Original Contribution

# Revised Framingham Stroke Risk Score, Nontraditional Risk Markers, and Incident Stroke in a Multiethnic Cohort

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***Background and Purpose***—Limited data exist on the performance of the revised Framingham Stroke Risk Score (R-FSRS) and the R-FSRS in conjunction with nontraditional risk markers. We compared the R-FSRS, original FSRS, and the Pooled Cohort Equation for stroke prediction and assessed the improvement in discrimination by nontraditional risk markers.

***Methods***—Six thousand seven hundred twelve of 6814 participants of the MESA (Multi-Ethnic Study of Atherosclerosis) were included. Cox proportional hazard, area under the curve, net reclassification improvement, and integrated discrimination increment analysis were used to assess and compare each stroke prediction risk score. Stroke was defined as fatal/nonfatal strokes (hemorrhagic or ischemic).

***Results***—After mean follow-up of 10.7 years, 231 of 6712 (3.4%) strokes were adjudicated (2.7% ischemic strokes). Mean stroke risks using the R-FSRS, original FSRS, and Pooled Cohort Equation were 4.7%, 5.9%, and 13.5%. The R-FSRS had the best calibration (Hosmer–Lemeshow goodness-of-fit, $\chi^2$=6.55; $P$=0.59). All risk scores were predictive of incident stroke. C statistics of R-FSRS (0.716) was similar to Pooled Cohort Equation (0.716), but significantly higher than the original FSRS (0.653; $P$=0.01 for comparison with R-FSRS). Adding nontraditional risk markers individually to the R-FSRS did not improve discrimination of the R-FSRS in the area under the curve analysis, but did improve category-less net reclassification improvement and integrated discrimination increment for incident stroke. The addition of coronary artery calcium to R-FSRS produced the highest category-less net reclassification improvement (0.36) and integrated discrimination increment (0.0027). Similar results were obtained when ischemic strokes were used as the outcome.

***Conclusions***—The R-FSRS downgraded stroke risk but had better calibration and discriminative ability for incident stroke compared with the original FSRS. Nontraditional risk markers modestly improved the discriminative ability of the R-FSRS, with coronary artery calcium performing the best. **(*Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.117.018928.)**

**Key Words:** atherosclerosis ■ epidemiology ■ risk factors ■ stroke



Stroke is a leading cause of morbidity and mortality in the United States.[1] Over 70% of strokes occur in those without a history of a prior stroke, emphasizing the importance of stroke primary prevention.[2] Several risk scores have been developed to identify persons at high risk for future strokes and overall atherosclerotic cardiovascular disease (ASCVD).[3–6] Over the past 15 to 20 years, stroke rates and risk factor prevalence have declined, and the implementation of ASCVD/stroke prevention therapies and strategies has improved.[7,8]

The Framingham Stroke Risk Score (FSRS) combines stroke risk factors (age, sex, systolic blood pressure, use of antihypertensives, presence/absence of left ventricular hypertrophy on ECG, prevalent cardiovascular disease, current smoking status, current/previous atrial fibrillation, and diabetes mellitus [DM]) to predict 10-year probability of stroke.[3] The original FSRS (O-FSRS) is based on stroke data from the 1960s and 1970s, and the application of the O-FSRS to contemporary cohorts shows overestimation of stroke risk.[9,10] A revised FSRS (R-FSRS) was developed to reflect temporal trends using updated stroke risk factors prevalence and stroke rate incidence and may be used for examining geographic/racial differences in stroke risk and the use of nontraditional risk markers in stroke prediction.[11]

Data from the Rotterdam Heart Study showed that the R-FSRS and O-FSRS had similar discriminative ability for primary stroke in whites.[12] Limited data exist on the performance of the R-FSRS in a multiethnic and ASCVD-free cohort and whether nontraditional ASCVD risk markers improve the discriminative ability of the R-FSRS.

We used data from the MESA (Multi-Ethnic Study of Atherosclerosis) to compare the calibration and discrimination of the O-FSRS, R-FSRS, and the ASCVD Pooled Cohort Equation (PCE) for incidence strokes with 10 years

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of adjudicated stroke outcomes. In addition, we assessed the ability of nontraditional risk markers (coronary artery calcium [CAC], carotid intima-media thickness [CIMT], ankle-brachial index [ABI], high-sensitivity CRP [C-reactive protein], and family history of stroke to improve the discrimination of the R-FSRS).

## Methods

The data that support the findings of this study are available at the National Heart, Lung, and Blood Institute-MESA website (www.mesa.nhlbi.org) and would be made available by the corresponding author on reasonable request.

### Study Population and Data Collection

The design for the MESA has been previously published.[13] MESA is a prospective population-based cohort study to investigate the prevalence, correlates, and progression of subclinical ASCVD in persons without known baseline ASCVD. The cohort includes 6814 women and men ages 45 to 84 years recruited from 6 US communities (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; northern Manhattan, NY; and St. Paul, MN). MESA included 38% white, 28% black, 22% Hispanic, and 12% Chinese adults. Demographics, medical history, anthropometric, and laboratory data for the present study were taken from the first examination (July 2000 to August 2002). The MESA study was approved by the institutional review boards of each study site, and written informed consent was obtained from all participants.

### Conventional Risk Factors

At baseline examination, traditional and additional ASCVD risk factor data were collected. Table I in the online-only Data Supplement shows the risk factors used in the O-FSRS, R-FSRS, and PCE for future stroke risk calculation. Current smoking was defined as having smoked a cigarette in the past 30 days. Medication use was based on medication inventory. DM was defined as self-reported history of DM, DM medication use, or fasting glucose ≥126 mg/dL. Participants who reported having DM should also be on antidiabetic medications and or have fasting blood glucose of ≥126 mg/dL to be counted as having DM in MESA. Resting blood pressure was measured 3× in the seated position, and the average of the second and third readings was recorded. Hypertension was defined as a systolic blood pressure of at least 140 mm Hg, diastolic blood pressure of at least 90 mm Hg, and or use of antihypertensive medication. Body mass index was calculated as weight (kg) divided by height ($m^2$). Total and HDL (high-density lipoprotein) cholesterol were measured from blood samples obtained after a 12-hour fast. LDL (low-density lipoprotein) cholesterol was estimated by the Friedewald equation.[14]

### Measurement of CIMT

Methods for measuring and interpreting CIMT were previously reported.[15] The mean of the maximum intima-media thickness of the common carotid artery was used. Reproducibility was assessed by blinded replicate readings of CIMT performed by 2 readers. One reader reread 66 studies for a between reader correlation coefficient of 0.84 (n=66), and a second reader reread 48 studies for a correlation coefficient of 0.86. The rescan and the reread coefficients of variation were 7.07% and 3.48%.

### Family History of Stroke

Family history of stroke was obtained and defined by asking participants whether any member in their immediate family (first-degree relatives: parents, siblings, and children) experienced fatal or nonfatal stroke. Type of stroke (ischemic or hemorrhagic) was not asked. In addition, the age at which the immediate family experienced a stroke was also not obtained, and thus, it is unclear whether experienced strokes were premature.

### High-Sensitivity CRP

HsCRP (high sensitivity C-reactive protein) was measured using the BNII nephelometer (N High-Sensitivity CRP; Dade Behring Inc, Deerfield, IL) at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, VT). Analytic intra-assay coefficient of variations ranged from 2.3% to 4.4%, and interassay coefficient of variation ranged from 2.1% to 5.7% with a detection level of 0.18 mg/L.

### CAC Score

Details of the MESA computed tomography (CT) scanning and interpretation methods have been previously reported.[16] Scanning centers assessed CAC by chest CT with either a cardiac-gated electron-beam CT scanner (Chicago, IL; Los Angeles, CA; and New York, NY, field centers) or a multidetector CT system (Baltimore, MD; Forsyth County, NC; and St Paul, MN, field centers). Certified technologists scanned all participants twice over phantoms of known physical calcium concentration. A radiologist or cardiologist read all CT scans at a central reading center (Los Angeles Biomedical Research Institute at Harbor–UCLA, Torrance, CA). We used the mean Agatston score[17] for the 2 scans in all analyses. Intraobserver and interobserver agreements were excellent (κ=0.93 and 0.90, respectively).

### Ankle-Brachial Index

Details of the MESA ABI measurement protocol have been previously published.[18] Systolic blood pressure measurements in the bilateral brachial, dorsalis pedis, and posterior tibial arteries were obtained in the supine position using a handheld Doppler instrument with a 5-mHz probe. To avoid potential bias from subclavian stenosis, the higher of the brachial artery pressures was used as the denominator. The ABI numerator used was the highest pressure (dorsalis pedis or posterior tibial) from that leg. Reproducibility of the ABI was evaluated using measurements of 43 participants by 2 technicians. The inter- and intrareader correlation coefficients were 0.845 and 0.937, respectively, with an intra- and inter-reader coefficient of variation of 5.14% and 3.27%, respectively. Participants with an ABI >1.4 were excluded.

### Risk Scores

The stroke risk for each MESA participant was calculated using the published equations of the O-FSRS,[3] R-FSRS,[11] and PCE.[6] For this analysis, we limited PCE predicted events to stroke.

### Event Ascertainment

Event ascertainment procedures and the adjudication process in MESA have been published.[19] Every 9 to 12 months from baseline examination, MESA participants (or proxies) were contacted to inquire about hospital admissions, ASCVD diagnosis, and death. Hospital and other documentation of possible stroke and deaths were obtained. Documentation was sent to at least 2 MESA morbidity and mortality committee members for adjudication using a standard protocol. Disagreements between adjudicators were settled by discussion until consensus was reached. Events adjudicated as stroke were classified as ischemic, hemorrhagic, or other, which includes those for whom the type of stroke is undetermined. Stroke adjudication in MESA required a focal deficit of 24 hours and was in most instances confirmed by neuroimaging. For the purposes of this study, we defined incident a stroke event as adjudicated fatal or nonfatal hemorrhagic or ischemic stroke as described by the MESA protocol (www.mesa.nhlbi.org).

### Statistical Analysis

Descriptive baseline statistics of demographic, clinical, and ASCVD risk factors were reported as mean (with SD) for

continuous variables and percentile for categorical variables. The stroke risk associated with 1 SD of the calculated O-FSRS, R-FSRS, and the PCE was assessed using Cox proportional hazard analysis. The Cox proportional hazard analysis assessing the association between R-FSRS and O-FSRS and incident stroke was further stratified by sex, race/ethnicity, and age (using 65 years as cutoff). We also assessed the associations between R-FSRS and O-FSRS for ischemic strokes, hemorrhagic strokes, and transient ischemic attacks. Calibration of each risk score was assessed by using the Hosmer–Lemeshow goodness-of-fit test and by comparing the mean predicted stroke risk of each risk score in the MESA cohort with the observed stroke event rate during the follow-up period. Predicted probabilities of the cohort were obtained from Cox proportional hazard models with the O-FSRS, R-FSRS, and PCE as the predictor variable and incident stroke events as the outcome of interest.

Discriminative ability of the O-FSRS, R-FSRS, and the PCE for incident stroke events was assessed using area under the curve analysis and C statistics. Improvement in discrimination of the O-FSRS and R-FSRS afforded by the addition of individual nontraditional ASCVD risk marker was assessed. The differences in C statistics of the O-FSRS or R-FSRS and R-FSRS plus each nontraditional risk marker were evaluated using the method by DeLong et al.[20]

We constructed a reclassification plot using predicted probabilities of the O-FSRS and R-FSRS to assess reclassification.[21,22] The predicted probabilities were obtained using the calculated risk scores (O-FSRS and R-FSRS) and observed stroke events in a Cox model. Category-less net reclassification index (NRI) was used to assess the improvement in discrimination afforded by the addition of nontraditional risk markers to the R-FSRS for incident stroke events. CAC, CIMT, CRP, and ABI were transformed [ln (Risk marker+1)] before introducing each individually into models. *P* value of <0.05 was considered significant for all calculations. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and Microsoft Excel.

## Results

Six thousand seven hundred twelve of 6814 (98.5%) of total MESA participants had complete data and were included in our analyses. After a mean follow-up of 10.7 years, 231 of 6712 (3.4%) participants had an adjudicated stroke (2.7% had an ischemic stroke, 0.7% hemorrhagic strokes). The mean age was 62±10 years with 53% female. Thirteen percent had DM, and 15% were on statin therapy, 20% on aspirin therapy, and 33% on antihypertensives. Further demographics and distribution of the nontraditional risk markers are in Table 1. The Hosmer–Lemeshow goodness-of-fit test for stroke for each risk score was as follows: O-FSRS ($\chi^2$=34.23; *P*=0.0002), R-FSRS ($\chi^2$=6.55; *P*=0.59), and PCE ($\chi^2$=28.7; *P*=0.003). As also shown in Figure 1, the R-FSRS is better calibrated than the O-FSRS when respective mean risk prediction is compared with the observed stroke event rate. The mean±SD risk of the R-FSRS was significantly lower than that of the O-FSRS (*P* value for *t* test=0.01) and the PCE (*P*=0.0001).

Consistent and significant associations existed between the O-FSRS and R-FSRS and incident stroke events across each defined stratum (sex, ethnicity, and age) and outcome (ischemic stroke, hemorrhagic stroke, and transient ischemic attack; Table II in the online-only Data Supplement).

The C statistics of the O-FSRS, R-FSRS, and PCE for stroke events were 0.653, 0.716, and 0.716, respectively (Figure 2). There was a significant difference in the C statistics between the O-FSRS and the R-FSRS/PCE (*P*=0.01 for each comparison). Figure 3 shows the improvement in discrimination

**Table 1. Clinical Characteristics of the Study Cohort (n=6712)**

| Baseline Characteristics | Mean (Median When Specified; SD or %) |
|---|---|
| Age, y | 62.2±10.2 |
| Female (%) | 52.8 |
| Race/Ethnicity (%) | |
| Whites | 32.3 |
| Chinese | 11.9 |
| Black | 27.6 |
| Hispanics | 22.2 |
| BMI, kg/m$^2$ | 28.3±5.5 |
| Cholesterol (mg/dL) | |
| Total | 194.2±35.7 |
| LDL | 117.2±31.4 |
| HDL | 51.0±14.8 |
| Triglycerides | 131.6±89.0 |
| Blood pressure, mm/Hg | |
| Systolic | 126.6±21.5 |
| Diastolic | 71.9±10.3 |
| Cigarette smoking status (%) | |
| Never | 50.3 |
| Former | 36.7 |
| Current | 13.0 |
| Diabetes mellitus (%) | 12.7 |
| Blood pressure medication use (%) | 33.2 |
| Statin use (%) | 14.8 |
| Aspirin use (%) | 20.0 |
| Original FSRS | 5.9±1.2 |
| Revised FSRS | 4.7±5.3 |
| Pooled Cohort Equation | 13.2±13.1 |
| CAC score (Agatston Units)* | |
| Median (IQR) | 0.0 (0.0–86.2) |
| CIMT, mm | |
| Median (IQR) | 0.8 (0.7–1.0) |
| High-sensitivity CRP, mg/L | |
| Median (IQR) | 3.8 (0.8–4.3) |
| ABI | |
| Median (IQR) | 1.1 (1.1–1.2) |
| Family history of stroke (First-degree relative) (%) | 32.6 |
| Total number of strokes | 231 (3.5%) |

IQR (Q1–Q3, 25th–75th percentile). ABI indicates ankle-brachial index; BMI, body mass index; CAC, coronary artery calcium; CIMT, carotid intima-media thickness; CRP, C-reactive protein; FSRS, Framingham Stroke Risk Score; HDL, high-density lipoprotein; IQR, interquartile range; and LDL, low-density lipoprotein.

*CAC range is significantly skewed given that median CAC score is 0.

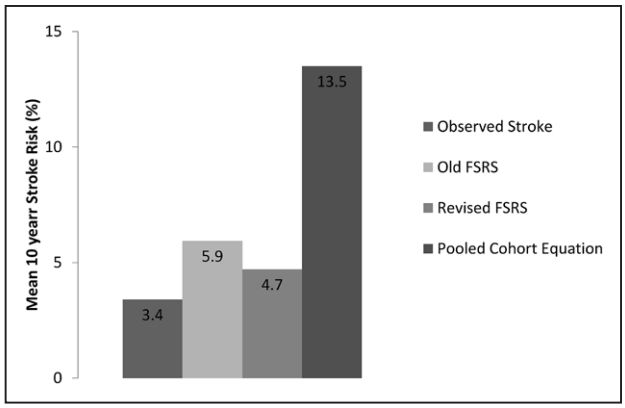


**Figure 1.** Comparing the mean calculated risk using the original Framingham Stroke Risk Scores (FSRS), revised FSRS, and Pooled Cohort Equation with observed stroke rate in the MESA (Multi-Ethnic Study of Atherosclerosis).

afforded by the addition of CAC, CIMT, CRP, ABI, and family history of stroke individually to the O-FSRS and the R-FSRS. Among the risk markers considered, only CAC modestly improved the C statistics of the O-FSRS for future stroke events (*P* valve for comparison of C statistics=0.04; Figure 3A). None of the risk markers improved the C statistics of the R-FSRS for future strokes (Figure 3B)

Figure 4 shows the reclassification plot comparing the improvement in reclassification of the R-FSRS (*y* axis) with the O-FSRS (*x* axis). A model that significantly improves reclassification will show more nonevents (blue dots) below the 45° line and more events (red dots) above the 45° line. The event (red dots) and nonevent (blue dots) category-less NRI when R-FSRS was compared with O-FSRS were −2.7% and 4.5%, respectively. Thus, despite overestimation of stroke risk for nonevent persons (Figure 4), overall the R-FSRS downgrades stroke risk in the MESA cohort. Table 2 shows the category-less NRI and integrated discrimination increment (IDI) when CAC, CIMT, CRP, ABI, and family history of stroke were added to the R-FSRS.

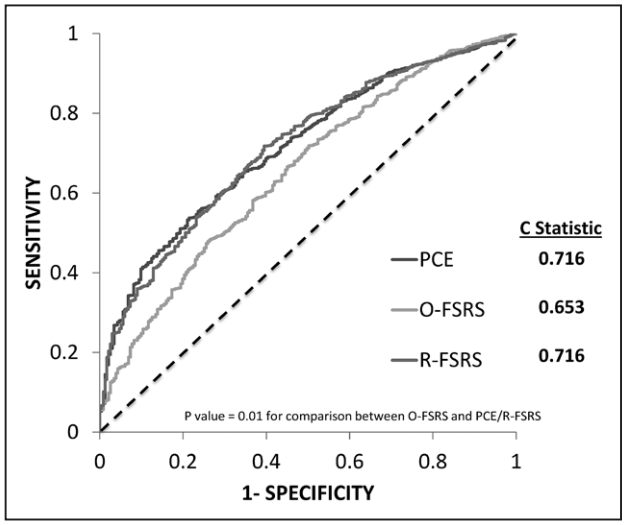


**Figure 2.** Receiver operator curves (ROC) assessing the discrimination for incident stroke of the original Framingham Stroke Risk Scores (O-FSRS), revised FSRS (R-FSRS), and Pooled Cohort Equation (PCE).

The addition of each nontraditional risk marker showed an improvement in the overall category-less NRI and absolute IDI (Table 2). CAC showed the most improvement (NRI=0.36; IDI=0.0027), whereas ABI showed the least (NRI=0.11, IDI=0.0013) improvement.

In our secondary analysis, both O-FSRS and R-FSRS were predictive of ischemic stroke and hemorrhagic stroke (Table II in the online-only Data Supplement). The C statistics for PCE, R-FSRS, and O-FSRS for ischemic strokes were 0.725, 0.727, and 0.653, respectively (*P* value for comparison=0.02). The C statistics when CAC, CIMT, CRP, ABI, and family history of stroke were individually added to the O-FSRS for ischemic stroke prediction were 0.702, 0.674, 0.663, 0.660, and 0.656, respectively, with only the addition of CAC being statistically significant (*P*=0.01). The C statistics when CAC, CIMT, CRP, ABI, and family history of stroke were individually added to R-FSRS for ischemic stroke prediction were 0.722, 0.717, 0.721, 0.730, and 0.720 (*P* value for not significant for each comparison with the C statistics for R-FSRS alone). The category-less NRI and IDI using ischemic strokes as the outcome were similar to that of all strokes in Table 2 (data not shown). Thus, the primary outcome (stroke) results seem to have been driven by ischemic stroke. The number of adjudicated hemorrhagic strokes (49 events) was too few, and, therefore, we were underpowered for such as analysis.

## Discussion

This study compared the calibration and discriminative ability of the R-FSRS, O-FSRS, and PCE for incident stroke and the improvement in discrimination afforded by the addition of nontraditional risk markers to the R-FSRS in a multiethnic US cohort free of baseline clinical ASCVD. We showed that the R-FSRS had the best calibration for stroke events compared with the O-FSRS or PCE. Despite the R-FSRS showing a modest but significantly higher discriminative ability (C statistic) compared with the O-FSRS, it downgrades stroke risk in this low-risk cohort (Figure 4). In our area under the curve analyses, none of the nontraditional risk markers improved the discrimination of the R-FSRS for future stroke prediction. However, in the category-less NRI and IDI analyses, all the nontraditional risk markers (CAC, CIMT, CRP, ABI, and family history of stroke) modestly improved discrimination of the R-FSRS, with CAC being the most useful (category-less NRI=0.36) and ABI the least (category-less NRI=0.05). To our knowledge, this is the first study to assess the improvement in discrimination afforded by the addition of nontraditional risk markers to the R-FSRS for future strokes.

Of the 3 stroke risk prediction scores available to clinicians for assessing stroke risk in the general US population, the O-FSRS and R-FSRS were developed in a white population (Framingham Heart Study),[3,11] validated in other cohorts,[10–12] and are recommended for stroke prediction.[3,10–12] The PCE was not primarily derived for stroke risk prediction, but rather for a broader primary ASCVD outcome, which includes fatal and nonfatal strokes.[6] A dilemma exists for clinicians, even if one assumes that the R-FSRS replaces the O-FSRS, as to which risk score to use in clinical practice for assessing primary stroke risk. In the present analysis, the PCE and R-FSRS have

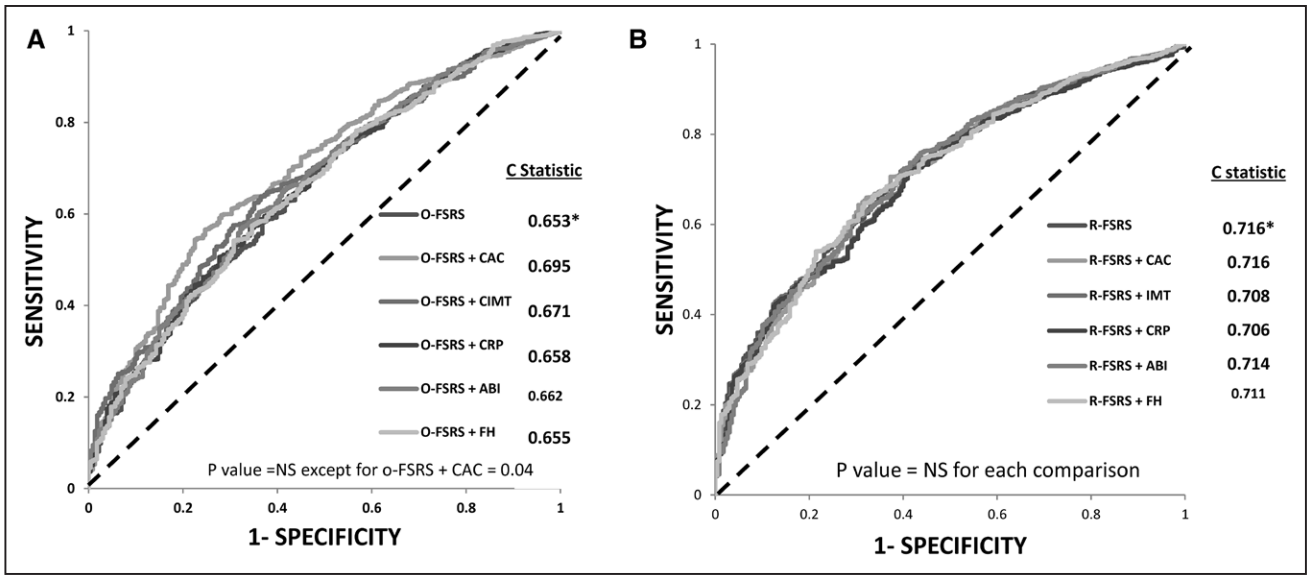


**Figure 3.** Receiver operator curves (ROC) assessing the improvement in discrimination afforded by the addition of coronary artery calcium (CAC), carotid intima-media thickness (CIMT), high-sensitivity CRP (C-reactive protein), ankle-brachial index (ABI), and family history of stroke (FHS) to the (**A**) original Framingham Stroke Risk Score (O-FSRS) and (**B**) revised FSRS (R-FSRS) for incident stroke events in MESA (Multi-Ethnic Study of Atherosclerosis). *Indicates reference.

similar discriminative ability (C statistics), and the R-FSRS has better calibration. Although the PCE overestimates stroke risk, the R-FSRS seems to downgrade stroke risk compared with the O-FSRS. Thus, based on our analysis, the R-FSRS seems to be superior to the PCE/O-FSRS for primary stroke prediction. The present study supports the use of the R-FSRS as the preferred primary stroke risk prediction tool for general clinical practice in the US population.

It should be noted that the category-less NRI and IDI do not take into consideration calculated stroke risk cutoffs/ranges that may warrant therapy and which modifiable risk factors to target to minimize this risk. Thus, although our data showed a modest improvement in discrimination when nontraditional risk markers are added to the R-FSRS for primary stroke prediction, the absence of R-FSRS risk cutoffs for the initiation of therapy limits our ability to infer whether the upward/downward reclassifications observed in our models when the nontraditional risk markers were added to the R-FSRS would have resulted in any clinically meaningful change in risk categories and hence a change in clinical decision making/therapy. The lack of established clinically meaningful cutoff of R-FSRS risk also makes it difficult, if not impossible, to determine the CAC levels or ranges associated with either upward/downward reclassification of individuals in our study similar to what is being established for ASCVD risk assessment.[23] Our study calls for more research to establish clinically meaning R-FSRS risk cut points/ranges associated with low, intermediate, and high 10-year risk of primary strokes to help guide therapeutic considerations in the US population similar to that established for ASCVD prevention.[6]

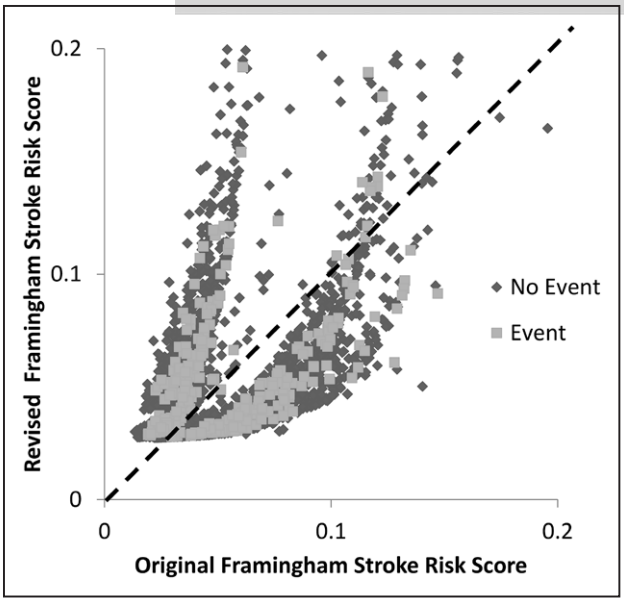


**Figure 4.** Reclassification plot of the predicted probabilities of the original and revised Framingham Stroke Risk Score for incident stroke events in MESA (Multi-Ethnic Study of Atherosclerosis). (Both axes truncated at 0.2 to eliminate outliers.)

Despite the large sample size, multiethnic nature of our cohort, long follow-up, and adjudicated stroke events used for this analysis, our study has significant limitations. First, our study is an observational study, and therefore, our results may be because of residual confounding. We did not account for treatment of risk factors in our participants with medications (such as antihypertensive medications, statins, etc) known to reduce stroke risk at baseline and during the follow-up period. Medication use may have resulted in a reduction in the observed stroke events during the follow-up period and may have affected our results. We also assessed the use of the 3 stroke risk prediction tools (PCE, O-FSRS, and R-FSRS) available in the United States in this cohort. However, unlike the O-FSRS and the R-FSRS, the PCE was developed to predict a composite outcome of fatal and nonfatal coronary heart diseases events and strokes. This may have resulted in the PCE having the worse calibration in our study. However, the

**Table 2. Category-Less NRI and IDI With the Addition of Subclinical Atherosclerotic Cardiovascular Disease Markers to the Revised FSRS for Incident Stroke**

| | No. of Participants | Revised FSRS >Revised FSRS+Marker (Downward) | Revised FSRS <Revised FSRS+Marker (Upward) | NRI | Total NRI | Absolute IDI |
|---|---|---|---|---|---|---|
| Revised FSRS+CAC | | | | | | |
| Event | 231 | 98 | 133 | 0.15 | 0.36 | 0.0028 |
| Nonevent | 6481 | 3928 | 2553 | 0.21 | | |
| Revised FSRS+CIMT | | | | | | |
| Event | 231 | 127 | 104 | –0.10 | 0.22 | 0.0013 |
| Nonevent | 6481 | 3996 | 2485 | 0.23 | | |
| Revised FSRS+CRP | | | | | | |
| Event | 231 | 110 | 121 | 0.05 | 0.25 | 0.0020 |
| Nonevent | 6481 | 3881 | 2600 | 0.20 | | |
| Revised FSRS+ABI | | | | | | |
| Event | 231 | 131 | 100 | –0.13 | 0.05 | 0.0010 |
| Nonevent | 6481 | 3803 | 2678 | 0.17 | | |
| Revised FSRS+FH | | | | | | |
| Event | 231 | 141 | 90 | –0.22 | 0.13 | 0.0014 |
| Nonevent | 6481 | 4383 | 2098 | 0.35 | | |

ABI indicates ankle-brachial index; CAC, coronary artery calcium; CIMT, carotid intima-media thickness; CRP, C-reactive protein; FH, family history of stroke; FSRS, Framingham Stroke Risk Score; IDI, integrated discrimination index; and NRI, net reclassification improvement.



discriminative ability of the PCE was similar to that of the R-FSRS for future stroke.

Third, the MESA cohort by design had no history of cardiovascular disease at baseline, and because the O-FSRS and R-FSRS were derived and validated in cohorts with and without history of cardiovascular disease, this may have affected the performance of these 2 risk scores. The PCE on the other hand was developed and validated in cohorts without history of cardiovascular disease. Thus, the PCE may have an unfair advantage over the O-FSRS and R-FSRS when compared in a cohort such as MESA. Nonetheless, our analysis comparing the discriminative ability of the O-FSRS and R-FSRS for future stroke should not be affected by this because both have history of cardiovascular disease as a component. In addition, because all these risk scores have stroke as a component of their composite outcome (PCE) or as their primary outcome (O-FSRS and R-FSRS), and were developed to predict future stroke in populations without history of cardiovascular disease (PCE) or populations with and without history of cardiovascular disease (O-FSRS and R-FSRS), there is validity in comparing future stroke prediction of these 3 risk scores in a primary prevention population such as MESA. Finally, our results may not be applicable to other race/ethnic groups and other populations with characteristics dissimilar to that of the MESA cohort.

## Conclusions

In this multiethnic cohort free of clinical ASCVD at baseline, the R-FSRS has better discriminative ability and calibration for incident stroke compared with the O-FSRS. Nontraditional risk markers modestly improve the discriminative ability of the R-FSRS, with CAC providing the greatest improvement. Further studies are needed to define R-FSRS risk levels/categories that warrant therapeutic treatment for primary stroke prevention similar to that available for the primary ASCVD prevention.



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## Disclosures

None.

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# Revised Framingham Stroke Risk Score, Nontraditional Risk Markers, and Incident Stroke in a Multiethnic Cohort

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# SUPPLEMENTAL MATERIAL

**Supplemental Table I. Risk factors included in each stroke prediction risk score.**

| Original Framingham Stroke Risk Score (O-FSRS) | Revised Framingham Stroke Risk Score (R-FSRS) | Pooled Cohort Equation (PCE) |
|---|---|---|
| Age | Age | Age |
| Systolic blood pressure | Systolic blood pressure | Systolic blood pressure |
| Use of antihypertensive medications | Use of antihypertensive medications | Use of antihypertensive medications |
| Diabetes mellitus | Diabetes mellitus | Diabetes mellitus |
| Current cigarette smoking | Current cigarette smoking | Current cigarette smoking |
| Prevalent cardiovascular disease | Prevalent cardiovascular disease | Sex |
| Atrial fibrillation | Atrial fibrillation | Race |
| Left ventricular hypertrophy(ECG) | | Total cholesterol |
| | | High density lipoprotein cholesterol |

**Supplemental Table II: Predictive valve of one standard deviation increase in Framingham Stroke Risk Scores (FSRS) for incident stroke in MESA**

| Outcome | # of CVA Events | Original FSRS (per 1 SD) HR (95% CI) | Revised FSRS (per 1SD) HR (95% CI) |
|---|---|---|---|
| **Stroke** | 231 | 1.78 (1.57 – 2.01) | 1.67 (1.54 – 1.80) |
| **Females** | 112 | 2.97(2.24-3.94) | 1.74(1.54-1.95) |
| **Males** | 119 | 2.81(2.27-3.46) | 1.62(1.46-1.80) |
| **Whites** | 82 | 2.17(1.75-2.68) | 1.80(1.59-2.04) |
| **Chinese** | 17 | 1.46(0.94-2.26) | 1.45(1.02-2.06) |
| **African Americans** | 66 | 1.37(1.08-1.73) | 1.45(1.23-1.71) |
| **Hispanics** | 66 | 1.92(1.54-2.41) | 1.74(1.53-1.98) |
| **>65 years** | 147 | 1.41(1.18-1.68) | 1.41(1.26-1.58) |
| **≤ 65 years** | 84 | 1.76(1.36-2.27) | 2.30(1.90-2.77) |
| **Ischemic Stroke** | 182 | 1.15 (1.00 – 1.33) | 1.23 (1.08 – 1.41) |
| **Hemorrhagic Stroke** | 49 | 1.43(0.95-2.14) | 1.41(1.13-1.25) |
| **TIA** | 84 | 1.63 (1.33 – 1.99) | 1.56 (1.36 – 1.80) |

Footnote: TIA: Transient ischemic attacks