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A comparison of the PROCAM and Framingham point-scoring systems for estimation of individual risk of coronary heart disease in the Second Northwick Park Heart Study

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Abstract

We have compared the predictive value of the PROCAM and Framingham risk algorithms in healthy UK men from the Second Northwick Park Heart Study (NPHS-II) (50–64 years at entry), followed for a median of 10.8 years for coronary heart disease (CHD) events. For PROCAM, the area under the receiver operating characteristic (ROC) curve was 0.63 (95% CI, 0.59–0.67), and not significantly different ($p = 0.46$) from the Framingham score, 0.62 (0.58–0.66). Sensitivities for a 5% false-positive rate (DR_5) were 13.8 and 12.4%, respectively. Calibration analysis for PROCAM gave a ratio of observed to expected events of 0.46 (Hosmer–Lemeshow test, $p < 0.0001$) and 0.47 for Framingham ($p < 0.0001$). Using measures taken at 5 years of high-density lipoprotein cholesterol and (estimated) low-density lipoprotein cholesterol levels increased the ROC by only 1%. An NPHS-II risk algorithm, developed using a 50% random subset, and including age, triglyceride, total cholesterol, smoking status, and systolic blood pressure at recruitment, gave an ROC of 0.64 (0.58–0.70) with a DR_5 of 10.7% when applied to the second half of the data. Adding family history and diabetes increased the DR_5 to 18.4% ($p = 0.28$). Adding lipoprotein(a) >26.3 mg/dL (relative risk 1.6, 1.1–2.4) gave a DR_5 of 15.5% ($p = 0.55$), while adding fibrinogen levels (relative risk for 1S.D. increase = 1.5, 1.1–2.0) had essentially no additional impact ($DR_5 = 16.9\%$, $p = 0.95$). Thus, the PROCAM algorithm is marginally better as a risk predictor in UK men than the Framingham score, but both significantly overestimate risk in UK men. The algorithm based on NPHS-II data performs similarly to those for PROCAM and Framingham with respect to discrimination, but gave an improved ratio of observed to expected events of 0.80 ($p = 0.01$), although no score had a high sensitivity. Any novel factors added to these algorithms will need to have a major impact on risk to increase sensitivity above that given by classical risk factors.

Keywords: PROCAM; Framingham; Receiver operator curve; Risk prediction; Myocardial infarction

1. Introduction

Many individual characteristics contribute to the risk of clinical coronary heart disease (CHD) including gender, age, blood lipid concentrations, blood pressure, glucose tolerance, adiposity, and cigarette smoking. The complexity of the interrelations between these risk factors makes assessment of individual 'global' risk difficult to evaluate in routine clinical practice, and statistical approaches have been developed, based on survival regression methods (e.g. Cox proportional hazards regression) or logistic regression. To simplify this approach for everyday use, point-scoring systems have been developed that permit the impact of several risk factors to be considered simultaneously [1,2]. The population distribution of each risk factor is divided into several categories (e.g. cigarette smoker: yes/no; high-density lipoprotein cholesterol (HDLc): <35, 35–54, 55+ mg/dL), and each category

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is given a risk score. These scores are totalled and the result converted into 10-year risk of a coronary event from tables.

Point-scoring schemes have been developed from the Framingham study in the USA [1] and the PROCAM study in Germany [2]. The PROCAM system includes age, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDLc), triglyceride, smoking, diabetes, family history of CHD, and systolic blood pressure as risk factors. The Framingham system does not include information on family history, diabetes, triglyceride, or LDLc, but does include total cholesterol and interactions of age with smoking and cholesterol. Both systems use acute CHD events as the end point. Not surprisingly, the Framingham system was not as accurate as the PROCAM system when applied to the PROCAM data set, and the proposal has been made that valid comparison of performance requires their application to a third and independent data set [2]. The Second Northwick Park Heart Study (NPHS-II), a prospective cardiovascular study of healthy middle-aged men, has provided the opportunity both for development of a point-scoring system using conventional and novel coronary risk factors [3–5], and comparison with Framingham and PROCAM in a British setting.

2. Methods

2.1. Subjects

Full details of the recruitment methods, participant characteristics, and baseline measurements have been published previously [3–5]. Serum HDLc was measured using polyethylene glycol 8000 and enzymatic colorimetry on the sample of plasma taken at year 5 [5] and values used to estimate LDLc for each subject using the Friedewald equation as described [5]. Briefly, NPHS-II is a prospective study of 3052 healthy middle-aged Caucasian men (50–64 years) recruited from nine United Kingdom general practices [4], followed for a median of 10.8 years. Each man answered a questionnaire involving lifestyle and medical history and was classified as a current smoker or other (i.e. ex- plus never-). A family history of CHD was determined by the response to the question: "Has any person in your family ever had a heart attack?" CHD end points were: (1) acute CHD events; sudden coronary death, fatal acute myocardial infarction, and non-fatal acute myocardial infarction. Details of possible events were obtained through general practices, hospitals, and coroners' offices. The clinical history, ECGs, cardiac enzymes, and pathology were assessed by independent review according to World Health Organization criteria [6], and normal limits for cardiac enzymes were those for the reporting laboratory; (2) a new major Q wave on the ECG after 5 years of follow-up (Minnesota codes 1_1, $1_{2.1}$ to $1_{2.7}$, and $1_{2.8}$ plus 5_1 or 5_2 [7]; (3) surgery for angina pectoris with CHD angiographically demonstrated.

In the 2732 men with complete trait data, by January 2004 there had been 219 CHD events comprising 153 acute CHD events, 45 coronary artery revascularisation procedures and 21 silent myocardial infarctions. The ethics committees of the participating institutions approved the study.

2.2. Statistical analysis

Calibration refers to the accuracy of the score in predicting the probability of an event. Both Framingham and PROCAM systems provide estimates of the 10-year risk of CHD for each subject allowing the calibration to be assessed. These estimated risks were compared with the event rate (restricted to acute CHD events for the calibration analysis) observed in NPHS-II after dividing the population into similarly sized groups by each score. Individuals without an event who had not yet completed 10 years of follow-up and those with events occurring after 10 years were excluded from this analysis. The Hosmer–Lemeshow test was used to test differences between the observed and expected rates. A significant p value for the Hosmer–Lemeshow test indicates poor calibration. The ability of different scoring systems to predict CHD was assessed using the area under the receiver operating characteristic (ROC) curve as a discriminatory test. Differences in the area under the curves were tested as suggested [8]. Detection rates (or sensitivities) for a 5% false-positive rate were calculated (DR_5). For each combination of variables, a Cox proportional hazards model was fitted and converted to a score by grouping each factor into intervals and increasing the score by an integer amount for each increment in factor level. Triglyceride and fibrinogen were log-transformed in the analysis. Estimates for systolic blood pressure, triglyceride, cholesterol, and fibrinogen were adjusted for regression to the mean by correction factors obtained by Rosner's intraclass correlation coefficient method [9] from repeat measures. The model assumed linearity for the quantitative risk factors. Each integer amount was a rounding of the coefficient from the model multiplied by the relevant increase above baseline. The estimated probability of CHD within 10 years can be calculated from the score for the complete model as $1 - 0.981^{\exp(0.1 \times \text{riskscore})}$.

3. Results

3.1. Application of PROCAM and Framingham scores to NPHS-II

The PROCAM and Framingham scoring systems were applied to the 2732 NPHS-II men with complete data. Serum HDLc and LDLc were not measured at baseline in NPHS-II and so levels for these variables were set to the average observed in a subset of over 2000 NPHS-II men after 5 years of follow-up (LDLc 4.0 mmol/L and HDLc 0.8 mmol/L). The ability of the scores to separate men with and without disease was assessed using ROC curve analysis (Fig. 1). The ROC area using PROCAM was 0.63 (95% CI, 0.59–0.67). This result did not differ significantly ($p = 0.46$) from that obtained