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New Pooled Cohort Risk equations: Application to a recent stroke patient population

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ABSTRACT

Background: Recently, Pooled Cohort Risk (PCR) equations, which incorporate new sex- and race-specific estimates of the 10-year risk for atherosclerotic cardiovascular disease (ASCVD) including stroke, for ASCVD-free adults were introduced. Given the importance of secondary stroke prevention and benefit of a potential tool to readily identify stroke patients at high intermediate-term vascular risk for appropriate treatment, we evaluated the prediction and discrimination of the PCR and Framingham Cardiovascular Risk (FCR) equations after a recent stroke.

Method: We conducted an analysis of Vitamin Intervention for Stroke Prevention dataset of 3555 recent non-cardioembolic stroke patients aged ≥35 years and followed for 2 years. Subjects were categorized as having low-PCR/low-FCR (<20%), high-PCR/high-FCR (≥20%), and known-ASCVD. Independent associations of high-PCR/high-FCR with recurrent stroke (primary outcome) and stroke/coronary heart disease (CHD)/vascular death (secondary outcomes) were assessed.

Results: Both PCR and FCR were independently related to both outcomes: compared with low-PCR, high-PCR was associated with stroke (adjusted hazard ratio, 1.79; 95% CI, 1.25–2.57) and stroke/CHD/vascular death (2.05; 1.55–2.70). Compared with low-FCR, high-FCR was associated with stroke (2.06; 1.34–3.16) and stroke/CHD/vascular death (1.57; 1.12–2.20). The c-statistic of PCR/FCR as a continuous variable for stroke was 0.56 (95% CI, 0.54–0.58) and 0.56 (0.54–0.57), respectively and for stroke/CHD/vascular death was 0.62 (0.60–0.63) and 0.61 (0.59–0.63), respectively.

Conclusions: Both PCR and FCR are significant predictors of recurrent vascular events among patients after a recent non-cardioembolic stroke, but neither one of them is an optimal model for discriminating intermediate-term ASCVD prediction among stroke patients already receiving secondary stroke prevention.

1. Introduction

Traditional risk factors such as age, sex, high blood pressure, dyslipidemia, diabetes, and smoking are major contributors to the development of atherosclerotic cerebrovascular disease (ASCVD), which is the leading cause of mortality and morbidity [1]. To reduce ASCVD and its unfavorable consequences, multivariable assessment has been advocated to estimate absolute ASCVD risk and to guide treatment of risk factors [2,3]. The use of validated prognostic risk scores derived from observational data is endorsed in expert consensus guidelines as a means of identifying high-risk individuals [4,5]. The most commonly used cardiovascular risk prediction formulation is the Framingham 10-year risk model.

However, the Framingham Coronary Heart Disease (CHD) risk model does not cover the full range of major cardiovascular diseases, including stroke [6], and while a Framingham prediction model was subsequently developed for prediction of sex-specific absolute risk of total CVD events (Framingham Cardiovascular Risk [FCR] equations) in subjects free of CVD, it had little validation in multiethnic populations [1].

To improve validation of the risk tool in an external population, the ACC/AHA recently provided the guideline on the Assessment of Cardiovascular Risk and developed new sex- and race-specific estimates of the 10-year risk for hard ASCVD events for African-American and White men and women as the ACC/AHA Pooled Cohort Risk (PCR) equations [7]. Unlike the FCR model, the PCR includes stroke in the combined end point of ASCVD rather than CHD only, and this model was validated to show a good discrimination of incident ASCVD risk in a population without ASCVD at baseline [8].

The validity of applying risk models developed in a given population to another is disputable [9], especially because of potential underlying environmental and genetic distinctions, as well as possible variations

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in definitions, case ascertainment, and length of follow-up. However, risk tools that are validated in other patient populations can hold substantive advantage over single physician clinical experience [10], perhaps even more so if they are broadly familiar, developed by recognized experts, and carry the imprimatur of national organizations [7,11].

In this study, we evaluated the prediction and discrimination of the PCR equations for ASCVD risk (including stroke) in the intermediate-term after a recent non-cardioembolic stroke. Since as far as we know, the FCR equations have not been specifically tested for validation in an external population, we also compared the prediction and discrimination of PCR vs. FCR equations.

2. Methods

2.1. Subjects and study

To determine the validity of the PCR for hard ASCVD risk, we reviewed data from the Vitamin Intervention for Stroke Prevention (VISP) trial comprising 3680 patients, aged ≥35 years, with a recent (onset ≤ 120 days before randomization) non-disabling (modified Rankin Scale ≤ 3) non-cardioembolic stroke [12]. The VISP trial was a multicenter, double-blind, randomized, controlled trial performed at centers across the United States, Canada, and Scotland. The original aim of the study was to determine whether high doses of multivitamin (folic acid, pyridoxine, and cobalamin) given to lower total homocysteine levels would reduce the risk of recurrent stroke and major vascular events [12]. Demographic, clinical, and laboratory data were collected at randomization, with subsequent clinical and laboratory information obtained at follow-up visits of 1, 6, 12, 18, and 24 months. Serum lipid samples were obtained in the fasting state. Subjects who had missing lipid value(s) of the PCR or FCR were excluded. Predicted vascular event at 2 years of follow-up was calculated using the original 10-year PCR equations [7] and modified version of ($S_0(t)$) at 2 years. We reviewed medication information from VISP database including antihypertensive, lipid-lowering (i.e. statin, ezetimibe, fenofibrate, niacin, or/and omega-3 fatty acids), and antithrombotic (antiplatelet or/and anticoagulation) medication uses during follow-up visits. Other ethnic groups (e.g. American-Indians, Asian-Americans, and Hispanics) were regarded as Whites to conduct calibration by the recommendation of the 2013 ACC/AHA guideline [7]. VISP study was approved by the local research committee or Institutional Review Board at each participating center and all participants provided written informed consent [12].

2.2. Atherosclerotic cardiovascular risk category

For the purpose of this analysis, study subjects were categorized into 3 groups based on ASCVD risk category: low-PCR (<20%), high-PCR (≥20%), and known-ASCVD (history of stroke, MI, angina, coronary angioplasty/stenting, or coronary artery bypass graft surgery) for the PCR approach; and low-FCR (<20%), high-FCR (≥20%), and known-ASCVD for the FCR approach. The discrimination of low and high risks at the threshold of 20% was done because a score of ≥20% in 10 years is known to predict high global CVD risk that requires more aggressive risk factor modification [1]. Since the PCR/FCR model was originally designed for ASCVD free adults, those with known-ASCVD were separately categorized. Subjects with known-ASCVD with missing PCR or FCR model component (n = 114) were included in the known-ASCVD group. VISP qualifying stroke was not included in known-ASCVD. The PCR model and FCR model were also assessed as continuous variables with subjects with complete data.

2.3. Outcome

The primary outcome for this analysis was ischemic stroke. Secondary outcome was a composite of stroke, CHD including myocardial infarction (MI), coronary revascularization, cardiac resuscitation, and fatal CHD, or vascular death as major vascular events.

2.4. Statistical analysis

Comparisons across the PCR and FCR categories were examined using the χ^2 test for categorical variables and one-way analysis of variance (ANOVA), followed by the Dunnett test for multiple comparisons, for continuous variables. The low-PCR and low-FCR were the referent groups for purposes of comparison. Baseline demographic and clinical covariates were preselected based on previous studies of factors that influence vascular events after ischemic stroke. Backward elimination Cox proportional hazard regression analyses were performed to estimate the risk of outcome events by the PCR and FCR categories in the following ways: (1) unadjusted; (2) after adjusting for baseline covariates that were associated with high-PCR or high-FCR ($P < 0.10$) (model I); and (3) after adjusting for aforementioned covariates plus age and sex (model II). Although both the PCR and FCR were sex-specific models, sex was further added, since these covariates were the major portion of each risk model [1,7]. Patients not having these events were censored at the date of nonvascular death, last follow-up examination, or last contact. Results are given by hazard ratio (HR) and its 95% confidence interval (CI). Above analyses were conducted using IBM SPSS Version 22.0 (IBM SPSS Inc., Chicago, IL). Accuracies of the PCR model and FCR model as continuous variables were assessed by calculating c-statistics (areas under the receiver operating characteristic curves [ROC]) and were compared using MedCalc software version 5.0 (Mariakerke, Belgium). A probability value of <0.05 was considered statistically significant.

3. Results

3.1. Subject characteristics by ASCVD risk category

Of the 3680 participants in the trial, 125 participants had missing lipid component(s) of PCR or FCR equations and were excluded from the final analysis, yielding a total of 3555 (96.6%) subjects (complete calibration available in 3441 subjects). Subjects aged <40 years were 22 (0.6%) and those aged ≥80 years were 360 (10.1%). Baseline demographic and clinical characteristics by 2 ASCVD risk categories are provided in Table 1. At baseline, 54.8% and 93.5% of study participants were taking lipid modifier (including statin mostly) and antithrombotics, respectively. For PCR category, compared with low-PCR, high-PCR was more likely to have higher serum levels of low-density lipoprotein cholesterol (LDL-C), higher National Institutes of Health Stroke Scale (NIHSS) score, higher frequency of hypertension, and higher histories of congestive heart failure and carotid endarterectomy, whereas body mass index, frequencies of lipid modifier use, high-dose vitamin therapy, and history of alcohol use were more likely to be lower. For FCR category, compared with low-FCR, high-FCR was more likely to have higher serum levels of LDL-C and triglycerides, higher NIHSS scores, higher frequencies of hypertension and lipid modifier use, and higher histories of congestive heart failure and carotid endarterectomy, whereas high-dose vitamin therapy and history of alcohol use were more likely to be lower.

3.2. Effect of each ASCVD risk category on vascular events

During an average of 20 months of follow-up, a total of 289 (8.1%) incident strokes and 598 (16.8%) stroke/CHD/vascular deaths were recorded in the PCR and FCR categories. Event of stroke was higher in high-PCR and high-FCR, whereas event of stroke/CHD/vascular death was higher in known-ASCVD (Table 2). Table 2 also provides results of the unadjusted and adjusted associations of PCR and FCR categories with vascular outcomes. In unadjusted analyses, occurrence of stroke was higher in high-PCR (HR, 1.90; 95% CI, 1.35–2.67) and in known-ASCVD (1.64; 1.18–2.27), when referenced to low-PCR. Occurrence of