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Special Report

Prediction of Coronary Heart Disease Using Risk Factor Categories

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Background—The objective of this study was to examine the association of Joint National Committee (JNC-V) blood pressure and National Cholesterol Education Program (NCEP) cholesterol categories with coronary heart disease (CHD) risk, to incorporate them into coronary prediction algorithms, and to compare the discrimination properties of this approach with other noncategorical prediction functions.

Methods and Results—This work was designed as a prospective, single-center study in the setting of a community-based cohort. The patients were 2489 men and 2856 women 30 to 74 years old at baseline with 12 years of follow-up. During the 12 years of follow-up, a total of 383 men and 227 women developed CHD, which was significantly associated with categories of blood pressure, total cholesterol, LDL cholesterol, and HDL cholesterol (all $P<.001$). Sex-specific prediction equations were formulated to predict CHD risk according to age, diabetes, smoking, JNC-V blood pressure categories, and NCEP total cholesterol and LDL cholesterol categories. The accuracy of this categorical approach was found to be comparable to CHD prediction when the continuous variables themselves were used. After adjustment for other factors, ≈28% of CHD events in men and 29% in women were attributable to blood pressure levels that exceeded high normal (≥130/85). The corresponding multivariable-adjusted attributable risk percent associated with elevated total cholesterol (≥200 mg/dL) was 27% in men and 34% in women.

Conclusions—Recommended guidelines of blood pressure, total cholesterol, and LDL cholesterol effectively predict CHD risk in a middle-aged white population sample. A simple coronary disease prediction algorithm was developed using categorical variables, which allows physicians to predict multivariate CHD risk in patients without overt CHD. **(*Circulation*. 1998;97:1837-1847.)**

Key Words: coronary disease ■ prediction ■ hypertension ■ cholesterol

Coronary heart disease continues to be a leading cause of morbidity and mortality among adults in Europe and North America.[1] Risk factors have included blood pressure, cigarette smoking, cholesterol (TC), LDL-C, HDL-C, and diabetes.[2–4] Factors such as obesity, left ventricular hypertrophy, family history of premature CHD, and ERT have also been considered in defining CHD risk.[5–7] Data from population studies enabled prediction of CHD during a follow-up interval of several years, based on blood pressure, smoking history, TC and HDL-C levels, diabetes, and left ventricular hypertrophy on the ECG. These prediction algorithms have been adapted to simplified score sheets that allow physicians to estimate multivariable CHD risk in middle-aged patients.[8]

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The present article develops a simplified coronary prediction model, building on the blood pressure, cholesterol, and LDL-C categories proposed by the JNC-V and NCEP ATP II.[7,9,10] The analysis evaluates the utility and accuracy of blood pressure, cholesterol, and LDL-C recommended categories in multivariable CHD prediction, using a Framingham Heart Study sample that pooled information for the original and offspring cohorts and followed them for 12 years. This approach emphasizes the established, powerful, independent, and biologically important factors. Family history for heart disease, physical activity, and obesity are not included because these factors work to a large extent through the major risk factors, and their unique contribution to CHD prediction can be difficult to quantify. The prediction of initial CHD events in a free-living population not on medication is emphasized. Consequently, ERT for postmenopausal women, treatment of high blood pressure, and therapy for high blood cholesterol are not included in the formulations.

Methods

The population-based sample used for this report included 2489 men and 2856 women 30 to 74 years old at the time of their Framingham Heart Study examination in 1971 to 1974. Participants attended either the 11th examination of the original Framingham cohort[11] or the initial examination of the Framingham Offspring Study.[12] Similar research protocols were used in each study, and persons with overt CHD at the baseline examination were excluded.

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Selected Abbreviations and Acronyms

CHD = coronary heart disease
ERT = estrogen replacement therapy
HDL-C = HDL cholesterol
JNC-V = Fifth Joint National Committee on Hypertension
LDL-C = LDL cholesterol
NCEP ATP II = National Cholesterol Education Program, Adult Treatment Panel II
TC = total cholesterol
VLDL-C = VLDL cholesterol

At the 1971–1974 examination, a medical history was taken and a physical examination was performed by a physician. Persons who smoked regularly during the previous 12 months were classified as smokers. Height and weight were measured, and body mass index (kg/m^2) was calculated. Two blood pressure determinations were made after the participant had been sitting at least 5 minutes, and the average was used for analyses. Hypertension was categorized according to blood pressure readings by JNC-V definitions[10]: optimal (systolic <120 mm Hg and diastolic <80 mm Hg), normal blood pressure (systolic 120 to 129 mm Hg or diastolic 80 to 84 mm Hg), high normal blood pressure (systolic 130 to 139 mm Hg or diastolic 85 to 89 mm Hg), hypertension stage I (systolic 140 to 159 mm Hg or diastolic 90 to 99 mm Hg), and hypertension stage II–IV (systolic ≥160 or diastolic ≥100 mm Hg). When systolic and diastolic pressures fell into different categories, the higher category was selected for the purposes of classification. Blood pressure categorization was made without regard to the use of antihypertensive medication.

Diabetes was considered present if the participant was under treatment with insulin or oral hypoglycemic agents, if casual blood glucose determinations exceeded 150 mg/dL at two clinic visits in the original cohort, or if fasting blood glucose exceeded 140 mg/dL at the initial examination of the Offspring Study participants. Blood was drawn at the baseline examination after an overnight fast, and EDTA plasma was used for all cholesterol and triglyceride measurements. Cholesterol was determined according to the Abell-Kendall technique,[13] and HDL-C was measured after precipitation of VLDL and LDL proteins with heparin-magnesium according to the Lipid Research Clinics Program protocol.[14] When triglycerides were <400 mg/dL, the concentration of LDL-C was estimated indirectly by use of the Friedewald formula[15]; for triglycerides ≥400 mg/dL, the LDL-C was estimated directly after ultracentrifugation of plasma and measurement of cholesterol in the bottom fraction (plasma density <1.006).[16]

Cutoffs for TC (<200, 200 to 239, 240 to 279, and ≥280 mg/dL), LDL-C (<130, 130 to 159, and ≥160 mg/dL), HDL-C (<35, 35 to 59, and ≥60 mg/dL), cigarette smoking, diabetes, and age were considered in this report. The cholesterol and LDL-C cutoffs are similar to those used for the NCEP ATP II guidelines and were partly dictated by the number of persons with higher levels of TC or LDL-C. For those reasons, we have provided information for cholesterol categories of 240 to 279 and ≥280 mg/dL and for LDL-C ≥160 mg/dL. Too few persons had LDL-C ≥190 mg/dL to provide stable estimates for CHD risk. Study subjects were followed up over a 12-year period for the development of CHD (angina pectoris, recognized and unrecognized myocardial infarction, coronary insufficiency, and coronary heart disease death) according to previously published criteria. "Hard CHD" events included total CHD without angina pectoris.[17] Surveillance for CHD consisted of regular examinations at the Framingham Heart Study clinic and review of medical records from outside physician office visits and hospitalizations.

Statistical tests included age-adjusted linear regression or logistic regression to test for trends across blood pressure, TC, LDL-C, and HDL-C categories.[18] Age-adjusted Cox proportional hazards regression and its accompanying c statistic were used to test for the relation between various independent variables and the CHD outcome and to evaluate the discriminatory ability of various prediction models.[19,20] The 12-year follow-up was used in the proportional hazards models, and results were adapted to provide 10-year CHD incidence estimates. Separate score sheets were developed for each sex using TC and LDL-C categories. These sheets adapted the results of proportional hazards regressions by use of a system that assigned points for each risk factor based on the value for the corresponding β-coefficient of the regression analyses.

The relative risk, but not the attributable risk, for TC and CHD declines with advancing age.[21] Quadratic terms for age were considered in the models for the score sheets. Furthermore, CHD risk is associated with HDL-C in the elderly,[22–24] and interaction terms for TC and age were also considered in the development of the prediction models.[22] Among women, an age-squared term was found to be significant in the prediction models and was incorporated into the score sheets. Neither age×TC nor age×LDL-C was found to be significant in either sex.

Score sheets for prediction of CHD using TC and LDL-C categorical variables were developed from the β-coefficients of Cox proportional hazards models. The TC range was expanded in 40-mg/dL increments to include ≥160 mg/dL and ≥280 mg/dL, the HDL-C range 35 to 59 mg/dL was partitioned to provide three levels for each sex, and both optimal and normal blood pressure categories were included. The score sheets provide comparison 10-year absolute risks for persons of the same age and sex for average total CHD, average hard CHD (total CHD without angina pectoris), and low-risk total CHD. Risk factors are shaded, ranging from very low relative risk to very high. Such distinctions are arbitrary but provide a foundation to determine the need for clinical intervention.

Results

At initial examination, study subjects ranged in age from 30 to 74 years, and the mean age±SD was 48.6±11.7 years for 2489 men and 49.8±12.0 years for 2856 women. Because there were relatively few persons at the higher stages of hypertension in the Framingham sample, stages II, III, and IV hypertension were combined into a single category in the analyses (Table 1). Approximately half of the subjects for each sex had blood pressure levels in the normal or optimal range.

The age-adjusted means for various risk factors according to blood pressure categories are shown for men and women in Table 2. Therapy for hypertension ($P<.001$ men, $P<.001$ women), more frequent diabetes ($P<.001$ men, $P<.001$ women), greater body

TABLE 1. Characteristics of Participants According to JNC-V Hypertension Categories*

	Blood Pressure			
	Systolic, mm Hg	Diastolic, mm Hg	Men, %	Women, %
Normal (including optimal)	<130	<85	44	55
High normal	130–139	85–89	20	15
Hypertension stage I	140–159	90–99	23	19
Hypertension stage II–IV	≥160	≥100	13	11

*Ignoring blood pressure therapy.

TABLE 2. Age-Adjusted Mean Levels and Prevalence of Risk Factors According to Blood Pressure Category

	Not Hypertensive		Hypertensive		*P*,
	Normal	High Normal	Stage I	Stage II–IV	Test for Trend*
Men	(n=1097)	(n=500)	(n=567)	(n=325)	
Hypertensive therapy, %	1.6	2.7	10.1	25.0	<.001
Body mass index, kg/m^2	25.8	26.7	27.5	28.3	<.001
Cigarette use, %	43.1	41.8	35.4	38.2	.010
Diabetes, %	3.6	6.1	4.0	11.2	<.001
TC, mg/dL	210.1	214.3	218.0	213.9	.004
LDL-C, mg/dL	142.7	143.4	144.5	139.7	.638
HDL-C, mg/dL	44.4	45.7	44.8	44.5	.674
Women	(n=1578)	(n=424)	(n=535)	(n=319)	
Hypertensive therapy, %	3.9	9.4	18.0	33.6	<.001
Body mass index, kg/m^2	23.9	25.8	26.3	26.9	<.001
Cigarette use, %	39.4	37.3	33.9	35.9	.071
Diabetes, %	2.6	3.4	4.9	9.8	<.001
TC, mg/dL	214.1	223.0	224.4	218.5	<.001
LDL-C, mg/dL	138.3	143.9	146.8	138.9	.031
HDL-C, mg/dL	58.6	58.2	55.9	55.7	<.001

*Test for linear trend across blood pressure categories after age adjustment. For dichotomous variables, logistic regression was done.

mass index ($P<.001$ men, $P<.001$ women), and higher TC level ($P=.004$ men, $P<.001$ women) were consistently associated with higher blood pressure categories in both sexes. Cigarette smoking was inversely associated with blood pressure in men ($P=.010$), but only a borderline association was present in women ($P=.071$). The lipoprotein fractions HDL-C ($P<.001$) and LDL-C ($P=.031$) were significantly associated with blood pressure category in women but not in men.

Age-adjusted 10-year CHD rates for blood pressure and cholesterol categories are shown for men and women in Table 3. In prediction models, the CHD rates were significantly associated with the specified categories of blood pressure, TC, HDL-C, and LDL-C (all $P<.001$ for both sexes). The number of CHD events arising at each blood pressure and cholesterol category is also given. For blood pressure, the greatest number of CHD cases arose from the stage I hypertension category for both sexes. Conversely, the greatest number of CHD cases arose from the highest lipoprotein cholesterol levels (LDL-C ≥160 mg/dL or cholesterol ≥240 mg/dL).

Multivariable risk calculations for TC categories are shown in Table 4. Normal or optimal blood pressure was used as the reference level, and estimated relative risk rose from 1.00 for normal or optimal blood pressure to 1.84 in men and 2.12 in women with stage II–IV hypertension. Similarly, for TC, the estimated relative risk rose from 1.00 for levels <200 mg/dL to 1.90 in men and 1.72 in women with TC ≥240 mg/dL. When typical HDL-C levels (35 to 59 mg/dL) were used as a reference, CHD risk was increased among men and women with low HDL-C (<35 mg/dL) and CHD risk was correspondingly decreased among subjects with high HDL-C (≥60 mg/dL). The population-attributable risk percent associated with hypertension was 6% for high normal, 13% for stage I, and 9% for stage II–IV hypertension among men. The corresponding values were 5% for high normal, 13% for stage I, and 12% for stage II–IV hypertension among women. An overall estimate of the attributable risk percent for blood pressure level greater than normal was 28% in men and 29% in women. When cholesterol <200 mg/dL was used as the reference range, attributable risks were 10% for TC 200 to 239 mg/dL and 17% for TC ≥240 mg/dL in men and 12% for TC 200 to 239 mg/dL and 22% for TC ≥240 mg/dL in women. The overall estimate of the attributable risk percent for TC level ≥200 mg/dL was 27% in men and 34% in women.

Multivariable risk calculations for LDL-C categories are shown in Table 5, and these results parallel the presentation in Table 4. When LDL-C <130 mg/dL is used as the reference range, a greater absolute CHD risk is associated with higher LDL-C categories, but the magnitude of the relative risk and its statistical significance are very similar to that observed for the categories of TC (Table 4).

The efficacy of prediction with continuous variables was compared with that obtained with categorical variables and a risk factor sum (Figs 1 and 2 for men and women, respectively). For calculation of the risk factor sum, the levels considered were age (≥45 years for men, ≥55 years for women), hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication), smoking, diabetes, elevated cholesterol (cholesterol ≥240 mg/dL or LDL-C ≥160 mg/dL), and HDL-C <35 mg/dL. One point was given for each risk factor, for a possible score of 0 to 7 points. A greater area under the curve indicated better predictive capability. The curves were nearly identical for the continuous and categorical formulations, TC and LDL-C categories had similar effects, and the risk factor sums tended to have the lowest predictive potential. The c statistic, a measure of the discriminatory ability of a model, equal to the area under the receiver operating characteristic curve, provides a guide to interpret the

TABLE 3. CHD Risk According to Blood Pressure and Lipid Categories

	Men			Women		
	Person-Years	No. of Events (%)	Age-Adjusted 10-Year Rate	Person-Years	No. of Events (%)	Age-Adjusted 10-Year Rate
Total	30 154	383 (100)		38 057	227 (100)	
Blood pressure						
Normal (including optimal)	13 524	110 (29)	7.8	20 747	66 (29)	2.9
High normal	6307	77 (20)	12.4	6056	36 (16)	7.1
Hypertension stage I	6695	115 (30)	16.0	7254	72 (32)	13.9
Hypertension stage II–IV	3628	81 (21)	20.9	4000	53 (23)	14.1
TC, mg/dL						
<200	11 591	103 (27)	8.2	13 289	39 (17)	3.1
200–239	11 792	148 (39)	12.0	12 683	80 (35)	6.6
≥240	6771	132 (34)	18.6	12 085	108 (48)	10.3
HDL-C, mg/dL						
<35	5601	97 (25)	15.8	1506	23 (10)	14.7
35–59	21 151	260 (68)	12.0	20 788	146 (64)	7.5
≥60	3409	26 (7)	8.2	15 761	58 (26)	3.9
LDL-C, mg/dL						
<130	11 142	104 (27)	7.3	15 835	50 (22)	2.3
130–159	10 384	124 (32)	11.3	10 455	64 (28)	6.5
≥160	8628	155 (41)	17.3	11 767	113 (50)	10.6

The age-adjusted 10-year CHD rates were calculated from the Cox proportional hazards model, based on 12 years of follow-up.

results plotted in Figs 1 and 2. The c statistics associated with TC categories were 0.74 in men and 0.77 in women for continuous variables by proportional hazards or accelerated failure models,[11] 0.73 in men and 0.76 in women for categorical variables, and 0.69 in men and 0.72 in women for the risk factor sum. The corresponding c statistics associated with LDL-C categories were 0.74 in men and 0.77 in women for continuous variables by proportional hazards or accelerated failure models,[11] 0.73 in men and 0.77 in women for categorical variables, and 0.68 in men and 0.71 in women for the risk factor sum.

TABLE 4. Multivariable-Adjusted Relative Risks for CHD According to TC Categories

	Men		Women	
	Relative Risk	95% CI	Relative Risk	95% CI
Age, y	1.05‡	1.04–1.06	1.04‡	1.03–1.06
Blood pressure				
Normal (including optimal)	1.00	Referent	1.00	Referent
High normal	1.31	0.98–1.76	1.30	0.86–1.98
Hypertension stage I	1.67†	1.28–2.18	1.73†	1.19–2.52
Hypertension stage II–IV	1.84‡	1.37–2.49	2.12†	1.42–3.17
Cigarette use (y/n)	1.68‡	1.37–2.06	1.47†	1.12–1.94
Diabetes (y/n)	1.50*	1.06–2.13	1.77†	1.16–2.69
TC, mg/dL				
<200	1.00	Referent	1.00	Referent
200–239	1.31*	1.01–1.68	1.51*	1.01–2.24
≥240	1.90‡	1.47–2.47	1.72†	1.15–2.56
HDL-C, mg/dL				
<35	1.47†	1.16–1.86	2.02†	1.29–3.15
35–59	1.00	Referent	1.00	Referent
≥60	0.56†	0.37–0.83	0.58†	0.43–0.79

The multivariate models were performed separately for men and women. Each model included simultaneously all variables listed in the table. All analyses used categorical variables.

*.01<P<.05, †.001<P<.01, ‡P<.001.

TABLE 5. Multivariate-Adjusted Relative Risks for CHD According to LDL-C Categories

	Men		Women	
	Relative Risk	95% CI	Relative Risk	95% CI
Age, y	1.05‡	1.04–1.06	1.04‡	1.03–1.06
Blood pressure				
Normal (including optimal)	1.00	Referent	1.00	Referent
High normal	1.32	0.98–1.78	1.34	0.88–2.05
Hypertension stage I	1.73‡	1.32–2.26	1.75†	1.21–2.54
Hypertension stage II	1.92‡	1.42–2.59	2.19‡	1.46–3.27
Cigarette use (y/n)	1.71‡	1.39–2.10	1.49†	1.13–1.97
Diabetes (y/n)	1.47*	1.04–2.08	1.80†	1.18–2.74
LDL-C, mg/dL				
<130	1.00	Referent	1.00	Referent
130–159	1.19	0.91–1.54	1.24	0.84–1.81
≥160	1.74‡	1.36–2.24	1.68†	1.17–2.40
HDL-C, mg/dL				
<35	1.46†	1.15–1.85	2.08†	1.33–3.25
35–59	1.00	Referent	1.00	Referent
≥60	0.61*	0.41–0.91	0.64†	0.47–0.87

The multivariate models were performed separately for men and women. Each model included simultaneously all variables listed in the table. All analyses used categorical variables.

*.01<*P*<.05, †.001<*P*<.01, ‡*P*<.001.

Score sheets were developed to predict CHD in men (Fig 3) and women (Fig 4) from the β-coefficients of Cox proportional hazards models (Table 6). Among women, an age-squared term was found to be significant and was incorporated into the score sheets. The average CHD risk over a period of 10 years tends to plateau slightly in the oldest men and women.

An illustrative example for Fig 3 follows. The subject is a 55-year-old man with a TC of 250 mg/dL, HDL-C of 39 mg/dL, and blood pressure of 146/88 who is diabetic and a nonsmoker. Proceeding through the steps gives us the following results: Step 1: Age 55=4 points. Step 2: TC 250 mg/dL=2 points. Step 3: HDL-C 39 mg/dL=1 point. Step 4: Blood pressure 146/88 mm Hg=2 points. Step 5: Diabetic=2 points. Step 6: Nonsmoker=0 points. Step 7: Point total was 4+2+1+2+2+0=11. Step 8: Estimated 10-year CHD risk is 31%. Step 9: The average and "low-risk" risks of CHD over a period of 10 years for a 55-year-old man are 16% and 7%, respectively (low risk was calculated for a person the same age, optimal blood pressure, TC 160 to 199 mg/dL, HDL-C 45 mg/dL for men or 55 mg/dL for women, nonsmoker, and no diabetes). Dividing the subject's risk by the

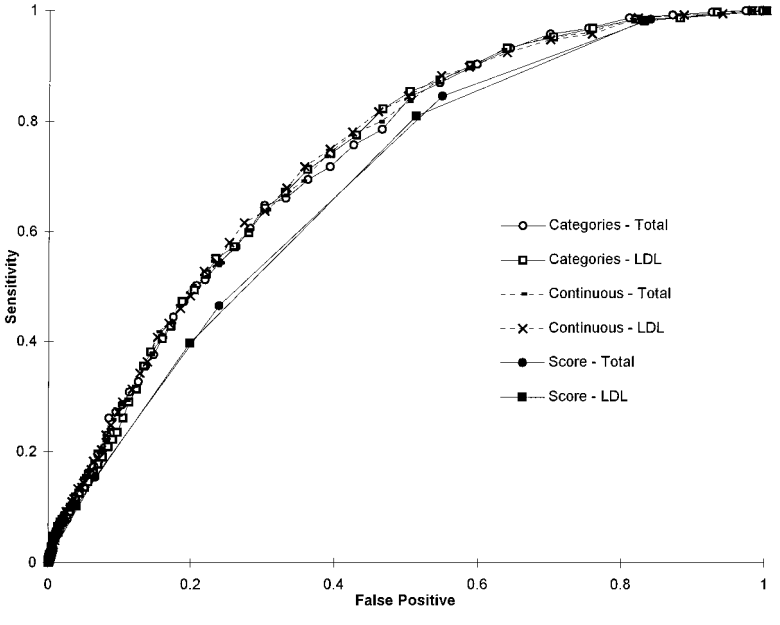


Figure 1. Receiver operating characteristic curves for prediction of CHD in Framingham men over a period of 12 years. Separate plots were used for continuous, categorical, and risk factor sum models, according to whether TC or calculated LDL-C was used.

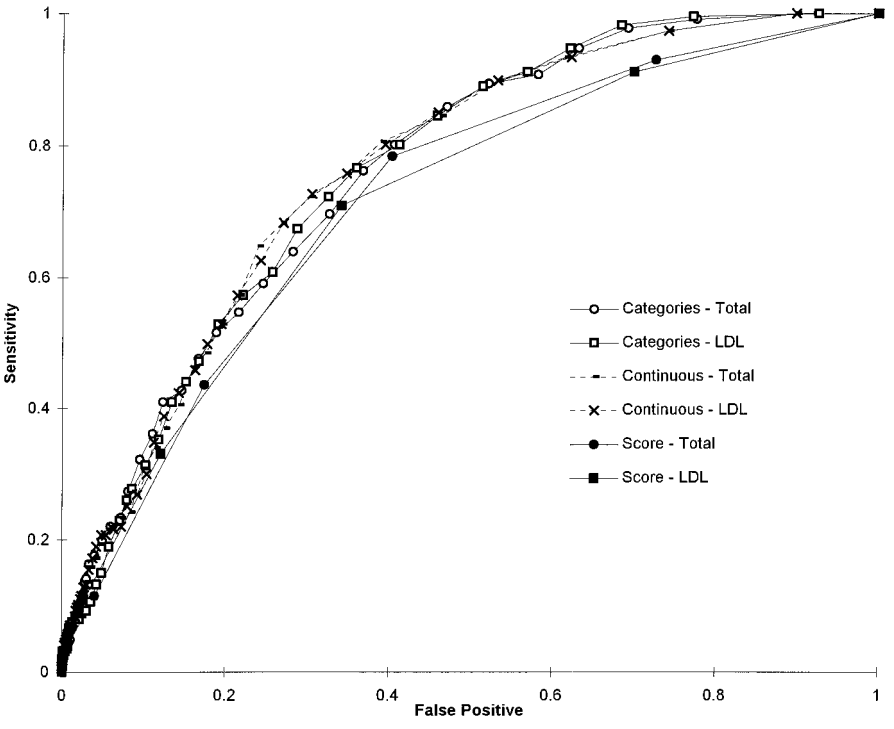


Figure 2. Receiver operating characteristic curves for prediction of CHD in Framingham women over a period of 12 years. Separate plots were used for continuous, categorical, and risk factor sum models, according to whether TC or calculated LDL-C were used.

average risk provides an estimate of the relative risk: 31% divided by 16%=1.94. Use of the LDL-C approach in the score sheets is appropriate when fasting LDL-C estimates are available, by use of ultracentrifugation techniques, the Friedewald formula, or newer LDL-C assays.[15,25,26] The approach is analogous to that shown for TC categories.

Discussion

For the past two decades it has been possible to estimate CHD risk by use of regression equations derived from observational studies, and the present study demonstrates similar results, predicting later CHD in a middle-aged white population sample. Prediction models have typically been based on the logistic function, although the Weibull distribution has also been used.[11,22] Formulations have often included age, sex, blood pressure, TC, HDL-C, smoking, diabetes, and left ventricular hypertrophy.[11] The prediction of CHD has taken the form of sex-specific equations that were developed from a single study and applied to other populations or individuals. Age, TC, HDL-C, and blood pressure were used in the equations as continuous variables, in contrast to dichotomous variables (yes/no) such as smoking, diabetes, and left ventricular hypertrophy.

The present study builds on the prior experience of CHD prediction with continuous variables and integrates the categorical approaches that have become part of the framework of blood pressure (JNC-V) and cholesterol (NCEP) programs in the United States.[6,7,10] As suggested in an earlier NCEP report,[27] our approach integrates blood pressure and cholesterol information and estimates both relative and absolute CHD risk with a risk factor weighting approach.

The NCEP ATP II guidelines defined hypertension as a yes/no variable, and it can be seen from Tables 3, 4, and 5 that additional blood pressure categories are important in predicting CHD risk. Higher levels of blood pressure are typically associated with abnormal cholesterol levels, greater body mass index, and an increased prevalence of diabetes (Table 2). Data from Tables 3 and 4 demonstrate that blood pressure, TC, LDL-C, and HDL-C categories are predictive of CHD and suggest that risk factor prevention and intervention programs should be integrated, as recently suggested.[28–30] Three reasons probably account for similar results when continuous or categorical formulations are used: (1) a large enough number of categories has been used to adequately describe the clinical data; (2) coronary prediction equations have limitations in their precision and accuracy; and (3) in the final steps of the prediction score sheet, the data are summarized, by use of point score totals, providing fewer than 20 combinations for CHD risk prediction.

The predictive capability of the continuous model described here is similar to the accelerated failure model used in an earlier Framingham CHD prediction equation,[11] and the continuous variable and categorical variable approaches have c-statistic values that are nearly identical, suggesting that predictability of the models is nearly the same in either instance. This result is in contradistinction to a comparison of the NCEP ATP II algorithm (<10 unique patterns) with a continuous variable approach in which the latter (using Framingham models) was thought to be statistically superior.[29] A risk factor sum model, considering 7 dichotomous variables, was used for comparison in the present study and showed a significant falloff in the level of the c statistic with this approach compared with formulations using categorical or continuous levels.

TC- and LDL-C–based approaches, whether continuous or categorical variables are used, are similar in their ability to predict initial CHD events in the models presented. This may result from indirect estimation of LDL-C, leading to reduced

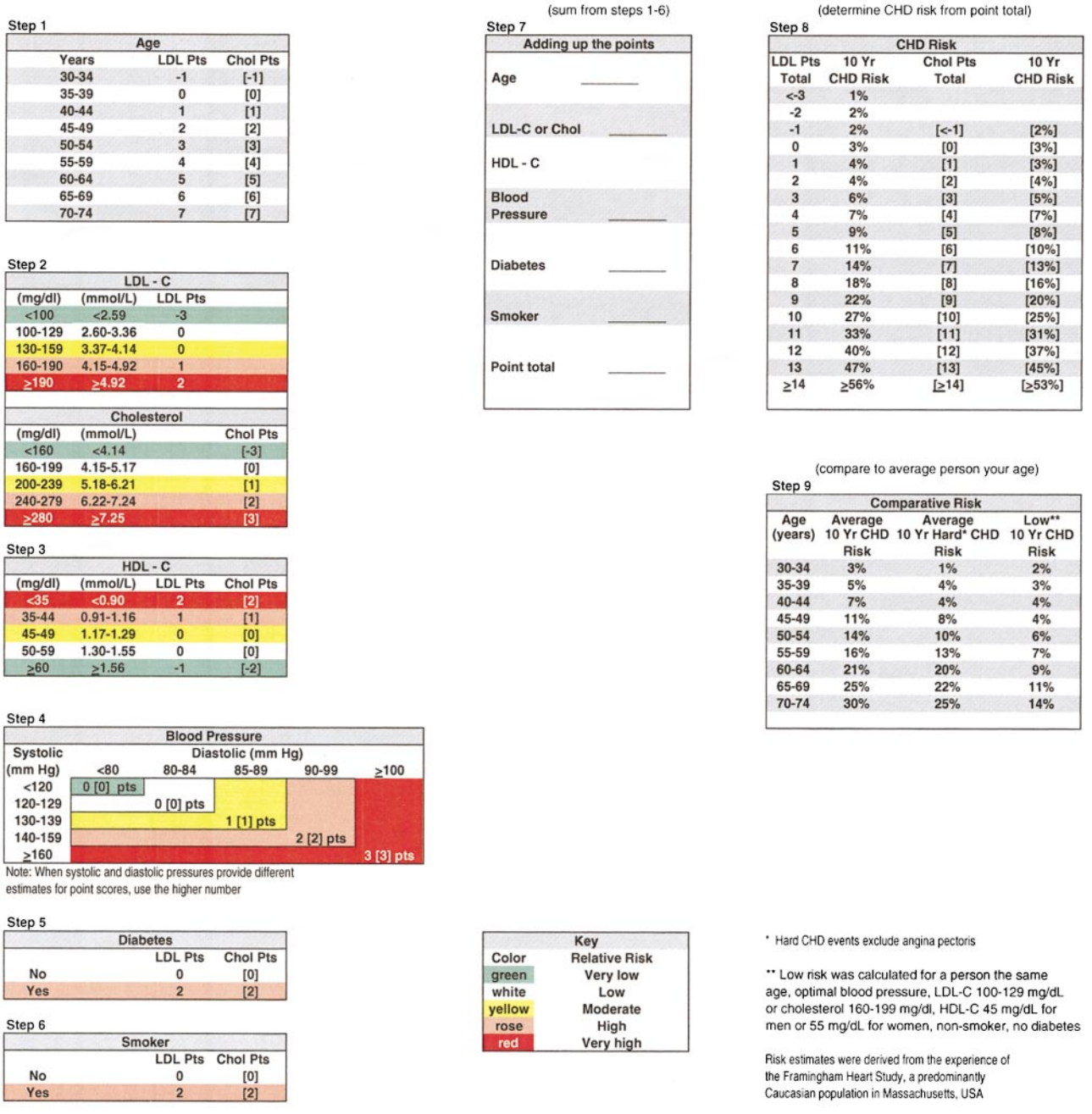
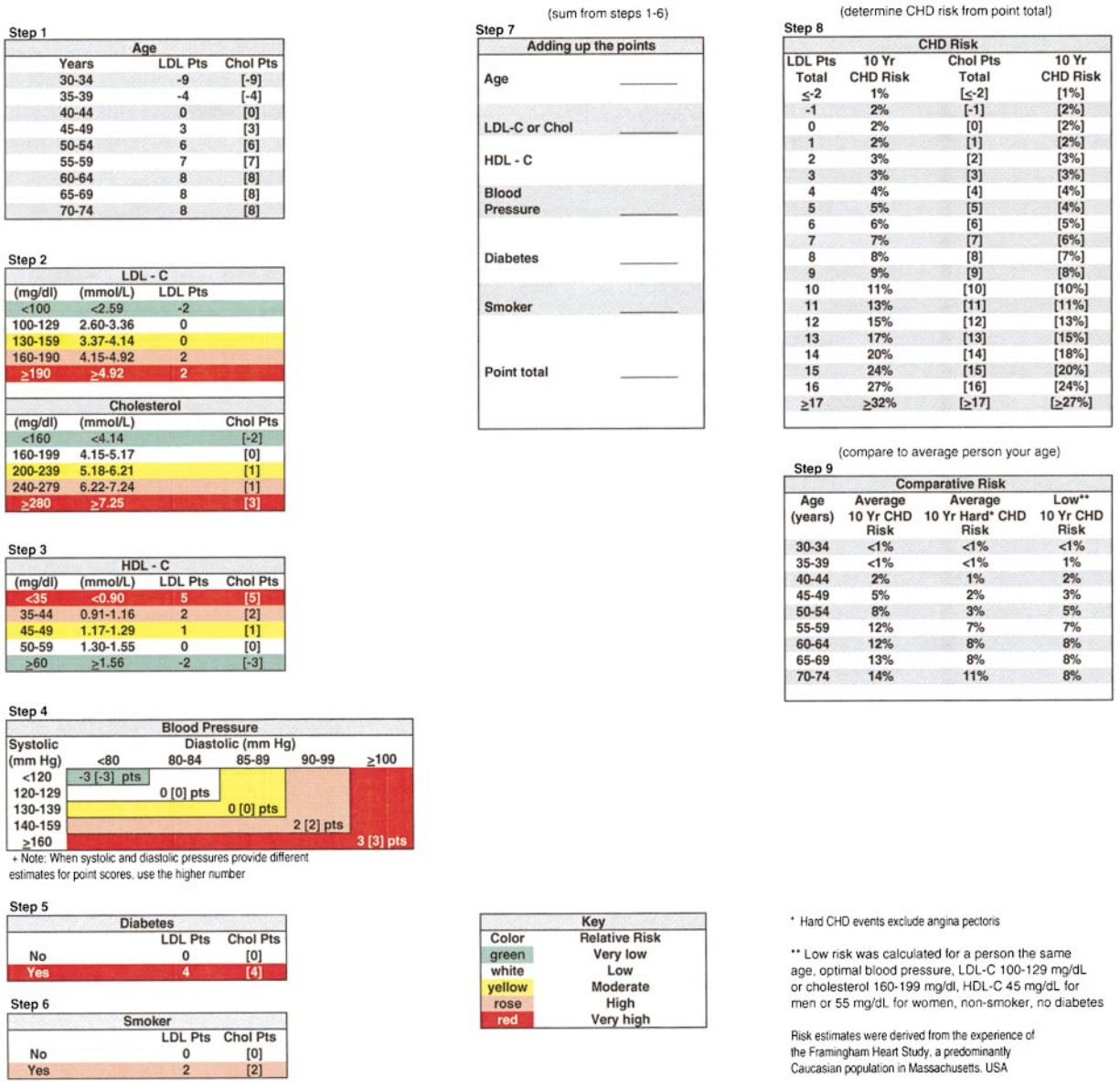


Figure 3. CHD score sheet for men using TC or LDL-C categories. Uses age, TC (or LDL-C), HDL-C, blood pressure, diabetes, and smoking. Estimates risk for CHD over a period of 10 years based on Framingham experience in men 30 to 74 years old at baseline. Average risk estimates are based on typical Framingham subjects, and estimates of idealized risk are based on optimal blood pressure, TC 160 to 199 mg/dL (or LDL 100 to 129 mg/dL), HDL-C of 45 mg/dL in men, no diabetes, and no smoking. Use of the LDL-C categories is appropriate when fasting LDL-C measurements are available. Pts indicates points.

accuracy and precision of LDL-C estimates from single blood measurements.[31,32] The CHD estimates in the present article represent the experience of a free-living population sample, and different results may be obtained when blood pressure or blood cholesterol has been treated aggressively.

Although the impact of TC and LDL-C on estimates of CHD risk is similar in Framingham data, such results may be more relevant to populations than to individuals. Extensive clinical data and clinical trial results suggest that LDL-C is the major atherogenic lipoprotein and that measurement of LDL-C levels in the clinical setting provides an advantage.[33–35] High or low levels of HDL-C within individuals can produce discrepancies between TC and LDL-C levels. In addition, TC and LDL-C levels are not always concordant in persons with hypertriglyceridemia. Thus, measurement of TC is only a crude surrogate for LDL-C in risk assessment or in estimating initial response to therapy, although it can be useful in initial detection or long-term monitoring of response.[31]

Several candidate variables were not used in the prediction equations. A family history of premature CHD, previously shown in the Framingham Study to increase the relative odds of CHD to ≈1.3,[36] was not uniformly



Step 1

Age		
Years	LDL Pts	Chol Pts
30-34	-9	[-9]
35-39	-4	[-4]
40-44	0	[0]
45-49	3	[3]
50-54	6	[6]
55-59	7	[7]
60-64	8	[8]
65-69	8	[8]
70-74	8	[8]

Step 2

LDL - C		
(mg/dl)	(mmol/L)	LDL Pts
<100	<2.59	-2
100-129	2.60-3.36	0
130-159	3.37-4.14	0
160-190	4.15-4.92	2
≥190	≥4.92	2

Cholesterol		
(mg/dl)	(mmol/L)	Chol Pts
<160	<4.14	[-2]
160-199	4.15-5.17	[0]
200-239	5.18-6.21	[1]
240-279	6.22-7.24	[1]
≥280	≥7.25	[3]

Step 3

HDL - C			
(mg/dl)	(mmol/L)	LDL Pts	Chol Pts
<35	<0.90	5	[5]
35-44	0.91-1.16	2	[2]
45-49	1.17-1.29	1	[1]
50-59	1.30-1.55	0	[0]
≥60	≥1.56	-2	[-3]

Step 4

Blood Pressure					
Systolic (mm Hg)	Diastolic (mm Hg) <80	80-84	85-89	90-99	≥100
<120	-3 [-3] pts				
120-129		0 [0] pts			
130-139			0 [0] pts		
140-159				2 [2] pts	
≥160					3 [3] pts

+ Note: When systolic and diastolic pressures provide different estimates for point scores, use the higher number

Step 5

Diabetes		
	LDL Pts	Chol Pts
No	0	[0]
Yes	4	[4]

Step 6

Smoker		
	LDL Pts	Chol Pts
No	0	[0]
Yes	2	[2]

(sum from steps 1-6)

Step 7

Adding up the points	
Age	_____
LDL-C or Chol	_____
HDL - C	
Blood Pressure	_____
Diabetes	_____
Smoker	_____
Point total	_____

(determine CHD risk from point total)

Step 8

CHD Risk			
LDL Pts Total	10 Yr CHD Risk	Chol Pts Total	10 Yr CHD Risk
≤-2	1%	[≤-2]	[1%]
-1	2%	[-1]	[2%]
0	2%	[0]	[2%]
1	2%	[1]	[2%]
2	3%	[2]	[3%]
3	3%	[3]	[3%]
4	4%	[4]	[4%]
5	5%	[5]	[4%]
6	6%	[6]	[5%]
7	7%	[7]	[6%]
8	8%	[8]	[7%]
9	9%	[9]	[8%]
10	11%	[10]	[10%]
11	13%	[11]	[11%]
12	15%	[12]	[13%]
13	17%	[13]	[15%]
14	20%	[14]	[18%]
15	24%	[15]	[20%]
16	27%	[16]	[24%]
≥17	≥32%	[≥17]	[≥27%]

(compare to average person your age)

Step 9

Comparative Risk			
Age (years)	Average 10 Yr CHD Risk	Average 10 Yr Hard* CHD Risk	Low** 10 Yr CHD Risk
30-34	<1%	<1%	<1%
35-39	<1%	<1%	1%
40-44	2%	1%	2%
45-49	5%	2%	3%
50-54	8%	3%	5%
55-59	12%	7%	7%
60-64	12%	8%	8%
65-69	13%	8%	8%
70-74	14%	11%	8%

Key	
Color	Relative Risk
green	Very low
white	Low
yellow	Moderate
rose	High
red	Very high

* Hard CHD events exclude angina pectoris

** Low risk was calculated for a person the same age, optimal blood pressure, LDL-C 100-129 mg/dL or cholesterol 160-199 mg/dl, HDL-C 45 mg/dL for men or 55 mg/dL for women, non-smoker, no diabetes

Risk estimates were derived from the experience of the Framingham Heart Study, a predominantly Caucasian population in Massachusetts, USA

Figure 4. CHD score sheet for women using TC or LDL-C categories. Uses age, TC, HDL-C, blood pressure, diabetes, and smoking. Estimates risk for CHD over a period of 10 years based on Framingham experience in women 30 to 74 years old at baseline. Average risk estimates are based on typical Framingham subjects, and estimates of idealized risk are based on optimal blood pressure, TC 160 to 199 mg/dL (or LDL 100 to 129 mg/dL), HDL-C of 55 mg/dL in women, no diabetes, and no smoking. Use of the LDL-C categories is appropriate when fasting LDL-C measurements are available. Pts indicates points.

available among the second-generation participants. Fibrinogen is now recognized as a CHD risk factor,[37] and levels were available for ≈1000 original cohort participants at a 1968–70 examination,[38,39] but fibrinogen measurements were not available for the Offspring Study participants. In addition, established methods for measuring fibrinogen are lacking, and the precise mechanism linking elevated fibrinogen levels to CHD is unclear. Other risk factors, such as smoking, diabetes, and hypertension, are often associated with abnormal fibrinogen levels, and fibrinogen measurements vary greatly within individuals.[37,40] Left ventricular hypertrophy on the ECG was used in previous CHD prediction algorithms, but it is highly associated with hypertension and was not included in the present formulation for a variety of reasons, including lack of standard universally accepted ECG criteria.[11]

Postmenopausal ERT was not used in the prediction algorithm, because estrogen dose was typically higher in the early 1970s[41] and the cardioprotective effects of hormonal replacement therapy that have been universally observed in more recent times[42–45] were not experienced by all Framingham women from the early 1970s to the mid 1980s.[46–48]

Persons who exercise typically have a lower risk of CHD.[49–51] Information on physical activity was not available at the baseline examinations used to develop this CHD risk prediction algorithm, but cigarette smoking, low HDL-C levels, and diabetes are less common among those who are physically active.[52–55] Regular and vigorous exercise is often

associated with higher levels of HDL-C, an important determinant for reduced CHD risk.[56–58] Similarly, body mass index, an obesity index that expresses weight in kilograms divided by height in meters squared, has been considered a candidate variable for the CHD prediction algorithm. Greater obesity has been associated with higher TC, lower HDL-C, higher blood pressure, and diabetes, and the residual impact of obesity on CHD has typically been slight after incorporation of these other variables into the regression model.[8]

Clinicians should exercise caution in generalizing from experience of the Framingham Study, a community sample of white subjects drawn from a suburb west of Boston. Use of the prediction models would be most appropriate for individuals who resemble the study sample. However, reasonable accuracy in predicting CHD has been demonstrated in the past, when earlier Framingham CHD prediction equations were applied to population samples from Honolulu, Puerto Rico, Albany, Chicago, Los Angeles, Minneapolis, Tecumseh, the Western Collaborative Group, and a national cohort.[59–62] Follow-up from the Framingham Study was also used to estimate CHD experience in men participating in the Multiple Risk Factor Intervention Trial.[63]

Coronary prediction estimates tend to be most reliable when the data are most concentrated and can be particularly useful when subjects have multiple mild abnormalities that act synergistically to increase CHD risk. It is uncommon for persons to have four or five risk factors, and estimates of CHD risk tend to be more precise for individuals with fewer risk factors. Score sheet approaches have been used to target persons for the primary prevention of coronary disease by use of a tabular format called a Sheffield table, in which the estimated absolute risk for CHD is used to establish a threshold for aggressive intervention.[64] The average CHD rates reported in those tables are roughly comparable to the myocardial infarction and coronary death rates among middle-aged men who participated in the West of Scotland trial of cholesterol lowering.[35,65] In contrast, our prediction equations estimate coronary disease risk over a period of 10 years for a larger age range and include total CHD (angina pectoris, myocardial infarction, and coronary death).

A study that considered CHD prediction using TC, LDL-C, TC/HDL-C ratio, and LDL-C/HDL-C ratio[66] concluded that "total cholesterol/HDL is a superior measure of risk for CHD compared with either total cholesterol or LDL cholesterol, and that current practice guidelines could be more efficient if risk stratification was based on this ratio rather than primarily on the LDL cholesterol level." Such an approach appears attractive, but at the extremes of the TC or LDL-C distribution, equal ratios may not signify the same CHD risk. Moreover, use of a ratio may make it harder for the physician to focus on the separate values for TC, LDL-C, and HDL-C that have to be borne in mind to make appropriate clinical decisions concerning therapy. The current approach builds on established blood pressure (JNC-V) and cholesterol (NCEP ATP II) foundations, requires fasting samples only if LDL-C score sheets are used, and is easy to implement as part of a screening program.

Estimation of CHD and other cardiovascular events is a dynamic field. The present formulation has attempted to provide a simplified approach to predict risk for initial CHD events in outpatients free of disease, drawing on national programs for treatment of elevated blood pressure and TC, without a loss in accuracy. Other factors, such as fibrinogen, lipoprotein(a), ERT, family history of premature CHD, and hypertensive therapy have been or will be evaluated as baseline data and greater follow-up experience become available.

TABLE 6. β-Coefficients Underlying CHD Prediction Sheets Using TC Categories

Variable	Men	Women
Age, y	0.04826	0.33766
Age squared, y		−0.00268
TC, mg/dL		
<160	−0.65945	−0.26138
160–199	Referent	Referent
200–239	0.17692	0.20771
240–279	0.50539	0.24385
≥280	0.65713	0.53513
HDL-C, mg/dL		
<35	0.49744	0.84312
35–44	0.24310	0.37796
45–49	Referent	0.19785
50–59	−0.05107	Referent
≥60	−0.48660	−0.42951
Blood pressure		
Optimal	−0.00226	−0.53363
Normal	Referent	Referent
High normal	0.28320	−0.06773
Stage I hypertension	0.52168	0.26288
Stage II–IV hypertension	0.61859	0.46573
Diabetes	0.42839	0.59626
Smoker	0.52337	0.29246
Baseline survival function at 10 years, S(t)	0.90015	0.96246

Appendix

Application of Tables 6 and 7

The β-coefficients given in Table 6 are used to compute a linear function. The latter is corrected for the averages of the participants' risk factors, and the subsequent result is exponentiated and used to calculate a 10-year probability of CHD after insertion into a survival function. The following explanation and an example treat each of these steps in a serial fashion, using Table 6 for the illustration below.

(Equation 1): $L\_Chol_{men} = 0.04826 \times age - 0.65945$ (if cholesterol <160) +0.0 (if cholesterol 160 to 199) +0.17692 (if cholesterol 200 to 239) +0.50539 (if cholesterol 240 to 279) +0.65713 (if cholesterol ≥280) +0.49744 (if HDL-C<35) +0.24310 (if HDL-C 35 to 44) +0.0 (if HDL-C 45 to 49) −0.05107 (if HDL-C 50 to 59) −0.48660 (if HDL-C ≥60) −0.00226 (if blood pressure [BP] optimal) +0.0 (if BP normal) +0.28320 (if BP high normal) +0.52168 (if BP stage I hypertension) +0.61859 (if BP stage II hypertension) +0.42839 (if diabetes present) +0.0 (if diabetes not present) +0.52337 (if smoker) +0.0 (if not smoker).

The function is evaluated at the values of the means for each variable. Call it G, where (Equation 1): $G\_Chol_{men} = 0.04826 \times 48.5926 - 0.65945 \times 0.07433 + 0.17692 \times 0.38851 + 0.50539 \times 0.16673 + 0.65713 \times 0.05826 +$

$0.49744\times0.19285+0.24310\times0.35476-0.05107\times0.19646-0.48660\times0.10727-0.00226\times0.20048+0.28320\times0.20048+0.52168\times0.22820+0.61859\times0.13057+0.42839\times0.05223+0.52337\times0.40458=3.0975$. Similarly, for women, G_Chol=9.92545. For the LDL score sheets, G_LDL for men is 3.00069 and for women 9.914136.

This value of G is subtracted from function L to produce function A (Equation 2), which is then exponentiated, to produce B (Equation 3). The latter represents the relative odds for CHD. The survival value s(t) is exponentiated by B and subtracted from 1.0 to calculate the 10-year probability of CHD (Equation 4).

(Equation 2): A=L−G (where G_Chol=3.0975 for men, 9.92545 for women; similarly for Table 7, G_LDL=3.00069 for men, 9.914136 for women).

(Equation 3): $B=e^{A}$.

(Equation 4): $P=1-[s(t)]^{B}$ [where s(t)_Chol 10 years=0.90015 for men, 0.96246 for women; similarly for Table 7, s(t)_LDL 10 years=0.90017 for men, 0.9628 for women].

Consider a 55-year-old man with cholesterol of 250 mg/dL, HDL-C of 39 mg/dL, blood pressure (146/88 mm Hg) that falls into stage I hypertension, and no diabetes, who is a smoker. In this instance, after Equation 1, $L=55\times0.04826+0.50539+0.24310+0.52168+0.52337=4.4478$. After Equation 2, $A=4.4478-3.0975=1.3503$, and after Equation 3, $B=e^{1.3503}=3.85874$. Finally, after Equation 4, $P=1-0.90015^{3.85874}=1-0.66637=0.3336$, for a 33% chance of developing CHD over 10 years. According to the point score sheet, 55 years old (4 points)+cholesterol of 250 mg/dL (2 points)+HDL-C of 39 mg/dL (1 point)+stage I blood pressure (2 points)+smoker (2 points)=11 points, corresponding to a 31% chance of developing CHD over 10 years. An average 55-year-old man has a 16% risk, and an ideal man has a 7% risk. Similar calculations can be done for women and for the LDL-C prediction models and score sheets.

TABLE 7. β-Coefficients Underlying CHD Prediction Sheets Using LDL-C Categories

Variable	Men	Women
Age, y	0.04808	0.33994
Age squared, y		−0.0027
LDL-C, mg/dL		
<100	−0.69281	−0.42616
100–129	Referent	Referent
130–159	0.00389	0.01366
160–189	0.26755	0.26948
≥190	0.56705	0.33251
HDL-C, mg/dL		
<35	0.48598	0.88121
35–44	0.21643	0.36312
45–49	Referent	0.19247
50–59	−0.04710	Referent
≥60	−0.34190	−0.35404
Blood pressure		
Optimal	−0.02642	−0.51204
Normal	Referent	Referent
High normal	0.30104	−0.03484
Stage I hypertension	0.55714	0.28533
Stage II–IV hypertension	0.65107	0.50403
Diabetes	0.42146	0.61313
Smoker	0.54377	0.29737
Baseline survival function at 10 years, S(t)	0.90017	0.9628

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