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External validation of the 2008 Framingham cardiovascular risk equation for CHD and stroke events in a European population of middle-aged men. The PRIME study

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ABSTRACT

Objective. To test the applicability of the sex-specific 2008 Framingham general cardiovascular risk equation for coronary heart disease (CHD) and stroke in European middle-aged men from Ireland and France.

Methods. In the PRIME study, 9638 healthy middle-aged men recruited in France and Ireland were surveyed for 10 years for the occurrence of first CHD and stroke events. The original Framingham equation, the partially calibrated Framingham equation (using the PRIME baseline survival at 10 years), and the completely calibrated Framingham equation (additionally using risk factor means calculated in PRIME) were assessed. Model fit (expected versus observed events) and discrimination ability were assessed using a modified Hosmer–Lemeshow Chi-square statistic and Harrell's c-index respectively.

Results. The original (uncalibrated) Framingham equation overestimated by 1.94-fold the risk of CHD and stroke combined in PRIME, and by 2.23 and 1.42-fold in PRIME-France and PRIME-Ireland respectively. Adequate fit was found after complete calibration. However, discrimination ability of the Framingham equation was poor as shown by Harrell's c-index lower than 0.70.

Conclusion. The (completely) calibrated 2008 Framingham equation predicted accurate number of CHD and stroke events but discriminated poorly individuals at higher from those at lower event risk in a European population of middle-aged men.

Introduction

Although several risk equations for cardiovascular disease (CVD) have been developed, Framingham equations (Anderson et al., 1991; D'Agostino et al., 1994, 2008; Wilson et al., 1998; Wolf et al., 1991) are the most widespread worldwide. They are derived from a Caucasian north-American population, and allow estimation of the absolute risk for several CVD endpoints, including coronary heart disease (CHD) and stroke. External validations of the Framingham equations have been mainly performed for CHD events (Barroso et al., 2010; Cooper et al., 2005; Ferrario et al., 2005; Koller et al., 2007; Reissigova and Zvarova, 2007; Vergnaud et al., 2008; Vrentzos et al., 2007). It is noteworthy that while the 1998 Framingham equation for CHD has been shown to be applicable to multiple ethnic American subpopulations (D'Agostino et al., 2001), discrepant results have been found when applied to various European populations (Barroso et al., 2010; Buitrago et al., 2011; Cooper et al., 2005; Empana et al., 2003; Ferrario et al., 2005; Reissigova and Zvarova, 2007; Scheltens et al., 2008; Simmons et al., 2008; Thomsen et al., 2002). Only a few studies on the applicability of the Framingham equations for stroke risk have been published and the results have

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been inconclusive (Bineau et al., 2009; Truelsen et al., 1994; Voko et al., 2004).

In 2008, a new sex-specific Framingham general risk equation was developed, allowing for the estimation of the ten-year absolute risk of CVD and its main components. This equation has the advantage of using simple, routinely available predictors of atherosclerosis, i.e. age, sex, smoking status, diabetes, blood pressure, antihypertensive treatment, and total and high-density lipoprotein (HDL) cholesterol. For comparison, previous published Framingham risk equations included signs of left ventricle hypertrophy on electrocardiogram, and atrial fibrillation, diagnoses that lack standardization. The possibility of estimating the risk of separate and combined cardiovascular events using the same sex-specific predictors represents an additional advantage of the 2008 Framingham equation. So far, its external validity has been evaluated in some populations (Collins and Altman, 2009; Khalili et al., 2012; Simmons et al., 2009; Zomer et al., 2011) for global CVD. To the best of our knowledge, the applicability of that equation to a European population for its main specific end points, i.e. CHD and stroke, has not yet been performed.

Our aim was to test the external validity of the 2008 Framingham cardiovascular equation in European middle-aged men to estimate their absolute 10-year risk of CHD and stroke events, considered individually and together. To this end, we took advantage of the 10-year follow-up of the PRIME study, a prospective cohort of healthy men from France and Ireland, allowing us to compare the validity of the equation in both a CVD low-risk (France) and high-risk (Ireland) country (Yarnell, 1998).

Methods

Study population

Details regarding recruitment and baseline examination of the PRIME study cohort have been previously described (Ducimetiere et al., 2001). The study protocol was approved by the institutional review board of the Broussais Hospital, Paris, France, and written informed consent was obtained for each participant. Overall, 10,602 men aged 50 to 59 were recruited between 1991 and 1993 by four collaborating WHO MONICA centers in Ireland (N = 2747) and in France (N = 7855). Among these, 891 men had a history of coronary disease or stroke at baseline examination. Sixty-three men had several missing baseline covariates and 10 men had no follow-up. These individuals were excluded from the original cohort.

Baseline characteristics

Briefly, a self-administered health questionnaire was completed by subjects at their homes and was subsequently verified by trained interviewers. A subset of biological measurements was carried out using fresh plasma for the entire cohort after overnight fasting.

Follow-up and verification of cases

During a 10-year follow-up period, subjects were contacted annually by letter and asked to complete a clinical event questionnaire. For all subjects reporting a possible event, clinical information was sought directly from hospital or general practitioner records. CHD and stroke events were validated by two independent medical committees. CHD events included stable and unstable angina, myocardial infarction and coronary death. Stroke was defined as a new neurological deficit with a rapid onset and of vascular origin, persisting for more than 24 h. Transient ischemic attacks and strokes caused by a blood disease, a cerebral tumor or metastasis, or secondary to a trauma, were excluded by the stroke medical committee.

Updated Framingham general equation in 2008

This equation provides a 10-year absolute risk estimate of CVD events and of its components, including CHD, stroke, peripheral artery disease and congestive heart failure. The baseline survival at the mean values of the risk factors (S_0) considers the hazard of all endpoints. At 10 years of follow-up its value was of 0.88936 for men. Predictors include age, serum total and high-density lipoprotein cholesterol (HDL-cholesterol), systolic blood pressure, anti-hypertensive treatment, smoking status and diabetes. Predictor estimates are provided in the paper by D'Agostino et al. (2008). Risk factors and CVD endpoint assessments differed in two aspects between Framingham and PRIME. First, the Framingham study additionally included "transient ischemic attacks" and "coronary insufficiency" in the event definitions for stroke and CHD respectively. Secondly, diabetes was defined according to fasting glucose level and antidiabetic treatment in Framingham while based on treatment for diabetes only in PRIME.

Statistical analysis

The distributions of baseline risk factors in PRIME and in Framingham populations were compared using Chi-square tests and analysis of variance for categorical and continuous variables respectively; no statistical comparison was done for diabetes as its definition differed between the two studies.

External validation of the Framingham risk equation in PRIME was conducted in three steps. First, we compared the hazard ratios (HRs) calculated in PRIME with those published in Framingham for CHD, stroke, and CHD and stroke combined. Second, we compared the number of events predicted by the Framingham equation with the number of observed events in PRIME, using the Hosmer–Lemeshow χ^2 statistic adjusted for censored data. We therefore computed the 10-year individual absolute risk of cardiovascular disease according to the published Framingham equation using the following formula, $1-S_0(t)^{\exp\{\sum\beta_k(x_k-\overline{X}_k)\}}$ where:

- $S_0(t)$ is the Framingham baseline survival at $t = 10$ years for global CVD,
- β_k are the Framingham regression coefficients for a set of risk factors k,
- x_k is the value of a given risk factor k for a given individual in PRIME,
- $\overline{X}_k$ is the mean value of the risk factor k calculated in Framingham.

As recommended by the authors of the Framingham general equation, individual predicted risks were then multiplied by calibration factors of 0.7174 for CHD, 0.1590 for stroke and 0.8764 (0.7174 + 0.1590) for CHD plus stroke. Individuals were thereafter ranked by decile of predicted risk. The number of observed events by decile of risk was derived from cumulative Kaplan–Meier survival rates at 10 years of follow-up (Viallon et al., 2009), while the number of predicted events was obtained by adding the Framingham predicted probabilities for individuals in a given decile of risk. Calibration of the Framingham risk equation was done (1) using the PRIME baseline survival (S_0) at 10 years of follow-up for each end point only (partial calibration) and (2) additionally using means of risk factors calculated in PRIME (complete calibration). We also used a local PRIME equation using regression coefficients, baseline survival (S_0) at 10 years of follow-up and means of the risk factors calculated in PRIME.

Third, the discrimination ability of the Framingham and the local PRIME equations was assessed by computing Harrell's c-index statistic. The discrimination ability of the Framingham equation was assessed considering results of the uncalibrated (original) equation since calibration does not affect discrimination.

Since analyses were performed for CHD, stroke and CHD or stroke (first) events, and by country, the threshold for statistical significance was set to 0.01 to correct for multiple testing. R software (R Foundation for Statistical Computing, http://cran.r-project.org/) was used for the statistical analysis.

Results

The median follow-up of the 9638 men was 10 years, during which 648 had a first CHD event and 138 a first stroke, corresponding to 763 individuals with a first CHD or stroke event (23 men experienced both events). Among men who did not experience any CVD event (N = 8875), 90% were followed over 10 years, 5% over 6 years and 5% less than 6 years.

Table 1 confirms the presence of significant differences in the baseline characteristics between Framingham and PRIME, and between PRIME-Ireland and PRIME-France.

With regards to CHD risk, age, total and HDL cholesterol, diabetes, smoking status, and treated or untreated systolic blood pressure, were independent predictors of CHD in PRIME, as in Framingham (Table 2). With regards to stroke risk, both studies found age, diabetes, smoking, and treated or untreated systolic blood pressure to be