The Inclusion of Stroke in Risk Stratification for Primary Prevention of Vascular Events

The Northern Manhattan Study

Mandip S. Dhamoon, MD, MPH; Yeseon Park Moon, MS; Myunghee C. Paik, PhD; Ralph L. Sacco, MD, MS; Mitchell S.V. Elkind, MD, MS

Background and Purpose—The Framingham coronary heart disease (CHD) risk score estimates 10-year risk of myocardial infarction (MI) and CHD death. Because preventive approaches to CHD and stroke are similar, a composite outcome may be more appropriate. We compared 10-year risk of (1) MI or CHD death; and (2) stroke, MI, or CHD death among individuals free of vascular disease.

Methods—The Northern Manhattan Study contains a prospective, population-based study of stroke- and CHD-free individuals ≥40 years of age followed for a median of 10 years for vascular events. Framingham coronary heart disease risk score was calculated for each individual and for each category of predicted risk, Kaplan–Meier observed 10-year cumulative probabilities were calculated for (1) MI or CHD death; and (2) stroke, MI, or CHD death. The cumulative probability of (1) was subtracted from (2), and 95% CIs for the difference were obtained with 1000 bootstrap samples. Using stratified analyses by race–ethnicity, we compared risk differences among race–ethnic groups.

Results—Among 2613 participants (53% Hispanic, 25% non-Hispanic black, and 20% non-Hispanic white), observed 10-year risk of MI or CHD death was 14.20%. With stroke in the outcome, observed risk was 21.98% (absolute risk difference, 7.78%; 95% CI, 5.86% to 9.75%). The absolute risk difference among blacks was significantly larger than among whites (P=0.01).

Conclusions—In this multiethnic urban population, adding stroke to the risk stratification outcome cluster resulted in a 55% relative increase in estimated risk and crossing of the absolute risk threshold (>20% over 10 years) considered for preventive treatments such as statins. (Stroke. 2011;42:2878-2882.)

Key Words: epidemiology ■ risk factors ■ stroke management
and 10% to 20%), the inclusion of stroke would result in the crossing of important clinical thresholds for preventive treatments. Finally, we hypothesized that the difference in risk between the 2 outcomes of interest (MI or CHD death versus stroke, MI, or CHD death) would differ among race–ethnic groups.

**Methods**

The Northern Manhattan Study is a prospective, population-based cohort of 3298 subjects. The primary goals of the study are to describe the prevalence of vascular risk factors and incidence of vascular outcomes in a community-based sample of a racially and ethnically diverse population. The study was approved by the Institutional Review Boards of Columbia University and the University of Miami, and informed consent was obtained from all participants.

**Cohort Selection**

The cohort was recruited between 1993 and 2001 as described elsewhere. Subjects were enrolled if they: (1) were at least 40 years of age; (2) lived in a predefined geographic area of northern Manhattan for at least 3 months in a household with a telephone; and (3) did not have a history of stroke. Subjects with coronary artery disease (angina, MI, cardiac bypass surgery, or coronary angioplasty) at enrollment were excluded from this analysis (n = 560). Subjects were contacted by random digit dialing of both published and unpublished telephone numbers. The telephone response rate was 91% (9% refused to be screened), and 87% of eligible subjects indicated willingness to participate. The enrollment response rate was 75%, resulting in an overall response rate of 68%.

**Baseline Assessment**

All participants underwent a thorough baseline examination including comprehensive medical history, physical examination, review of medical records, and fasting blood samples. Standardized questions were adapted from the Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System. Race–ethnicity was based on self-identification modeled after the US census. Smoking was defined as either nonsmoker or smoker (within the last year). Blood pressure was measured at baseline, and the use of blood pressure medication was recorded. Diabetes mellitus was defined by self-report, fasting blood glucose level ≥ 126 mg/dL, or insulin/oral hypoglycemic use. Fasting high-density lipoprotein and total cholesterol were obtained using a Hitachi 705 automated spectrophotometer (Boehringer Mannheim, Mannheim, Germany), and low-density lipoprotein levels were derived from the Friedwald equation.

**Prospective Follow-Up**

Subjects were followed up annually by telephone. Only 2 subjects were completely lost to follow-up after their baseline examination, and the average annual contact rate was 99%. The telephone interview assessed any change in vital status, neurological or cardiac symptoms and events, and hospitalizations. A positive screen for any potential cardiac or neurological event was followed up by an in-person assessment to determine whether a vascular outcome had occurred. We prospectively screened all admissions and discharges to detect hospitalizations and outcomes that may not have been captured by telephone interview. Nearly 70% of vascular events led to hospitalizations at Columbia-Presbyterian Hospital.

**Classification of Outcomes**

Hospital records were reviewed to classify all outcomes as previously reported. The 3 main outcomes of interest included stroke, MI, and CHD death. Stroke included ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage but not transient ischemic attack or venous sinus thrombosis. At least 2 stroke neurologists verified and classified every case of stroke. MI was defined by criteria adapted from the Cardiac Arrhythmia Suppression trial and the Lipid Research Clinics Coronary Primary Prevention trial requiring at least 2 of the 3 following criteria: (1) ischemic cardiac pain determined to be typical angina; (2) cardiac marker abnormalities defined as abnormal creatine kinase–myocardial isoenzyme fraction or troponin I values; and/or (3) ischemic electrocardiographic abnormalities. The presence of an MI was adjudicated by cardiologists independently after review of all the clinical data. Death was classified as related to CHD based on information from family, medical records, death certificate, and primary care physicians. CHD death was death due to MI, heart failure, and cardiac arrhythmia.

**Statistical Analysis**

Our hypothesis was not that adding stroke to the vascular outcome cluster would result in an increase in estimated risk; this is tautological. However, we were interested in modeling the amount of increase in risk to ascertain whether this increase is clinically significant. Furthermore, we are not comparing several models that predict the same outcome; rather, we are comparing models that have different outcomes. Hence, traditional and newer reclassification statistics cannot be applied to this problem.

The distributions of individuals in each race–ethnic category, and with major vascular risk factors, were calculated. We calculated, for each individual, the FRS, which is interpreted as the predicted 10-year risk of MI or CHD death, using sex and baseline values of age, high-density lipoprotein, total cholesterol, systolic blood pressure, use of antihypertensive medications, and smoking status. For all analyses, the original FRS model was used, without population-specific calibrations, to approximate clinical practice, in which clinicians would use available online tools for risk stratification. We grouped individuals into categories of predicted risk using cutoffs that are based on clinically relevant thresholds for primary and secondary preventive treatment of vascular disease: <5%, 5% to 10%, 10% to 20%, and >20%. Focusing on those within the intermediate categories of 5% to 10% and 10% to 20%, for whom changes in risk strata would be most likely to be clinically significant, we estimated separate 10-year cumulative probabilities of (1) MI or CHD death; and (2) stroke, MI, or CHD death using the Kaplan–Meier method. The cumulative probability of MI or CHD death was subtracted from that of stroke, MI, or CHD death, and the 95% CI of the difference was obtained by constructing 1000 bootstrap samples.

We conducted a similar analysis in which we calculated, for each individual, the FGS, which is interpreted as the estimated 10-year risk of a global vascular outcome (CHD, cerebrovascular events, peripheral vascular disease, and heart failure) based on using the previously described baseline variables along with the presence or absence of diabetes. To visually depict the course of vascular events over follow-up, we obtained Kaplan–Meier curves of observed survival free of the 2 outcomes of interest (MI and CHD death; and stroke, MI, and CHD death) stratified by predicted risk. In 1 set of curves, the FRS was used to create categories of predicted risk (5% to 10% and 10% to 20%), and in another, the FGS was used.

We conducted several secondary analyses. Because the Framingham risk scores were derived from cohorts with age <80 years of age, we analyzed those with age <80 years. We also conducted stratified analyses among each category of race–ethnicity, from which we calculated the difference in actual risk (risk of MI or CHD death subtracted from risk of stroke, MI, or CHD death) with 95% CI for each category of predicted risk (5% to 10% and 10% to 20%) for each race–ethnic category (non-Hispanic white and black, and Hispanic). To test for significant differences among race–ethnic categories in the difference in actual risk, we subtracted the difference in actual risk for 1 race–ethnic category (eg, white) from that for another category (eg, black) and calculated 95% CI from 1000 bootstrap samples for each category of intermediate risk (5% to 10% and 10% to 20%).

**Results**

Baseline characteristics of the study population are described in Table 1. Median follow-up was 10 years (interquartile range 7–13 years). The distributions of individuals in each race–ethnic category, and with major vascular risk factors, were calculated. We calculated, for each individual, the FRS which is interpreted as the predicted 10-year risk of MI or CHD death, using sex and baseline values of age, high-density lipoprotein, total cholesterol, systolic blood pressure, use of antihypertensive medications, and smoking status. For all analyses, the original FRS model was used, without population-specific calibrations, to approximate clinical practice, in which clinicians would use available online tools for risk stratification.

We grouped individuals into categories of predicted risk using cutoffs that are based on clinically relevant thresholds for primary and secondary preventive treatment of vascular disease: <5%, 5% to 10%, 10% to 20%, and >20%. Focusing on those within the intermediate categories of 5% to 10% and 10% to 20%, for whom changes in risk strata would be most likely to be clinically significant, we estimated separate 10-year cumulative probabilities of (1) MI or CHD death; and (2) stroke, MI, or CHD death using the Kaplan–Meier method. The cumulative probability of MI or CHD death was subtracted from that of stroke, MI, or CHD death, and the 95% CI of the difference was obtained by constructing 1000 bootstrap samples.
range, 7.6 to 11.3 years). Table 2 lists the observed Kaplan–Meier 10-year risk of the 2 outcome clusters of interest (MI or CHD death versus stroke, MI, or CHD death) stratified by category of predicted risk. The differences in observed risk between the 2 outcome clusters, along with 95% CIs, are also described. Eight hundred sixty-seven participants had 10% to 20% predicted 10-year risk based on the FRS. Among these, the estimated 10-year cumulative probability of MI or CHD death from the Kaplan–Meier method was 14.20%. When stroke was added to the outcome cluster, the cumulative probability was 21.98%, a 55% relative increase, and the absolute difference in survival probability between the 2 outcome clusters was 7.78% (95% CI, 5.86 to 9.75%; Figure).

Table 2. Kaplan–Meier Observed 10-Year Risk of Vascular Events

<table>
<thead>
<tr>
<th>Predicted 10-Y Risk</th>
<th>Observed Kaplan–Meier 10-Y Risk (%)</th>
<th>Observed Kaplan–Meier 10-Y Risk (%)</th>
<th>Difference in Observed Risks (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>of MI or CHD Death</td>
<td>(No. of Events)</td>
<td>(No. of Events)</td>
<td></td>
</tr>
<tr>
<td>10%–20% (n=876)</td>
<td>14.20 (105)</td>
<td>21.98 (166)</td>
<td>7.78 (5.86–9.75)</td>
</tr>
<tr>
<td>&gt;20% (n=558)</td>
<td>22.88 (104)</td>
<td>30.71 (144)</td>
<td>7.82 (5.45–10.42)</td>
</tr>
<tr>
<td>Using FRS for risk prediction</td>
<td>2.76 (15)</td>
<td>4.96 (27)</td>
<td>2.20 (1.09–3.48)</td>
</tr>
<tr>
<td>&lt;5% (n=598)</td>
<td>8.91 (47)</td>
<td>13.64 (74)</td>
<td>4.73 (3.10–6.67)</td>
</tr>
<tr>
<td>5%–10% (n=590)</td>
<td>14.20 (105)</td>
<td>21.98 (166)</td>
<td>7.78 (5.86–9.75)</td>
</tr>
<tr>
<td>10%–20% (n=867)</td>
<td>22.88 (104)</td>
<td>30.71 (144)</td>
<td>7.82 (5.45–10.42)</td>
</tr>
<tr>
<td>Using FRS for risk prediction</td>
<td>1.32 (1)</td>
<td>1.32 (1)</td>
<td>0</td>
</tr>
<tr>
<td>&lt;5% (n=76)</td>
<td>2.45 (6)</td>
<td>4.17 (10)</td>
<td>1.72 (0.37–3.75)</td>
</tr>
<tr>
<td>5%–10% (n=268)</td>
<td>6.50 (42)</td>
<td>10.55 (70)</td>
<td>4.05 (2.63–5.85)</td>
</tr>
<tr>
<td>10%–20% (n=731)</td>
<td>14.48 (222)</td>
<td>21.52 (330)</td>
<td>7.69 (6.31–9.23)</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; CHD, coronary heart disease; FRS, Framingham coronary heart disease risk score; FGS, Framingham general cardiovascular disease risk score; CI, confidence interval.

Seven hundred thirty-one participants had 10% to 20% predicted 10-year risk based on the FGS. Among these, the estimated 10-year cumulative probability of MI or CHD death was 6.50%. When stroke was added to the outcome cluster, the cumulative probability was 10.55%, and the absolute difference in survival probability between the 2 outcome clusters was 4.05% (95% CI, 2.63 to 5.85%; Figure).

When these analyses were limited to those with age ≤80 years, the observed survival probabilities were slightly lower, but the differences in observed risk between the 2 outcome clusters were unchanged (data not shown).

Table 3 shows the differences in observed risk between the 2 outcome clusters for each race–ethnic category. Of note, there was heterogeneity among different race–ethnic categories in the category of 5% to 10% 10-year predicted risk of CHD with a larger difference among blacks than among whites (7.57%; 95% CI, 2.02% to 13.56%). There was no significant heterogeneity in the category of 10% to 20% 10-year predicted risk of CHD.

Discussion

In this multiethnic urban population, adding stroke to the cardiovascular risk stratification outcome cluster resulted in a 55% relative increase in observed 10-year risk among those with predicted risk of 10% to 20%. Adding stroke to the outcomes of MI and CHD death also resulted in crossing of the threshold (>20% over 10 years) considered for preventive treatments such as statins for this intermediate-risk group. Among the low-intermediate risk group of 5% to 10% predicted risk, there was a similar increase in observed 10-year risk (53%) and a crossing of the threshold (10% over 10 years) considered for treatments such as aspirin. Results were similar when analyses were limited to those of age ≤80 years, which is the upper age limit for which the FRS was intended.

The mainstays of current preventive approaches to cardiovascular disease such as antiplatelet and statin medications reduce risk of both stroke and cardiac disease, and the importance of considering both outcomes when predicting risk, instead of cardiac disease alone, is increasingly recognized. One implication of our findings is that including stroke in the risk prediction outcome cluster has a clinically significant impact on the absolute value of risk and results in crossing of clinically significant thresholds for treatment. These findings are particularly robust because of the large size of the cohort studied, the minimal loss to follow-up, the long duration of follow-up, the precision of outcome definitions, and the multiethnic composition of the source population.

We also found that the effect of adding stroke to the outcome cluster for risk prediction may have an even greater impact in blacks, among whom prior research has shown an increased stroke incidence compared with whites. For example, in the Atherosclerosis Risk in Communities study, the age-adjusted rate ratio for ischemic stroke comparing blacks with whites was 2.41. The causes of this increased incidence among blacks are not fully characterized, but our findings suggest that, by not accounting for the risk of stroke, the FRS may be drastically underestimating overall cardio-
vascular risk among blacks in the low- to intermediate-risk category.

We did not use population-specific calibrations of the Framingham equations, because none are available for the Northern Manhattan community. Furthermore, the FRS and FGS are generally used by practitioners without population-specific calibrations, and we wanted to reflect the general use of these risk prediction equations. In other publications, we have demonstrated that the addition of other anthropometric variables to the traditional FRS variables with coefficients that were optimized for our population have improved the prediction of stroke, MI, and vascular death. The aim of this analysis was not to evaluate the applicability of the FRS to our population, but rather to demonstrate the incremental cardiovascular risk that occurs when stroke is added to the outcome cluster.

Limitations of this study include the unique race–ethnic composition of the cohort, which may limit comparability of the findings to other populations. However, we believe that a strength of this population is the ability to detect differences in the performance of the Framingham risk prediction schemes by race–ethnic category, which is particularly relevant because the source population of the Framingham study is predominantly white, and the association between individual risk factors and outcome has been shown to differ by race–ethnicity.

Further research is needed to clarify the optimal use of primary risk stratification schemes, particularly those that predict risk of a composite vascular outcome and particularly among minority populations. Relevant questions are whether different clinical thresholds of risk should be used with a composite vascular outcome and which vascular events should be included in a composite vascular outcome. Ultimately, the addition of stroke to the outcome cluster of cardiovascular risk will improve the identification of those at moderate to high risk, particularly among minority populations, and expand the demand for more effective prevention programs for cardiovascular disease and stroke.

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Disclosures
R.L.S. has received research grants from the National Institute of Neurological Disorders and Stroke (NINDS); served as a past consultant to Boehringer Ingelheim, Sanofi Aventis, and Glaxo Smith Kline; and received honorarium for continuing medical education speaking from Boehringer Ingelheim and Sanofi Aventis. M.S.V.E. serves as Resident and Fellow Section Editor for Neurology; serves as a consultant to Bristol-Myers Squibb/Sanoﬁ Pharmaceuticals Partnership, GlaxoSmithKline, Jarvik Heart, and Tethys Bioscience, Inc; serves on speakers’ bureaus for Boehringer-Ingelheim, Inc, and Bristol-Myers Squibb/Sanoﬁ Pharmaceuticals Partnership; and receives research support from diaDexus, Inc, Bristol-Myers Squibb/Sanoﬁ Pharmaceuticals Partnership, and from the National Institutes of Health/NINDS (R01 NS050724 [Principal

### Table 3. Differences in Observed Risks (Survival Probability of Stroke, MI, or CHD Death Subtracted From the Probability of MI or CHD Death Over 10 Years) Among Racial/Ethnic Subgroups

<table>
<thead>
<tr>
<th></th>
<th>Differences in Observed Risks (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5%–10% Predicted 10-Y Risk of CHD†</td>
</tr>
<tr>
<td>Entire sample</td>
<td>4.73 (3.10–6.67)</td>
</tr>
<tr>
<td>White</td>
<td>2.75 (0.00–6.00)</td>
</tr>
<tr>
<td>Black</td>
<td>10.32* (5.41–15.70)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2.71 (1.07–4.74)</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; CHD, coronary heart disease; CI, confidence interval.

*The difference among blacks is significantly larger than the difference among whites (7.57; 95% CI, 2.02–13.56).

†Estimated by the Framingham heart risk score.
Investigator], NS048134 [Principal Investigator], P50 NS049060 [Project Principal Investigator], R27 NS029993 [Co-Principal Investigator], R01 NS55809 [Co-Investigator], and R01 NS062820 [Co-Investigator]); and has given expert testimony on behalf of Novartis (Zelnorm and stroke litigation).

References


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