

## Original Contributions

# Identifying Adults at Increased Risk of Coronary Disease

## How Well Do the Current Cholesterol Guidelines Work?

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**Objective.**—To assess the accuracy of lipid screening strategies to identify individuals at increased risk of coronary heart disease mortality.

**Patients.**—The 15% random sample of adults recruited into the Lipid Research Clinic Prevalence and Follow-up Studies, which included 3678 men and women aged 35 to 74 years. Total plasma cholesterol levels, lipoprotein fractions, and other coronary risk factors at study entry were compared with subsequent coronary heart disease mortality (mean follow-up, 12.2 years).

**Main Outcome Measures.**—The areas under receiver operating characteristic curves for blood lipids, lipid ratios, the screening guidelines proposed by the National Cholesterol Education Program, those of the Canadian Consensus Conference on Cholesterol, and a coronary risk model that used Framingham data.

**Main Results.**—The current National Cholesterol Education Program guidelines (area under the curve, 0.74) were significantly ( $P=.03$ ) more accurate than the old National Cholesterol Education Program guidelines (area, 0.72). The ratio of total plasma cholesterol level to high-density lipoprotein cholesterol level (area, 0.72) was as accurate as current National Cholesterol Education Program guidelines. The coronary risk model (area, 0.85) was superior ( $P<.003$ ) to all other screening maneuvers. Compared with the current National Cholesterol Education Program guidelines, the risk model demonstrated superior test sensitivity (70% vs 45%) with only slightly reduced specificity (82% vs 86%).

**Conclusion.**—The ratio of total plasma cholesterol level to high-density lipoprotein cholesterol level is as accurate as current American screening guidelines. Future guidelines should better incorporate high-density lipoprotein cholesterol levels and nonlipid risk factors to target high-risk individuals accurately.

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TOTAL plasma cholesterol (TC) and specific lipoproteins have increasingly become the focus of screening and treat-

ment programs to prevent the development of coronary heart disease (CHD). These initiatives are supported by the strong and consistent relation between the development of CHD and elevations in TC and low-density lipoprotein cholesterol (LDL) levels.<sup>1-7</sup> Depressed levels of high-density lipoprotein cholesterol (HDL) have also been shown to be independently associated with CHD development.<sup>3,6</sup> In Canada and the United States, panels of experts have been convened to consider these epidemiological data and the results of successful clinical

trials to prevent the development of CHD through lipid modification. These deliberations have resulted in expert or consensus guidelines to identify individuals at high risk of CHD and to treat these individuals according to their perceived overall coronary risk.<sup>9,11</sup> Subsequent analyses have demonstrated that a substantial number of Americans and Canadians would require dietary intervention or pharmacotherapy if these guidelines were followed.<sup>12,13</sup> However, there has been little evaluation of these guidelines to determine whether they accurately target high-risk individuals, particularly those who have not yet developed symptoms of CHD.

In preparing the guidelines, panels of experts have drawn heavily on previously published epidemiologic research, in particular the Framingham Heart Study.<sup>13-17</sup> Accordingly, the experts were faced with the difficult task of distilling multivariate statistical data from the Framingham Study into scientifically sound but reasonable guidelines. These guidelines resulted in the categorization of low-, intermediate-, and high-risk groups of individuals as complex data had to be simplified to be clinically useful.

Given the uncertainty surrounding the accuracy of current cholesterol management guidelines, we used receiver operating characteristic (ROC) curve analyses to evaluate the predictive value of the original National Cholesterol Education Program guidelines (NCEP I), the updated guidelines (NCEP II), the Canadian Consensus Conference on Cholesterol guidelines (CCCC), and a computer simulation model based on the original Framingham multivariate equations.<sup>18,11,14</sup>

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## PATIENTS AND METHODS

### Lipid Research Clinic (LRC) Prevalence and Follow-up Studies

We used public-use data tapes provided by the LRC Program Prevalence and Follow-up Studies. The Prevalence Study was conducted from 1972 to 1976 in 10 North American clinics to determine the prevalence of dyslipoproteinemias and related factors.<sup>15-17</sup> A 15% random sample of these participants, plus all individuals with abnormal lipid values, were invited to return to a second visit (visit 2). The group with abnormal lipid values was not included in this analysis. This group included all participants taking lipid-lowering medication, and those with abnormal lipid values defined primarily by age- and sex-specific threshold levels for plasma TC and triglycerides (TG).<sup>18</sup> Accordingly, only individuals in the 15% random sample were the focus of this analysis, which supports the generalizability of our results to the general population.

Among the 15% random sample, we excluded individuals who (1) had definite CHD or myocardial ischemia at study entry, (2) had had a stroke or reported symptoms consistent with peripheral vascular disease, (3) used digitalis, antiarrhythmics, or lipid-altering medication, (4) were missing values for TC or lipoproteins, (5) were pregnant, (6) were younger than 35 or older than 74 years at study entry, or (7) had been fasting less than 12 hours before lipid testing. Disease criteria were defined by the LRC. Patients considered to have definite CHD or myocardial ischemia were those in whom a myocardial infarction or angina pectoris had been diagnosed, who used digitalis or medications for arrhythmias or angina, or who had undergone surgery for a coronary bypass or aortic aneurysm. Peripheral vascular disease was defined as calf pain on walking that was unrelieved unless the individual stopped or slowed down (in which case it was relieved in 10 minutes or less), or a history of surgery for poor circulation for a condition other than varicose veins. Cerebrovascular disease was defined as present if the individual had a history of stroke. After these exclusions, 3678 (75%) of the 4917 random-sample participants remained in the dataset.

All men and women were followed up prospectively to provide data on subsequent mortality. Telephone or mail contact began annually in July 1977, and individuals were followed up through June 1987, for an average follow-up of 12.2 years. Specific causes of mortality were ascertained by death certificate and hospital records, and the vital status of 99% of the participants was es-

tablished at least once during the follow-up period.<sup>8</sup> Details of laboratory and quality control procedures have been published elsewhere.<sup>15,18</sup>

### Screening Strategies

We compared the accuracy of various screening strategies to identify those at increased risk of CHD mortality. Lipid screening strategies were based on single lipid values or lipid ratios at visit 2 that included TC, HDL, LDL, TG, TC/HDL, LDL/HDL, and TG/HDL. Corrected TG values were used in this analysis, the LRC having adjusted for the amount of free glycerol in the plasma for persons with plasma TG levels exceeding 3.39 mmol/L (300 mg/dL).<sup>18</sup>

### Data Analysis

For our analyses, CHD deaths included those classified by the LRC protocol as "definite" or "suspected" CHD deaths.<sup>19</sup> Two-tailed *t* tests were used to compare the mean values of continuous variables among those who did and did not die of CHD. Categorical variables were compared by means of the  $\chi^2$  statistic.

### ROC Analyses

Quartiles were calculated for each of the plasma lipid levels and lipid ratios among LRC subjects. Risk strata were also determined according to specific lipid guidelines. A series of decision thresholds was then considered, based on four strata, to test the sensitivity and specificity of each screening method. Three 2x2 contingency tables were constructed for each strategy.

The resulting tables for each screening strategy provided a series of three true-positive rates and three false-positive rates with which to test the accuracy of each screening method to predict CHD mortality by means of ROC curve analysis. An ROC curve plots the true-positive rate (test sensitivity) for a given decision threshold on the y-axis and the corresponding false-positive rate (1 - test specificity) on the x-axis. The area under the resulting fitted curve represents the discriminating ability of that particular screening method<sup>20</sup> and is assumed to be normally distributed. An area of 0.5 below the 45° line represents a nondiscriminant screening test where the true-positive rate equals the false-positive rate.

For each screening strategy, maximum likelihood estimates of the parameters of binomial ROC curves were calculated and the areas under the fitted smooth curves were obtained. The statistical significance of the differences between the two estimated ROC curve areas was calculated by means of univariate *z* scores.<sup>21</sup>

### American and Canadian Screening Guidelines

To compare the results of US and Canadian screening guidelines with the computer simulation model of Framingham data, we restricted our analysis to adults aged 35 to 74 years who had not yet developed symptomatic cardiovascular disease. The NCEP I and NCEP II screening recommendations are summarized in Figure 1.<sup>10,11</sup> Both guidelines categorize adults into four risk strata based on lipoprotein levels and the presence of additional nonlipid risk factors.

The CCCC recommendations are summarized in Figure 2.<sup>9</sup> These recommendations focus only on serum lipoprotein levels and stratify individuals into three risk groups. To compare accurately the three risk strata of the CCCC with the four outlined by the NCEP, we added a fourth risk group to the Canadian guidelines. Although this fourth risk group was not explicitly stated by the CCCC, we believe that its identification is consistent with the CCCC guidelines.

### The Computer Risk Model Based on Framingham Data

The CHD Prevention Model is based primarily on the logistic regression equations reported by the Framingham Heart Study.<sup>14</sup> This model calculates the lifetime distribution of CHD events, CHD death, and non-CHD death for individuals free of symptomatic coronary disease at entry into the model. These annual probabilities are based on the Framingham equations, Canadian Life Tables Statistics, and data from the Canada Health Survey.<sup>12,22,23</sup> The annual risk of coronary events is a function of a subject's age, sex, diastolic blood pressure, TC level, HDL level, and the presence or absence of left ventricular hypertrophy, glucose intolerance, and cigarette smoking.

It should be emphasized that the CHD Prevention Model is based on a different cohort of patients from those recruited into the LRC cohort. As such, the LRC data represent an "independent" validation of the model. Each individual in the LRC cohort was assigned a 12-year CHD mortality risk based on his or her specific risk factors. All individuals were then rank ordered according to their risk, and the cohort was divided into quartiles. An ROC curve based on the CHD deaths in each quartile was then produced.

### Risk Assessment Among Those With Hyperlipidemia

While the computer risk model incorporates lipid levels into the calculation of overall CHD risk, it does not specifi-

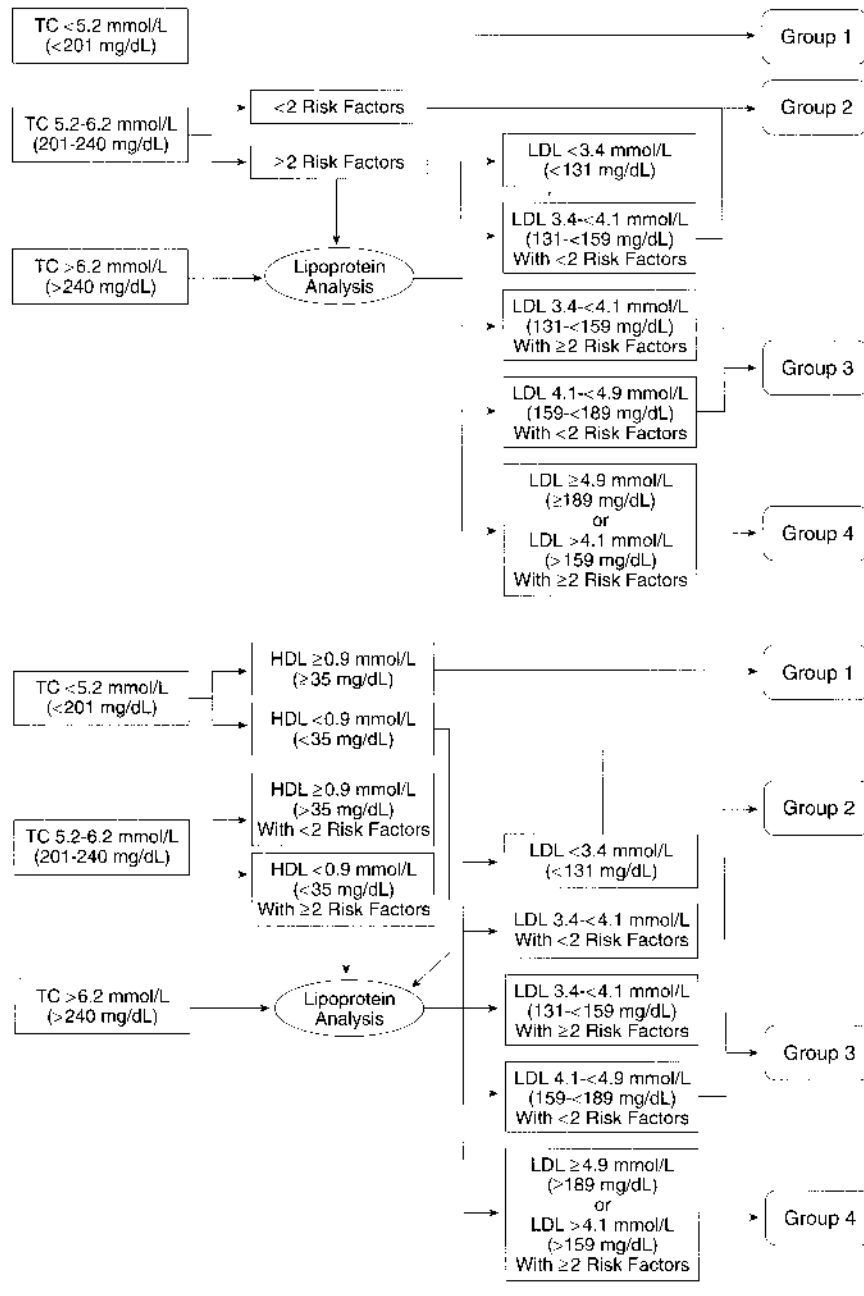


Figure 1.—Overview of the first (top) and second (bottom) National Cholesterol Education Program guidelines that allocated adults to four coronary risk strata based on lipid measurements and the presence of nonlipid risk factors such as male age of 45 years or more, female age of 55 years or more or premature menopause without estrogen replacement therapy, a family history of premature coronary heart disease, current cigarette smoking, hypertension or use of antihypertensive medication, a low HDL level, and diabetes mellitus. See references 10 and 11 for more specific details. TC indicates total plasma cholesterol; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

ally identify high-risk individuals who also have hyperlipidemia. Accordingly, we evaluated the usefulness of adding the model to screening strategies for hyperlipidemia, by first identifying individuals with an elevated TC level ( $\geq 5.2$  mmol/L [ $\geq 201$  mg/dL]).

These individuals were then classified according to a 12-year risk of CHD mortality based on the CHD Prevention

Model and their specific risk factors and rank ordered into tertiles. When these three risk strata were added to the low-risk group with TC level less than 5.2 mmol/L (201 mg/dL), the resulting four strata were used to compare the "risk model screening strategy" with those categories delineated by the CCCC, NCEP I, NCEP II, or quartiles of specific blood lipid measurements.

Among 3678 individuals without symptomatic cardiovascular disease, 77 CHD deaths occurred during the 12.2 years of follow-up. Univariate analyses demonstrated the usual risk factors significantly associated with coronary mortality, including advancing age, male sex, increasing body mass, increasing blood pressure, and the presence of cigarette smoking or diabetes (Table 1). As expected, increasing levels of TC, LDL, and TG were significantly associated with CHD mortality, as were decreasing levels of HDL. Ratios of TC, LDL, or TG divided by HDL were also strong significant risk factors.

The ability of each test or strategy to discriminate between those who would and those who would not die of CHD was calculated by means of ROC curve analyses. The area under each ROC curve represents the discriminating ability of a specific test or strategy. For instance, if two individuals (one who will develop CHD and one who will not) are randomly selected from the population, each ROC curve area describes the likelihood of correctly identifying the individual who will develop CHD. A perfect test has an area of 1.00 and a useless test has an area of 0.50, which is no better than chance. The areas ( $\pm$ SD) for single lipid measurements were similar and ranged from  $0.64 \pm 0.04$  for TG,  $0.66 \pm 0.03$  for HDL, and  $0.68 \pm 0.03$  for LDL or TC. The areas under the ROC curves for TC/HDL ( $0.72 \pm 0.04$ ) and LDL/HDL ( $0.72 \pm 0.03$ ) were similar but superior ( $P < .05$ ) to the area for TG/HDL ( $0.65 \pm 0.04$ ). The ratio of TC/HDL was also a better discriminator than TC alone, as previously described.<sup>24</sup> The LDL/HDL ratio was better than LDL alone, but the TG/HDL ratio was not better than TG alone. This failure of TG/HDL to improve over TG alone probably results from the strong inverse correlation between TG and HDL.<sup>25</sup> Also, in this cohort, both TG and the TG/HDL ratio were relatively weak predictors of CHD.

When ROC curves were constructed for each of the expert guidelines as well as the CHD Prevention Model, the CCCC guidelines proved to be the least accurate, with an area of  $0.70 \pm 0.03$  (Figure 3). A simple ratio of TC/HDL with an area of  $0.72 (\pm 0.04)$  was not significantly less accurate than the NCEP II ( $P = .54$ ) or CCCC guidelines ( $P = .50$ ). The updated NCEP II guidelines were also significantly better than the old NCEP I guidelines ( $0.74 \pm 0.03$  vs  $.72 \pm .03$ ;  $P = .03$ ).

The CHD Prevention Model based on Framingham data demonstrated an ROC area of  $0.85 \pm 0.02$ , which was signifi-

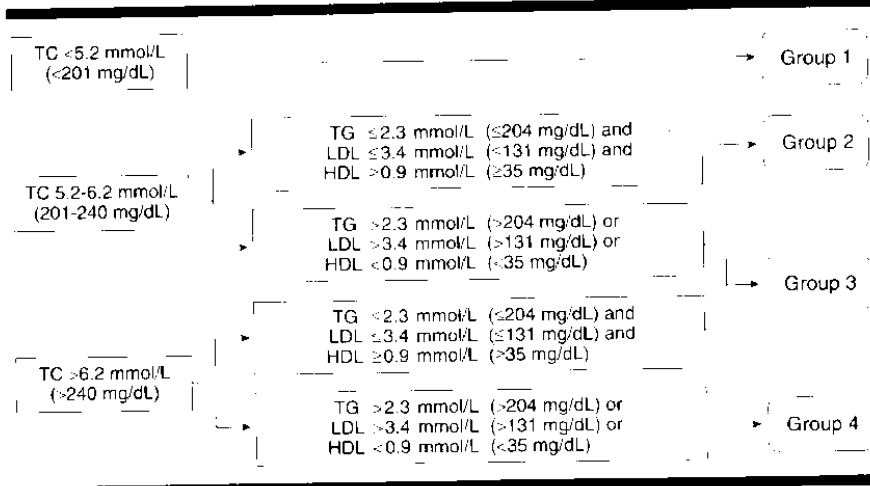


Figure 2.—Overview of the Canadian Consensus Conference on Cholesterol guidelines that allocated adults (aged  $\geq 30$  years) to three coronary risk strata based on lipid measurements. A fourth, very high-risk group has been added (see the "Patients and Methods" section) to allow comparison with the four strata of the National Cholesterol Education Program. TC indicates total plasma cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and TG, triglycerides.

Table 1.—Risk Factors Associated With Coronary Death\*

	Coronary Death		P
	No (n=3601)	Yes (n=77)	
Age, y	48.8 ± 9.6	57.2 ± 9.6	<.001
Blood pressure, mm Hg			
Systolic	124.2 ± 18.1	141.8 ± 26.5	<.001
Diastolic	79.7 ± 10.5	88.0 ± 13.7	<.001
Cholesterol, mmol/L (mg/dL)			
TC	5.4 ± 1.0 (209 ± 39)	6.0 ± 0.9 (232 ± 35)	<.001
HDL	1.4 ± 0.4 (54 ± 15)	1.2 ± 0.6 (46 ± 23)	.02
LDL	3.5 ± 0.9 (135 ± 35)	4.2 ± 0.9 (162 ± 35)	<.001
TG, mmol/L (mg/dL)	1.4 ± 1.0 (124 ± 89)	1.7 ± 0.9 (151 ± 80)	.01
TC:HDL ratio	4.3 ± 1.8	5.5 ± 1.7	<.001
LDL:HDL ratio	2.9 ± 1.3	3.9 ± 1.4	<.001
TG:HDL ratio	1.2 ± 1.6	1.7 ± 1.1	.001
Body mass index, kg/m <sup>2</sup>	25.6 ± 4.1	27.3 ± 5.8	.01
Sex, No. (%) M	1856 (51.5)	55 (71.4)	.001
Smokers, No. (%)	1187 (33.0)	38 (49.4)	.003
Diabetic, No. (%)	118 (3.3)	15 (19.5)	<.001
Left ventricular hypertrophy, No. (%)	13 (0.4)	0 (0.0)	.60

Mean follow-up was 12.2 years. Values are expressed as mean ± SD unless otherwise stated. TC indicates total plasma cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and TG, triglycerides.

cantly better ( $P=.003$ ) than any of the expert guidelines (Figure 3). Even if the model was applied only to those with hyperlipidemia (TC level  $\geq 5.2$  mmol/L [ $\geq 201$  mg/dL]), the resulting ROC area of  $0.80 \pm 0.4$  was still significantly ( $P<.01$ ) better than the CCCC or NCEP I (not shown). Compared with the NCEP II guidelines, the model's larger ROC area was of borderline significance ( $P=.06$ ).

We also evaluated the expected results of screening in terms of test sensitivity, specificity, and disease labeling (true-positive and false-positive results). As summarized in Table 2, if those with the highest risk quartile in each lipid category are targeted for lipid modification, then by design, 25% of the population would be classified as high risk

but only 45% to 58% of the individuals eventually dying of CHD would be identified (test sensitivity). However, the test specificities are approximately 75%.

Among the expert guidelines, the NCEP II performed the best, as 15% of the population was designated high risk and 45% of eventual CHD deaths occurred in this risk category. As an overall screening strategy, TC measurement followed by the risk model (for all adults  $\geq 5.2$  mmol/L [ $\geq 201$  mg/dL]) demonstrated superior sensitivity compared with the NCEP II (70% vs 45%), with only slightly reduced specificity (82% vs 86%). Moreover, 70% of those who eventually died of CHD were identified, yet only 19% of the population was classified as high risk.

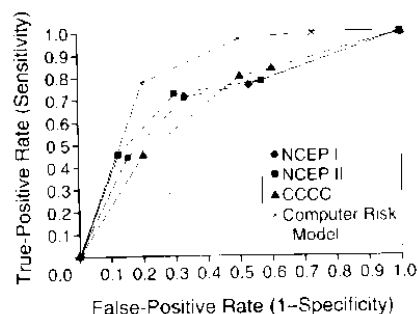


Figure 3.—Receiver operating characteristic curves for screening guidelines including the first and second National Cholesterol Education Programs (NCEP I and II) and the Canadian Consensus Conference on Cholesterol (CCCC). The 45° line (broken line) represents a nondiscriminating test where the true-positive rate equals the false-positive rate. The NCEP II guidelines performed the best with an area ( $\pm$ SD) beneath the curve of  $0.74 \pm 0.03$ , followed by the NCEP I ( $0.72 \pm 0.03$ ) and the CCCC ( $0.70 \pm 0.03$ ). The NCEP II guidelines also performed significantly ( $P=.03$ ) better than the NCEP I in predicting coronary deaths. The computer risk model had an area of  $0.85 \pm 0.02$  and was a significantly ( $P=.03$ ) better discriminator than any of the expert guidelines.

## COMMENT

Using the LRC data set, we previously demonstrated that the ratio of TC to HDL level is the best lipid discriminator of increased coronary risk.<sup>24</sup> This is particularly true for individuals younger than 60 years, in whom the association between TC level and coronary risk is strong. In this present study, we have shown that the TC/HDL ratio is as accurate as current screening guidelines.

We should note the substitution of CHD mortality for total CHD risk as the LRC follow-up data included only fatal events. This will underestimate the absolute risk of fatal and nonfatal CHD. Nevertheless, these data can be used to compare the relative accuracy of different coronary risk screening strategies given the strong association between fatal and nonfatal events. We also note that these analyses focus only on screening for primary prevention and do not evaluate the accuracy of the current guidelines for secondary prevention among those with diagnosed CHD.

The CCCC recommendations categorize individuals into specific risk groups solely based on ranges of lipid abnormalities.<sup>5</sup> The original NCEP guidelines (NCEP I) expand on the CCCC recommendations as they recognize the presence or absence of nonlipid risk factors.<sup>25</sup> The updated NCEP guidelines (NCEP II) further develop the relationship between nonlipid risk factors and CHD risk and also give additional importance to the HDL level.<sup>26</sup> Finally, the CHD

Table 2.—CHD Risk Classification According to Lipid Levels and Screening Guidelines: Test Sensitivity and Specificity†

	Total Population (N=3678)		With CHD Death (n=77)			Without CHD Death (n=3601)		
	Low Risk, No.	High Risk, No. (%)	Low Risk, No.	High Risk, No.	Test Sensitivity, %	Low Risk, No.	High Risk, No.	Test Specificity, %
Cholesterol								
TC	2764	914 (25)	41	36	47	2723	878	76
HDL	2709	969 (26)	40	37	48	2669	932	74
LDL	2769	909 (25)	41	36	47	2728	873	76
TG	2778	900 (24)	42	35	45	2736	865	76
TC/HDL ratio	2759	919 (25)	32	45	58	2727	874	76
LDL/HDL ratio	2763	915 (25)	33	44	57	2730	871	76
TG/HDL ratio	2759	919 (25)	42	35	45	2717	884	75
CCCC	2905	773 (21)	43	34	44	2862	739	79
NCEP								
I	3043	635 (17)	43	34	44	3000	601	83
II	3132	546 (15)	42	35	45	3090	511	86
Lipids and risk model‡	2963	715 (19)	23	54	70	2940	661	82

†CHD indicates coronary heart disease; TC, total plasma cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; CCCC, Canadian Consensus Conference on Cholesterol; NCEP I, National Cholesterol Education Program (original guidelines); and NCEP II, National Cholesterol Education Program (revised guidelines). High risk corresponds to either the highest quartile for TC, LDL, TG, TC/HDL, LDL/HDL, or TG/HDL, the lowest quartile for HDL, or the highest risk strata defined by each of the expert guidelines.

‡Those with a TC level less than 5.2 mmol/L (201 mg/dL) are at low risk. Those with a TC level of 5.2 mmol/L (201 mg/dL) or greater are further stratified according to the computer risk model, and the highest risk tercile is classified as "high risk."

Prevention Model imparts additional weight to nonlipid risk factors by actually calculating CHD risk.<sup>14</sup> Accordingly, at each increasing level of complexity, one must ask whether the additional information results in improved identification of those who will die of CHD.

The ratios of TC/HDL and LDL/HDL are the best lipid discriminators for identifying those at increased risk of CHD mortality. This suggests that, while all of the current guidelines focus attention on TC and LDL levels, the relative importance of HDL level may be undervalued. In the CCCC and NCEP I, the importance of HDL level is only recognized if it is below 0.9 mmol/L (35 mg/dL).<sup>10</sup> One of the reasons that the NCEP II is a significant improvement on the earlier recommendations is that HDL levels now play a major role as part of the initial risk classification.<sup>11</sup> Moreover, the reduction in coronary risk associated with an increased HDL level above 1.6 mmol/L (62 mg/dL) is also recognized by the NCEP II.

The TC/HDL ratio was as accurate as the LDL/HDL ratio in this analysis. The reasons for this are not obvious, given our current understanding of the more direct role of LDL vs total TC in the development of atherosclerotic plaque formation. The TC/HDL ratio may perform as well as the LDL/HDL ratio because TC is measured directly but LDL is only estimated from the direct measurement of TC, HDL, and TG. Estimates of LDL may be particularly undervalued by the large coefficient of variation reported for TG measurements.<sup>20</sup> Accordingly, while LDL may remain the primary target of lipid-lowering efforts, its susceptibility to the cumulative er-

rors in TC, TG, and HDL measurement may weaken its predictive value.<sup>27</sup> These analyses support the use of TC/HDL ratio as the optimal lipid screening measurement because of its relative accuracy, availability, and low cost.<sup>24</sup>

The importance of nonlipid risk factors in the determination of overall coronary risk is well recognized. The major shortcoming of the CCCC is that it does not explicitly integrate the presence or absence of nonlipid risk factors into the final determination of coronary risk.<sup>9</sup> The resulting discriminating ability of the CCCC recommendations was inferior to both the NCEP I and NCEP II, which explicitly consider the presence of nonlipid risk factors in the global assessment of risk.<sup>10,11</sup> However, this global risk assessment is based only on the presence of risk factors, not their relative importance nor the degree to which a specific risk factor deviates from the norm.

For instance, in the NCEP II, all positive risk factors are considered equally important, including male age of 45 years or more, female age of 55 years or more or premature menopause without estrogen replacement therapy, a family history of premature CHD, current cigarette smoking, hypertension (defined as a blood pressure  $\geq 140/90$  mm Hg or the use of antihypertensive medication), a low HDL level, and diabetes mellitus.<sup>11</sup> However, Framingham data indicate that not all risk factors are equal. For instance, among women, the presence of diabetes mellitus increases coronary risk more than the presence of cigarette smoking, while among men, the opposite appears to be true.<sup>1,28</sup>

Recognizing the need to simplify the classification of nonlipid risk factors into

easily remembered and clinically useful categories, the NCEP II panel had to compromise further the information contained in continuous risk factors, such as age, blood pressure, and HDL level, by dichotomizing these variables. Accordingly, when the discriminating ability of the CHD prevention model is compared with that of the NCEP II guidelines, the model performs better. This underscores the importance of fully evaluating nonlipid risk factors. Simply enumerating the number that are present may not be sufficient. At the least, both the relative weights of each risk factor and the degree to which they deviate from the norm should be considered, such that a 55-year-old woman with diabetes is not considered to be equal to a 55-year-old woman with a blood pressure of 140/90 mm Hg or a 60-year-old woman with a blood pressure of 160/95 mm Hg.<sup>11</sup>

These analyses indicate that we are making progress, as the NCEP II guidelines are superior to those of NCEP I. Nevertheless, they also indicate there is room for improvement, as the knowledge gained from the Framingham Heart Study is not being fully incorporated into current guidelines. The use of sophisticated computer simulation models, such as that used in this analysis, is one possible answer.<sup>14</sup> However, this would require routine computer analyses of data from individual patients, which may not be readily available in current everyday clinical practice. Simpler solutions should also be considered. Framingham data have been distilled into a coronary heart disease risk factor prediction chart by the American Heart Association.<sup>29-31</sup> This chart has been pro-

posed as one means for assessing the overall coronary risk of individual patients before embarking on a treatment plan for hyperlipidemia.

Finally, this study underscores the importance of verifying the validity of clinical guidelines whenever feasible. Consensus panels face a tremendous challenge in bringing a group of independent experts together to develop guidelines that are scientifically sound and yet clinically feasible. The costs of screening and the cost-effectiveness of preventive interventions must also be considered.<sup>12,31,32</sup> The final solution must

then be evaluated in daily clinical practice to ensure that theoretical efficacy translates into real clinical effectiveness. Independent validation of clinical decision rules is only a first step in this lengthy process.<sup>33,34</sup> Data sets like the LRC Follow-up Cohort afford the opportunity to provide the evaluation and feedback that are critical to the ongoing evolution of clinical practice guidelines. This information must then be used to target those at increased risk of disease and reassure those whose overall risk remains low despite the presence of an abnormal test result.

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