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

Jong-Ho Park [a,b], Hyung-Min Kwon [c], Bruce Ovbiagele [b,*]

[a] Department of Neurology, Myongji Hospital, Goyang, South Korea
[b] Department of Neurosciences, Medical University of South Carolina, Charleston, SC, United States
[c] Department of Neurology, SMG-SNU Boramae Medical Center, Seoul, South Korea

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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

* Corresponding author at: Department of Neurosciences, Medical University of South Carolina, 96 Jonathan Lucas St., CSB 301, MSC 606, Charleston, SC 29425–6160, United States. Tel.: +1 843 792 1414; fax: +1 858 657 6788.
E-mail address: Ovibes@musc.edu (B. Ovbiagele).

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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

Table 1
Baseline characteristics of study subjects by atherosclerotic cardiovascular risk category.

Model components	Pooled Cohort Risk		Known-ASCVD* (n = 1598)	Framingham Cardiovascular Risk		P†	P‡
	Low (<20%; n = 889)	High (≥20%; n = 1068)		Low (<20%; n = 622)	High (≥20%; n = 1335)		
Age, years	57.8 ± 8.5[c]	71.9 ± 8.4[a]	67.2 ± 10.5[b]	59.0 ± 10.8[c]	68.6 ± 9.6[a]	<0.001	<0.001
Male	461 (51.9)	694 (65.0)	1076 (67.3)	223 (35.9)	932 (69.8)	<0.001	<0.001
African-American	135 (15.2)	162 (15.2)	223 (14.0)	110 (17.7)	187 (14.0)	0.591	0.059
Total cholesterol, mg/dL	206.0 ± 44.5	205.8 ± 49.9[a]	196.7 ± 45.1[b]	199.4 ± 42.0	208.9 ± 49.6[a]	<0.001	<0.001
HDL-C, mg/dL	48.0 ± 15.1[a]	45.1 ± 15.2	44.0 ± 15.6[b]	52.0 ± 17.4[a]	43.8 ± 13.4	<0.001	<0.001
Systolic BP, mm Hg	133.4 ± 16.5[c]	147.8 ± 17.8[a]	140.1 ± 18.5[b]	129.8 ± 14.5[c]	146.6 ± 18.0[a]	<0.001	<0.001
Treatment for high BP	620 (69.7)	911 (85.3)	1360 (85.1)	403 (64.8)	1128 (84.5)	<0.001	<0.001
Diabetes mellitus	140 (15.7)	370 (34.6)	545 (34.1)	69 (11.1)	441 (33.0)	<0.001	<0.001
Smoker	150 (16.9)	191 (17.9)	261 (16.3)	80 (12.9)	261 (19.6)	0.578	0.001
Body mass index, kg/m^2	28.8 ± 6.5[a]	27.9 ± 5.3	28.3 ± 5.4[b]	28.4 ± 6.8	28.3 ± 5.4	0.003	0.922
LDL-C, mg/dL	123.3 ± 39.2[a]	125.5 ± 42.5	118.5 ± 39.8[b]	117.3 ± 36.8	127.9 ± 42.5[a]	<0.001	<0.001
Triglycerides, mg/dL	171.0 ± 109.2	177.4 ± 222.2	175.5 ± 117.9[a]	150.9 ± 84.8[b]	185.6 ± 209.1	0.652	<0.001
Homocystein, μmol/L	14.3 ± 7.1	13.8 ± 4.9	14.2 ± 6.0	14.2 ± 7.3	14.0 ± 5.3	0.161	0.755
Qualifying stroke NIHSS						0.083	0.011
0	326 (36.7)	329 (30.8)	542 (33.9)	243 (39.1)	412 (30.9)		
1–4	493 (55.5)	656 (61.4)	925 (57.9)	335 (53.9)	814 (61.0)		
≥5	70 (7.9)	83 (7.8)	131 (8.2)	44 (7.1)	109 (8.2)		
Hypertension	676 (76.0)	940 (88.0)	1388 (86.9)	439 (70.6)	1177 (88.2)	<0.001	<0.001
Antithrombotic use	821 (92.4)	1003 (93.9)	1499 (93.8)	574 (92.3)	1250 (93.6)	0.292	0.409
Lipid modifier use	456 (51.3)	528 (49.4)	964 (60.3)	299 (48.1)	685 (51.3)	<0.001	<0.001
High-dose B vitamin	433 (48.7)	503 (47.1)	825 (51.6)	303 (48.7)	633 (47.4)	0.061	0.068
History							
Congestive heart failure	18 (2.0)	34 (3.2)	136 (8.6)	13 (2.1)	39 (2.9)	<0.001	<0.001
Carotid endarterectomy	35 (3.9)	66 (6.2)	141 (8.8)	20 (3.2)	81 (6.1)	<0.001	<0.001
Alcohol use	557 (64.5)	611 (58.8)	888 (56.9)	373 (61.8)	795 (61.2)	0.001	0.026

Values provided are number (%) or mean ± SD, as appropriate, otherwise stated. a > b, $P < 0.05$; b > c, $P < 0.05$.
ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BP, blood pressure; NIHSS, National Institutes of Health Stroke Scale.
* Defined as history of stroke, myocardial infarction, angina, coronary angioplasty/stenting, or coronary artery bypass graft surgery.
† Among Pooled Cohort Risk (low, high) and known-ASCVD.
‡ Among Framingham Cardiovascular Risk (low, high) and known-ASCVD.

Table 2
Estimates of hazard ratio (HR) of vascular outcomes and comparison of discrimination in populations with recent stroke by each atherosclerotic cardiovascular risk category.

	Pooled Cohort Risk (PCR) category				Framingham Cardiovascular Risk (FCR) category			
	High-PCR (≥20%)[a]		Known-ASCVD[a]		High-FCR (≥20%)[a]		Known-ASCVD[a]	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Stroke								
Events, n	105 (9.8)		136 (8.5)		122 (9.1)		136 (8.5)	
Unadjusted	1.90 (1.35–2.67)	<0.001	1.64 (1.18–2.27)	0.003	1.89 (1.27–2.80)	0.002	1.77 (1.20–2.61)	0.004
Adjusted								
Model I[b]	1.79 (1.25–2.57)	0.001	1.56 (1.10–2.22)	0.012	2.06 (1.34–3.16)	0.001	1.87 (1.21–2.87)	0.005
Model II[c]	1.79 (1.25–2.57)	0.001	1.56 (1.10–2.22)	0.012	2.06 (1.34–3.16)	0.001	1.87 (1.21–2.87)	0.005
C-statistic (95% CI)[d]	0.56 (0.54–0.58)				0.56 (0.54–0.57)			
Sensitivity	73.1				54.1			
Specificity	38.2				56.5			
P for differences	0.638							
Stroke/CHD[e]/vascular death								
Events, n	197 (18.4)		320 (20.0)		222 (16.6)		320 (20.0)	
Unadjusted	2.13 (1.65–2.76)	<0.001	2.33 (1.82–2.97)	<0.001	1.91 (1.43–2.56)	<0.001	2.35 (1.77–3.12)	<0.001
Adjusted								
Model I[b]	2.11 (1.60–2.77)	<0.001	2.15 (1.65–2.80)	<0.001	1.94 (1.42–2.67)	<0.001	2.23 (1.63–3.04)	<0.001
Model II[c]	2.05 (1.55–2.70)	<0.001	2.07 (1.58–2.70)	<0.001	1.57 (1.12–2.20)	0.009	1.83 (1.31–2.54)	<0.001
C-statistic (95% CI)[d]	0.62 (0.60–0.63)				0.61 (0.59–0.63)			
Sensitivity	70.5				58.6			
Specificity	47.6				60.1			
P for differences	0.432							

ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol.
[a] Referent group is patients with each of corresponding group with low risk score (low-PCR or low-FCR).
[b] For PCR category, adjusted for body mass index, LDL-C, stroke severity, hypertension, lipid modifier use, vitamin therapy, history of congestive heart failure, history of carotid endarterectomy, and history of alcohol use; for FCR category, adjusted for ethnicity (African-American vs. White), LDL-C, triglycerides, stroke severity, hypertension, lipid modifier use, vitamin therapy, history of congestive heart failure, history of carotid endarterectomy, and history of alcohol use.
[c] Adjusted for model I plus age and sex.
[d] As a continuous variable (n = 3441 subjects with complete data).
[e] Defined as myocardial infarction, coronary revascularization, cardiac resuscitation, and fatal CHD.

stroke was higher in the high-FCR (1.89; 1.27–2.80) and in known-ASCVD (1.77; 1.20–2.61), when referenced to lower-FCR. Occurrence of stroke/CHD/vascular death was higher in high-PCR (2.13; 1.65–2.76) and in known-ASCVD (2.33; 1.82–2.97), when referenced to low-PCR. Occurrence of stroke/CHD/vascular death was higher in high-FCR (1.91; 1.43–2.56) and in known-ASCVD (2.35; 1.77–3.12), when referenced to low-FCR. In multivariable backward elimination Cox models, compared with low-PCR, high-PCR and known-ASCVD were associated with an increased risk of stroke (1.79; 1.25–2.57 and 1.56; 1.10–2.22, respectively) and these associations remained constant after further adjustment for age and sex. Compared with the low-FCR, high-FCR and known-ASCVD had a higher risk of stroke (2.06; 1.34–3.16 and 1.87; 1.21–2.87, respectively) and these associations also remained constant after further adjustment for age and sex. Fig. 1 displays cumulated incidence of stroke by PCR category (A) and FCR category (B) after adjusting for multivariable covariates including age and sex. For major vascular events, high-PCR and known-ASCVD were associated with an increased risk of stroke/CHD/vascular death (2.11; 1.60–2.77 and 2.15; 1.65–2.80, respectively) and these associations persisted significant after further adjustment for age and sex (2.05; 1.55–2.70 and 2.07; 1.58–2.70, respectively). The high-FCR and known-ASCVD were associated with a higher risk of stroke/CHD/vascular death (1.94; 1.42–2.67 and 2.23; 1.63–3.04, respectively) and these associations attenuated after further adjustment for age and sex (1.57; 1.12–2.20 and 1.83; 1.31–2.54, respectively). The adjusted HRs of covariates included in the multivariable model appear in Supplementary Table I. Of note, lipid modifier use was a potent predictor of lesser risk of both stroke and major vascular events in the PCR or FCR category. The PCR and FCR as a continuous variable was also independently associated with an increased risk of stroke (1.01; 1.00–1.01 for all) and major vascular events (1.01; 1.01–1.02 for all, Supplementary Table II). As was shown in Supplementary Table III, when $S_0(t)$ at 10 years of the PCR equations was calibrated into $S_0(t)$ at 2 years, PCR as a continuous variable was significantly linked to an increased risk of major vascular events (1.06; 1.04–1.08), but not of recurrent stroke (categorical analysis could not be conducted because of small numbers of high-PCR subjects (n = 14)).

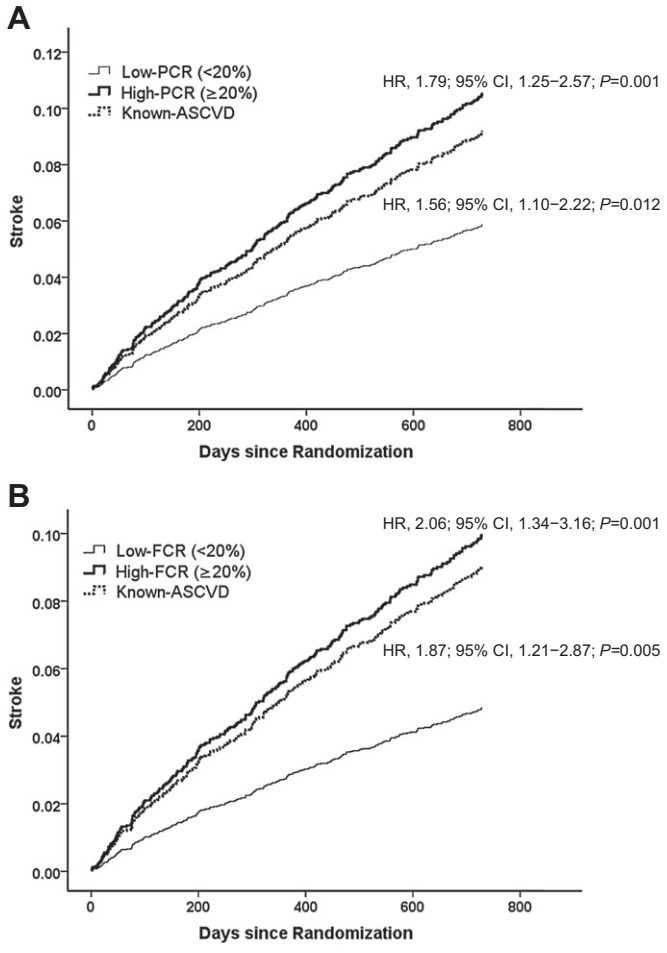

Fig. 1. Cumulative incidence of stroke at 2 years after non-cardioembolic stroke by Pooled Cohort Risk (PCR) category (A) and Framingham Cardiovascular Risk (FCR) category (B) after adjusting for covariates including age and sex. Low-PCR and low-FCR as reference groups. ASCVD, atherosclerotic cardiovascular disease.

3.3. Comparison of model discrimination

Results of c-statistic for each of ASCVD risk model (continuous variable) in predicting vascular events are shown in Table 2. For stroke and major vascular events, all the c-statistics of the PCR and FCR were significant. For stroke, the discrimination of the PCR and FCR was 0.56 (0.54–0.58) and 0.56 (0.54–0.57), respectively, in which the difference was not significant ($P = 0.638$). The PCR model has a higher sensitivity for stroke than the FCR (73.1 vs. 54.1). For major vascular events, the discrimination of the PCR and FCR was 0.62(0.60–0.63) and 0.61 (0.59–0.63), respectively and comparable ($P = 0.432$). The PCR seemed more sensitive than the FCR in identifying major vascular events (70.5 vs. 58.6). For a 2-year PCR model, c-statistic was 0.62 (0.60–0.63) for major vascular events and 0.55 (0.54–0.57) for stroke (Supplementary Table III for full data).

4. Discussion

This study provides the first test of the potential utility of the new PCR model in patients with stroke. In our analysis of subjects with a recent non-cardioembolic stroke, 30% and 38% of those without known-ASCVD had high-PCR and high-FCR, respectively. In subjects with stroke without known-ASCVD, high-PCR was independently associated with a 1.8-fold higher risk of stroke over a 2-year period, which was numerically lower than the association observed with the FCR model (vs. 2.1); while high-PCR was independently associated with a 2.1-fold higher risk of stroke/CHD/vascular death over a 2-year period, which was numerically higher than the association observed with the FCR model (vs. 1.6). Nevertheless, c-statistics by the ROC curve were fairly compatible with PCR and FCR for each vascular outcome.

The PCR model appeared more sensitive than the FCR in identifying vascular events including stroke, but our analyses of VISP dataset suggest that neither the PCR nor FCR has modest discriminative capacity for prediction of recurrent ASCVD risk because of low c-statistics (<0.70) [13].

Other analyses indicate that the ACC/AHA PCR model significantly overestimates ASCVD risk in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) and Multi-Ethnic Study of Atherosclerosis (MESA) external cohorts [14]. A recent analysis of the Rotterdam Study also revealed similar overestimations [15].The 2013 ACC/AHA cholesterol treatment guidelines recommend using the 10-year risk PCR equations to predict ASCVD risk and to help guide the decision to initiate statin therapy for primary prevention in adults without clinical ASCVD or diabetes, and with LDL-C levels between 70 and 189 mg/dL in their study [16]. However, since REGARDS study participants have not been followed up for 10 years, Muntner et al [8] modified into 5-year risk equations and restricted to participants aged 45 to 79 years without taking statins at baseline, for which the PCR model was specifically designed to be used, thereby likely yielding better discrimination. In our study, a 2-year modified PCR model was significantly linked to the risk of major vascular events but did not improve discrimination, which is a fairly similar pattern to the finding seen with the original 10-year

model. In VISP populations, age was ranged from 35 to 89 years and 45% had vascular comorbidities including known-ASCVD, heart failure and 7% revascularization (i.e. carotid endarterectomy). Furthermore, in VISP, there is the possibility that higher frequencies of lipid modifier use (54.8%) and antithrombotic medication (93.5%) for secondary prevention may have attenuated the discrimination power of vascular outcome events (overestimation). Other potential factors for the varied results between our VISP analysis and the Muntner et al. study [8] include differences in black race (37.6% vs. 14.6%), and population size (10997 vs. 3555). Recently however, Cook et al. pointed out that overestimation of the PCR is not explained by statin use, revascularization procedures, or underascertainment of ASCVD events through evaluation of the Women's Health Study, suggesting the PCR model needs be recalibrated within more contemporary populations [17].

Of note, the finding that high-FCR was associated with the risk of recurrent stroke conflicts with results of a previously published analysis of VISP participants using the Framingham CHD risk model, which observed that high risk (≥20%) was associated with a higher risk of future MI and vascular death, but not of recurrent stroke [6]. We speculate that the non-inclusion of diabetes in Framingham CHD risk model (vs. FCR) may have contributed to the disparate finding between the Framingham risk model and the outcome of recurrent stroke. Diabetes is associated with progression [18] and severity [19] of intracranial atherosclerosis, which is one of the most common causes of stroke worldwide [20]. Interestingly, while on one hand, the effect of known-ASCVD on the incidence of the secondary composite outcome was higher than that of high-PCR and high-FCR, a contrary result was seen for the primary outcome of stroke, perhaps suggesting that the contribution of preexisting ASCVD to the occurrence of various major vascular events after stroke may be greater than the sum of its traditional vascular risk factor parts. We also found that lipid modifier use (mostly statins) was significantly associated with lower vascular event risk, a finding that is in accord with those seen in a meta-analysis [21] showing that statins significantly reduce the risk of recurrent stroke (relative risk 0.84; 95% CI, 0.71–0.99) and major cardiovascular events (0.80; 0.69–0.92).

This study has limitations. It is a post hoc exploratory analysis of a completed randomized trial and many of the study participants were having vascular comorbidities and receiving secondary prevention including lipid modifiers. Furthermore, all study participants experienced non-cardioembolic strokes thereby limiting our results extrapolated to general stroke patients. This study included subjects aged <40 (n = 22) and those aged ≥80 years (n = 360), all of whom are not evaluated the validity in the new PCR equations. Nevertheless, the study was strengthened by prospective nature of data collection in VISP, rigorous trial procedures, and a fairly large sample size [12].

In conclusion, both the PCR and FCR were significant predictors of recurrent vascular events in patients with non-cardioembolic stroke enrolled in the VISP study. The FCR model appears not to be inferior to the PCR for predicting vascular outcomes, but the PCR seems to be more sensitive than the FCR in identifying both stroke and major vascular events. However, neither of them may be an optimal model to discriminate intermediate-term ASCVD prediction among recent stroke patients already receiving secondary prevention. Nevertheless, this study suggests that for health care professionals taking care of patients with ischemic stroke, awareness that those with high-PCR or high-FCR may be at higher risk for the untoward consequences of recurrent stroke, might facilitate more attention for suboptimal risk factor control, with the goal of promptly conducting evidence-based strategies to reduce recurrent vascular events.

The PCR model was originally designed to predict 10-year ASCVD risk in ASCVD free population [7]. The accuracy of the PCR model for discriminating vascular risk after stroke needs to be explored in other datasets, but to enhance discrimination, adding novel risk factors (i.e. high sensitivity C-reactive protein, microalbuminuria, coronary artery calcium score, etc.) to the PCR equations should be considered [7,8].

Disclosure

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jns.2014.11.028.

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