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.
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 36 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 cardiovascular 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 civilan population, carried out between 1976 and 1980.\(^6\) 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.\(^6\) 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.\(^6\)

We used the Framingham equations\(^\text{9,10}\) 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 al\(^\text{9}\) as follows: 1 − exp(−exp[(ln(10) − µ)/α]), where µ = 4.4284 + m, and α = −0.3171 − 0.2825 × m. For men, m = a − 1.6346 × ln(age) − 0.2082 × diabetes for 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) − 0.7150 × 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 1.—NCEP II Treatment Criteria*\(^\text{1}\)

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Men</th>
<th>Women</th>
<th>No. of Required Cardiac Risk Factors†</th>
<th>LDL Cholesterol, mmol/L (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–34</td>
<td>20 to menopause</td>
<td>0</td>
<td>≥5.7 (220)</td>
<td></td>
</tr>
<tr>
<td>20–34</td>
<td>20 to menopause</td>
<td>≥2</td>
<td>4.9–5.7 (190–220)</td>
<td></td>
</tr>
<tr>
<td>≥35</td>
<td>Postmenopause</td>
<td>0</td>
<td>≥4.9 (190)</td>
<td></td>
</tr>
<tr>
<td>≥35</td>
<td>Postmenopause</td>
<td>≥2</td>
<td>4.1–4.9 (160–190)</td>
<td></td>
</tr>
</tbody>
</table>

*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.

| Cardiac risk factors: (1) men, age 45 years or more, or women, age 55 years or more; (2) family history of premature coronary heart disease; (3) current cigarette smoking; (4) hypertension (blood pressure at least 140/90 mm Hg or taking antihypertensive medication); (5) high-density lipoprotein cholesterol level less than 0.91 mmol/L (35 mg/dL); and (6) diabetes mellitus. Subtract 1 risk factor if high-density lipoprotein cholesterol level is at least 1.6 mmol/L (60 mg/dL).

### Table 2.—Revised Treatment Criteria*\(^\text{1}\)

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Points Assigned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>+ 1 for every decade over 35 y</td>
</tr>
<tr>
<td>Women</td>
<td>+ 1 for every decade over 45 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>

*Hypocholesterolemic intervention 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. LDL 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.\(^1\)^\(^1\)^\(^2\)^\(^1\) 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.\(^1\)

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 1.0; a scale with no discrimination ability would have an AUC of 0.5.\(^1\) Ninety-five percent confidence intervals (CIs) for the AUCs were calculated by bootstrap
methods, which make no distributional assumptions about the variables.15

Levels of CHD risk for groups of indivi-
duals are expressed as the 10th to
90th percentiles of 10-year risk of CHD
event. The full range of risk is not pre-
sented since all scales include a few very
low-risk and very high-risk persons, ob-
scuring 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 Preva-
ience and Follow-up Study (LRC) to
test the performance of the revised and
NCEP systems. This investigation was a
prospective cohort study of risk fac-
tors 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 speci-
cificity 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 la-
beled “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 clas-
sification 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 well,
with the AUC falling to 0.81.

The revised scales performed sub-
stantially 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 classifica-
tion 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 dem-
strates 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 re-
vised system than under the NCEP II
system (Figure 2). Note that there are
fewer treated individuals in the oldest
age group (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 in-
dividuals would be treated using the re-
vised system (with a 3-point cutoff) rela-
tive to that of the NCEP, with a corre-
sponding increase in levels of CHD risk
(Table 3). For the revised system, a sub-
stantially 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 sys-
tem are possible. Finer gradations of
cutoff would occur in the levels of risk
and number of individuals designated
“higher-risk” if the number of risk fac-
tors used as the cutoff is varied from 2 to
4 and starting age cut point is lower-
er 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 be-
cause of the older age criteria, and there
would be a corresponding decline in the
number of persons recommended for hy-
polipidemic therapy. Regardless of how
the revised system is modified, the de-
gree of overlap in CHD risk between the
lower-risk group and the higher-risk

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Table 3.—Area Under the ROC Curve, Number of Persons Recommended for Lipid-Lowering Treatment,
and Levels of CHD Risk Under Alternative Risk-Stratification Scales*

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Scale</th>
<th>Area Under ROC Curve (95% CI)</th>
<th>10-y CHD Risk Among Those Recommended for Treatment, % (10th-90th Percentiles)</th>
<th>No. of Persons Recommended for Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adults</td>
<td>NCEP II</td>
<td>0.90 (0.87-0.92)</td>
<td>7-29</td>
<td>15 570 000</td>
</tr>
<tr>
<td></td>
<td>Revised, ≥2 points</td>
<td>0.94 (0.92-0.96)</td>
<td>5-27</td>
<td>21 950 000</td>
</tr>
<tr>
<td></td>
<td>Revised, ≥3 points</td>
<td>0.97 (0.95-0.98)</td>
<td>10-30</td>
<td>14 700 000</td>
</tr>
<tr>
<td></td>
<td>Revised, ≥4 points</td>
<td>0.97 (0.96-0.98)</td>
<td>14-32</td>
<td>9 230 000</td>
</tr>
<tr>
<td>Men ≥35 y, women ≥55 y</td>
<td>NCEP II</td>
<td>0.81 (0.76-0.85)</td>
<td>7-30</td>
<td>14 650 000</td>
</tr>
<tr>
<td></td>
<td>Revised, ≥2 points</td>
<td>0.94 (0.91-0.97)</td>
<td>7-28</td>
<td>18 270 000</td>
</tr>
<tr>
<td></td>
<td>Revised, ≥3 points</td>
<td>0.96 (0.93-0.97)</td>
<td>10-30</td>
<td>14 160 000</td>
</tr>
<tr>
<td></td>
<td>Revised, ≥4 points</td>
<td>0.94 (0.91-0.96)</td>
<td>14-33</td>
<td>9 040 000</td>
</tr>
</tbody>
</table>

*ROC indicates receiver operating characteristic; CHD, coronary heart disease; LDL, low-density lipoprotein; CI, confidence interval; and NCEP II, updated National Cholesterol Education Program guidelines. Data are for persons 20 to 74 years of age with an LDL cholesterol level of at least 4.1 mmol/L (160 mg/dL).

Figure 1.—Receiving operating characteristic (ROC) curves for the updated National Cholesterol Education Program guidelines (NCEP II) and the revised system (3-point cutoff), for the subgroup of men at least 35 years old and women at least 55 years old with a low-density lipoprotein cholesterol level of at least 4.1 mmol/L (160 mg/dL) in the NHANES II (Second National Health and Nutrition Examination Survey) data set. Dashed line represents lower limit of a ROC curve where the area under the curve equals 0.5.

Figure 2.—Age distributions of those designated “higher-risk” by the updated National Cholesterol Education Program guidelines (NCEP II) and the revised system (3-point cutoff) among persons 20 to 74 years old with a low-density lipoprotein cholesterol level of at least 4.1 mmol/L (160 mg/dL) in the NHANES II (Second National Health and Nutrition Examination Survey) data set. The revised system (3-point cutoff) is modified, the degree of overlap in CHD risk between the lower-risk group and the higher-risk group is less.
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 individuals have greater absolute risk for CHD, but the association between hypercholesterolemia and CHD is attenuated in the elderly.\textsuperscript{27} In post hoc subgroup analyses from 3 recent clinical trials, older higher-risk individuals appeared to benefit from treatment with a hydroxymethylglutaryl-CoA reductase inhibitor (statin). At the time of randomization, subjects aged 55 to 64 years,\textsuperscript{15} 60 to 70 years,\textsuperscript{19} and 60 to 75 years\textsuperscript{20} showed significant benefits of therapy with statins. In 2 of these trials, however, the magnitude of benefit was attenuated in the older subgroups,\textsuperscript{15,19} though in the third study, the opposite was true.\textsuperscript{20}

The efficacy of therapy in older individuals, 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.\textsuperscript{21} 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 trials 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 cholesterol levels must be revised as more data become available. At this point,
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