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General Cardiovascular Risk Profile for Use in Primary Care
The Framingham Heart Study

Ralph B. D'Agostino, Sr, PhD; Ramachandran S. Vasan, MD; Michael J. Pencina, PhD; Philip A. Wolf, MD; Mark Cobain, PhD; Joseph M. Massaro, PhD; William B. Kannel, MD

Background—Separate multivariable risk algorithms are commonly used to assess risk of specific atherosclerotic cardiovascular disease (CVD) events, ie, coronary heart disease, cerebrovascular disease, peripheral vascular disease, and heart failure. The present report presents a single multivariable risk function that predicts risk of developing all CVD and of its constituents.

Methods and Results—We used Cox proportional-hazards regression to evaluate the risk of developing a first CVD event in 8491 Framingham study participants (mean age, 49 years; 4522 women) who attended a routine examination between 30 and 74 years of age and were free of CVD. Sex-specific multivariable risk functions ("general CVD" algorithms) were derived that incorporated age, total and high-density lipoprotein cholesterol, systolic blood pressure, treatment for hypertension, smoking, and diabetes status. We assessed the performance of the general CVD algorithms for predicting individual CVD events (coronary heart disease, stroke, peripheral artery disease, or heart failure). Over 12 years of follow-up, 1174 participants (456 women) developed a first CVD event. All traditional risk factors evaluated predicted CVD risk (multivariable-adjusted $P<0.0001$). The general CVD algorithm demonstrated good discrimination (C statistic, 0.763 [men] and 0.793 [women]) and calibration. Simple adjustments to the general CVD risk algorithms allowed estimation of the risks of each CVD component. Two simple risk scores are presented, 1 based on all traditional risk factors and the other based on non–laboratory-based predictors.

Conclusions—A sex-specific multivariable risk factor algorithm can be conveniently used to assess general CVD risk and risk of individual CVD events (coronary, cerebrovascular, and peripheral arterial disease and heart failure). The estimated absolute CVD event rates can be used to quantify risk and to guide preventive care. **(*Circulation*. 2008;117: 743-753.)**

Key Words: cardiovascular diseases ■ coronary disease ■ heart failure ■ risk factors ■ stroke

It is widely accepted that age, sex, high blood pressure, smoking, dyslipidemia, and diabetes are the major risk factors for developing cardiovascular disease (CVD).[1] It also is recognized that CVD risk factors cluster and interact multiplicatively to promote vascular risk.[2] This knowledge led to the development of multivariable risk prediction algorithms incorporating these risk factors that can be used by primary care physicians to assess in individual patients the risk of developing all atherosclerotic CVD[3–12] or specific components of CVD, ie, coronary heart disease,[9,13–17] stroke,[18] peripheral vascular disease,[19] or heart failure.[20] Multivariable assessment has been advocated to estimate absolute CVD risk and to guide treatment of risk factors.[2,6] For instance, the Framingham formulation for predicting coronary heart disease (CHD) was incorporated into the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).[9] The Framingham CHD risk assessment tool has been validated in whites and blacks in the United States[9,10,21] and are transportable (with calibration) to culturally diverse populations in Europe, the Mediterranean region, and Asia.[9,10,22,23] Similar CHD risk prediction algorithms have been developed by other investigators worldwide and have been demonstrated to perform well.[14,15,17]

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Despite the availability of several validated risk prediction algorithms, their use has lagged in primary care.[24] One potential reason for physician inertia in using risk prediction instruments is the multiplicity of such algorithms, each for

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From Boston University, Department of Mathematics and Statistics (R.B.D., M.J.P.), School of Medicine (R.S.V., P.A.W., W.B.K.), and Department of Biostatistics (J.M.M.), Boston, Mass; Framingham Heart Study, Framingham, Mass (R.B.D., R.S.V., M.J.P., P.A.W., J.M.M., W.B.K.); and Unilever Research, Corporate Biology, Colworth Park, UK (M.C.).

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Correspondence to R.B. D'Agostino, PhD, Chairman, Professor of Mathematics/Statistics and Public Health, Boston University, Department of Mathematics and Statistics, 111 Cummington St, Boston, MA 02215.

predicting an individual CVD component. Indeed, there are occasions when a physician would like to target risk assessment and preventive measures to a specific cardiovascular end point such as myocardial infarction or stroke depending, for example, on an individual patient's family history, age, diabetic status, or predisposition to a particular outcome by valve disease. However, with this exception, primary care physicians engaged in preventive health maintenance want to assess risk of developing any major atherosclerotic CVD event using a general CVD risk assessment tool. Accordingly, the purpose of the present investigation was to formulate a single multivariable risk assessment tool that would enable physicians to identify high-risk candidates for any and all initial atherosclerotic CVD events using measurements readily available at the clinic or office.

Methods

Study Design and Sample

The design and selection criteria for the original Framingham Heart Study and the Framingham Offspring Study have been detailed elsewhere.[25,26] Detailed descriptions of the examination procedures and criteria for CVD events also have been reported.[27] Participants were eligible for the present investigation if they attended the 11th biennial examination cycle of original cohort (1968 to 1971, when measurement of high-density lipoprotein [HDL] cholesterol was available) or the first (1971 to 1975) or third (1984 to 1987) examination cycles of the Offspring cohort and were free of CVD. All participants provided written informed consent, and the study protocol was approved by the Institutional Review Board at the Boston Medical Center.

The study sample consisted of attendees of the baseline examinations free of prevalent CVD who were 30 to 74 years of age with nonmissing data on covariates. After exclusions, 8491 participants (mean age, 49 years; 4522 women) remained eligible.

Measurement of CVD Risk Factors

At each heart study examination, participants underwent a physical examination, anthropometry, blood pressure determination, and phlebotomy for vascular risk factors. Blood pressure measurements were made on the left arm of the seated participants with a mercury-column sphygmomanometer and an appropriately sized cuff; the average of 2 physician-obtained measures constituted the examination blood pressure. Serum total and HDL cholesterol levels were determined with standardized enzymatic methods. Cigarette smoking status was ascertained by self-report. Diabetes was defined as fasting glucose ≥126 mg/dL (offspring cohort) or 140 mg/dL (original cohort) or use of insulin or oral hypoglycemic medications. Antihypertensive medication use was ascertained by the physician examiner at the heart study and based on self-report.

Follow-Up and Outcome Events

All study participants were under continuous surveillance for the development of CVD events and death. The Framingham Heart Study defines CVD as a composite of CHD (coronary death, myocardial infarction, coronary insufficiency, and angina), cerebrovascular events (including ischemic stroke, hemorrhagic stoke, and transient ischemic attack), peripheral artery disease (intermittent claudication), and heart failure.[1] Information about CVD events on follow-up was obtained with the aid of medical histories, physical examinations at the study clinic, hospitalization records, and communication with personal physicians. All suspected new events were reviewed by a panel of 3 experienced investigators who evaluated all pertinent medical records. A separate review committee that included a neurologist adjudicated cerebrovascular events, and a heart

Statistical Analyses

Multivariable Models and Estimation of General CVD Risk Functions

We used sex-specific Cox proportional-hazards regressions[28] to relate risk factors to the incidence of a first CVD event during a maximum follow-up period of 12 years after confirming that the assumption of proportionality of hazards was met. From these models, we estimated mathematical CVD risk functions,[28] referred to as a general CVD risk function (Appendix); these functions were used to estimate 10-year absolute CVD risk.

Covariates included in Cox models were age, total cholesterol, HDL cholesterol, systolic blood pressure, antihypertensive medication use, current smoking, and diabetes status. Other variables such as diastolic blood pressure, body mass index, and triglycerides also were considered, but they were not statistically significant. The use of low-density lipoprotein cholesterol did not improve model fit or performance. All the continuous variables were naturally logarithmically transformed to improve discrimination and calibration of the models and to minimize the influence of extreme observations. We adjusted for the use of antihypertensive medication by modeling the impact of a participant's systolic blood pressure differently on the basis of use of such medications.

Assessment of Model Performance

We evaluated the ability of the risk prediction model to discriminate persons who experience a CVD event from those who do not using an overall c statistic,[29,30] expanding on a suggestion by Harrell et al.[31] This c statistic is analogous to the area under the receiver-operating characteristic curve. Briefly, 2 subjects are described as comparable if we can determine which one survived longer and concordant if their predicted probabilities of survival and survival times go in the same direction, and we can define the overall c statistic as the probability of concordance given comparability. The degree of overoptimism resulting from model assessment on the same data on which it was developed was estimated on the basis of bootstrap resampling of the original set.

We evaluated the calibration of our risk prediction model, a measure of agreement between observed and predicted events within 10 years, using a modified Hosmer-Lemeshow χ^2 statistic with 9 *df*.[29] For this purpose, we used the Kaplan-Meier estimator to obtain the observed incidence of CVD events, which was then compared with the CVD risk predicted by the model and classified into deciles.[29] We also calculated the proportion of CVD events that occurred in the top quintile of predicted risk (ie, sensitivity of the top quintile of predicted risk for identifying CVD events) and the proportion of individuals without events who are not in the top quintile of predicted risk (ie, specificity of the top quintile for CVD events).

The performance of the new CVD risk prediction model presented here was compared with that of another popular Framingham risk score developed by Wilson et al.[16] Because the latter score was developed for predicting CHD and not CVD, we performed a simple recalibration by multiplying the risk of each individual by the ratio of CVD incidence rate and the mean predicted risk based on the CHD risk function. Thus, we assessed how well the Framingham CHD risk functions[16] predicted CVD relative to the new CVD prediction model. A test for difference in 2 correlated c statistics proposed by Antolini et al[32] was used, along with the net reclassification improvement proposed by Pencina et al.[33] Reclassification improvement is defined as an increase in risk category for individuals who develop events and as a decrease for those who do not. Net reclassification improvement accounts for movement between categories in the wrong direction and applies different weights to events and nonevents. We used 0% to 6%, 6% to 20%, and >20% as risk categories.

Performance of General CVD Risk Prediction Model for Predicting Individual CVD Components

After generating sex-specific general CVD risk functions as detailed

Table 1. Summary Statistics for Risk Factors Used in Risk Models

Characteristics	Women (n=4522, 28% FOC)	Men (n=3969, 22% FOC)
Age, mean (SD), y	49.1 (11.1)	48.5 (10.8)
Total-C, mean (SD), mg/dL	215.1 (44.1)	212.5 (39.3)
HDL-C, mean (SD), mg/dL	57.6 (15.3)	44.9 (12.2)
Systolic BP, mean (SD), mm Hg	125.8 (20.0)	129.7 (17.6)
BP treatment, n (%)	532 (11.76)	402 (10.13)
Smoking, n (%)	1548 (34.23)	1398 (35.22)
Diabetes, n (%)	170 (3.76)	258 (6.50)
Incident CVD events, n (%)	456 (10.08)	718 (18.09)

FOC indicates Framingham original cohort; Total-C, total cholesterol; HDL-C, HDL cholesterol; and BP, blood pressure.

of CVD (CHD, stroke, intermittent claudication, congestive heart failure) after multiplication of the probability predicted by the general risk function by the proportion of all CVD events that were constituted by an individual component (ratio of Kaplan-Meier event rates). These were contrasted with models that we developed for individual CVD components using the same predictors.

Sex-Specific General CVD Risk Scores Sheets and Heart Age

General CVD risk functions were translated into sex-specific risk score sheets by use of previously described methods.[34] To facilitate easier understanding of the concept of risk, we also constructed "heart age" sheets. An individual's heart age is calculated as the age of a person with the same predicted risk but with all other risk factor levels in normal ranges. Although called heart age for simplicity of risk communication in primary care, the heart age really reflects vascular age. In the following, we use heart age/vascular age.

Simpler CVD Risk Prediction Models Using Nonlaboratory Predictors Routinely Ascertained in Primary Care

In addition to the main CVD risk prediction models described above, we developed simplified sex-specific models that used simple office-based predictors that are routinely obtained in primary care and do not require laboratory testing. These variables included age, body mass index, systolic blood pressure, antihypertensive medication use, current smoking, and diabetes status. The same modeling principles and model assessment techniques were applied to these simplified models.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

The risk factor characteristics of men and women in our sample at the baseline examinations are shown in Table 1. In our middle-aged sample, mean levels of serum total cholesterol and systolic blood pressure were similar in men and women, as were the prevalences of cigarette smoking and use of antihypertensive treatment. The prevalence of diabetes was substantially higher in men, whereas mean serum HDL levels were higher in women.

General CVD Risk Prediction Models

The multivariable-adjusted regression coefficients and hazard ratios for incident CVD events are presented in Table 2. We observed highly statistically significant relations of all risk factors evaluated and incident CVD.

The sex-specific CVD functions performed well in terms of both model discrimination and calibration. The c statistics for the risk function ranged from 0.763 (95% confidence interval [CI], 0.746 to 0.780) in men to 0.793 (95% CI, 0.772 to 0.814) in women. The degree of overoptimism was estimated at 0.001 for men and 0.003 for women, partly reflecting a large number of events and the potential limitation of the bootstrap resampling approach for assessing overoptimism.

The calibration χ^2 statistics for the CVD prediction models were 13.48 in men and 7.79 for the women, indicating excellent goodness of fit (for the lack of fit, $P=0.14$ and

Table 2. Regression Coefficients and Hazard Ratios

Variable	β*	P	Hazard Ratio	95% CI
Women [So(10)=0.95012]				
Log of age	2.32888	<0.0001	10.27	(5.65–18.64)
Log of total cholesterol	1.20904	<0.0001	3.35	(2.00–5.62)
Log of HDL cholesterol	−0.70833	<0.0001	0.49	(0.35–0.69)
Log of SBP if not treated	2.76157	<0.0001	15.82	(7.86–31.87)
Log of SBP if treated	2.82263	<0.0001	16.82	(8.46–33.46)
Smoking	0.52873	<0.0001	1.70	(1.40–2.06)
Diabetes	0.69154	<0.0001	2.00	(1.49–2.67)
Men [So(10)=0.88936]				
Log of age	3.06117	<0.0001	21.35	(14.03–32.48)
Log of total cholesterol	1.12370	<0.0001	3.08	(2.05–4.62)
Log of HDL cholesterol	−0.93263	<0.0001	0.39	(0.30–0.52)
Log of SBP if not treated	1.93303	<0.0001	6.91	(3.91–12.20)
Log of SBP if treated	1.99881	<0.0001	7.38	(4.22–12.92)
Smoking	0.65451	<0.0001	1.92	(1.65–2.24)
Diabetes	0.57367	<0.0001	1.78	(1.43–2.20)

So(10) indicates 10-year baseline survival; SBP, systolic blood pressure.

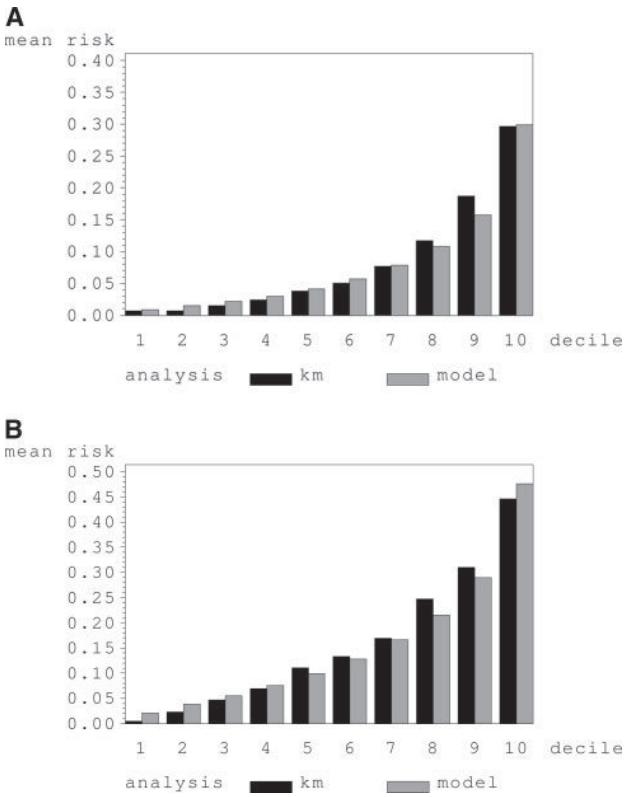

Figure. Calibration by decile for CVD function for women (A) and men (B). Vertical bars represent observed (Kaplan-Meier [km]; black) and model-based predicted (decile specific means; gray) probabilities of CVD event in 10 years in deciles of model-based predicted probabilities.

P=0.56, respectively). The Figure displays the calibration plots comparing predicted deciles of risk and actual observed risk in men and women. The top sex-specific quintiles of predicted risk identified ≈49% of men and 60% of women who experienced a first CVD event on follow-up (sensitivity). Proportions of men and women without CVD events who were not in the top quintile of predicted risk were 85% and 84%, respectively (specificity).

The Framingham CHD risk functions (Wilson et al[16]) performed less well for predicting CVD risk: The c statistics were lower (0.756 [95% CI, 0.739, 0.773] in men; for difference compared with our new model, P=0.051; 0.778 [95% CI, 0.756, 0.799] in women; for difference compared with our new model, P=0.003) and calibration was worse (χ^2=32.37 in men and 12.42 in women) relative to that noted above for the new CVD risk prediction models. The sensitivity of the top quintile of predicted risk using the CHD risk functions was slightly lower (47% in men and 56% in women) although specificity was similar (85% in men and 83% in women). The net reclassification improvement from using the new model was statistically significant for both men and women and reached 6.65% (P<0.001) and 7.95% (P=0.003), respectively.

Performance of General CVD Risk Prediction Model for Predicting Individual CVD Components

Tables 3 and 4 assess the performances of the sex-specific

Table 3. Performance Summary: Modified CVD Model Versus Event-Specific Own Model for Women

	CVD Model	Own Model
CHD (n=216)		
C	0.787	0.789
95% CI for C	(0.762–0.812)	(0.764–0.815)
χ^2	14.79	17.52
P for χ^2	0.097	0.041
Sensitivity of top quintile	57.55	56.38
Specificity of top quintile	81.94	81.88
Calibration factor	0.6086	
So(10)		0.9704
Stroke (n=84)		
C	0.769	0.774
95% CI for C	(0.715–0.822)	(0.721–0.828)
χ^2	5.26	6.86
P for χ^2	0.811	0.651
Sensitivity of top quintile	61.56	63.91
Specificity of top quintile	80.82	80.86
Calibration Factor	0.2385	
So(10)		0.9898
CHF (n=44)		
C	0.847	0.851
95% CI for C	(0.803–0.891)	(0.804–0.897)
χ^2	9.32	8.82
P for χ^2	0.408	0.454
Sensitivity of top quintile	76.49	83.73
Specificity of top quintile	80.58	80.65
Calibration factor	0.1250	
So(10)		0.9962
IC (n=66)		
C	0.829	0.848
95% CI for C	(0.786–0.872)	(0.810–0.887)
χ^2	11.33	11.63
P for χ^2	0.254	0.235
Sensitivity of top quintile	70.25	70.07
Specificity of top quintile	80.77	80.76
Calibration factor	0.1862	
So(10)		0.9918

C indicates model discrimination (c statistic); Sensitivity of top quintile, percent events captured by the top quintile of predicted risk; Specificity of top quintile, percent nonevents captured by the bottom 4 quintiles of predicted risk; So(10), baseline survival rate at 10 years; and IC, intermittent claudication.

specific algorithms for predicting risk of CHD, stroke, intermittent claudication, and heart failure. To apply the CVD functions for a specific component, the CVD-predicted probabilities were multiplied by the "calibration factor" given in Tables 3 and 4. For example, to compute the 10-year probability of CHD from the general CVD risk function in women, the CVD probability is calculated and then multiplied by 0.61, the proportion of first CVD events in women

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