Framingham Stroke Risk Function in a Large Population-Based Cohort of Elderly People

The 3C Study

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Background and Purpose—External validation of the Framingham stroke risk function has been rarely performed. We assessed its predictive ability in a population-based cohort of French elderly.

Methods—The sample comprised 6913 subjects from the 3C Study, aged 65 to 84 at baseline, who were followed up to 6 years. Predictive accuracy of the original Framingham stroke risk function was assessed in a 3-step procedure: comparison between the Framingham and 3C cohorts of the prevalence of selected risk factors and the associated relative risks (RR) for stroke, comparison of the predicted to the observed number of stroke events (calibration), and ability to separate high-risk from low-risk participants (discrimination). We also compared predictive performances of the original Framingham, the recalibrated Framingham, and the local stroke risk functions.

Results—During follow-up, 110 incident strokes occurred. For most risk factors, RRs were comparable between the 2 cohorts, except for age in women. The original Framingham stroke risk function applied to the 3C cohort overestimated the 6-year absolute risk for stroke by a factor of 3.7 for men and 4.4 for women. However, the recalibrated Framingham and 3C functions did not show any over- or underestimation of stroke risk. The 3 stroke risk functions (original, recalibrated, and 3C) provided acceptable discrimination with areas under the ROC curve ranging from 0.67 to 0.73.

Conclusions—The original Framingham stroke risk function strongly overestimated the stroke risk for 3C participants. Derived Framingham stroke score sheets should not be directly used by physicians in the French elderly population. (Stroke. 2009; 40:1564-1570.)

Key Words: stroke ■ risk ■ aging ■ cohort studies

Cerebrovascular disease is a major cause of death.1 Almost 90% of deaths attributed to stroke occur among people aged 65 years or older.2 Stroke is an important public health problem, especially in the elderly, as population ageing has given rise to significant increases in stroke incidence.

Epidemiological studies have identified numerous stroke risk factors such as age, blood pressure, atrial fibrillation, heart failure, and diabetes mellitus.3,4 Prediction models have subsequently been developed to assess the individual absolute risk of developing stroke.5-9 Several widely used risk functions for stroke have been drawn from the Framingham Heart Study (FHS), one of the well-known studies in this field.5,6,9 Primary prevention based on such tool should help to decrease stroke incidence, stroke-related mortality, and long-term disability among the elderly.

However, the Framingham cohort has certain particularities which may preclude generalization of these risk functions to other samples including the large proportion of white, middle-aged, suburban Americans included, and the low prevalence of subjects treated for classical cardiovascular risk factors. To apply FHS risk functions to other populations, external validation studies are therefore required.

Implementation of the Framingham stroke risk functions has been rarely investigated in other geographic settings and in elderly populations taking multiple medications.7,10,11 The aim of the present study was to assess the external validity of the Framingham stroke risk functions in a large cohort of French people aged 65 years and over, the Three-City (3C) Study.

Materials and Methods

Study Population

The 3C Study is an ongoing French prospective multicenter population-based cohort study whose main objective is to estimate...
Two separate measures of systolic and diastolic blood pressure were performed using a digital electronic tensiometer (OMRON M4). The mean was used for these analyses. Diabetes mellitus was defined as being present if the participant was under hypoglycaemic treatment (insulin or oral blood glucose lowering drugs) or if glycaemia was greater than 1.26 g/dL (7 mmol/L). A diagnosis of atrial fibrillation history was made either by ECG or self-report. Although left ventricular hypertrophy based on ECG was used in the Framingham risk function, it was not assessed in the 3C Study, therefore for this factor a missing value was attributed to all participants.

Follow-Up and Case Ascertainment

At each follow-up examination (2, 4, and 6 years after enrolment), information was collected concerning suspicion of stroke occurrence. In participants who reported incident stroke (during interview or by self-administered questionnaire), further medical data were collected from general practitioners, specialists, and hospital records where possible.

An end point adjudication committee reviewed source documentation for all individuals with a suspected stroke or those who died during follow-up. Outcomes were coded according to the tenth revision of the International Classification of Diseases. A stroke was classified as nonfatal if the patient was alive 28 days after stroke onset.

**Framingham Stroke Risk Function**

Sex-specific Framingham stroke risk functions used in the present study were derived from a Framingham Study sample, which included 2372 men and 3362 women, aged 55 to 84 years old, who were free of stroke history in 1966 (examination 9) or in 1976 (examination 14). Subjects were followed over 10 years. The outcome of interest was occurrence of a first ischemic/hemorrhagic stroke. Stroke risk factors included were: age, systolic blood pressure, antihypertensive therapy, cigarette smoking, diabetes mellitus, cardiovascular disease (history of myocardial infarction, angina pectoris, coronary insufficiency, intermittent claudication, or congestive heart failure), atrial fibrillation, and left ventricular hypertrophy by ECG (LVH-ECG).

There are 2 published versions of the stroke risk function: the second one, used in the present study, being an update of the original one by adding the interaction term between antihypertensive therapy and systolic blood pressure.

**Statistical Analysis**

**Cox Proportional Hazards Model**

Sex-specific Cox proportional hazards models were constructed incorporating the stroke risk factors identified from the Framingham Study. Underlying validity assumptions (proportionality and linearity) were tested and fulfilled by the 3C data. For the prediction of the 6-year absolute risk of stroke, we used the following model:

\[
P = 1 - S_0(t)e^{[Cox \times [X \times M]]}
\]

with \(f(x,M) = \beta_1(x_1,M_1) + \cdots + \beta_p(x_p,M_p)\). Here, \(\beta_1 \ldots \beta_p\) are the Cox regression coefficients associated with the \(p\) risk factors included in the model, \(x_1 \ldots x_p\) are the risk factor levels for an individual \(i\), \(M_1 \ldots M_p\) are the mean values of each of the \(p\) risk factors in the cohort, and \(S_0(t)\) is the average incidence rate at time \(t\), ie, the survival rate at the mean values of the risk factors at time \(t\) (here, \(t = 6\) years).

Cox proportional hazards model were computed from a sample of 6913 individuals (Figure 1). No stroke occurred during follow-up in 3C women participants who smoked at baseline, and therefore no Cox coefficient could be estimated. To keep these subjects in the analyses, we assigned to all subjects belonging to this group the same Cox coefficient as the one estimated from the Framingham cohort data for women who smoked.
Performances of the Framingham Prediction Function

The performances of the Framingham prediction function applied to 3C participants was assessed using 3 classical steps: (1) Relative risks comparison; (2) calibration; (3) discrimination.\textsuperscript{17}

Relative Risks Comparison

We compared multivariate-adjusted relative risk (RR) for each risk factor between the Framingham and 3C cohorts. In multivariate analyses of the 3C data, RR were additionally adjusted for the center (Dijon, Bordeaux, or Montpellier). For the comparison, we extracted regression coefficients generated from Cox models computed in both samples. For a given risk factor, a 2-tailed $z$ statistic was generated to compare Framingham and 3C regression coefficients, where $z=(\beta_{[F]} - \beta_{[3C]})/\text{SE}$. $\beta_{[F]}$ and $\beta_{[3C]}$, being respectively, the regression coefficients of the Framingham and the 3C models. The SE is the standard error of the difference in coefficients and $\text{SE}=(\text{SE}_{[F]}^2 + \text{SE}_{[3C]}^2)^{1/2}$, with $\text{SE}_{[F]}$ and $\text{SE}_{[3C]}$ being respectively the standard errors of $\beta_{[F]}$ and $\beta_{[3C]}$. The degree of significance was set to $P<0.10$.\textsuperscript{17,19}

Calibration

This step consisted in a comparison of the 6-year predicted number of events to the 6-year observed number. Distribution of 6-year risk predicted by the model was categorized into deciles. The goodness-of-fit Hosmer–Lemeshow (H-L) $\chi^2$ test assessed the difference between predicted and observed number of events categorized in deciles. It is compared to a $\chi^2$ distribution with $n=90$ degrees of freedom (df), with $g=10$ (number of deciles) and $n$ whose value depends on the study population.\textsuperscript{20} A $\chi^2$ statistic with a degree of significance of less than 0.01 indicated a lack of calibration. In the framework of a Cox survival model with censored observations, we estimated data fit. Thus, in the recalibrated Framingham risk function, $\hat{\gamma}$ is the observed incidence of stroke events and the Cox estimator yields the observed incidence of stroke events.\textsuperscript{22,23} For both sexes, there were more subjects taking antihypertensive medication in 3C. The smoking rate and the prevalence of cardiovascular diseases were lower among 3C participants, whereas comparable diabetes mellitus and atrial fibrillation prevalence rates were observed in the 2 cohorts.

Discrimination

To assess the ability of the Framingham stroke risk function to distinguish high-risk participants who actually had a stroke from low-risk participants who had no stroke, we calculated the area under the receiver operating characteristic (ROC) curve or $c$ statistic which assesses the discrimination of the function. We used the traditional following thresholds for the area under the ROC curve: 0.5, no discrimination; 0.5 to 0.7, poor discrimination; $\geq0.7$ acceptable discrimination; $\geq0.8$ excellent discrimination; $\geq0.9$ outstanding discrimination.\textsuperscript{24}

Original Framingham, Recalibrated Framingham, and 3C Functions

To compare the predictive abilities of the original Framingham risk function, we repeated these 3 steps for 2 other Framingham risk functions: the recalibrated Framingham risk function and the 3C “local” risk function.\textsuperscript{17} The 3 risk functions differ in terms of average incidence rate $S_0(t)$, the $\beta$ Cox regression coefficients and mean values of the $p$ risk factors $M_p$. In the original Framingham risk function, these 3 parameters are all estimated from the Framingham cohort. When an overestimation or underestimation of risk by the original Framingham function is suspected, recalibration may optimize data fit. Thus, in the recalibrated Framingham risk function, mean values of risk factors and average incidence rate are derived from the 3C data. Finally, in the 3C “local” risk function, which represents the best possible risk function for the 3C data, the $\beta$ coefficients, mean values of risk factors and average incidence rate are all estimated from the 3C data (Table 1).

All statistical analyses were performed with SAS software, version 9.1 (SAS Institute).

Results

From the 3C subsample selected for this analysis ($n=6913$), the follow-up rate at the 6-year assessment among partici-
among Framingham participants (Men: RR_{3C} = 2.29 versus RR_{F} = 1.63, P = 0.27; Women: RR_{3C} = 3.51 versus RR_{F} = 2.01, P = 0.09).

In the calibration analysis, the H-L $\chi^2$ value was 95.8 for men ($P < 0.001$; 10 df) with a global ratio of predicted over observed strokes of 3.70 (95% CI, 2.84 to 4.80). Average estimated 6-year stroke risk by deciles in men ranged from 2.8 to 18.9%. For women, the H-L $\chi^2$ was 158.9 ($P < 0.001$; 10 df) with a global ratio of predicted over observed strokes of 4.35 (95% CI, 3.34 to 5.67). Average estimated 6-year stroke risk by deciles in women ranged from 1.7% to 17.3%.

The recalibrated Framingham stroke risk function overestimated expected stroke rate in 3C men and women (Figure 2). In the discrimination analysis, the areas under the ROC curve were acceptable, 0.67 (95% CI, 0.59 to 0.74) for men and 0.70 (95% CI, 0.64 to 0.76) for women (Table 4).

In the calibration analysis using the recalibrated Framingham risk function (ie, $\beta$ coefficients extracted from the Framingham Cox model, but mean values of risk factors and average incidence rate estimated from the 3C cohort), the H-L $\chi^2$ was 7.6 for men ($P = 0.07$; 10 df) with a global ratio of predicted over observed strokes of 1.17 (95% CI, 0.90 to 1.52). Average estimated 6-year stroke risk by deciles in men ranged from 0.9 to 6.2%. The H-L $\chi^2$ was 16.9 for women ($P = 0.08$; 10 df) with a global ratio of predicted over observed strokes of 0.85 (95% CI, 0.65 to 1.11). Average estimated 6-year stroke risk by deciles in women ranged from 0.3 to 3.5%. Therefore, the recalibrated Framingham stroke risk function did not overestimate expected stroke rate among 3C men and women compared to the observed ones (Figure 2). As expected, the areas under the ROC curve were not affected by recalculation (Table 4).

In the calibration analysis using the 3C risk function, the H-L $\chi^2$ was 20.1 for men ($P = 0.02$; 9 df) with a global ratio of predicted over observed strokes of 1.13 (95% CI, 0.87 to 1.47). Average estimated 6-year stroke risk by deciles in men ranged from 0.8 to 7.4%. The H-L $\chi^2$ was 8.8 among women ($P = 0.46$; 9 df) with a global ratio of predicted over observed strokes of 0.97 (95% CI, 0.75 to 1.26). Average estimated 6-year stroke risk by deciles in women ranged from 0.3 to 4.5%. Therefore, the 3C stroke risk function did not overestimate stroke rates observed among 3C men and women (Figure 2). In the discrimination analysis, the areas under the ROC curve were acceptable, 0.68 (95% CI, 0.61 to 0.75) for men and 0.73 (95% CI, 0.67 to 0.79) for women (Table 4).

**Discussion**

We assessed the external validity of the Framingham stroke risk function in a French cohort of noninstitutionalized people aged 65 to 84 years, the 3C Study. Overall, the original Framingham stroke risk function overestimated the 6-year absolute risk of stroke in the 3C sample by a factor of 3.7 in men and 4.4 in women.

The overestimation of stroke risk using the original Framingham risk function may be explained in a number of ways. First, the Framingham stroke risk function estimated in fact the risk of incident stroke (atherothrombotic brain infarction, cerebral embolus, intracranial hemorrhage) and transient ischemic attacks pooled together and accounting for 78% and 22% of the events, respectively. In the 3C Study, only incident stroke was an event of interest, as has been the case in most other recent studies. Second, differences in stroke incidence and risk factor levels between the 2 countries, especially over the past 3 decades, could also explain this overestimation. There are large differences in stroke incidence between the high-risk American Framingham cohort and the low-risk French 3C cohort. Third, the original Framingham stroke risk function was estimated based on data gathered in the 1980s whereas the 3C data were collected in 2000. But, over the past 30 years, preventive and therapeutic...
strategies have evolved considerably, especially in the cardiovascular area, causing significant decreases in stroke incidence.\textsuperscript{25} For example, the Framingham stroke risk function takes into account only treatment for high blood pressure and not treatment for diabetes, hypercholesterolemia, or atrial fibrillation.\textsuperscript{6} Fourth, although 3C participants were asked, at each wave, whether they had a stroke since last examination, levels of screening and surveillance were not comparable between 3C and the Framingham studies, and we cannot exclude a few incident cases were missed among 3C participants. Finally, 3C participants were older than Framingham participants (mean age in the 3C study was 73 years old compared to 66 in the Framingham study). This important age difference could influence the results and explain, at least partly, why several of the stroke risk factors of the Framingham risk function were not associated with stroke risk in the 3C cohort. Despite this important age difference, effect of age was statistically similar between the 2 cohorts in men (RR comparison in men, $P=0.27$) and only slightly different in women (RR comparison in women, $P=0.09$). Other relative risks associated with factors included in the Framingham risk function were not statistically significantly different between

Table 4. Comparison of Discrimination Evaluations of the Original Framingham, Recalibrated Framingham, and 3C Stroke Risk Functions in the 3C Cohort

<table>
<thead>
<tr>
<th>Stroke Risk Functions</th>
<th>3C Cohort</th>
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<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AUROC</td>
<td>95% CI</td>
<td>AUROC</td>
</tr>
<tr>
<td>Original Framingham</td>
<td>0.67</td>
<td>(0.59–0.74)</td>
<td>0.70</td>
</tr>
<tr>
<td>Recalibrated Framingham</td>
<td>0.67</td>
<td>(0.59–0.74)</td>
<td>0.70</td>
</tr>
<tr>
<td>3C</td>
<td>0.68</td>
<td>(0.61–0.75)</td>
<td>0.73</td>
</tr>
</tbody>
</table>

\*AUROC curve: Area Under the ROC Curve, indicate discriminatory capacities by applying stroke risk functions to 3C data.
the 3C and the Framingham cohort. Moreover, magnitude and direction of the association were globally similar between the 2 cohorts. We may therefore assume that age differences between the 2 studies are likely to have only a limited impact on the overestimation observed.

Transposition of the Framingham risk function to other elderly populations has given conflicting results. In a European study of hypertensive patients, no global overestimation of predicted stroke risk was observed. However, a subanalysis among French patients in this European sample showed that the use of the Framingham risk function led to a predicted/observed strokes ratio of 2.0, which is close to our findings. In a cohort of Dutch elderly, the original Framingham stroke risk function had good predictive performance. However, calibration was adequate only in persons with a low to moderate 5-year predicted risk (<5%), whereas overestimation was reported in higher deciles of risk. Compared to the 3C sample, Dutch participants were younger, had lower mean systolic blood pressure, used less antihypertensive medication, were more often smokers, and had more cardiovascular diseases. Moreover, it should be noted that the authors reported that the predictive performance of the Framingham function was reduced when applied to older persons. Differences between population characteristics could partly explain the Framingham predictive value in the 3C sample. In a cohort of American elderly, the original Framingham stroke risk function gave good prediction of stroke. There was a 15-fold incidence gradient between the highest and the lowest quintile of predicted risk showing powerful discrimination. Framingham model gave similar predictive to the 3C sample with areas under the ROC curve of 0.69 for men and 0.73 for women.

Our study has several strengths, including the large cohort size, the high follow-up rate, and the standardized and centralized procedures for both data recording and incident events validation. It also has some potential limitations. In the 3C Study, participants were volunteers and thus likely to have a better health and medical follow-up than the French general population. In the Framingham Study, participants were also volunteers, but they were enrolled at a younger age and the healthy volunteer bias related to the outcome of interest is likely to be smaller than in the 3C study. However, it is difficult to estimate the consequences of selection participation on the observed results. It should also be noted that all 3C participants were of white ethnicity, and our findings are not generalizable to other ethnicities.

Compared to the original Framingham stroke risk function, the recalibrated Framingham and 3C functions showed good agreement between predicted and observed stroke rates, without over- or underestimation of stroke risk. The abilities of the 3 original Framingham, recalibrated Framingham, and 3C stroke risk functions to separate 3C participants who had stroke from those who had not were fairly acceptable with areas under the ROC curve ranging from 0.67 to 0.73, which are similar to those reported in other studies.

Caution should be exercised by clinicians in applying the original Framingham risk function within the French context, as it is likely to strongly overestimate the 6-year risk of stroke. From the patient perspective, it could result in inappropriate treatment with unjustified side effects. In terms of public health, it could also have negative consequences such as increased costs and overestimation of the burden of stroke in France. The recalibrated Framingham risk function gave reliable and accurate correction of the risk of overestimation and may thus be a useful primary approach in French elderly populations. Its predictive performance can be easily compared with similar studies in other settings. The 3C “local” risk function using only 3C data showed satisfactory predictive performance, despite the restriction of having to adhere to the Framingham cardiovascular risk factors. However, its performances did not improve substantially those of the recalibrated Framingham risk function.

Further analyses of the 3C cohort may enable us to develop our own risk function to study the predictive power of other potential clinical, biological, and radiological risk factors such as walking speed, serum creatinine, hypercholesterolemia, carotid intima-media thickness and plaques, or white matter hyperintensity volume on brain MRI. Adjustments on therapies such as statins, blood glucose lowering drugs, or antiplatelets/anticoagulants agents could also be explored. Such predictions would be 3C-specific and thus closer to the current health status of the French elderly population. However, sensitivity analyses showed us that the integration of some of these “nonclassical” stroke risk factors in the model did not substantially modify the prediction of stroke in the 3C sample (data not shown). Indeed, overestimation of cardiovascular risk between the United States and France is traditionally related to the average incidence rate \( S_i(t) \) heterogeneity between the 2 countries, which is probably attributable to currently unknown differences of lifestyle, alimentation, or socio-cultural risk backgrounds.

To conclude, we found that the Framingham stroke risk function strongly overestimated the 6-year absolute risk of stroke in a population-based cohort of French elderly, the 3C Study. Thus, score sheets developed from this model should not be directly used by physicians in stroke prevention in the French elderly population. Recalibration process corrected this overestimation. The recalibrated Framingham stroke risk function seems to be an interesting alternative between the misuse of a well-known risk function and the development of a too-specific local population risk function. Finally, in the area of the cerebrovascular primary prevention for French elderly people, further development is needed to elaborate an adequate risk function which could be based on the recalibrated Framingham stroke risk function.

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Disclosures

None.

References

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