Improving the Prediction of Coronary Heart Disease to Aid in the Management of High Cholesterol Levels

What a Difference a Decade Makes

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Context.—A patient's coronary heart disease (CHD) risk must be correctly classified to successfully apply risk-based guidelines for treatment of hypercholesterolemia.

Objective.—To determine the classification accuracy of the National Cholesterol Education Program (NCEP) CHD risk-stratification system and compare it with a simple revised system that gives greater weight to age as a CHD risk factor.

Design.—Modeling of 10-year CHD risk, using equations from the Framingham Heart Study applied to a cross-sectional survey of the US population.

Subjects.—The 3284 subjects aged 20 to 74 years surveyed in the Second National Health and Nutrition Examination Survey (1978-1982) who had fasting lipid levels measured.

Main Outcome Measures.—The area under the receiver operating characteristic curve (AUC) for 10-year CHD risk for the NCEP and revised scales.

Results.—Among all adults with a low-density lipoprotein cholesterol value of at least 4.1 mmol/L (160 mg/dL), the NCEP system showed fairly good discrimination (AUC=0.90), though there was a substantial decline among men 35 to 74 years old and women 55 to 74 years old (AUC=0.81). By contrast, the revised system showed superior performance in all hypercholesterolemic adults (AUC=0.94-0.97) as well as in the subgroup of men 35 to 74 years old and women 55 to 74 years old (AUC=0.94-0.96).

Conclusions.—Simple modifications of the NCEP treatment criteria result in a substantially improved ability to discriminate between higher and lower CHD risk groups. Unlike the NCEP system, this revised system retains its classification ability in all age groups studied.

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nate between higher-risk and lower-risk individuals.

METHODS

Comparing the classification performance of the NCEP II system with a revised scale required estimating the 10-year risk of CHD for each subject in a population-based data set, and generating a measure of discrimination with which to test each scale. We limited our analysis to adults aged 20 to 74 years without a history of CHD.

Defining Scale Criteria

The NCEP II algorithm for intervention is detailed in Table 1. In this system, men younger than 35 years and premenopausal women are recommended for treatment if their low-density lipoprotein (LDL) level is at least 5.7 mmol/L (220 mg/dL) or if their LDL cholesterol level is at least 4.9 mmol/L (190 mg/dL) and at least 2 other cardiac risk factors are present. The same strategy is recommended for older persons, with LDL cholesterol thresholds reduced by 0.8 mmol/L (30 mg/dL).

For the revised scale (Table 2), we substituted the following rule for the NCEP age criteria: men are assigned 1 point for every decade of age, beginning at 35 years, and women acquire age points beginning at 45 years. Thus, a woman is assigned 1 point if she is 45 to 54 years old, 2 points if she is 55 to 64 years old, and so on. One additional point is added if the LDL cholesterol level is at least 5.2 mmol/L (200 mg/dL). The other risk factors (hypertension, diabetes, smoking, and low high-density lipoprotein [HDL] cholesterol) are retained as specified in the NCEP II guidelines, as is the “negative risk factor” of a high HDL cholesterol level. For example, a 60-year-old woman (+2 points) with hypertension (+1 point), an LDL cholesterol level of 4.1 mmol/L (160 mg/dL) (no additional points), and an HDL cholesterol level of 1.8 mmol/L (70 mg/dL) (+1 point) would receive a total of 2 points.

Under the revised system, treatment of elevated cholesterol levels is indicated for persons with an LDL cholesterol level of at least 4.1 mmol/L (160 mg/dL) and a specified number of high-risk points. We performed separate analyses of the revised scale for “higher-risk” cutoffs of 2, 3, or 4 points.

Assigning CHD Risk to Population-Based Data

To estimate the distribution of CHD risk in US adults aged 20 to 74 years, we used data from the Second National Health and Nutrition Examination Survey (NHANES II), a population-based survey of the US noninstitutionalized civilian population, carried out between 1978 and 1982.4 We included the 3284 subjects who had full measurements of lipids following at least a 9-hour fast. Because data from the more recent NHANES III had not yet been released at the time of this analysis, we used published summary estimates from NHANES III to adjust total cholesterol and HDL values for changes that have occurred since NHANES II was performed.9 Expansion weights were used in all calculations and 1996 US Bureau of the Census population projections were used to convert percentages of the population into absolute numbers.10

We used the Framingham equations11 to estimate the 10-year CHD risk for each respondent in the NHANES II data set. This value was calculated by the method of Anderson et al12 as follows: 1 – exp(–exp(ln(10) – μ/σ)), where μ = 4.4284 + m, and σ = exp(–0.3171 – 0.2825 × m). For men, m = a – 1.6346 × ln(age) – 0.2082 × diabetes; for women, m = a – 6.5306 + 2.1059 × (ln(age/74))^2 – 0.4055 × diabetes. For both men and women, a = 11.0938 – 0.8670 × ln(diastolic blood pressure) – 0.2789 × smoking – 0.7142 × ln(total cholesterol/HDL cholesterol) – 0.7156 × ECG-LVH, where “smoking” is defined as current smoker and “ECG-LVH” is the presence of left ventricular hypertrophy on the electrocardiogram (set to 0 since this variable was not present in the NHANES II data set).

<table>
<thead>
<tr>
<th>Table 1.—NCEP II Treatment Criteria*</th>
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<tbody>
<tr>
<td><strong>Men</strong></td>
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<tr>
<td>20-34</td>
</tr>
<tr>
<td>20-34</td>
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<tr>
<td>≥35</td>
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*Hypcholesterolemic intervention is indicated for individuals without preexisting coronary heart disease who meet any of the criteria shown. LDL indicates low-density lipoprotein; NCEP II, updated National Cholesterol Education Program guidelines.

Table 2.—Revised Treatment Criteria*

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Points Assigned</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>Men</td>
</tr>
<tr>
<td>≥54</td>
<td>+1 for every decade over 35 y</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>+1 for levels ≤5.2 mmol/L (200 mg/dL)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>+1 for levels ≤0.91 mmol/L (35 mg/dL)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>+1 for presence of diabetes mellitus</td>
</tr>
<tr>
<td>Smoking</td>
<td>+1 if patient is a current cigarette smoker</td>
</tr>
<tr>
<td>Hypertension</td>
<td>+1 if blood pressure is at least 140/90 mm Hg or person is taking antihypertensive medications</td>
</tr>
</tbody>
</table>

*Low-density lipoprotein is indicated for individuals with a low-density lipoprotein (LDL) cholesterol level of at least 4.1 mmol/L (160 mg/dL) who exceed a chosen cutoff of “high-risk points” based on the risk factors shown. HDL indicates high-density lipoprotein.

Measurement of Discrimination

We used the area under the receiver operating characteristic (ROC) curve as the primary measure of the classification performance of the scales.11,12 Unlike typical ROC curves, which plot sensitivity against 1–specificity, these curves plot the positive predictive value against 1–negative predictive value. The ROC curves were constructed by first ranking all NHANES II respondents according to their CHD risk. As the cut point separating “higher-risk” from “lower-risk” persons was incrementally increased from a 10-year CHD risk of 0% to 100%, positive and negative predictive values were calculated. For example, if the cut point between higher- and lower-risk individuals is chosen as a 10-year risk of 10%, the positive predictive value of the NCEP system is 0.993 while the 1–negative predictive value is 0.638. If the cut point is increased to a 10-year risk of 11%, the corresponding values are 0.989 and 0.611. Thus, these curves incorporate the changing prevalence of “higher-risk” individuals as the cut point of CHD risk increases. The area under the curve (AUC) was calculated with the trapezoidal rule. All analyses were performed with Stata statistical software, version 5.0.13

These AUCs can be interpreted as follows: if 1 individual is randomly selected from the group labeled “higher-risk” and another is randomly chosen from the group labeled “lower-risk,” the AUC is the probability that the higher-risk individual has a CHD risk greater than that of the lower-risk individual. This interpretation was verified by Monte Carlo simulations. A scale with perfect discrimination would have an AUC of 1; a scale with no discrimination ability would have an AUC of 0.5. Ninety-five percent confidence intervals (CIs) for the AUCs were calculated by bootstrap


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Levels of CHD risk for groups of individuals are expressed as the 10th to 90th percentiles of 10-year risk of CHD event. The full range of risk is not presented since all scales include a few very low-risk and very high-risk persons, obscuring differences in the general levels of risk associated with the application of the different systems.

These analyses were performed for 2 groups: all adults aged 20 to 74 years with an LDL cholesterol level of at least 4.1 mmol/L (160 mg/dL), and all men 35 to 74 years of age and women 55 to 74 years of age with an elevated LDL cholesterol level (>4.1 mmol/L [160 mg/dL]).

**Validation**

In a separate analysis, we used data from the Lipid Research Clinics Prevalence and Follow-up Study (LRC) to test the performance of the revised and NCEP systems. This investigation was a prospective cohort study of risk factors for CHD death, beginning in 1977. The available LRC data set contained data on 2919 hypercholesterolemic (LDL, >4.1 mmol/L [160 mg/dL]) subjects who were at least 30 years old and free of CHD at baseline, and who were followed for an average of 12.2 years. Ascertainment of deaths was 99% complete; 131 CHD deaths were identified during the follow-up period.

In these analyses, each subject in the LRC data set was designated “higher-risk” or “lower-risk” according to the NCEP and revised criteria (using 3 points as the cutoff for the latter). We then calculated the sensitivity and specificity of each scale for the outcome of definite or suspected CHD death (note that sensitivity and specificity, rather than predictive values, were calculated since this data set contained actual clinical outcomes, not simply estimated CHD risk). Comparison of the sensitivities, specificities, and numbers of subjects labeled “higher-risk” was performed with McNemar test for matched pairs.

**RESULTS**

Among all adults aged 20 to 74 years, the NCEP II criteria showed good classification performance, with an AUC of 0.90 (Table 3). In large part, this was due to the correct classification of most young adults as lower risk. Among men aged 35 to 74 years and women aged 55 to 74 years, the scale performed less well, with the AUC falling to 0.81.

The revised scales performed substantially better than the NCEP criteria (Table 3). Depending on the number of points used as the criterion for “higher-risk,” the AUCs ranged from 0.94 to 0.97 for all adults and 0.94 to 0.96 for the older subgroup. In nearly all cases, there was no overlap in the CIs of the 2 classification systems. Visual comparison of the ROC curves generated by using the NCEP II system and the revised system (using the 3-point cutoff) for the older hypercholesterolemic subgroup demonstrates a substantially greater AUC for the revised system (Figure 1).

Reflecting the explicit incorporation of advancing age as a CHD risk factor, those individuals identified as “higher-risk” tended to be older under the revised system than under the NCEP II system (Figure 2). Note that there are fewer treated individuals in the oldest age groups (ages 65-74 years) than in the next younger group only because there are fewer persons in the older age group in the United States.

In the subgroup of all adults with an LDL cholesterol level of at least 4.1 mmol/L (160 mg/dL), slightly fewer individuals would be treated using the revised system (with a 3-point cutoff) relative to that of the NCEP, with a corresponding increase in levels of CHD risk (Table 3). For the revised system, a substantially greater number of individuals would be candidates for drug treatment if a cutoff of 2 points were chosen; many fewer would be so eligible if a cutoff of 4 points were used.

Other modifications of the revised system are possible. Finer gradations of change would occur in the levels of risk and number of individuals designated “higher-risk” if the number of risk factors used as the cutoff is varied from 2 to 4 and the starting age cut point is lowered or raised by 5 years (Table 4). For example, if the revised system is used with a 3-point cutoff and an age criteria starting at 40 years for men and 50 years for women, the AUC for this scale would be 0.96. The overall levels of risk found in the lower-risk (untreated) and higher-risk (treated) groups would increase because of the older age criteria, and there would be a corresponding decline in the number of persons recommended for hypolipidemic therapy. Regardless of how the revised system is modified, the degree of overlap in CHD risk between the lower-risk group and the higher-risk group is unlikely to be significantly reduced.
specificity, %

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Revised,

$\text{All adults 2917 85 93 52 56 1462 (51) 1353 (46)}$

National Cholesterol Education Program guidelines.

and the number of subjects classified as "higher-risk" by the 2 risk-stratification systems. NCEP II indicates updated

Revised,

$\text{the older man’s risk is approximately}$

10-year CHD risk of about 0.5%, while

Yet the young woman has a predicted

no other cardiac risk factors would not.

terol level of 4.1 mmol/L (160 mg/dL) and

cholesterol level of 5.7 mmol/L (220 mg/dL).

terial-CoA reductase inhibitor (statin). At the time of randomization, subjects aged 55 to 64 years,14 60 to 70 years,19 and 60 to 75 years20 showed significant benefits of therapy with statins. In 2 of these trials, however, the magnitude of benefit was attenuated in the older subgroups,18,19 though in the third study, the opposite was true.25

The efficacy of therapy in older individ- uals, who are at greater absolute CHD risk, is critical to determining the optimal age at which to begin medical therapy for elevated cholesterol levels, as is consideration of all relevant costs and benefits. Some have argued that hypolipidemic therapy should be provided to younger patients for greater preventive effectiveness.28 However, this strategy requires treating larger numbers of people for much longer periods with costly drugs that currently have limited evidence of long-term safety. Clinical tri- als currently under way should provide important information regarding the relative and absolute benefits of cholesterol-lowering therapy in older individuals; all strategies for treating high cho- lesterol levels must be revised as more data become available. At this point,

that of the NCEP. Though these men have an average 10-year CHD risk of 19%, one sixth of them (those with no other cardiac risk factors) are designated “lower-risk” by the NCEP II classification system and are not recommended to receive cholesterol-reducing treatment.

Decisions regarding the appropriate age at which to initiate cholesterol-lowering therapy are difficult. Older individ- uals have greater absolute risk for CHD, but the association between hypercholes- terolemia and CHD is attenuated in the elderly.27 In post hoc subgroup analyses from 3 recent clinical trials, older higher-risk individuals appeared to benefit from treatment with a hydroxymethylglu- taryl-CoA reductase inhibitor (statin). At the time of randomization, subjects aged 55 to 64 years,14 60 to 70 years,19 and 60 to 75 years20 showed significant benefits of therapy with statins. In 2 of these trials, however, the magnitude of benefit was attenuated in the older subgroups,18,19 though in the third study, the opposite was true.25

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given the paucity of data in individuals older than 75 years, we do not recommend extrapolation of the revised scale to older individuals.

Modifications to the revised scale can be made, depending on one's view regarding the level of CHD risk that warrants hypcholesterolemic drug therapy. For example, if the cut point were increased from 3 to 4 points, the 10th to 90th percentiles of CHD risk in the higher-risk group would increase from 10% to 30% to 14% to 32%, with a corresponding decrease in the number of higher-risk persons from about 15 million to 9.2 million (Table 4). If, instead, the cutoff were kept at 3 points but the age cut points were increased from 35 to 40 years for men and from 45 to 50 years for women, more modest changes would result. In this case, the 10th to 90th percentile of risk in the higher-risk group would increase to about 12% to 32%, with a reduction in the number of higher-risk individuals to approximately 11.4 million (Table 4).

Limitations of these analyses should be noted. First, they are based on the Framingham risk equations. While these formulas were carefully developed, they were derived from a predominantly middle-class white population in 1 region of the United States, and may not generalize well to other populations. Given the need for accurate classification, further development and validation of CHD risk-estimation models is urgently needed. Second, these risk-estimation techniques do not incorporate other CHD risk-reduction strategies, such as prophylactic aspirin therapy. Without considering these alternative interventions, all variants of these scales may overestimate an individual's true CHD risk. The NHANES II data that we used are now several years old. To address this concern, we adjusted the lipid levels for respondents in NHANES II to reflect recent changes. We did not include family history of premature CHD as a risk factor. This variable was not included in the Framingham risk equations, and it is not clear how much independent CHD risk (beyond that attributed to the other cardiac risk factors) is associated with such a family history. In summary, simple modifications of the current NCEP-recommended system for classifying CHD risk result in a substantially improved ability to discriminate higher-risk from lower-risk individuals. This revised system can be easily incorporated into routine clinical practice and can be adapted by individual clinicians to reflect their personal views regarding risk thresholds for the treatment of elevated cholesterol levels. Use of the revised system could result in a more consistent approach to the management of elevated cholesterol levels for the prevention of CHD.

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References


