Utility of Framingham Coronary Heart Disease Risk Score for Predicting Cardiac Risk After Stroke

Amytis Towfighi, MD; Daniela Markovic, MS; Bruce Ovbiagele, MD, MS

Background and Purpose—Coronary heart disease (CHD) is a major cause of mortality among stroke patients after the acute period. Simple risk stratification of stroke patients without known CHD may permit prompt implementation of CHD-specific management strategies for those who are at high risk for cardiac events. We assessed the utility of the Framingham Coronary Heart Disease Risk Score (FCRS) as a prognosticator in stroke patients without known CHD.

Methods—Post hoc analysis of a trial dataset of 3509 recent ischemic stroke patients who were aged 35 years or older, recruited from 56 centers, and followed-up for 2 years. Patients were categorized as having known CHD, high FCRS (≥20%), and low/intermediate FCRS (<20%). The predictive values between baseline FCRS and primary (myocardial infarction [MI]), secondary (MI or vascular death), and tertiary (recurrent stroke) outcomes were assessed in multivariate analyses.

Results—Rates of first MI at 2 years were 6.34%, 4.65%, and 1.44% for the known CHD, high FCRS, and low/intermediate FCRS groups. Compared with stroke patients with low/intermediate FCRS, individuals with high FCRS had a higher risk of MI (adjusted hazard ratio, 3.70; 95% confidence interval, 2.14–6.38) and MI or vascular death (adjusted hazard ratio, 2.21; 95% confidence interval, 1.48–3.28). High FCRS did not predict recurrent stroke.

Conclusion—Among patients with a recent ischemic stroke without known CHD, high FCRS was associated with a higher risk of MI and vascular death, but not stroke. FCRS could be a simple way to identify recent stroke patients who may benefit from additional CHD-specific management. *(Stroke. 2012;43:2942-2947.)*

Key Words: coronary atherosclerosis ■ coronary heart disease ■ myocardial infarction ■ outcome ■ risk ■ stroke ■ vascular death

Stroke patients often harbor asymptomatic coronary atherosclerosis.1 Beyond the acute period, stroke survivors are at a higher risk for death attributable to cardiac rather than recurrent cerebrovascular events.2,3 The high risk of coronary events among stroke survivors4 has prompted a discussion of whether stroke should be considered a coronary heart disease (CHD) risk equivalent, along with symptomatic carotid artery disease, peripheral arterial disease, abdominal aortic aneurysm, and diabetes mellitus.5–8 Although symptomatic carotid artery disease is among the listed CHD risk equivalents, atherosclerosis develops in many sites within the aortocervicocephalic circulation other than the carotid artery,9 and several race–ethnic minorities who tend to have more strokes because of atherosclerosis in the intracranial arterial circulation10 may be overlooked by this approach. A review of hospital-based and population-based studies appears to support the designation of stroke as an additional CHD risk equivalent.7 However, the review included individuals with known CHD, giving little information for the risk of future cardiac events among those without known CHD.12,13 In addition, considering every stroke as a CHD risk equivalent could potentially expose individuals with a low risk of subsequent coronary events to unnecessary treatments. Stroke is substantially more heterogeneous in etiology than myocardial infarction (MI) and includes diverse nonatherosclerotic mechanisms such as vasculitis, migraine, dissection, and hypercoagulable states. Intensively treating all stroke patients with therapies like statins could have untoward clinical implications without conferring benefit. Therefore, there have been calls to develop strategies to identify patients at high risk who could benefit from CHD-specific treatment.8,9,12 A recent American Heart Association scientific statement highlighted the need to develop a validated risk prediction instrument for risk of cardiac disease after stroke.14

Coronary risk stratification among stroke patients would allow practitioners to develop a more effective, targeted, and cost-effective preventive strategy.9 Although recurrent stroke and CHD preventive therapies are similar, key differences exist. For example, β-blockers are an integral part of CHD
preventive regimens but may be less effective for stroke prevention compared with other classes of antihypertensive agents. Furthermore, although statins are recommended for CHD prevention, their utility in nonatherosclerotic stroke remains in question. The Framingham Coronary Heart Disease Risk Score (FCRS) is a simple, widely recognized, readily available tool for estimating 10-year risk for CHD outcomes in the general population. The utility of FCRS in predicting risk of coronary events in the short-term to intermediate-term among stroke patients is unknown. This study aimed to assess whether baseline FCRS could delineate the risk of subsequent (1) MI, (2) MI or vascular death, and (3) recurrent stroke among recent ischemic stroke patients.

Subjects and Methods

Patient Population

We conducted a post hoc analysis of the Vitamin Intervention for Stroke Prevention (VISP) trial, a double-blind, randomized, controlled trial assessing whether best medical therapy and high-dose folic acid, pyridoxine, and cobalamin administered to lower homocysteine levels would reduce the incidence of recurrent stroke in patients with a nondisabling ischemic stroke within the preceding 120 days. Details of the trial protocol and main results have been published previously. In brief, from September 1996 to May 2003, VISP enrolled 3680 recent ischemic stroke patients aged 35 years or older from centers across the United States (n=45), Canada (n=10), and Scotland (n=1). Ischemic stroke was defined as brain infarction characterized by the sudden onset of a neurological deficit lasting ≥24 hours or evident on computed tomography or magnetic resonance imaging. Infarcts attributable to cardioembolism (atrial fibrillation within 30 days of stroke, prosthetic cardiac valve, intracardiac thrombus or neoplasm, or valvular vegetation) were excluded. One month after randomization, at 6 months, and every 6 months thereafter (up to 24 months), participants returned for evaluation including interview, examination, medication use assessment, stroke symptom questionnaire, stroke scales, and medical follow-up questionnaire. All subjects received best available medical and surgical management as determined by their primary physician, including risk factor modification and often aspirin 325 mg daily. A Cardiovascular End Point Review Committee adjudicated CHD end points. Myocardial infarction was defined by new ECG changes including Q waves or marked ST-T changes plus abnormal cardiac enzymes, cardiac symptoms plus abnormal enzymes, or symptoms plus hyperacute ECG changes resolving with thrombolytic, a Cerebrovascular End Point Review Committee adjudicated recurrent stroke end points. Recurrent stroke was defined by sudden onset of neurological symptoms lasting ≥24 hours with an increase in the National Institutes of Health Stroke Scale on a section not abnormal in the previous examination. When symptoms were not accompanied by an increased National Institutes of Health Stroke Scale score in an area that was previously normal, recurrent stroke was diagnosed using cranial computed tomography or magnetic resonance imaging evidence of new infarction consistent with the clinical presentation. The Ethics Committee or Institutional Review Board at each site approved the trial, and all participants provided written informed consent. VISP did not find high-dose vitamin therapy superior to the low-dose regimen in recurrent stroke prevention, so data for all enrolled patients were combined and included in these analyses.

Statistical Analysis

Patients were categorized into 3 categories: known CHD (defined as history of MI, angina, coronary angioplasty or stenting, or coronary artery bypass graft surgery); high FCRS (FCRS ≥20%); and low/intermediate FCRS (FCRS <20%). FCRS was determined using formulas published by Wilson et al. The low and intermediate FCRS groups were combined for the purpose of this analysis, because clinical management is typically similar for low and intermediate groups. Of 3680 participants in the trial, 171 participants were missing a component of FCRS and were excluded from the final analysis, yielding a total of 3509 subjects. We compared baseline clinical factors and assessed rates of MI, stroke, vascular death, and all-cause death among the 3 groups.

We assessed the prevalence and clinical predictors of high FCRS in VISP subjects without known CHD. Baseline demographic and clinical covariates were preselected based on previous studies of factors that influence vascular events after ischemic stroke. We used multivariate logistic regression to examine the association between the following variables simultaneously and cardiac risk status: race (black, white, other); history of stroke; severity of index stroke (National Institutes of Health Stroke Scale score: 0, 1–5, ≥6); history of congestive heart failure; history of carotid endarterectomy; body mass index (BMI, normal, overweight, obese); alcohol use in the previous year; antidyssipidemic use; antithrombotic use; low-density lipoprotein cholesterol level >100 mg/dL; and triglyceride level >150 mg/dL. Final models were selected using backwards stepwise search with P<0.25 as the retention criterion. We examined the association between baseline factors and high FCRS in the following ways: (1) without adjustment for any of the individual FCRS components (model I); (2) after adding age to the model (model II); and (3) after adding both age and sex to the model (model III). Age was added to the models because FCRS places a large weight on age as a risk factor.

We used Cox models with competing risks to assess the independent association of baseline cardiac risk status with the primary (MI), secondary (MI or vascular death), and tertiary (stroke) outcomes, adjusting for covariates using backward stepwise search with <0.25 as the retention criterion. The Cox models for MI and stroke were adjusted for the competing risk of all-cause mortality. The Cox model for MI or vascular death was adjusted for the competing risk of nonvascular mortality. Subjects who did not experience the event of interest or the corresponding competing event were censored. For each outcome, we assessed the association with and without age added to the model. We computed the area under the curve (concordance) as a measure of prediction accuracy for each model.

To determine if assessing FCRS as a continuous variable would provide more useful information than assessing FCRS as a categorical variable, we assessed linearity between the FCRS continuous score vs the risk of MI by fitting a restricted cubic splines model with 5 knots. To compare the nonlinear model containing the spline terms to the linear model not containing the spline terms, we computed the probability value using the likelihood ratio test with 3 degrees of freedom. Results showed that the nonlinear model tended to fit the data better than the linear model (P<0.056). Although linearity was approximately satisfied for a FCRS range of ≥10% or higher, linearity did not seem to hold at FCRS <10%, where slope was close to zero. Therefore, we decided to use a categorical model with a clinically defined FCRS threshold of low/intermediate risk vs high risk.

To evaluate whether FCRS conveys, as originally postulated, greater information than the sum of its parts, we compared multivariate models containing 6 non-FCRS vascular risk factors significantly associated with outcome using backwards stepwise search plus 1 individual FCRS components most strongly associated with outcome (model I); (2) FCRS (model II); and (3) FCRS plus FCRS components most strongly associated with outcome (model III). Models were compared using Akaike information criteria. The overall significance level for the study was P<0.05 using a 2-sided test. We computed the concordance statistic (area under the curve) to assess prediction accuracy of each model as per the procedure proposed by Wolbers et al. The aforementioned model accuracy statistics were calculated after 5-fold cross-validation to obtain more accurate estimates of model performance while allowing us to use all the data. Model fit also was assessed using modifications of methods by Hosmer and Lemeshow. We assessed the interaction between VISP treatment category and high FCRS in predicting...
the risk of MI by including the appropriate interaction terms in the model. All analyses were performed with SAS statistical software version 9.2.

### Results
Comparing baseline characteristics between patients with and without missing FCRS, those with missing values had a slightly higher systolic blood pressure (143.9 vs 141.2 mm Hg; \(P=0.01\)), were more likely to have diabetes (32% vs 26%; \(P=0.07\)), and were less likely to use lipid modifiers (29% vs 38%; \(P=0.07\)). Of the 3509 individuals included in this analysis, 31% had known CHD. Among subjects without known CHD, prevalence of high FCRS was 37% (n=933).

Table 1 shows the baseline characteristics of individuals with low/intermediate FCRS, high FCRS, and known CHD. Compared with those with low/intermediate FCRS, individuals with high FCRS were less likely to have National Institutes of Health Stroke Scale score 0 (29.8% vs 35.7%; \(P=0.01\)), more likely to be overweight (44.0% vs 39.4%; \(P=0.02\)), and had higher mean triglyceride (191.8 vs 162.0 mg/dL; \(P<0.001\)) and mean low-density lipoprotein cholesterol levels (131.3 vs 120.9 mg/dL; \(P<0.001\); Table 1).

Several baseline factors were associated with high FCRS (Supplementary Table I). The following factors were simultaneously associated with high FCRS in all 3 multivariate models (regardless of adjustment for age and sex): National Institutes of Health Stroke Scale score 1 to 4 vs 0; triglyceride level >150 mg/dL; and low-density lipoprotein level >100 mg/dL (\(P\leq 0.05\)). Persons of black/other race and obese individuals were more likely to have high FCRS after also controlling for age and sex.

At 2 years, 104 individuals had MI, 190 had a stroke, and 166 had MI or died of vascular causes. At 2 years, risks of MI in individuals with low/intermediate FCRS, high FCRS, and known CHD were 1.44%, 4.65%, and 6.34%, risks of stroke were 7.63%, 9.72%, and 9.01%, and risks of vascular death were 1.87%, 3.05%, and 5.91% (Table 2).

The final multivariate model showed that 6 non-FCRS factors were associated with higher risk of MI: history of stroke; congestive heart failure; abstinence from alcohol in past year; history of carotid endarterectomy; lower BMI (<25 kg/m²); and not using lipid modifiers. Compared with individuals with low/intermediate FCRS, those with high FCRS had significant higher risk of MI (4.65% vs 1.44%; \(P=0.001\)).
models (regardless of adjustment for age and sex): National Institutes of Health Stroke Scale score 1 to 4 vs 0; triglyceride level >150 mg/dL; and low-density lipoprotein level >100 mg/dL (P \leq 0.05). Persons of black/other race and obese individuals were more likely to have high FCRS after also controlling for age and sex.

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The final multivariate model showed that 6 non-FCRS factors were associated with higher risk of MI: history of stroke; congestive heart failure; abstinence from alcohol in past year; history of carotid endarterectomy; lower BMI (<25 kg/m²); and not using lipid modifiers. Compared with individuals with low/intermediate FCRS, those with high FCRS had a higher risk of the primary outcome (MI) after adjusting for these 6 factors (hazard ratio [HR], 3.70, 95% confidence interval [CI], 2.14–6.38). Further adjustment for age attenuated the results (HR, 3.33; 95% CI, 1.90–5.84; Table 3; Figure). The effect of high FCRS was slightly more pronounced for patients receiving low-dose vitamin therapy (HR, 5.63) than for patients receiving high-dose vitamin therapy (HR, 2.51); however, this interaction was not significant (P=0.14). Compared with those with low/intermediate FCRS, individuals with known CHD were more likely to have a subsequent MI (HR, 4.43; 95% CI, 2.58–7.59). The association persisted after further adjustment for age (HR, 4.05; 95% CI, 2.34–7.01; Table 3; Figure).

The final multivariate model assessing the association between high FCRS and risk of MI or vascular death adjusted for the following covariates that were significant in backwards stepwise regression model: previous stroke; mean systolic blood pressure in trial; congestive heart failure; history of stroke; mean in trial systolic blood pressure; coronary heart failure, carotid endarterectomy; body mass index, stroke severity, antithrombotic use; and antithrombotic use.

### Table 2. Unadjusted Clinical Outcomes at 2 Years by Cardiac Risk Category Among 3509 Patients With a Recent Ischemic Stroke

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low/Intermediate FCRS</th>
<th>High FCRS</th>
<th>Known CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N of patients</td>
<td>1614</td>
<td>933</td>
<td>962</td>
</tr>
<tr>
<td>MI (risk at 2 y, %; 95% CI)</td>
<td>1.44 (0.82–2.05)</td>
<td>4.65 (3.26–6.05)</td>
<td>6.34 (4.74–7.94)</td>
</tr>
<tr>
<td>Stroke (risk at 2 y, %; 95% CI)</td>
<td>7.63 (6.29–8.96)</td>
<td>9.72 (7.75–11.68)</td>
<td>9.01 (7.12–10.89)</td>
</tr>
<tr>
<td>Stroke, MI, or vascular death (risk at 2 y, %; 95% CI)</td>
<td>9.84 (8.35–11.33)</td>
<td>15.05 (12.69–17.40)</td>
<td>17.76 (15.27–20.26)</td>
</tr>
<tr>
<td>All-cause death (risk at 2 y, %; 95% CI)</td>
<td>4.19 (3.15–5.23)</td>
<td>6.72 (5.04–8.40)</td>
<td>10.01 (8.01–12.01)</td>
</tr>
<tr>
<td>Vascular death (risk at 2 y, %; 95% CI)</td>
<td>1.87 (1.16–2.57)</td>
<td>3.05 (1.91–4.19)</td>
<td>5.91 (4.34–7.48)</td>
</tr>
</tbody>
</table>

CHD indicates coronary heart disease; CI, confidence interval; FCRS, Framingham Coronary Heart Disease Risk Score; MI, myocardial infarction.

### Table 3. Multivariate Models Assessing Risk of Myocardial Infarction, Myocardial Infarction and Vascular Death, and Stroke in Individuals With High Framingham Coronary Risk Score or Known Coronary Heart Disease vs Low/Intermediate Framingham Coronary Risk Score

<table>
<thead>
<tr>
<th>Sample Size, n</th>
<th>N of Events</th>
<th>High Framingham Coronary Risk Score</th>
<th>Known Coronary Heart Disease</th>
<th>Cross-Validated AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI*</td>
<td>3384</td>
<td>113</td>
<td>3.70 (2.14–6.38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MI§</td>
<td>3384</td>
<td>113</td>
<td>3.33 (1.90–5.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI or vascular death†</td>
<td>3470</td>
<td>190</td>
<td>2.21 (1.48–3.28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MI or vascular death§</td>
<td>3470</td>
<td>190</td>
<td>1.96 (1.31–2.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Tertiary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke‡</td>
<td>3416</td>
<td>274</td>
<td>1.19 (0.89–1.58)</td>
<td>0.24</td>
</tr>
<tr>
<td>Stroke§</td>
<td>3416</td>
<td>274</td>
<td>1.16 (0.87–1.55)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

AUC indicates area under the curve; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.

*Adjusted for previous stroke, coronary heart failure, alcohol intake, carotid endarterectomy, body mass index, and antidysepidemic use.
†Adjusted for prior stroke, mean in trial systolic blood pressure, coronary heart failure, carotid endarterectomy, body mass index, stroke severity, antidysepidemic use, and antithrombotic use.
‡Adjusted for previous stroke, mean in trial systolic blood pressure, coronary heart failure, alcohol intake, carotid endarterectomy, stroke severity, and antithrombotic use.
§Adjusted for aforementioned covariates plus age.
Figure. Adjusted cumulative incidence of myocardial infarction (MI) after recent ischemic stroke among individuals with low/intermediate Framingham Coronary Heart Disease Risk Score (FCRS), high FCRS, and known coronary heart disease (CHD).

carotid endarterectomy; BMI; stroke severity; antidysslipidemic use; and antithrombotic use. After adjusting for those 8 covariates, high FCRS was associated with higher risk of MI or vascular death compared with low/intermediate FCRS (HR, 2.21; 95% CI, 1.48–3.28; Table 3). Further adjustment for age attenuated the magnitude (HR, 1.96; 95% CI, 1.31–2.95). Individuals with known CHD had a higher risk of subsequent MI or vascular death compared with those with low/intermediate FCRS (HR, 3.37; 95% CI, 2.30–4.92). Adjustment for age attenuated the results (HR, 3.06; 95% CI, 2.09–4.47).

After multivariate analysis, neither high FCRS nor known CHD was associated with a higher risk of stroke compared with low/intermediate FCRS. The model for predicting the risk of MI had the highest discrimination (cross-validated area under the curve, 70.1%), whereas the model for predicting the risk of stroke had the lowest discrimination (cross-validated area under the curve, 63.4%; Table 3).

The individual FCRS components associated with risk of MI after adjusting for previous stroke, congestive heart failure, alcohol intake, carotid endarterectomy, BMI, and antidysslipidemic use were age, male sex, diabetes, and smoking (Supplementary Table II, model I). Compared with low/intermediate FCRS, high FCRS was associated with higher incidence of MI, even after adjustment for the FCRS predictor (Supplementary Table II, model II) and FCRS components that were significantly associated with outcome (HR, 2.17; 95% CI, 1.16–4.09; Supplementary Table II, model III). The model that included the individual FCRS components without the FCRS predictor had slightly but not significantly better discrimination than the model that included the FCRS predictor alone without including the individual FCRS components (cross-validated area under the curve: 74.0% vs 70.1%, P=0.17; Supplementary Table II). The addition of FCRS to the model including the individual FCRS components did not further improve model prediction (cross-validated area under the curve: 74.4% vs 74.0%, P=0.91; Supplementary Table II).

Discussion
In this analysis of patients with a recent ischemic stroke, more than one-third of those without CHD had high FCRS. High FCRS was associated with a nearly 4-fold higher risk of MI and 2-fold risk of MI or vascular death over a 2-year period, after adjusting for numerous sociodemographic and clinical factors. These findings suggest that beyond its established utility as a prognosticator of long-term CHD risk in the general population, FCRS also might be a useful tool for predicting intermediate-term MI risk among individuals with recent stroke. Even though all FCRS components are risk factors for both MI and stroke, and although we studied a population with known stroke without known CHD, high FCRS was not associated with risk of recurrent stroke. The null finding for any link between FCRS and stroke is not surprising because the score was originally developed and validated for CHD events. FCRS does not include stroke-specific risk factors such as atrial fibrillation (which is included in the Framingham Stroke Risk Score). Interestingly, the effect of high FCRS on incidence of MI remained even after adjusting for its individual components, suggesting that contribution of high FCRS to MI risk after stroke may be greater than the sum of its traditional vascular risk factor parts.

These findings suggest that FCRS may be a useful tool for identifying stroke survivors with a high risk of MI or vascular death within the next 2 years. These individuals may benefit from additional CHD-specific agents or further diagnostic evaluation for silent cardiac ischemia, a condition that confers the same poor prognosis as symptomatic ischemia. Guidelines have not been established for treatment of stroke patients with asymptomatic CHD or high risk of future cardiac disease; however, counseling, diagnostic evaluation, and CHD-specific risk factor control have been suggested.

Beyond the issue of additional CHD-specific treatment in stroke patients with high FCRS is whether tighter control of FCRS components or modifications of vascular risk factors linked to high FCRS may boost CHD outcomes after stroke. Among modifiable FCRS components, diabetes and smoking were independently linked to incident MI. In addition, high FCRS was associated with modifiable non-FCRS vascular risk factors, including higher BMI, triglyceride, and low-density lipoprotein cholesterol levels. The SPARCL trial supports an approach of intensive risk factor treatment to avert CHD events in recent stroke patients without known CHD. In SPARCL, individuals with a history of TIA/stroke without symptomatic CHD were treated with high-dose atorvastatin (vs placebo) and experienced a substantial reduction in risk of a major coronary event (defined as death from cardiac causes, nonfatal MI, or resuscitation after cardiac arrest; HR, 0.65; 95% CI, 0.49–0.87), an acute coronary event (HR, 0.65; 95% CI, 0.50–0.84), and any coronary event (odds ratio, 0.58; 95% CI, 0.46–0.73). Low-density lipoprotein cholesterol levels declined by 45% in the high-dose statin group vs 4% in the placebo group. Of note, the high-dose statin appeared more efficacious in preventing the secondary outcome of major CHD events than it was in preventing the primary outcome of recurrent stroke.

This study has limitations. First, because it is a retrospective analysis of participants with noncardioembolic stroke enrolled in a clinical trial, the findings may not be generalizable to the general stroke population. Individuals with cardioembolic stroke would be expected to have a higher risk.
of cardiac events, possibly because of underlying cardiac disease. Second, although we conducted multivariate analyses, unmeasured confounding is possible. For example, although we controlled for baseline medication use, we were unable to control for medication use during the trial. In addition, the post hoc nature of the study limited us to examining only the variables collected in the original study. Furthermore, the VISP trial was conducted mainly in the early 2000s, so its relevance to stroke patients encountered today could be questioned. However, the baseline characteristics (mean age, sex, pretrial symptomatic cerebrovascular disease, known diabetes or hypertension, mean BMI, current smoking, and baseline blood pressure) of a recent large secondary stroke prevention trial are comparable with those seen in VISP. Finally, the lack of association between FCRS and recurrent stroke risk is perhaps not surprising because FCRS has not been shown to predict stroke risk in the general population. Further studies could assess if the Framingham Stroke Risk Score or FCRS is predictive of risk of recurrent stroke among stroke survivors. The strengths of the study include the rigorous procedures of the VISP trial design, multiple measurements/contacts for each subject, and consistency of effect direction across primary, secondary, and tertiary outcomes.

Acknowledgments
The authors are grateful to the Vitamin in Stroke Prevention (VISP) Investigators (NINDS R01 NS34447), especially Dr Chambless for making the dataset available to the authors.

Sources of Funding
NIH-NINDS (U01 NS079179) and American Heart Association National Scientist Development Program.

Disclosures
The abstract of this study was the winner of the 2012 Robert G. Siekert Award and was presented in oral form at the Plenary Session of American Heart Association International Stroke Conference on February 1, 2012, in New Orleans, Louisiana.

References
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Stroke. 2012;43:2942-2947; originally published online September 4, 2012; doi: 10.1161/STROKEAHA.112.668319
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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**SUPPLEMENTAL MATERIALS**

**Supplementary Table 1.** Multivariate logistic model results for baseline factors associated with high FCRS*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Model I†</th>
<th>p value</th>
<th>Model II‡</th>
<th>p value</th>
<th>Model III§</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of carotid endarterectomy</td>
<td>1.51 (1.05-2.17)</td>
<td>0.03</td>
<td>1.34 (0.91-1.97)</td>
<td>0.14</td>
<td>--</td>
<td>ns</td>
</tr>
<tr>
<td>NIHSS: 1-4 vs. 0</td>
<td>1.34 (1.11-1.61)</td>
<td>0.002</td>
<td>1.30 (1.07-1.59)</td>
<td>0.008</td>
<td>1.26 (1.00-1.58)</td>
<td>0.04</td>
</tr>
<tr>
<td>NIHSS: ≥5 vs. 0</td>
<td>1.30 (0.93-1.81)</td>
<td>0.13</td>
<td>1.38 (0.96-1.98)</td>
<td>0.08</td>
<td>1.15 (0.76-1.73)</td>
<td>0.51</td>
</tr>
<tr>
<td>BMI: overweight vs. normal weight</td>
<td>1.29 (1.05-1.58)</td>
<td>0.02</td>
<td>1.51 (1.21-1.88)</td>
<td>&lt;0.001</td>
<td>1.28 (0.99-1.66)</td>
<td>0.06</td>
</tr>
<tr>
<td>BMI: obese vs. normal weight</td>
<td>1.10 (0.88-1.38)</td>
<td>0.39</td>
<td>1.49 (1.17-1.91)</td>
<td>0.002</td>
<td>1.66 (1.25-2.20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides &gt;150 mg/dL</td>
<td>1.64 (1.38-1.94)</td>
<td>&lt;0.001</td>
<td>2.02 (1.67-2.43)</td>
<td>&lt;0.001</td>
<td>2.85 (2.28-3.56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL &gt;100 mg/dL</td>
<td>1.68 (1.37-2.06)</td>
<td>&lt;0.001</td>
<td>1.80 (1.45-2.24)</td>
<td>&lt;0.001</td>
<td>2.64 (2.06-3.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antithrombotic use</td>
<td>1.13 (0.96-1.34)</td>
<td>0.15</td>
<td>1.15 (0.96-1.38)</td>
<td>0.12</td>
<td>1.14 (0.93-1.41)</td>
<td>0.21</td>
</tr>
<tr>
<td>Alcohol use in prior year</td>
<td>--</td>
<td>ns</td>
<td>1.23 (1.02-1.48)</td>
<td>0.03</td>
<td>0.73 (0.59-0.92)</td>
<td>0.006</td>
</tr>
<tr>
<td>Race: black vs. white</td>
<td>--</td>
<td>ns</td>
<td>1.69 (1.14-2.50)</td>
<td>0.009</td>
<td>1.73 (1.09-2.74)</td>
<td>0.02</td>
</tr>
<tr>
<td>Race: other vs. white</td>
<td>--</td>
<td>ns</td>
<td>1.35 (1.03-1.76)</td>
<td>0.03</td>
<td>1.78 (1.31-2.43)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Antidyslipidemic medication use, history of congestive heart failure and history of prior stroke were not significant at p<0.25 in any model.

†Adjusted for race, stroke severity, carotid endarterectomy, body mass index (BMI), alcohol intake, antithrombotic use, low density lipoprotein cholesterol (LDL) >100 mg/dL and serum triglycerides >150 mg/dL.

‡Adjusted for above factors and age

§Adjusted for above factors, age and sex
**Supplementary Table 2.** Association between high FCRS and individual FCRS components with risk of MI in VISP subjects (n=3384 persons with complete data)*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Unadjusted</th>
<th>Model I†</th>
<th>Model II‡</th>
<th>Model III§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p value</td>
<td>HR (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>Age, per year</td>
<td>1.04 (1.02-1.06)</td>
<td>&lt;0.001</td>
<td>1.04 (1.02-1.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>0.63 (0.43-0.94)</td>
<td>0.02</td>
<td>0.53 (0.34-0.83)</td>
<td>0.01</td>
</tr>
<tr>
<td>SBP, per mm Hg</td>
<td>1.01 (1.00-1.02)</td>
<td>0.23</td>
<td>--</td>
<td>ns</td>
</tr>
<tr>
<td>DBP, per mm Hg</td>
<td>0.98 (0.97-1.00)</td>
<td>0.06</td>
<td>--</td>
<td>ns</td>
</tr>
<tr>
<td>Tot chol, per mg/dl</td>
<td>1.002 (0.998-1.005)</td>
<td>0.36</td>
<td>1.004 (1.002-1.007)</td>
<td>0.002</td>
</tr>
<tr>
<td>HDL, per mg/dl</td>
<td>0.98 (0.97-1.00)</td>
<td>0.04</td>
<td>--</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.37 (1.67-3.36)</td>
<td>&lt;0.001</td>
<td>2.26 (1.51-3.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoker</td>
<td>1.11 (0.71-1.74)</td>
<td>0.66</td>
<td>1.64 (1.00-2.68)</td>
<td>0.05</td>
</tr>
<tr>
<td>High FCRS (vs. low/intermediate FCRS)</td>
<td>3.45 (2.04-5.84)</td>
<td>&lt;0.001</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>AIC</td>
<td>1727.34</td>
<td>1768.67</td>
<td>1722.97</td>
<td>1722.97</td>
</tr>
<tr>
<td>Cross-validated AUC (SE)</td>
<td>0.740 (0.056)</td>
<td></td>
<td>0.701 (0.061)</td>
<td></td>
</tr>
</tbody>
</table>

* All models were adjusted for six additional factors using backwards stepwise search (prior stroke, CHF, alcohol intake, CEA, BMI, and antidyslipidemic use)

† Model I contains the subset of individual FCRS components most strongly associated with the outcome, not containing FCRS predictor

‡ Model II contains the FCRS predictor, but does not contain the individual FCRS components

§ Model III contains the FCRS predictor and the subset of individual FCRS components most strongly associated with outcome

NS: not significant at p<0.15