Primary and subsequent coronary risk appraisal: New results from The Framingham Study

Ralph B. D'Agostino, PhD,[a] Mason W. Russell, MAPE,[b] Daniel M. Huse, MA,[b] R. Curtis Ellison, MD,[c] Halit Silbershatz, PhD,[a] Peter W.F. Wilson, MD,[d] and Stuart C. Hartz, ScD[b] *Boston, Burlington, and Framingham, Mass*

Background Coronary heart disease continues to be one of the most common chronic illnesses in the United States and most of the developed world. Clinicians and health authorities have interest in identifying individuals at increased risk of CHD. The Framingham Heart Study has over the years produced mathematical "health risk appraisal models" that relate risk factors to the probability of developing CHD.

Methods and Results New sex-specific models from The Framingham Heart Study for primary and secondary (subsequent) CHD have been produced. The primary CHD models are appropriate for assessing CHD risk in persons free of cardiovascular disease and contain risk factors such as triglyceride levels, alcohol use, and menopausal status, risk factors not included in previously published models. The subsequent CHD models are applicable for persons with a history of CHD or ischemic stroke who have survived the acute period after the event. Age, blood lipid levels (total cholesterol and HDL cholesterol), and diabetes status are significant for men and women. In addition, systolic blood pressure and cigarette smoking are significant predictors of subsequent CHD in women.

Conclusions These new models are useful tools for better understanding the relation between risk factors and the occurrences of CHD events in individuals who are free of cardiovascular disease as well as persons who have had a prior CHD event or stroke. With the development of these latter models, the importance of blood lipid levels, diabetes, and, in women, systolic blood pressure and cigarette smoking as independent predictors of risk is once again underscored. (Am Heart J 2000;139:272-81.)

Coronary heart disease (CHD) continues to be one of the most common chronic illnesses in the United States and most of the developed world. Current estimates of CHD prevalence in the United States range as high as 13.5 million persons.[1] Although the annual case-fatality rate has declined by nearly 30% since the early 1980s, more than one fifth of total annual deaths in the United States are attributable to CHD-related causes.[1]

Clinicians and health authorities for many years have expressed interest in methods of identifying individuals who are at increased risk of CHD. For more than 30 years, The Framingham Heart Study investigators have developed mathematic predictive models (known as health risk appraisal functions) that relate risk factors measured among disease-free individuals in the Framingham population to the probability of cardiovascular disease (CVD) developing, including CHD, stroke, and other manifestations. The first such models were published in the mid-1960s[2]; subsequent models have been based on larger and more recent follow-up and have used better predictive variables and increasingly more sophisticated statistical methods, including logistic regression,[3] Cox proportional hazards regression,[4,5] and accelerated failure time analysis.[6,7]

Our understanding of the multifactorial nature of cardiovascular disease and the interrelations among risk factors has improved with the passage of time. The ability to examine these relations quantitatively in the Framingham database has improved with the addition of data from recent follow-up examinations. A number of new variables, including triglyceride levels[5,8-12] and ethyl alcohol consumption,[13,14] have been incorporated in the models to explore their roles as independent risk predictors and the extent to which risk prediction is improved by their inclusion. Also, in keeping with the growing public interest in secondary prevention of CHD, attention has begun to turn to models that predict risk of recurrent or subsequent CHD events in persons with a history of coronary or cardiovascular disease.

From the [a]Department of Mathematics, College of Arts and Sciences, Boston University; [b]Medical Research International, Burlington; [c]Department of Preventive Medicine, Boston University School of Medicine; and [d]The Framingham Heart Study, Framingham.
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Reprint requests: Ralph B. D'Agostino, PhD, Department of Mathematics, Boston University, 111 Cummington St, Boston, MA 02215.
E-mail: ralph@math.bu.edu

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Table I. Descriptive statistics for risk factors

Variable	CVD free				History of CHD/ischemic stroke			
	Mean	SD	Min	Max.	Mean	SD	Min	Max
Men								
Age (y)	49.44	9.21	35	74	60.37	8.42	35	74
Total cholesterol (mg/dL)	213.18	38.16	100	444	221.44	42.13	71	450
HDL cholesterol (mg/dL)	44.24	11.83	12	129	40.74	12.63	14	132
ln (Total cholesterol/HDL cholesterol)	1.59	0.31	0.535	3.005	1.72	0.33	0.511	3.094
Triglycerides (mg/dL)	359.41	344.83	15	7995	NA*			
SBP (mm Hg)	129.47	17.14	88	229	136.56	20.47	89	225
ln (SBP) (mm Hg)	4.86	0.13	4.477	5.434	4.91	0.15	4.489	5.416
SBP/antihypertensive Rx interaction	1.72	5.11	0	20.25	5.23	7.79	0	20.25
Prevalence of diabetes	0.039	0.192	0	1	0.153	0.359	0	1
Prevalence of cigarette smoking	0.341	0.474	0	1	0.333	0.472	0	1
Alcohol consumption (oz/wk)	5.32	6.43	0	57.15	4.96	6.73	0	42.59
Women								
Age (y)	49.89	9.55	35	74	59.59	8.06	37	74
Prevalence of menopause	0.542	0.498	0	1	0.937	0.244	0	1
Age/menopause interaction	30.40	28.52	0	74	59.31	16.70	0	74
Total cholesterol (mg/dL)	215.53	43.10	52	511	243.34	46.80	132	509
HDL cholesterol (mg/dL)	56.84	15.11	14	139	50.51	14.85	21	118
ln (Total cholesterel/HDL cholesterol)	1.35	0.32	0.123	2.958	1.60	0.33	0.766	2.767
Triglycerides (mg/dL)	265.59	254.34	6	6539	NA*			
SBP (mm Hg)	125.40	19.25	77.5	220	141.47	23.67	86	225
ln (SBP) (mmHg)	4.82	0.148	4.35	5.394	4.94	0.16	4.454	5.416
SBP/antihypertensive Rx interaction	1.84	5.25	0	20.25	6.82	8.3	0	20.25
Prevalence of diabetes	0.025	0.155	0	1	0.150	0.356	0	1
Prevalence of cigarette smoking	0.342	0.474	0	1	0.273	0.446	0	1
Alcohol consumption (oz/wk)	2.24	3.19	0	34.20	1.52	3.12	0	31.92

*Not measured in cohort examination 15.

Estimation of such models has become feasible only recently with the accumulation of additional longitudinal data on survivors of CHD or CVD events.

In this article we present updates from The Framingham Study for the relation between risk factors and the occurrence of CHD events in the form of health risk appraisal models for men and women. Separate models are reported for persons who are free of CVD and for persons with a history of CHD or ischemic stroke. The 4 models reflect the combined experience of the original Framingham cohort and participating offspring and their spouses.

Methods

Subjects, risk factors, and end points

Members of the original Framingham cohort and the Offspring-Spouse Study were eligible for inclusion in this study if they had participated since the 1970s in 1 or more clinic visits at which fasting blood lipid levels were measured and were 35 to 74 years of age at time of examination. Clinic visits by cohort members are referred to as examinations, which are numbered sequentially from the first examination (1948 to 1950) and occur on average at 2-year intervals. Clinic visits by offspring began in 1971 and have occurred at roughly 4-year intervals since the late 1970s; these are referred to as cycles. For the initial CHD event models, examination 11 (1968 to 1971) for the cohort and cycles 1 (1971 to 1975), 2 (1979 to 1982), and 3 (1984 to 1987) for offspring were used; the subsequent CHD event models also included examination 15 (1977 to 1979) for the cohort. This population has been described elsewhere.[6] As in earlier investigations,[15-17] use of the technique of pooled repeated measures allowed subjects to contribute multiple person-examinations to the analysis if data on covariates were available at each examination.

For inclusion in the analysis of initial CHD events, participants had to be free of all of the following CVDs before examination: CHD (includes myocardial infarction, coronary insufficiency, and angina pectoris), stroke (ischemic or hemorrhagic), transient ischemic attack, congestive heart failure, and intermittent claudication. For the analysis of subsequent CHD events, participants had to have had at least 1 CHD event or ischemic stroke before examination and have survived the acute stage of that event. Subsequent CHD includes mostly hospitalized events consisting of myocardial infarction, coronary insufficiency, angina pectoris, and sudden and nonsudden coronary death.

Risk factors considered in the analyses included age, the average of 2 clinic measurements of systolic blood pressure (SBP) (in millimeters of mercury), cigarette smoking status (1 if current smoker, 0 otherwise), fasting lipid level (in milligrams per deciliter) (total cholesterol by the Abell-Kendall method, HDL cholesterol measured after heparin-manganese precipitation, and triglycerides by the Kessler method), presence of left ventricular hypertrophy (LVH) as measured by the electrocardiogram, physician diagnosis of diabetes at the cur-

Table II. Numbers of initial and subsequent CHD events

	Initial				Subsequent			
	Men		Women		Men		Women	
Event	Frequency	%	Frequency	%	Frequency	%	Frequency	%
Myocardial infarction	117	52.2	39	36.1	96	45.1	37	47.4
Angina pectoris	91	40.7	61	56.5	40	18.8	17	21.8
Coronary insufficiency	3	1.3	6	5.6	24	11.3	11	14.1
Sudden CHD death	10	4.5	2	1.8	33	15.5	4	5.1
Nonsudden CHD death	3	1.3	0	0.0	20	9.4	9	11.5
Totals	224	100.0	108	100.0	213	100.0	78	100.0

rent or a previous examination, ethyl alcohol consumption in equivalent ounces per week, use of antihypertensive medication (yes/no), postmenopausal status in women (yes/no), and body mass index in kilograms per meter squared. In the analyses of subsequent CHD events, several temporal covariates (time since first CVD event, time since last CVD event, and year of examination) were also considered.

All subjects were monitored for up to 4 years after an examination to observe the occurrence of initial or subsequent CHD events. Event occurrence was determined by a panel of physicians blinded to risk factor measurements who reviewed information from regular clinic visits and subjects' medical records. Criteria for diagnosis of each type of CHD event have been reported elsewhere.[16]

Statistical modeling

Preliminary models for men and women were estimated with the Weibull accelerated failure regression model[6,7,18] for up to 4 years of follow-up, with myocardial infarction (recognized or unrecognized), CHD, and CVD as alternative end points. Initially all the risk factors described were included in the models. Risk factors were dropped from a given model through backward elimination if their estimated β coefficients did not differ significantly from zero ($P < .10$ for initial event models, $P < .20$ for subsequent event models) in preliminary analyses.

Even though the variable that measured presence of LVH has been demonstrated to be a potent predictor of risk in previous analyses[6] and would have qualified for inclusion based on statistical significance criteria, we chose to exclude it for 2 reasons. First, consistent population data on this condition are not available for forecasting purposes. Also, preliminary analyses indicated that the estimated β coefficients of other covariates were insensitive to the inclusion of LVH in the models, thus suggesting that its relation to CHD risk is essentially independent of those for other risk factors.

The Weibull regression model applied to the data was evaluated for nonproportionality of the underlying hazard[6,7,18] for the models with up to 4 years of follow-up by testing whether estimated β coefficients of risk factors were sensitive to the inclusion of time-dependent variables. Estimates did not significantly vary when such variables were added to the regression models, and thus the assumption of proportionality was deemed appropriate. Use of the Weibull model offers a simple multivariate parametric approach for the estimation of risk over any follow-up time up to 4 years. For example, estimates of 1- or 2-year risks for various profiles of the risk functions could be estimated.

In both the initial CHD and subsequent CHD models, total and HDL cholesterol were entered as the log ratio of total to HDL cholesterol to reduce the effects of skewness in their distributions and to avoid the need to include age interaction terms with each measure.[6] This composite measure has been found to result in better statistical fit than either or both measures stated in natural or logarithmic units.[5,6] Skewness in the distributions of SBP and triglycerides was also addressed through logarithmic transformation. Use of antihypertensive medication was included as an interaction with SBP between 110 and 200 mm Hg inclusive based on findings from an earlier investigation concerning stroke[19] that found that including a blood pressure/medication interaction term in a stroke risk appraisal model significantly improved statistical fit.

Results

Subjects and risk factors

A total of 10,156 person-examinations (4823 men, 5333 women) for individuals free of CVD, and 1176 person-examinations (718 men, 458 women) for individuals with history of CHD or ischemic stroke, were included in the initial CHD and subsequent CHD event models, respectively. Descriptive statistics (mean, SD, range) for risk factors included in the initial CHD and subsequent CHD models are reported in Table I.

CHD events

Numbers of initial and subsequent CHD events occurring during the 4-year intervals after the selected person-examinations among men and women are reported in Table II.

Health risk appraisal models for initial CHD

CHD risk appraisal functions for men and women free of CVD at the time of examination are summarized in Table III. As a consequence of the Weibull specification, a negative β coefficient for a risk factor indicates that larger values of the risk factor are associated with shorter time to event and thus with increased risk of an event. Log triglycerides proved to be statistically signifi-

Figure 1

Age		HDL-C									
35-39	0	Total-C	25	30	35	40	45	50	60	70	80
40-44	1	160	8	7	5	5	4	3	2	1	0
45-49	3	170	8	7	6	5	4	4	2	1	0
50-54	4	180	9	7	6	5	5	4	3	2	1
55-59	6	190	9	8	7	6	5	4	3	2	1
60-64	7	200	9	8	7	6	5	5	3	2	1
65-69	9	210	10	8	7	6	6	5	4	3	2
70-74	10	220	10	9	8	7	6	5	4	3	2
		230	10	9	8	7	6	6	4	3	2
		240	10	9	8	7	7	6	5	4	3
		250	11	9	8	8	7	6	5	4	3
		260	11	10	9	8	7	6	5	4	3
		270	11	10	9	8	7	7	5	4	3
		280	11	10	9	8	8	7	6	5	4
		290	12	10	9	9	8	7	6	5	4
		300	12	11	10	9	8	7	6	5	4

Diabetes	Cigs
No = 0	No=0
Yes = 3	Yes = 4

SBP			
if untreated		if treated	
<110	0	<110	0
110-124	1	110-114	1
125-144	2	115-124	2
145-164	3	125-134	3
165-184	4	135-144	4
185-214	5	145-154	5
>=215	6	155-215	6
		>=215	6

Pts	2 -yr Probabilities	Pts	2 -yr Probabilities	Pts	2 -yr Probabilities
0	0%	14	1%	28	17%
2	0%	16	2%	30	24%
4	0%	18	3%	32	32%
6	0%	20	4%	34	43%
8	0%	22	6%		
10	1%	24	9%		
12	1%	26	12%		

Probability of initial CHD within 2 years for men aged 35 to 74 and free of cardiovascular disease.

Table III. Health risk appraisal functions, initial CHD events

	Men		Women			
			Without triglycerides		With triglycerides	
Variable	Coeff	P	Coeff	P	Coeff	P
Intercept	12.7868	.0001	20.4049	.0001	20.9717	.0001
Age	-0.0405	.0001	-0.0622	.02	-0.0621	.04
Menopause	–	–	-3.8236	.02	-3.8522	.01
Age × menopause	–	–	0.0717	.04	0.0726	.02
ln (total cholesterol/HDL)	-0.9494	.0001	-0.8902	.0001	-0.6256	.02
ln (SBP)	-1.0163	.001	-2.3607	.0004	-2.2449	.0001
Antihypertensive therapy/SBP interaction	-0.0161	.09	-0.0097	.003	-0.098	.3
Diabetes	-0.4412	.08	-0.5734	.22	-0.5243	.03
Smoker	-0.6042	.0001	-0.4041	.02	-0.3777	.02
ln (triglycerides)	–	–	–	–	-0.2688	.04
Alcohol	–	–	0.0461	.03	0.0529	.07
Extreme value scale parameter	0.7764		0.7333		0.7467	

Coeff, Coefficient.

cant ($P < .04$) when included in the model for women, but it did not add significantly to the regression model for men. The addition of an interaction term for antihypertensive therapy/SBP contributed to improved statistical fit in the models for men and women, as did the inclusion of an age/menopause interaction in the model for women. Use of alcohol within the range observed in the data appears to be slightly protective for women. The relation of other risk factors to CHD risk was consistent with that estimated in previous studies.

Health risk appraisal models for subsequent CHD

CHD risk appraisal functions for men and women with prior CHD or stroke at time of examination are

Figure 2

If not Menpausal, Age		Total-C	HDL-C 25	30	35	40	45	50	60	70	80
35-39	0	160	5	4	3	3	2	2	1	1	0
40-44	1	170	5	4	4	3	3	2	1	1	0
45-49	3	180	5	5	4	3	3	2	2	1	0
50-54	4	190	5	5	4	4	3	3	2	1	1
55-59	6	200	6	5	4	4	3	3	2	1	1
60-64	7	210	6	5	5	4	3	3	2	2	1
65-69	9	220	6	5	5	4	4	3	2	2	1
70-74	10	230	6	6	5	4	4	3	3	2	1
If Menpausal, Age		240	6	6	5	5	4	4	3	2	2
35-49	17	250	7	6	5	5	4	4	3	2	2
50-74	16	260	7	6	5	5	4	4	3	3	2
		270	7	6	6	5	5	4	3	3	2
		280	7	6	6	5	5	4	3	3	2
		290	7	6	6	5	5	4	4	3	2
		300	7	7	6	5	5	5	4	3	3

Diabetes	Cigs
No = 0	No=0
Yes = 3	Yes = 2

alcohol oz/wk	
0-4	0
6 to 40	-1

SBP if untreated		if treated	
<110	0	<114	0
110-114	1	115-124	2
115-124	2	125-134	3
125-134	3	135-144	4
135-154	4	145-154	5
155-164	5	155-164	6
165-184	6	165-194	7
185-194	7	195-214	8
195-214	8	215-234	9
215-234	9	>=235	10
>=235	10		

if has prevalent menopause use:

Pts	2 -yr Probabilities	Pts	2 -yr Probabiliti	Pts	2 -yr Probabilities
0	0%	14	0%	28	3%
2	0%	16	0%	30	6%
4	0%	18	0%	32	11%
6	0%	20	0%	34	18%
8	0%	22	1%	36	31%
10	0%	24	1%		
12	0%	26	2%		

if does not have prevalent menopause use:

Pts	2 -yr Probabilities	Pts	2 -yr Probabilities
0	0%	14	2%
2	0%	16	3%
4	0%	18	5%
6	0%	20	9%
8	0%	22	16%
10	1%	24	27%
12	1%	26	43%

Probability of initial CHD within 2 years for women aged 35 to 74 and free of cardiovascular disease: Model without triglycerides.

summarized in Table IV. For men, only age, log ratio of total to HDL cholesterol, and diabetes remained in the model after backward elimination criteria were applied. Log-transformed SBP and smoking also remained in the model for women after backward elimination in addition to the log ratio of total to HDL cholesterol and diabetes.

Discussion

The Framingham health risk appraisal models developed over the last 3 decades have proven to be useful to clinicians in understanding the multifactorial nature of CHD and the extent to which risk factor modification can ameliorate risk of CHD in the future. Models suitable for use by a lay audience have also been developed in recent years at the request of the American Heart Association. Heretofore all models have been based on the experience of persons free of CVD at baseline, and thus their predictions have not been appropriate for persons with a history of CHD or ischemic stroke. With the development of models to predict risk of subsequent CHD events for men and women with history of CHD or stroke, the importance of blood lipid levels, diabetes, and, in women, SBP and cigarette smoking as independent predictors of risk is once again underscored.

The initial event models reported herein differ in several respects from those reported by Anderson et al[6] and Odell et al,[7] which have been widely disseminated in recent years among cardiologists and primary care clinicians. Our primary purpose in designing these models was to facilitate risk estimation over a relatively short time horizon ranging from 1 to 4 years. In contrast, the other model is designed for risk estimation over considerably longer time horizons ranging from 4 to 14 years, and in fact excluded all CHD events occurring within 4 years of examination from model fitting. We also endeavored to estimate separate models for men and women, whereas the other model pooled both sexes for purposes of model fitting. Our models also explored the independent contributions of risk factors, such as ethyl alcohol consumption and triglyceride level to CHD risk and avoided the use of electrocardiographically detected LVH as an independent predictor of CHD risk. Finally, we estimated sex-specific models for subsequent CHD events in addition to initial events, whereas the other model strictly focused on initial events.

Computation of probability estimates for initial and subsequent CHD can proceed in 2 ways, a point system generated from the mathematic function valid for 2-year estimates (presented in Figures 1 through 5) and direct computation with the Weibull models.

Figure 3

If not Menpausal, Age		Total-C	HDL-C 25	30	35	40	45	50	60	70	80
35-39	0	160	3	3	2	2	2	1	1	0	0
40-44	1	170	4	3	3	2	2	2	1	1	0
45-49	3	180	4	3	3	2	2	2	1	1	0
50-54	4	190	4	3	3	2	2	2	1	1	0
55-59	6	200	4	3	3	3	2	2	1	1	1
60-64	7	210	4	4	3	3	2	2	2	1	1
65-69	9	220	4	4	3	3	3	2	2	1	1
70-74	10	230	4	4	3	3	3	2	2	1	1
If Menpausal, Age		240	5	4	4	3	3	3	2	2	1
		250	5	4	4	3	3	3	2	2	1
35-39	19	260	5	4	4	3	3	3	2	2	1
40-64	18	270	5	4	4	3	3	3	2	2	2
65-74	17	280	5	4	4	4	3	3	2	2	2
		290	5	5	4	4	3	3	3	2	2
		300	5	5	4	4	3	3	3	2	2

Diabetes	Cigs
No = 0	No=0
Yes = 2	Yes = 2
alcohol	oz/wk
0-4	0
6 to 40	-1
Triglycerides	
<20	0
25-94	2
95-194	3
195-354	4
355+	5

SBP if untreated		if treated	
<110	0	<114	0
110-114	1	115-124	2
115-124	2	125-134	3
125-134	3	135-144	4
135-154	4	145-154	5
155-164	5	155-174	6
165-184	6	175-204	7
185-204	7	205-224	8
205-224	8	225-244	9
225-244	9	>=245	10
>=245	10		

if has prevalent menopause use: Pts	2 -yr Probabilities	Pts	2 -yr Probabilities	Pts	2 -yr Probabilities
0	0%	14	0%	28	3%
2	0%	16	0%	30	5%
4	0%	18	0%	32	8%
6	0%	20	0%	34	14%
8	0%	22	0%	36	23%
10	0%	24	1%	38	37%
12	0%	26	1%		

if does not have prevalent menopause use: Pts	2 -yr Probabilities	Pts	2 -yr Probabilities
0	0%	14	1%
2	0%	16	2%
4	0%	18	4%
6	0%	20	7%
8	0%	22	12%
10	0%	24	21%
12	1%	26	34%

Probability of initial CHD within 2 years for women aged 35 to 74 and free of cardiovascular disease: Model with triglycerides.

Table IV. Health risk appraisal functions, subsequent CHD events

Variable	Men Coeff	Men P	Women Coeff	Women P
Intercept	4.995	.0001	13.537	.001
Age	-0.0145	.11	-0.0225	.24
ln (total cholesterol/HDL)	-0.6738	.002	-0.834	.03
ln (SBP)	–	–	-1.3713	.10
Diabetes	-0.3042	.08	-0.7829	.006
Smoker	–	–	-0.3669	.182
Extreme value scale parameter	0.9994		1.0313	

Computation with the estimated initial CHD models is illustrated below. Consider a 55-year-old man free of CVD who has the following profile:

- Lipid values of total cholesterol of 260 mg/dL, HDL of 30 mg/dL
- Nondiabetic
- Current cigarette smoker
- SBP of 140 mm Hg, currently taking antihypertensive medication

Figure 1 may be used to estimate the 2-year probability of developing CHD for men. With this table, points are assigned to each risk factor as follows:

- Age = 6 points
- Lipid values = 10 points
- No diabetes = 0 points
- Current cigarette smoker = 4 ponts
- SBP, but being treated = 4 points

The points total 24, which by use of the column for the 2-year probabilities in Figure 1 corresponds to a 2-year probability of 9%.

The probability can also be obtained with the Weibull model. The initial CHD risk appraisal model estimated for men is: $m = 12.7868 - 0.0405 \times (\text{age}) - 0.9494 \times [\ln(\text{TC/HDL})] - 1.0163 \times [\ln(\text{SBP})] - 0.0161 \times [(\text{anti-}$

Figure 4

Age		HDL-C										Diabetes
35-39	0	Total-C	25	30	35	40	45	50	60	70	80	No = 0
40-44	1	160	10	9	7	6	5	4	3	1	0	Yes = 4
45-49	3	170	11	9	8	7	6	5	3	2	1	
50-54	4	180	11	10	8	7	6	5	4	2	1	
55-59	6	190	12	10	9	8	7	6	4	3	2	
60-64	7	200	12	11	9	8	7	6	5	3	2	
65-69	9	210	13	11	10	9	7	7	5	4	2	
70-74	10	220	13	11	10	9	8	7	5	4	3	
		230	13	12	10	9	8	7	6	4	3	
		240	14	12	11	10	9	8	6	5	4	
		250	14	13	11	10	9	8	6	5	4	
		260	15	13	12	10	9	8	7	5	4	
		270	15	13	12	11	10	9	7	6	5	
		280	15	14	12	11	10	9	7	6	5	
		290	16	14	13	11	10	9	8	6	5	
		300	16	14	13	12	11	10	8	7	6	

Pts	2 -yr Probabilities	Pts	2 -yr Probabilities	Pts	2 -yr Probabilities
0	3%	14	9%	28	25%
2	4%	16	11%	30	29%
4	4%	18	13%		
6	5%	20	14%		
8	6%	22	17%		
10	7%	24	19%		
12	8%	26	22%		

Probability of subsequent CHD within 2 years for men aged 35 to 74 with CHD or stroke.

hypertensive medication × [(200 - SBP) × (SBP - 110)/100] - 0.4412 × (diabetes) - 0.6042 × (smoker); and $s = 0.7764$, where s is the extreme value scale parameter. Note the antihypertensive medication adjustment is only used for SBP between 110 and 200; it is zero otherwise. Based on these risk factor values, the value of m is calculated to be 2.59. The probability (P) of occurrence of an initial CHD event during a time period t (between 1 and 4 years) is given by: $P = 1 - \exp(-\exp[u])$, where u is $[\ln(t) - m]/s$. For example, the probability of an initial CHD event occurring within 2 years (ie, $t = 2$) is $1 - \exp(-\exp[-2.443])$, or approximately 0.0832. This probability estimate is basically the same obtained from Figure 1. Tables and Weibull model estimates may differ because of round-off error in generating the point system of the tables.

Note that the use of the Weibull model directly can be used to produce probability estimates for any time between 0 and 4 years. Figures 1 through 5 are all designed only for 2-year estimates.

Our understanding of the importance of risk management in patients with existing CHD has improved considerably in recent years.[20] The subsequent CHD risk appraisal functions described here consider risk of subsequent events in persons with prior CHD or ischemic stroke who have survived the acute stage of their most recent event, a relatively restrictive definition of CVD. At a minimum, alternative population subgroups (eg, persons with any prior CVD) and study end points should be considered. Also, as more follow-up data are accumulated on Framingham participants with CVD and the numbers of event survivors grow, sample sizes for analyses of subsequent cardiovascular or CHD events will increase and thus improve statistical power (ie, the ability to detect statistically significant relations between other covariates and CHD risk where they in fact exist).

In addition, it is important to note that the subsequent CHD risk appraisal functions reported here do not include assessments of symptoms or data pertaining to additional testing. As a consequence, they should be considered only approximate guides to risk prediction in the populations of interest.[20] For example, the functions do not include the electrocardiographic LVH variable for reasons noted previously, even though it is known to have a strong direct association with CHD

Figure 5

Age		HDL-C										Diabetes	Cigs	SBP	
35-39	0	Total-C	25	30	35	40	45	50	60	70	80	No = 0	No=0		
40-44	1	160	10	9	7	6	5	4	3	1	0	Yes = 8	Yes = 4	<110	0
45-49	2	170	11	9	8	7	6	5	3	2	1			110-114	1
50-54	3	180	11	10	8	7	6	5	4	2	1			115-124	3
55-59	4	190	12	10	9	8	7	6	4	3	2			125-134	4
60-64	5	200	12	11	9	8	7	6	5	3	2			135-144	5
65-69	6	210	13	11	10	9	8	7	5	4	2			145-154	6
70-74	7	220	13	12	10	9	8	7	5	4	3			155-164	7
		230	14	12	11	9	8	7	6	4	3			165-184	8
		240	14	12	11	10	9	8	6	5	4			185-194	9
		250	14	13	11	10	9	8	7	5	4			195-214	10
		260	15	13	12	11	9	9	7	6	4			215-224	11
		270	15	13	12	11	10	9	7	6	5			225-244	12
		280	15	14	12	11	10	9	8	6	5			245+	13
		290	16	14	13	12	10	10	8	7	5				
		300	16	14	13	12	11	10	8	7	6				

Pts	2 -yr Probabilities	Pts	2 -yr Probabilities	Pts	2 -yr Probabilities
0	1%	14	3%	28	9%
2	1%	16	3%	30	11%
4	1%	18	4%	32	13%
6	1%	20	5%	34	16%
8	2%	22	5%	36	19%
10	2%	24	7%	38	22%
12	2%	26	8%		

Probability of subsequent CHD within 2 years for women aged 35 to 74 with CHD or stroke.

risk. More detailed information pertaining to symptom status and coronary function, among other factors, may improve the accuracy of risk prediction in persons with existing CVD.

The updated models for initial CHD events incorporate larger and more current follow-up than those previously reported and offer additional insight to the roles of several new variables in predicting occurrence of initial CHD events. As demonstrated in previously reported stroke risk profiles,[19] adjustment for use of antihypertensive medication among persons with SBP between 110 and 200 mm Hg inclusive improved statistical fit and was associated with higher risk. This finding suggests that achieving a given SBP level through treatment is associated with higher event risk than if that level had been achieved naturally. Future health risk appraisal functions should explore the extent to which the same may or may not be true for glycemic therapy among older diabetics and lipid therapy in persons with dyslipidemia.

Consumption of ethyl alcohol was associated with a slight reduction in risk in women, but the association failed to remain statistically significant once log triglycerides were added to the model. The population on which these models was estimated included very few heavy drinkers (more than 20 ounces per week); the estimated relation is therefore based almost exclusively on light to moderate alcohol consumption. It is quite possible that different results would be obtained if the population included more heavy drinkers. It therefore would be inappropriate to conclude from these findings that risk modification resulting from alcohol use is directly proportional to the level of consumption. Further investigation of the relation between alcohol consumption and CHD risk is clearly warranted before inferences regarding the true association can be made.

Although inclusion of log triglycerides did not significantly add to the regression models for men, it improved goodness-of-fit and was associated with a significant reduction in risk when added to the model for women. One might have expected triglycerides to not remain statistically associated with an outcome once HDL cholesterol is included in a regression analysis because of the former's inherently larger biological variation.[21] This was not the case. A comparison of the

β coefficients for models including and excluding log triglycerides suggests that the inclusion of a triglyceride measure in the model reduces the magnitude of the β coefficient of the log ratio of total to HDL cholesterol but not those of other covariates. Previous research found that log triglycerides but not triglycerides expressed in natural units was statistically significant even with diabetes, SBP, and cigarette smoking included in the analysis.[5,22,23] The importance of triglycerides as an independent risk factor for major coronary events has been demonstrated recently also in an 8-year epidemiologic follow-up of middle-aged German men who were either free of CHD or who had a history of angina at time of examination.[24]

Previous research suggests that the log-transformed ratio of total to HDL cholesterol is a better predictor of CHD risk than either measure alone, both measured in natural or logarithmic units, or other lipid measures (eg, LDL cholesterol).[6,25] This does not imply that LDL cholesterol and other lipid measures should be disregarded for purposes of clinical decision making in favor of the composite measure used in these risk appraisal functions. In clinical practice, the decision to intervene through diet or pharmacologic therapy is often made on the basis of LDL cholesterol levels, as recommended in National Cholesterol Education Program guidelines. Of course, for most patients LDL values are calculated from objective measures of total and HDL cholesterol and triglycerides, and clinicians who intervene based on LDL levels generally have total and HDL cholesterol values at their disposal. Thus these models can be used by clinicians for purposes of individual risk assessment quite apart from information used in making treatment decisions.

Certain caution should be exercised in the interpretation and use of the risk equations. First, the predictions may not be appropriate for persons with risk factor values in the highest or lowest percentiles of their distributions. Second, generalization of risk functions to general populations should always be undertaken with care. However, previous Framingham CHD risk functions have effectively predicted vascular disease in other settings.[26,27] Furthermore, extensive research is underway in testing their generalizability. Results of these investigators are forthcoming.

The Framingham Study has been successful in producing health risk appraisal functions for 30 years. Those reported here are useful tools for better understanding the relation between risk factors and the occurrence of CHD events in individuals who are free of CVD as well as persons who have had a prior CHD event or stroke. As such, they underscore the importance of risk factor control and intervention in the prevention of initial and subsequent CHD events.

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