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

The Framingham coronary heart disease risk score (FRS)$^{1,2}$ was designed to estimate the 10-year risk of myocardial infarction (MI) and coronary heart disease (CHD) death and is used to risk stratify individuals for vascular disease primary prevention. Because the preventive approaches to CHD and stroke are similar, a composite outcome including both cardiac disease and stroke may be more appropriate, and estimating the risk of cardiac events alone may underestimate an individual’s overall risk of cardiovascular disease.$^{3}$ Furthermore, it is important to assess the performance of the FRS among minority groups such as Hispanics, who may have a different relative burden of stroke and heart disease.$^{4}$ The Framingham general cardiovascular disease risk score (FGS)$^{5}$ was recently developed to calculate the risk of a composite vascular outcome (CHD, cerebrovascular events, peripheral vascular disease, and heart failure), but guidelines have not yet incorporated this score, and appropriate risk thresholds are not yet established.

A population-based prospective cohort study with long-term follow-up provides an opportunity to assess the absolute differences in risk that would result from using a composite vascular outcome instead of a cardiac outcome. We sought, in the Northern Manhattan Study, to compare the observed 10-year risk of MI or CHD death with the 10-year risk of stroke, MI, or CHD death among individuals free of vascular disease after categorizing individuals into clinically relevant groups of predicted FRS risk ($<5\%$, $5\%$ to $10\%$, $10\%$ to $20\%$, and $>20\%$).$^{2}$ We also used the FGS to calculate predicted risk. Our hypothesis was that including stroke in the outcome cluster in primary prevention risk prediction results in a clinically significant increase in risk. We further hypothesized that for those in intermediate risk categories ($5\%$ to $10\%$
Criteria adapted from the Cardiac Arrhythmia Suppression trial and verified and classified every case of stroke. MI was defined by 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%).
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>CHD Death (No. of Events)</td>
<td>MI or Stroke, MI, or CHD Death (No. of Events)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5% (n=598)</td>
<td>2.76 (15)</td>
<td>4.96 (27)</td>
<td>2.20 (1.09–3.48)</td>
</tr>
<tr>
<td>5%–10% (n=590)</td>
<td>8.91 (47)</td>
<td>13.64 (74)</td>
<td>4.73 (3.10–6.67)</td>
</tr>
<tr>
<td>10%–20% (n=867)</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>
</tbody>
</table>

Using FRS for risk prediction
| <5% (n=76) | 1.32 (1) | 1.32 (1) | 0 |
| 5%–10% (n=268) | 2.45 (6) | 4.17 (10) | 1.72 (0.37–3.75) |
| 10%–20% (n=731) | 6.50 (42) | 10.55 (70) | 4.05 (2.63–5.85) |
| >20% (n=1533) | 14.48 (222) | 21.53 (330) | 7.69 (6.31–9.23) |

Using FGS for risk prediction

SD indicates standard deviation.

*As defined in the text.

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. 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-

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.
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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References


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