Circulation
Volume 117, Issue 6, 12 February 2008; Pages 743-753
https://doi.org/10.1161/CIRCULATIONAHA.107.699579

EPIDEMIOLOGY

General Cardiovascular Risk Profile for Use in Primary Care

The Framingham Heart Study

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Abstract: ***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.

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

Received February 27, 2007; accepted November 30, 2007.

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 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 study neurologist examined most participants with suspected stroke.

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 above, we applied them to predict the risk of individual components 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.

Table 1. Summary Statistics for Risk Factors Used in Risk Models (Table view)

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.		

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.

Table 2. Regression Coefficients and Hazard Ratios (Table view)

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

Variable	β*	P	Hazard Ratio	95% CI
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.				
*Estimated regression coefficient				

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 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).

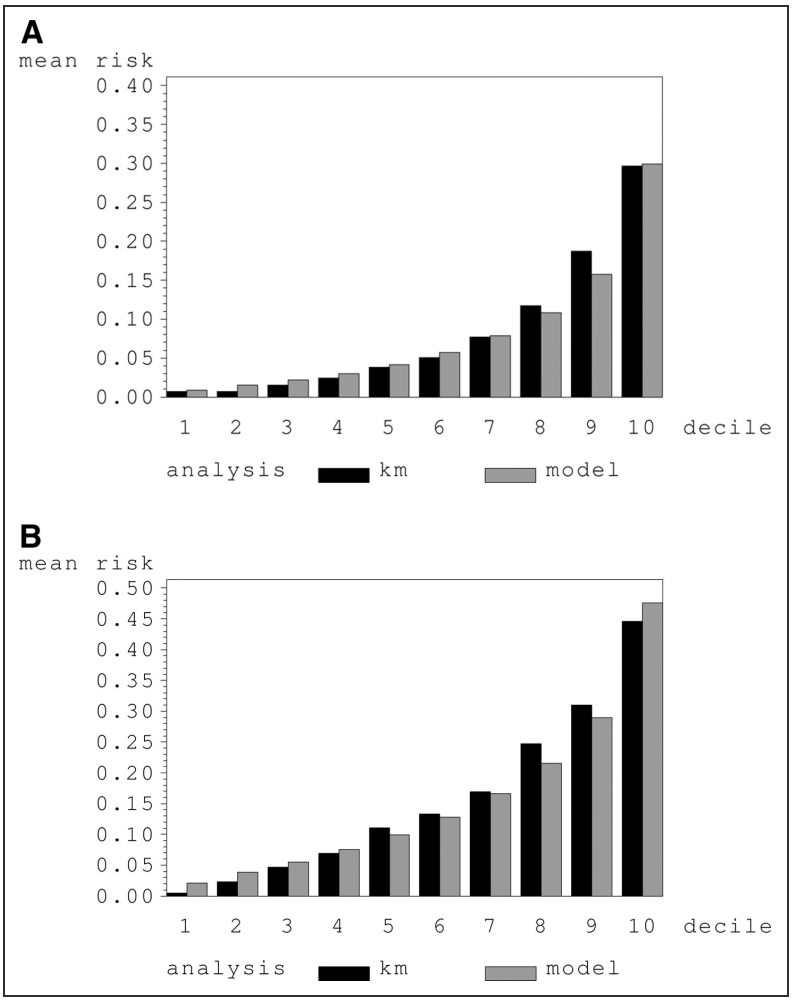

Figure. Calibration by decile for CVD function for women (A) and men (B). Vertical bars represent observed (Kaplan-Meier [km]; black) and model-based predicted (decile specific means; gray) probabilities of CVD event in 10 years in deciles of model-based predicted probabilities.

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 general CVD risk functions by comparing them with disease-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 that were CHD events.

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

	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

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.

	CVD Model	Own Model
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.

Table 4. Performance Summary: Modified CVD Model Versus Event-Specific Own Model for Men (Table view)

	CVD Model	Own Model
CHD (n=425)		
C	0.733	0.735
95% CI for C	(0.712–0.754)	(0.714–0.756)
χ^2	18.20	18.36
P for χ^2	0.033	0.031
Sensitivity of top quintile	45.94	45.70
Specificity of top quintile	83.23	83.20
Calibration factor	0.7174	
So(10)		0.9167
Stroke (n=93)		
C	0.826	0.835
95% CI for C	(0.789–0.863)	(0.797–0.874)
χ^2	26.11	9.21
P for χ^2	0.002	0.418
Sensitivity of top quintile	71.64	76.05
Specificity of top quintile	81.30	81.41
Calibration factor	0.1590	
So(10)		0.9883
CHF (n=67)		
C	0.841	0.845
95% CI for C	(0.799–0.883)	(0.802–0.888)
χ^2	27.23	15.30
P for χ^2	0.001	0.083
Sensitivity of top quintile	80.55	82.59
Specificity of top quintile	81.09	81.13
Calibration factor	0.1148	
So(10)		0.9927
IC (n=105)		
C	0.813	0.820
95% CI for C	(0.780–0.847)	(0.787–0.853)
χ^2	19.05	8.18

Abbreviations as in Table 3.

	CVD Model	Own Model
P for χ^2	0.025	0.516
Sensitivity of top quintile	60.29	66.65
Specificity of top quintile	81.15	81.34
Calibration factor	0.1804	
So(10)		0.9852
Abbreviations as in Table 3.		

From the comparison of discrimination and χ^2 statistics, it is evident that the general CVD risk formulation provides discrimination of individual CVD outcomes that is as good as the individual disease-specific multivariable risk formulations and is well calibrated. Similarly, the sensitivity of the upper quintile of the CVD risk function is comparable to that of the top quintile of disease-specific functions in both sexes (Tables 3 and 4). In the analyses of individual components, the regression coefficients for cholesterol were higher for CHD and intermittent claudication (relative to that for stroke and congestive heart failure [CHF]; data not shown). Systolic blood pressure was more strongly associated with stroke and CHF (compared with CHD and intermittent claudication), and smoking was more strongly associated with intermittent claudication (data not shown).

Derivation of CVD Prediction Scores and Heart Age/Vascular Age

Tables 5 and 6 and 7 and 8 provide score sheets that can be used for estimating the multivariable risk of CVD for women and men, respectively. Tables 9 and 10 give a different quantification of the same risk in the form of heart age/vascular age. We illustrate the use of these tables in the Appendix, and they are available at www.framinghamheartstudy.org/risk/index.html.

Table 5. CVD Points for Women (Table view)

Points	Age, y	HDL	Total Cholesterol	SBP Not Treated	SBP Treated	Smoker	Diabetic	
−3				<120				
−2		60+						
−1		50–59			<120			
0	30–34	45–49	<160	120–129		No	No	
1		35–44	160–199	130–139				
2	35–39	<35		140–149	120–129			
3			200–239		130–139	Yes		
4	40–44		240–279	150–159			Yes	
5	45–49		280+	160+	140–149			
6					150–159			
7	50–54				160+			
8	55–59							
9	60–64							
SBP indicates systolic blood pressure.								

Points	Age, y	HDL	Total Cholesterol	SBP Not Treated	SBP Treated	Smoker	Diabetic	
10	65–69							
11	70–74							
12	75+							
Points allotted								Total
SBP indicates systolic blood pressure.								

Table 6. CVD Risk for Women (Table view)

Points	Risk, %
≤−2	<1
−1	1.0
0	1.2
1	1.5
2	1.7
3	2.0
4	2.4
5	2.8
6	3.3
7	3.9
8	4.5
9	5.3
10	6.3
11	7.3
12	8.6
13	10.0
14	11.7
15	13.7
16	15.9
17	18.5
18	21.5
19	24.8
20	28.5
21+	>30

Table 7. CVD Points for Men (Table view)

Points	Age, y	HDL	Total Cholesterol	SBP Not Treated	SBP Treated	Smoker	Diabetic	
−2		60+		<120				
−1		50–59						

Points	Age, y	HDL	Total Cholesterol	SBP Not Treated	SBP Treated	Smoker	Diabetic	
0	30–34	45–49	<160	120–129	<120	No	No	
1		35–44	160–199	130–139				
2	35–39	<35	200–239	140–159	120–129			
3			240–279	160+	130–139		Yes	
4			280+		140–159	Yes		
5	40–44				160+			
6	45–49							
7								
8	50–54							
9								
10	55–59							
11	60–64							
12	65–69							
13								
14	70–74							
15	75+							
Points allotted								Total

Table 8. CVD Risk for Men (Table view)

Points	Risk, %
≤−3 or less	<1
−2	1.1
−1	1.4
0	1.6
1	1.9
2	2.3
3	2.8
4	3.3
5	3.9
6	4.7
7	5.6
8	6.7
9	7.9
10	9.4
11	11.2
12	13.2
13	15.6

Points	Risk, %
14	18.4
15	21.6
16	25.3
17	29.4
18+	>30

Table 9. Heart Age/Vascular Age for Women (Table view)

Points	Heart Age, y
<1	<30
1	31
2	34
3	36
4	39
5	42
6	45
7	48
8	51
9	55
10	59
11	64
12	68
13	73
14	79
15+	>80

Table 10. Heart Age/Vascular Age for Men (Table view)

Points	Heart Age, y
<0	<30
0	30
1	32
2	34
3	36
4	38
5	40
6	42
7	45
8	48
9	51
10	54
11	57

Points	Heart Age, y
12	60
13	64
14	68
15	72
16	76
≥17	>80

Simpler CVD Risk Prediction Models Using Nonlaboratory Predictors

The simple office-based CVD risk prediction function that incorporated body mass index (instead of total and HDL cholesterol) performed reasonably well (Table I of the online Data Supplement). The discrimination c statistics was 0.749 (95% CI, 0.731, 0.767) for men and 0.785 (95% CI, 0.764, 0.806) for women (for difference compared with our full model, $P<0.001$ and 0.013, respectively). Calibration χ^2 statistics were 13.61 (for the lack of fit, $P=0.14$) for men and 10.24 for women (for the lack of fit, $P=0.33$). The top sex-specific quintiles of predicted CVD risk identified ≈48% of men and 58% of women who experienced a first CVD event on follow-up (sensitivity). Proportions of men and women without events who were not in the top quintile of risk were 85% and 83%, respectively (specificity). Tables IIA through IIC and IIIA through IIIC in the Data Supplement provide score sheets that can be used to estimate the multivariable risk of CVD and heart age/vascular age for women and men, respectively, using the office-based nonlaboratory predictors.

Discussion

It is widely accepted that CVD constitutes a major public health problem in the United States[35] and worldwide.[36] The lifetime risk of CVD is substantial,[37] and the condition is often silent or may strike without warning, underscoring the importance of prevention. Investigators have identified key risk factors that account for most CVD burden in the community, and numerous reports have demonstrated the clustering and conjoint influences of multiple risk factors in mediating disease vascular risk.[2,4,6,7,38–41] Consequently, researchers have devised multivariable risk prediction tools that synthesize vascular risk factor information to yield estimates of absolute CVD risk (also referred to as global CVD risk) in individual patients.[4,7,8,10–12,42] The estimation of global CVD risk facilitates the matching of the intensity of risk factor lowering with the estimated probability of disease, thereby rendering treatment most cost-effective.[38,42–44] For instance, national cholesterol guidelines link treatment thresholds and goals to global coronary heart disease risk.[9] In addition to reducing the number needed to treat to prevent a CVD event, multivariable risk assessment also avoids overlooking high-risk CVD candidates with multiple marginal risk factors and avoids needlessly alarming persons with only 1 isolated risk factor. Furthermore, analyses that fail to examine risk factors in combinations usually greatly overestimate the population-attributable risks associated with individual risk factors.[45]

Researchers also have developed disease-specific formulations to predict risk of developing specific CVD events such as CHD events or stroke.[13–16,18–20] The present investigation is based on the premise that although the impacts of risk factors vary from 1 specific CVD type to another, there is

sufficient commonality of risk factors to warrant generating a single general CVD risk prediction instrument that could accurately predict global CVD risk and the risk of individual components. Our study was motivated by our presumption of a need to simplify risk prediction in office-based practices by replacing disease-specific algorithms with a single general CVD prediction tool.

Framingham investigators formulated a general CVD risk function several years ago.[46] Using a multivariable-logistic regression model, we reported that an algorithm that identified persons at high risk of atherosclerotic CVD in general also was effective for identifying persons at risk for each of the specific events, including CHD, stroke, intermittent claudication, and heart failure. However, that risk formulation was developed in 1976; was based on a limited number of events; did not include HDL cholesterol, a powerful influence on lipid atherogenesis; and did not focus on estimates of absolute risk. A subsequent CVD risk function used a parametric model, but that investigation did not evaluate the ability of a general CVD risk profile to predict individual outcomes.[3]

The present investigation extends and expands on the previous general CVD risk formulation on the basis of a larger number of events, incorporates HDL cholesterol, and estimates absolute CVD risk. We propose a general CVD risk function that demonstrates very good discrimination and calibration both for predicting CVD and for predicting risk of individual CVD components (comparable to disease-specific algorithms). The parallelism between atherosclerosis in different vascular territories in terms of sharing a common set of risk factors explains why the general CVD risk function performs well for predicting the individual components. The C statistic for the general CVD risk prediction models ranged from 0.76 to 0.79, suggesting that additional risk factors may be considered in future studies for inclusion in the models to further improve model discrimination. The general CVD risk prediction function performed better than the Framingham CHD risk function[16] for predicting CVD risk. The specific focus on CVD risk and the modeling of risk factors as continuous variables (as opposed to the use of categories in the CHD risk function developed by Wilson et al[16]) may explain the better performance of the former.

Comparison With Other CVD Risk Prediction Tools

Although several instruments have been formulated to predict CHD,[9,14,15,17] tools that predict CVD are fewer. For instance, the scoring system developed by the Prospective Cardiovascular Munster Study (PROCAM) investigators[14] focuses on prediction of acute coronary events. The British[4] and New Zealand[7] guidelines use an older Framingham equation[3] to facilitate prediction of global CVD risk. The present report offers an updated risk function based on a greater number of CVD events in a more contemporary time period with evaluation of calibration and “exchangeability” for disease-specific risk profiles.

Ridker et al[10] recently published a Reynolds risk score for predicting CVD in women. The Reynolds risk score incorporates family history of CVD, high-sensitivity C-reactive protein, and hemoglobin A_{1c} (the latter in individuals with diabetes). In addition, the Reynolds risk score was developed in women alone and did not include some CVD end points (such as intermittent claudication), and its transportability to other samples or its exchangeability for disease-specific profiles is unknown. It is conceivable that the general CVD risk algorithm proposed in the present investigation and the Reynolds risk score could be sequential components of a staged approach: The former is a simpler formulation using only lipids from several eligible candidate biomarkers, and the

latter is a strategy that could be applied to a specific subgroup identified by the former that is targeted for measurement of additional biomarkers. The validity of such a premise of sequential testing warrants further research.

The Systematic Coronary Risk Evaluation (SCORE) project[5] formulated a CVD risk estimation algorithm (HEARTSCORE) that has been adopted by the Joint European Societies' guidelines on CVD prevention.[6] Whereas the SCORE risk functions have the advantage of being based on European epidemiological studies, the HEARTSCORE predicts only fatal CVD, which can result in an underestimation of the total CVD burden.

More recently, 2 CVD risk scores have been formulated by investigators in the United Kingdom.[11,12] Brindle et al[11] have formulated a CVD risk prediction algorithm (QRISK) using data on >1 million nondiabetic patients in general practice in the United Kingdom. The QRISK (risk score using the QRESEARCH database) algorithm incorporates family history and social deprivation (in addition to the risk factors included in the Framingham risk score) and calibrates better to the UK population than the older Framingham CVD risk functions formulated by Anderson et al,[3] but clinical CVD events were not formally adjudicated with a review process (as is done at Framingham).[11] A formal comparison of these 2 scores on a third cohort could prove very useful.

The second risk score (ASSIGN; ASsessing cardiovascular risk using SIGN guidelines to assign potential patients to preventive treatment) from the United Kingdom was developed by investigators using >12 000 individuals from the Scottish Heart Health Extended cohort.[12] The ASSIGN score also incorporated family history and deprivation and performed marginally better than the older Framingham CVD risk functions.[3,12] Additional investigations are warranted to formally compare the performance of the QRISK[11] and ASSIGN[12] scores relative to the new CVD risk functions proposed here. It is conceivable that addition of other risk factors variables (such as family history or deprivation) may improve the performance of the general CVD risk function proposed in this investigation. It also is likely that risk scores for CVD developed within countries may be better calibrated for risk estimation than the Framingham general CVD risk function.

The metabolic syndrome, a much-debated multivariable risk profile, also can be used to predict CVD. This syndrome has been compared with the Framingham risk score as a predictor of CHD.[47] The presence of the metabolic syndrome was found to be a significant predictor of CHD, but it was not quite as good a predictor as the Framingham risk score.

Strengths and Limitations

The large community-based sample that is under continuous surveillance using the same standardized criteria for CVD incidence and the assessment of model performance measures such as discrimination, calibration, and exchangeability with disease-specific profiles strengthen the present investigation. However, several limitations of the present study must be acknowledged. Given the predominantly white Framingham sample, the transportability of the CVD risk function in other samples must be evaluated. Other Framingham risk functions have shown themselves to be transportable,[19] at times with a recalibration.[19–21] Additionally, it has been emphasized that risk scores per se do not translate to better patient outcomes unless they are used appropriately by physicians using risk communication tools and the communicated risks are well understood by the patients.[24,48]

Implications

Individuals with a high global CVD risk (eg, a 10-year risk of a CVD event >20%) require more aggressive risk factor modification. The goal of therapy of dyslipidemia, diabetes, and hypertension should be linked to the global CVD risk. Although atherosclerotic disease-specific profiles are available, a multivariable risk formulation for global CVD made up of standard risk factors is particularly relevant for primary prevention of atherosclerotic CVD because it is intuitive that measures taken to prevent any 1 CVD outcome can be expected to also prevent risk of the other CVD outcomes. Therefore, use of a general CVD risk score is an attractive option in office-based primary care practices. Serial assessment of global CVD risk could be used to monitor progress of patients on treatment and improvement in their multivariable risk scores.

Other risk factors not included in the general risk profile must be taken into account in evaluating risk and selecting the most efficacious treatment. These include abdominal obesity, ECG evidence of left ventricular hypertrophy, indications of insulin resistance, triglycerides, and a strong family history of premature CVD. Obesity is not included because its influence is largely attributable to its promotion of insulin resistance and its attendant CVD risk factors.

Presentations

The CVD risk functions of Table 2 are easily programmed, for example, as an Excel spreadsheet or as the score sheets of Tables 5 through 10. This was done with the Adult Treatment Panel III cholesterol guidelines and the SCORE equations.[5,9,12] In this investigation, we also present a new concept of heart age/vascular age. Here, the CVD risk of an individual is transformed to the age of a person with the same risk but all other risk factors at the normal level (nontreated systolic blood pressure of 125 mm Hg, total cholesterol of 180 mg/dL, HDL of 45 mg/dL, nonsmoker, nondiabetic). As seen in the example given in the Appendix, a 61-year-old woman with risk factors above normal levels has the heart age/vascular age of a 73-year-old female with normal risk factors; similarly a 53-year-old man with risk factors has the heart age/vascular age of a man 64 years of age with normal risk factors.

Conclusions

The present investigation presents a sex-specific multivariable risk factor algorithm that can be conveniently used to assess general CVD risk and risk of individual CVD events (coronary, cerebrovascular, and peripheral artery disease and heart failure). The estimated absolute CVD event rates predicted can be used to quantify risk and to guide preventive primary care. The validity and transportability of the proposed general CVD risk function should be evaluated in future studies.

Appendix

Risk Estimation From Cox Model and From Score Sheet

The following examples illustrate the direct application of the Cox model and the use of the score sheet to estimate CVD risk in women and men.

General formula: equation

$$\hat{p} = 1 - S_0(t)^{\exp(\sum_{i=1}^{p} \beta_i X_i - \sum_{i=1}^{p} \beta_i \bar{X}_i}$$

where $S_0(t)$ is baseline survival at follow-up time t (here t=10 years; see Table 2), βi is the estimated regression coefficient (log hazard ratio; see Table 2), Xi is the log-transformed value of the ith risk factor, (if continuous), $\bar{X}_i$ is the corresponding mean, and p denotes the number of risk factors.

Case 1—Women (baseline 10-year survival=0.95012). A 61-year-old woman not treated for high blood pressure has a total cholesterol of 180 mg/dL, HDL of 47 mg/dL, and systolic blood pressure of 124 mm Hg and is a current smoker but is not diabetic (see Table 11).

Table 11. Case 1 (Table view)

Risk Factor	Value	Points
Age	61	9
Total cholesterol	180	1
HDL	47	0
Nontreated SBP	124	0
Treated SBP	…	0
Smoker	Yes	3
Diabetes	No	0
Point total	13	
Estimate of risk, %	10.0	
Heart age/vascular age, y	73	
SBP indicates systolic blood pressure.		

The risk estimate based on the Cox model is computed as follows: equation

$$\sum_{i=1}^{p} \beta_i X_i = 2.32888*\log(\mathbf{61}) + 1.20904*\log(\mathbf{180})$$

$$-0.70833*\log(\mathbf{47}) + 2.76157*\log(\mathbf{124}) + 2.82263*$$

$$+0.52873*\mathbf{1} + 0.69154*\mathbf{0} = 26.9653.$$

equation

$$\sum_{i=1}^{p} \beta_i \bar{X}_i = 2.32888*3.8686 + 1.20904*5.350$$

$$-0.70833*4.0176 + 2.76157*4.2400$$

$$+2.82263*0.5826 + 0.52873*0.3423$$

$$+0.69154*0.0376 = 26.1931.$$

equation

$$\hat{p} = 1 - S_0(t)^{\exp(\Sigma_{i=1}^{p} \beta_i X_i - \Sigma_{i=1}^{p} \beta_i \bar{X}_i)} = 1 - 0.95012^{\exp(26.9653 - 26.19}$$

equation

$$= 0.1048 \approx 10.5\%$$

The points system gives a 10-year estimate of risk of 10.0%. Using the Cox model directly gives 10.5%. The Cox estimate for a 61-year-old woman of normal risk is 6.7%.

Case 2—Men (baseline 10-year survival=0.88936). A 53-year-old man on treatment for systolic blood pressure has a total cholesterol of 161 mg/dL, HDL of 55 mg/dL, and systolic blood pressure of 125 mm Hg and is diabetic but is not a current smoker (see Table 12).

Table 12. Case 2 (Table view)

Risk Factor	Value	Points
Age	53	8
Total cholesterol	161	1
HDL	55	−1
Nontreated SBP	…	0
Treated SBP	125	2
Smoker	No	0
Diabetes	Yes	3
Point total	13	
Estimate of risk, %	15.6	
SBP indicates systolic blood pressure.		

Risk Factor	Value	Points
Heart age/vascular age, y	64	
SBP indicates systolic blood pressure.		

The risk estimate based on the Cox model is computed as follows: equation

$$\sum_{i=1}^{p} \beta_i X_i = 3.06117*\log(\mathbf{53}) + 1.12370*\log(\mathbf{161})$$

$$-0.93263*\log(\mathbf{55}) + 1.93303*\mathbf{0} + 1.99881*\log(\mathbf{12}$$

$$+0.65451*\mathbf{0} + 0.57367*\mathbf{1} = 24.3509.$$

equation

$$\sum_{i=1}^{p} \beta_i \bar{X}_i = 3.06117*3.8560 + 1.12370*5.3420$$

$$-0.93263*3.7686 + 1.93303*4.3544 + 1.99881*0.501$$

$$+0.65451*0.3522 + 0.57367*0.0650 = 23.9802.$$

equation

$$\hat{p} = 1 - S_0(t)^{\exp(\Sigma_{i=1}^{p} \beta_i X_i - \Sigma_{i=1}^{p} \beta_i \bar{X}_i)} = 1 - 0.88936^{\exp(24.3509 - 23.98}$$

$$= 0.1562 \approx 15.6\%$$

The points system gives a 10-year estimate of risk of 15.6%. Using the Cox model directly gives 15.6%. The Cox estimate for a 53-year-old man of normal risk is 9.1%.

CLINICAL PERSPECTIVE

Cardiovascular disease (CVD) remains the leading cause of mortality and morbidity. A plethora of effective drugs for the major risk factors of CVD such as blood pressure, high cholesterol, and diabetes control exists. Prevention strategies assessing the risk of CVD and identifying the risk factors associated with the risk have become major approaches for reducing CVD and its unfavorable consequences. Presently, many of these strategies involve focusing on a component of CVD such as hard coronary disease consisting of myocardial infarction and coronary death, assessing the risk by mathematical risk functions or scoring functions, and designing treatment (behavioral and/or drug) according to the level of risk. Our belief is that, especially in the primary care setting, CVD risk should not be directed only to a component of CVD such as coronary disease or stroke but rather to all manifestation of CVD. In particular, individuals with high overall CVD risk require aggressive risk factor modification. In the present article, we present simple sex-specific risk functions that assess the 10-year risk (probability) of developing overall CVD. These functions involve inputs of blood pressure, cholesterol levels, diabetes, and smoking. Thus, not only is the overall risk quantified, but the source of the risk can be identified for treatment. Simple scoring sheets are presented that make the CVD functions immediately usable. Finally, straightforward adjustments to the functions can be used also to assess the risk for specific components of CVD.

Article Information

Notes

Guest Editor for this article was Eric B. Rimm, ScD.

The online Data Supplement can be found with this article at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107. 699579/DC1.

Article Information

Published online January 22, 2008.

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Acknowledgments

Sources of Funding

Support was received from the National Heart, Lung, and Blood Institute's Framingham Heart Study, National Institutes of Health, as well as from National Institutes of Health grant 5R0l-NS17950. Framingham Heart Study research is supported by NIH/NHLBI contract No. N01-HC-25195. Dr Kannel was supported by the Visiting Scientist Program supported by AstraZeneca. Dr Vasan is supported in part by 2K24 HL04334 (NHLBI). Dr Cobain was supported by Unilever Research. Dr Massaro was supported in part by a grant from Unilever Research.

Disclosures

Dr D'Agostino has served on as a consultant or on the advisory board for Sanofi and Pfizer. Dr Cobain has ownership interest in Milife.com. Dr Kannel has served on the speakers' bureau and received honoraria from BMS/Sanofi. The other authors report no conflicts.

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