stroke)

- Clinical Trials
 - Limited by selection bias and short-term follow-up
 - 10 trials from 2000-2008 were analyzed for cardiac risk, stroke risk, and combined risk
 - Annual cardiac risk: 1.6% to 3.8%
 - Annual stroke risk: 0.4% to 1.4%
 - Annual combined risk: 2.5% to 5.1%

Inclusion of Stroke in the Vascular Outcome Cluster

- Summary
 - Inclusion of stroke as an outcome could lead to an increase in the absolute risk of vascular events of 5-10%
 - May be larger in some minority populations
 - Inclusion of stroke as an outcome measure in risk prediction instruments may therefore better capture overall risk of cardiovascular disease

Inclusion of Stroke in International Guidelines that Address Cardiovascular Disease Prevention

- None of the current guidelines provides an estimate of the extent to which inclusion of stroke as an outcome contributes to the global CVD risk.
- None of the current guidelines consider heterogeneity of stroke.
 - Some factors, such as high blood cholesterol, have different impact on hemorrhagic and ischemic stroke.
- There are problems in estimating risk for non-Caucasian populations, which may have a higher risk of stroke and lower risk of ischemic heart disease.

Inclusion of Stroke in International Guidelines that Address Cardiovascular Disease Prevention

- There is heterogeneity among published guidelines with regard to the inclusion of cerebrovascular disease among conditions at high absolute risk.
- Guidelines also differ in that some include only fatal or both fatal and non-fatal events, and use different risk prediction instruments.

Recommendations and Conclusions

- 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 equivalents **(Class I, Level of Evidence B)**.
- Ischemic stroke can reasonably be considered a relevant outcome along with coronary heart disease outcomes in cardiovascular disease risk prevention instruments used in primary and secondary prevention **(Class IIa, Level of Evidence B)**.

Recommendations and Conclusions

- Ischemic stroke subtypes other than large vessel atherosclerosis, including small vessel disease, may be considered as CHD risk equivalents, though further research is needed (**Class IIb, Level of Evidence B**).
- Hemorrhagic strokes and strokes of undetermined subtypes may be included among outcomes in general cardiovascular disease risk prediction instruments used in primary and secondary prevention (**Class IIb, Level of Evidence B**).

Recommendations and Conclusions

- 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)**.
- 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.