Impact of Evidence-Based “Clinical Judgment” on the Number of American Adults Requiring Lipid-Lowering Therapy Based on Updated NHANES III Data

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Background: When the National Cholesterol Education Program Adult Treatment Panel II (ATP II) guidelines were published, National Health and Nutrition Examination Survey III data for 1988 to 1991 were used to estimate the number of Americans requiring lipid-lowering therapy based on ATP II cut points. However, the guidelines recommend using clinical judgment to determine whether to initiate drug therapy in individuals whose low-density lipoprotein cholesterol levels remain above treatment goals with diet therapy but below the initiation level for drug therapy.


Results: Assuming a 10% low-density lipoprotein cholesterol reduction with diet, an estimated 10.4 million American adults require drug therapy based on ATP II cut points. If we include individuals for whom the guidelines recommend clinical judgment, the estimate increases to 28.4 million. The largest increase occurs in individuals without known coronary heart disease but with 2 or more risk factors: from 5.5 to 17.5 million. These high-risk individuals have low-density lipoprotein cholesterol concentrations similar to those in patients with coronary heart disease.

Conclusions: Since the ATP II guidelines were published, clinical judgment has been informed by abundant clinical trial evidence establishing the safety and benefit of lipid-lowering therapy. The large number of individuals at high risk for coronary heart disease emphasizes the need for cost-effective therapy to extend treatment to the greatest number of individuals who may benefit.

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SUBJECTS AND METHODS

DATA SOURCE

National Health and Nutrition Examination Survey III was conducted by the National Center for Health Statistics from October 1988 to October 1994 in two 3-year phases (1988-1991 and 1991-1994). Each phase was designed to represent the entire civilian noninstitutionalized US population aged 2 months and older. This survey included an oversampling of the 2 largest racial minorities, African Americans and Mexican Americans, known to be under-represented in previous NHANES databases; children aged 2 to 5 years; and persons aged 60 years and older. As noted, data on the prevalence of hypercholesterolemia from the first phase were published previously; the present study includes data from both phases for computation of more accurate and recent national estimates because individual phase estimates may be highly variable. A detailed description of the survey design and methods has already been published.4

Basic demographic characteristics were obtained for all persons (N = 39 695) selected to participate in NHANES III. The survey consisted of an interview followed by a physical examination. Overall, 33 994 participants completed the household questionnaire; 18 825 were adults aged 20 years and older. Information on cardiovascular disease history—including questions on family history of heart attack; history, knowledge, and treatment of high blood pressure, high blood cholesterol, and diabetes; and history of heart attack, stroke, transient ischemic attacks, and congestive heart failure—was obtained. Responses to the Rose questionnaire for angina pectoris5 were also included. Current and past use of cigarettes and lipid-lowering, antihypertensive, and hypoglycemic medications was also assessed, based on the participant's self-report.

Physical examinations were performed in 99% (n = 17 030) of interviewed adults. The medical examination included blood pressure measurement and venipuncture to obtain blood samples. Those interviewed were randomly assigned to either a 12-hour morning fasting sample (morning subgroup) or a 6-hour fasting sample (nonmorning subgroup). For the present analysis, we used data from the 8476 adults aged 20 years or older assigned to the morning subgroup.

LABORATORY MEASUREMENTS

Lipids

All lipid analyses were based on a single venous blood sample collected at the mobile examination center or at the home of persons who were unable to go to the mobile examination center. Measurements of serum total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglyceride levels were made in milligrams per deciliter at The Johns Hopkins University Lipid Research Clinical Laboratory, Baltimore, Md. This laboratory was standardized according to the criteria of the Centers for Disease Control–National Heart, Lung, and Blood Institute Lipid Standardization Program.6

Low-density lipoprotein cholesterol levels were calculated in people with triglyceride levels of 400 mg/dL or less (≤4.52 mmol/L) by using the equation developed by Friedewald et al7 (all units are milligrams per deciliter): LDL-C = total cholesterol – [HDL-C + (triglyceride/5)].

Participants in the morning subsample who had fasted less than 9 hours, had triglyceride levels greater than 400 mg/dL (>4.32 mmol/L), had hemophilia, or had type 1 diabetes mellitus were excluded from this analysis because their LDL-C level could not be accurately calculated (n = 1680 [19.8%]). Thus, prevalence estimates were based on 6796 subjects with valid LDL-C levels. Because all treatment decisions in the ATP II guidelines are based on LDL-C level, the analyses in this study are based on LDL-C level.

Plasma Glucose

The plasma glucose level was measured after an overnight fast lasting 9 to 24 hours in individuals who had not been

RESULTS

In the 155.0 million individuals represented in this analysis, the mean total cholesterol level was 204.1 mg/dL (5.28 mmol/L) and the mean LDL-C level was 127.4 mg/dL (3.29 mmol/L). Of these individuals, an estimated 107.1 million did not have CHD and had less than 2 risk factors, 38.5 million did not have CHD and had 2 or more risk factors, and 9.4 million had known CHD. Overall, the LDL-C level was above the level recommended in the ATP II guidelines in 28.8% of individuals (≥160 mg/dL [≥4.14 mmol/L] in individuals without CHD who had <2 risk factors, ≥130 mg/dL [≥3.36 mmol/L] in individuals without CHD who had ≥2 risk factors, and >100 mg/dL [≥2.59 mmol/L] in individuals with CHD). In each risk category, most individuals had normal to mildly elevated LDL-C levels (Figure 1). The mean LDL-C level in the respective risk categories was 122.6 mg/dL (3.17 mmol/L), 139.5 mg/dL (3.61 mmol/L), and 132.8 mg/dL (3.43 mmol/L).

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Blood Pressure

Blood pressure was measured on 2 separate occasions following the American Heart Association standardized protocol. In the present analysis, we used the average of 3 blood pressure measurements obtained at the participant’s home and 3 obtained at the mobile examination center.

CLASSIFICATION OF RISK CATEGORIES

Participants were classified according to the ATP II risk categories: (1) with CHD, defined in this analysis as a self-reported history of a heart attack or a positive score for angina on the Rose questionnaire; (2) without CHD and with 2 or more risk factors (see subsection titled “Risk Stratification in Primary Prevention”); and (3) without CHD and with less than 2 risk factors.

RISK STRATIFICATION IN PRIMARY PREVENTION

In participants without CHD, risk factors were defined as in the ATP II algorithm for primary prevention (Table 2), with the following qualifications reflecting NHANES III data collection: family history of premature CHD was defined as a first-degree relative (parent, sibling, or offspring) of either sex who had a heart attack before the age of 50 years, and patients were considered to be diabetic if they had ever been told by a physician that they had diabetes and were taking insulin or oral diabetes medication or if they had a fasting plasma glucose level of 126 mg/dL or greater ($\geq 7.0$ mmol/L). Per the ATP II guidelines, a risk score was calculated for each individual by adding 1 point for each risk factor present and subtracting 1 point from the total score if the HDL-C level was 60 mg/dL or greater ($\geq 1.55$ mmol/L), eg, a 52-year-old woman who was a current smoker with hypertension would have a risk score of 2, but if she also had a high HDL-C level, the risk score would be 1.

DATA ANALYSIS

Sampling weights reflecting the survey design were used to produce national estimates. Adjustments for nonresponse in NHANES III did not reveal evidence of nonresponse bias (T. M. Ezzati, MS, and M. Khare, MS, unpublished data, 1992). The weights were adjusted to reduce bias from nonresponse at the interview and examination stages. The weighted total was 154,987,478 adults aged 20 years or older as of October 1991, the midpoint of NHANES III. To assess potential nonresponse bias for LDL-C level, the weighted distributions of individuals in the selected sample, individuals in the interviewed sample, and individuals with and without LDL-C values in the fasting morning subsample for various demographic and health-related factors were obtained. To estimate the total number of participants with an elevated cholesterol level who might require lipid-lowering drug therapy, we considered 4 scenarios in which dietary intervention would uniformly reduce LDL-C levels by 0%, 5%, 10%, or 15%, which was consistent with previous analyses conducted by Sempos et al.

In addition, we examined the percentage reduction in LDL-C level required by individuals qualifying for drug therapy according to the ATP II guidelines, assuming a 10% reduction in LDL-C level with dietary therapy. A sensitivity analysis was performed on the range of 20% to 50% LDL-C reduction needed to achieve ATP II goals by aggregating people across CHD risk strata. Computer software (Microsoft Access 97; Microsoft Corp, Redmond, Wash) was used to perform descriptive analyses and summation of weights based on various criteria. For quality control, the analyses were reconstructed using additional software (Statistical Export and Tabulation System; US Department of Health and Human Services, National Center for Health Statistics, Hyattsville, Md).

The number and percentage of individuals in each risk category whose LDL-C level was at or above the initiation level for diet or diet plus drug therapy, assuming LDL-C reductions of 0%, 5%, 10%, and 15% with diet alone, are shown in Table 3. However, the total number of individuals who require therapy would be higher, because the sample includes individuals whose LDL-C level has already been lowered by diet or diet plus drug therapy and might otherwise be above the initiation level. Lipid-lowering drug therapy was estimated to be used by 4.5 million individuals: 1.4 million (1.3%) with less than 2 risk factors, 2.1 million (5.4%) with 2 or more risk factors, and 1.0 million (11.1%) with CHD. The LDL-C treatment goals recommended by the ATP II guidelines were achieved in 72.8%, 30.2%, and 16.6% of the respective risk categories.

Clearly, the broader application of clinical judgment as defined in the guidelines would lead to a marked increase in the number of individuals who might require lipid-lowering drug therapy (Figure 2 and Table 3), although the actual number of individuals for whom therapy would be appropriate would be somewhere between the extremes defined by conservative and broader applications of clinical judgment. The most striking increase with a broader application is in the group with 2 or more risk factors. Of the 38.5 million individuals without CHD who have 2 or more risk factors, 23.0 million have an LDL-C level of 130 mg/dL or greater ($\geq 3.36$ mmol/L), i.e., above the level recommended by the ATP II guidelines. Within this risk category, estimates of the number of individuals requiring drug therapy using a “conservative” approach range from 3.7 million (9.7%) based on 15% LDL-C reduction with diet to 11.1 million (28.8%) based on 0% LDL-C reduction with diet. Using a broader application of clinical judgment, the respective numbers requiring drug therapy range from 13.7 million (35.6%) to 23.0 million (59.8%).

Because the group of individuals without CHD and with 2 or more risk factors represents the largest number of individuals potentially requiring therapy, we further examined whether individuals in this group with “borderline” LDL-C levels of 130 to 159 mg/dL (3.36–4.13 mmol/L)
higher LDL-C levels (CHD that is at least as high as many in the subgroup with application of the ATP II cut points, have a global risk for group, who would not qualify for drug therapy under a strict application of the ATP II algorithm for primary prevention suggests that a large number of individuals in the borderline LDL-C subgroup of individuals with 2 or more risk factors and an LDL-C level of 160 mg/dL or greater ($3.36 \text{ mmol/L}$) had an LDL-C level of 160 mg/dL or greater ($3.36 \text{ mmol/L}$) compared with 42.1% who had an LDL-C level of 130 mg/dL or greater ($3.36 \text{ mmol/L}$). The subgroup of individuals with 2 or more risk factors and an LDL-C level of 160 mg/dL or greater ($3.36 \text{ mmol/L}$) was similar in size to the subgroup with an LDL-C level of 130 to 159 mg/dL (3.36-4.14 mmol/L) (64.1%) than had an LDL-C level of 160 mg/dL or greater ($3.36 \text{ mmol/L}$) (35.9%). Of the 0.2 million Mexican Americans with an LDL-C level of 130 mg/dL or more ($3.36 \text{ mmol/L}$) and diabetes mellitus, 57.9% had an LDL-C level of 130 to 159 mg/dL (3.36-4.13 mmol/L), compared with 42.1% who had an LDL-C level of 160 mg/dL or greater ($3.41 \text{ mmol/L}$).

Although broader application of clinical judgment would require treating more high-risk patients, the vast majority of individuals with an elevated LDL-C level have only mild elevations and, therefore, need a 30% reduction or less in LDL-C level to achieve the appropriate ATP II goal (Figure 3). Assuming a 10% reduction in LDL-C level with diet and treating the maximum number of individuals potentially qualifying for drug therapy under the ATP II guidelines, 94.3% of individuals without CHD with and with less than 2 risk factors, 91.4% of individuals without CHD and with 2 or more risk factors, and 68.7% of individuals with CHD would reach the LDL-C goal recommended by the ATP II guidelines with only a 30% or less reduction in LDL-C level. Treating only individuals qualifying for drug therapy by a strict application of the ATP II cut points, 85.0%, 72.7%, and 36.1% of individuals in the respective risk categories would achieve goal with 30% or less reduction in LDL-C level. Figure 4 illustrates the estimated percentages of individuals in the 3 risk categories combined who can achieve LDL-C goals recommended by the ATP II guidelines with broader application of clinical judgment at different LDL-C reductions. With 20% and 30% reductions in LDL-C level, 66.8% and 86.4% of US adults, respectively, would reach ATP II goals. However, the increment in the percentage of patients reaching the goal is small beyond an LDL-C reduction of 35% to 40%.

**Table 1. Adult Treatment Panel II Low-Density Lipoprotein Cholesterol (LDL-C) Action Limits**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Initiation Level</th>
<th>Goal</th>
<th>Conservative</th>
<th>Broad</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without CHD and with &lt; 2 other risk factors</td>
<td>≥ 160</td>
<td>&lt; 160</td>
<td>≥ 190</td>
<td>≥ 160</td>
<td>&lt; 160</td>
</tr>
<tr>
<td>Without CHD and with ≥ 2 other risk factors</td>
<td>≥ 130</td>
<td>&lt; 130</td>
<td>≥ 160</td>
<td>≥ 130</td>
<td>&lt; 130</td>
</tr>
<tr>
<td>With CHD or other atherosclerotic disease</td>
<td>&gt; 100</td>
<td>≥ 100</td>
<td>≥ 130</td>
<td>&gt; 100</td>
<td>≤ 100</td>
</tr>
</tbody>
</table>

*Data from the National Cholesterol Education Program (public domain).1,2
†A description of the risk factors is given in Table 2. CHD indicates coronary heart disease.
‡To convert LDL-C levels from milligrams per deciliter to millimoles per liter, multiply milligrams per deciliter by 0.02586.
§In middle-aged or older individuals without CHD who have less than 2 risk factors (see Table 2) and an LDL-C level of 160 to 189 mg/dL, in individuals without CHD who have 2 or more risk factors and an LDL-C level of 130 to 159 mg/dL, and in individuals with CHD whose LDL-C level remains at 100 to 129 mg/dL, the physician should exercise clinical judgment in deciding whether to initiate drug therapy.

**Table 2. Adult Treatment Panel II Risk Factors in Primary Prevention**

<table>
<thead>
<tr>
<th>Positive risk factors</th>
<th>Initiative Level</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: 45 years or older in men; 55 years or older, or premature menopause without estrogen-replacement therapy in women</td>
<td>≥ 130</td>
<td>&lt; 130</td>
</tr>
<tr>
<td>Family history of premature coronary heart disease: myocardial infarction or sudden death before the age of 55 years in father or other male first-degree relative or before the age of 65 years in mother or other female first-degree relative</td>
<td>≥ 130</td>
<td>&lt; 130</td>
</tr>
<tr>
<td>Current cigarette smoking</td>
<td>≥ 130</td>
<td>&lt; 130</td>
</tr>
<tr>
<td>Hypertension: blood pressure ≥ 140/90 mm Hg or taking antihypertensive medication</td>
<td>≥ 130</td>
<td>&lt; 130</td>
</tr>
<tr>
<td>Low HDL-C level: &lt; 35 mg/dL (&lt; 0.90 mmol/L)</td>
<td>≥ 130</td>
<td>&lt; 130</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>≥ 130</td>
<td>&lt; 130</td>
</tr>
<tr>
<td>Negative risk factor†</td>
<td>High HDL-C level: ≥ 60 mg/dL (≥ 1.55 mmol/L)</td>
<td></td>
</tr>
</tbody>
</table>

*Data from the National Cholesterol Education Program (public domain).1,2
†If present, subtract 1 from the number of risk factors.

were at lower “global” risk for CHD events if all major risk factors were examined and individuals with LDL-C levels of 160 mg/dL or greater ($≥ 3.36 \text{ mmol/L}$) that 2 or more risk factors, and gave disproportionately higher percentage had an LDL-C level of 130 to 159 mg/dL (3.36-4.13 mmol/L) (64.1%) than and had an LDL-C level of 160 mg/dL or greater ($≥ 4.14 \text{ mmol/L}$) (35.9%). Of the 0.2 million Mexican Americans with an LDL-C level of 130 mg/dL or more ($≥ 3.36 \text{ mmol/L}$) and diabetes mellitus, 57.9% had an LDL-C level of 130 to 159 mg/dL (3.36-4.13 mmol/L), compared with 42.1% who had an LDL-C level of 160 mg/dL or greater ($≥ 4.14 \text{ mmol/L}$).

Although broader application of clinical judgment would require treating more high-risk patients, the vast majority of individuals with an elevated LDL-C level have only mild elevations and, therefore, need a 30% reduction or less in LDL-C level to achieve the appropriate ATP II goal (Figure 3). Assuming a 10% reduction in LDL-C level with diet and treating the maximum number of individuals potentially qualifying for drug therapy under the ATP II guidelines, 94.3% of individuals without CHD with and with less than 2 risk factors, 91.4% of individuals without CHD and with 2 or more risk factors, and 68.7% of individuals with CHD would reach the LDL-C goal recommended by the ATP II guidelines with only a 30% or less reduction in LDL-C level. Treating only individuals qualifying for drug therapy by a strict application of the ATP II cut points, 85.0%, 72.7%, and 36.1% of individuals in the respective risk categories would achieve goal with 30% or less reduction in LDL-C level. Figure 4 illustrates the estimated percentages of individuals in the 3 risk categories combined who can achieve LDL-C goals recommended by the ATP II guidelines with broader application of clinical judgment at different LDL-C reductions. With 20% and 30% reductions in LDL-C level, 66.8% and 86.4% of US adults, respectively, would reach ATP II goals. However, the increment in the percentage of patients reaching the goal is small beyond an LDL-C reduction of 35% to 40%.

**COMMENT**

The ATP II guidelines were farsighted in their inclusion of clinical judgment instead of a narrow application of...
Figure 1. Distribution of low-density lipoprotein cholesterol (LDL-C) levels. A, in individuals without coronary heart disease (CHD) who had less than 2 risk factors; B, in individuals without CHD who had 2 or more risk factors; and C, in individuals with CHD. The LDL-C level was normal to mildly elevated in most individuals in each risk category. Individuals with “borderline” LDL-C levels would be considered for drug therapy using a broader application of clinical judgment as recommended in the Adult Treatment Panel II (ATP II) guidelines. Bar height indicates the number of individuals in each LDL-C range. To convert LDL-C levels from milligrams per deciliter to millimoles per liter, multiply milligrams per deciliter by 0.02586.
patients with mildly to moderately elevated LDL-C levels and drug therapy. Subsequently, however, the use of arbitrary cut points. Since the ATP II guidelines and the previous NHANES III report on prevalence of hypercholesterolemia were published in 1993, clinical trial data have dramatically changed evidence-based clinical judgment. When the guidelines were developed, most of the published clinical trials of lipid-lowering drug therapy used agents with low efficacy and adverse effect profiles that limited compliance; because these agents were not shown to improve total mortality, questions remained about the relative benefit vs risk of using drug therapy to lower elevated LDL-C levels. Accordingly, the ATP II guidelines recommended the use of clinical judgment to weigh “potential benefit, possible side effects, and costs” in determining whether to initiate drug therapy in patients with LDL-C levels between the cut points for diet and drug therapy. Subsequently, however, the use of statin therapy has become widespread, and long-term data have become available, establishing the safety and enhanced efficacy of the statins. In 5 major clinical event trials enrolling almost 31,000 patients, the benefits of statin therapy on CHD morbidity and mortality have been demonstrated in primary and secondary prevention in patients with a broad range of LDL-C levels before therapy. Patients with severely elevated LDL-C levels were examined in the secondary prevention Scandinavian Simvastatin Survival Study with simvastatin and in the primary prevention West of Scotland Coronary Prevention Study with pravastatin sodium. Patients with mildly to moderately elevated LDL-C levels were studied in the secondary prevention Cholesterol and Recurrent Events trial and in the Long-Term Intervention With Pravastatin in Ischaemic Disease study, both with pravastatin, and in the primary prevention Air Force/Texas Coronary Atherosclerosis Prevention Study with lovastatin. In all these studies, statin therapy produced a consistent reduction in relative risk for coronary events without any significant increase in noncardiovascular death, cancer, myopathy, or transaminase elevations greater than 3 times normal. Similarly, in angiographic trials of statin therapy, CHD progression has been shown to be significantly reduced with therapy not only in patients with severely elevated LDL-C levels but also in patients whose LDL-C level was only mildly to moderately elevated. Taken together, these clinical trial results have demonstrated that patients with a range of CHD risk pro-

Table 3. Adult Americans Needing Therapy to Lower an Elevated LDL-C Level

<table>
<thead>
<tr>
<th>Therapy</th>
<th>LDL-C Level Lowered With Diet, %</th>
<th>Clinical Judgment†</th>
<th>US Adult Population Aged ≥20 y‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;2 RF</td>
<td>≥2 RF</td>
<td>CHD</td>
</tr>
<tr>
<td>Diet</td>
<td>0.0</td>
<td>14.0 (9.0)</td>
<td>23.0 (14.9)</td>
</tr>
<tr>
<td>Diet and drug</td>
<td>0.0</td>
<td>4.6 (3.0)</td>
<td>11.1 (7.1)</td>
</tr>
<tr>
<td></td>
<td>Broad</td>
<td>8.4 (5.4)</td>
<td>23.0 (14.9)</td>
</tr>
<tr>
<td></td>
<td>Conservative</td>
<td>2.9 (1.9)</td>
<td>7.8 (5.1)</td>
</tr>
<tr>
<td></td>
<td>Broad</td>
<td>6.0 (3.8)</td>
<td>20.2 (13.0)</td>
</tr>
<tr>
<td></td>
<td>Conservative</td>
<td>1.8 (1.0)</td>
<td>5.3 (3.6)</td>
</tr>
<tr>
<td></td>
<td>Broad</td>
<td>4.1 (2.7)</td>
<td>17.5 (11.3)</td>
</tr>
<tr>
<td></td>
<td>Conservative</td>
<td>0.7 (0.5)</td>
<td>3.7 (2.4)</td>
</tr>
<tr>
<td></td>
<td>Broad</td>
<td>2.3 (1.5)</td>
<td>13.7 (8.8)</td>
</tr>
</tbody>
</table>

Table 4. Distribution of Risk Factors Among Adult Americans With 2 or More Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>LDL-C Level, mg/dL (mmol/L)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥160 (4.14)</td>
</tr>
<tr>
<td>Diabetes mellitus‡</td>
<td>1.3 (12.2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7.1 (64.5)</td>
</tr>
<tr>
<td>HDL-C level ≤ 35 mg/dL (&lt;0.90 mmol/L)</td>
<td>2.5 (22.4)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>4.9 (44.2)</td>
</tr>
<tr>
<td>Age, men ≥ 45 y and women ≥ 55 y</td>
<td>8.8 (79.3)</td>
</tr>
<tr>
<td>Family history of premature CHD§</td>
<td>2.2 (20.3)</td>
</tr>
<tr>
<td>≥ 3 of the above risk factors</td>
<td>3.2 (28.8)</td>
</tr>
</tbody>
</table>

‡| LDL-C indicates low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; and CHD, coronary heart disease.
†| Data are given as number (percentage) of persons, with the number given in millions. Percentages are based on the total number of individuals in the respective column.
‡| Data are given as number (percentage) of persons, with the number given in millions. Percentages are based on the total number of individuals in the respective column.
§| National Health and Nutrition Examination Survey definition: individuals with a fasting plasma glucose level of 126 mg/dL (7.0 mmol/L), those taking insulin or oral diabetes medication, or those ever told by a physician that they had diabetes.
files, including an LDL-C level that would be considered “average,” benefit from aggressive lipid-lowering therapy. While the responsible application of clinical judgment also encompasses the exclusion of individuals for whom drug therapy is inappropriate, the clinical trial evidence supports the extension of treatment to individuals who would not be treated with lipid-lowering drugs under a strict application of the ATP II cut points for drug therapy.

The majority of patients with CHD do not have markedly elevated LDL-C levels. Because too often the first symptom of CHD is sudden death, primary prevention in high-risk patients is essential. However, a conservative application of the ATP II guidelines would mean that the majority of people at risk would not be treated. This analysis of NHANES III data estimates that of the 9.4 million individuals with documented CHD, 7.3 million (78%) have an LDL-C level less than 160 mg/dL (<4.14 mmol/L) (Figure 1, C); the majority of individuals who do not have known CHD but who have multiple risk factors and are, therefore, at increased risk for developing CHD symptoms also have an LDL-C level less than 160 mg/dL (<4.14 mmol/L). At the time the guidelines were developed, it was reasonable to assume that pharmacological therapy for primary prevention in patients with multiple risk factors and an LDL-C level of 160 mg/dL or greater (≥4.14 mmol/L) would provide greater relative risk reduction than in patients with an LDL-C level less than 160 mg/dL (<4.14 mmol/L). However, this assumption was not borne out in the Air Force/Texas Coronary Atherosclerosis Prevention Study, conducted in 6605 men and women without any coronary or vascular disease who had an LDL-C level of 130 to 159 mg/dL (3.6-4.13 mmol/L) and 160 mg/dL or greater (≥4.14 mmol/L), then the decision to initiate drug treatment should be based on the absolute risk for CHD. Among individuals with 2 or more risk factors, more individuals with an LDL-C level of 130 to 159 mg/dL (3.6-4.13 mmol/L) have at least 3 risk factors compared with individuals with an LDL-C level of 160 mg/dL or greater (≥4.14 mmol/L). The present guidelines focus heavily on LDL-C level rather than the absolute risk of the individual; after trichotomizing patients into 3 broad risk categories, the ATP II guidelines use LDL-C level as the basis for determining the initiation and monitoring the effectiveness of treatment. However, the absolute risk for a CHD event may be higher in an individual with 3 risk factors and an LDL-C level less than 160 mg/dL (<4.14 mmol/L) than in an individual with no other risk factors and an LDL-C level greater than 190 mg/dL (≥4.91 mmol/L). In the West of Scotland Coronary Prevention Study, men aged 55 to 64 years without a previous myocardial infarction had CHD event rates of 1% or less per year if they only had a high LDL-C level, whereas their event rates were higher than 2% per year if they also had any one of the following risk factors: minor electrocardiographic abnormalities, preexisting vascular disease, current smoking, HDL-C level less than 43 mg/dL (<1.11 mmol/L), hypertension, or family history of premature CHD. As we look ahead to ATP III, the inclusion of absolute risk, as in other national and international guidelines, may help identify high-risk patients.

Limitations of the NHANES III data likely led to underestimation of the number of high-risk patients. Inferences from survey participants to the entire population are limited by potential sources of bias. Consistent with observations of other investigations, various demographic and clinical characteristics were similarly distributed between persons assigned to the morning subgroup and the interviewed sample. However, people with hypertension, a high cholesterol level, and diabetes were underrepresented among responders to the LDL-C analysis, partly because diabetic patients taking insulin were excluded from the morning subgroup, which requires a 9-hour fasting blood sample. Data from self-reported smoking may also have a potential for underreporting and recall bias, particularly among ethnic minorities, older persons, and people with a lower socioeconomic sta-
tus. These subgroups are more likely to have CHD risk factors than the entire population. Furthermore, persons with CHD may have been misclassified in the absence of a validating clinical diagnosis or if the presence of other atherosclerotic disease was not ascertained. Overall, these biases likely resulted in an underestimation of the numbers of people in the higher-risk groups who require therapy to lower LDL-C levels under the ATP II guidelines.

Although the ATP II algorithm for primary prevention weights all risk factors equally, recent studies suggest that some risk factors, such as diabetes or low HDL-C level, may confer greater risk than other risk factors. Diabetic patients without known CHD have been reported to have the same incidence of fatal or nonfatal myocardial infarction as patients with known CHD. Among individuals with 2 or more risk factors, a larger percentage of those with an LDL-C level of 130 to 159 mg/dL (3.36-4.13 mmol/L) have diabetes than of those with an LDL-C level of 160 mg/dL or greater (≥4.14 mmol/L) (Table 4), and as noted the actual number of diabetic individuals is likely higher than the estimates reported herein because individuals unable to provide a fasting blood sample have been excluded. In the Scandinavian Simvastatin Survival Study and the Cholesterol and Recurrent Events trial, patients with diabetes had the highest absolute risk for CHD events, and lipid-lowering therapy produced greater absolute risk reductions for clinical events in diabetic patients than in patients overall. Despite the increased incidence of diabetes among Mexican Americans, high-risk Mexican Americans, most of whom have an LDL-C level of 130 to 159 mg/dL (3.36-4.13 mmol/L) (Table 4), may be less likely to be recommended for drug therapy than other ethnic groups. Because of the importance of diabetes as a risk factor and because most diabetic patients eventually die of CHD, the American Diabetes Association recommends more aggressive treatment of hyperlipidemia in patients with diabetes.

Another important risk factor is HDL-C level. Particularly in individuals with a borderline LDL-C level, a low HDL-C level may greatly increase the risk for CHD. In the Lipoprotein and Coronary Atherosclerosis Study, conducted in patients with CHD and a mildly to moderately elevated LDL-C level of 115 to 190 mg/dL (2.97-4.91 mmol/L), patients with a baseline HDL-C level less than 35 mg/dL (<0.9 mmol/L) had more angiographic progression than patients with a higher HDL-C level; however, patients with a low HDL-C level also had more benefit from lipid-lowering therapy with fluvastatin sodium. In a number of trials that used diverse methods to identify high-risk subgroups that may receive the most benefit from therapy, including ultracentrifugation to measure intermediate-density lipoprotein and very LDL, LDL density measurement, apolipoprotein and lipoprotein particle assessment, and LDL-C cut points in patients with hyperapolipoprotein B-100, the high-risk group was also characterized by a lower HDL-C level. In the Air Force/Texas Coronary Atherosclerosis Prevention Study, conducted in patients with below-average HDL-C levels (≤45 mg/dL [≤1.16 mmol/L] in men and ≤47 mg/dL [≤1.22 mmol/L] in women), benefit on first major coronary event was similar across all tertiles of baseline HDL-C level, although patients in the lowest tertile were at the highest absolute risk; among patients assigned placebo, an estimated 6.7% with baseline HDL-C levels of 34 mg/dL or less (≤0.89 mmol/L) had events compared with 4.1% with HDL-C levels of 40 mg/dL or greater (≥1.02 mmol/L). Although overall relative risk reductions in the statin trials were impressive, the wide range of absolute risk reductions and numbers needed to treat highlight the importance of treating patients according to their absolute risk. Relatively simple tools to assess the absolute risk for CHD are available, such as the most recent Framingham algorithm, which includes categorical variables for age, blood pressure, and diabetes and smoking status, as well as LDL-C and HDL-C levels. Targeting therapy to those most likely to receive benefit would also allow for more cost-effective treatment.

With the accumulation of clinical trial evidence, the issues surrounding lipid-lowering drug therapy have shifted from scientific questions regarding efficacy to cost-effectiveness concerns. With the increasing number of individuals who may benefit from therapy comes the growing problem of allocation of resources. To extend treatment to the largest number of individuals who might benefit, algorithms have been devised to maximize cost-effectiveness by targeting high-risk patients, improving treatment efficacy (including increased compliance to diet and exercise), and minimizing the cost of therapy. The National Heart, Lung, and Blood Institute is sponsoring a large prospective study that should provide better information not only on the predictive value of newer diagnostic tests for detecting subclinical CHD but also on the cost-effectiveness of these tests. Another important means of reducing the cost of treatment is to match therapy to the patient by using less expensive agents when they are sufficient to achieve LDL-C targets. The subset of individuals without known CHD but with multiple risk factors and mildly to moderately elevated LDL-C levels represents the largest segment of the US adult population needing lipid-lowering therapy by either a broad or a conservative application of clinical judgment. Most of these patients need only moderate LDL-C reductions to achieve goal: based on the latest NHANES III data, 91% of patients with multiple risk factors but without documented CHD could reach the ATP II goal with only a 30% or less reduction in LDL-C level. Advances in evidence-based medicine, which extend the benefit of lipid-lowering therapy to patients with mildly to moderately elevated LDL-C levels, provide the necessary basis for informed clinical judgment as recommended in the ATP II guidelines.

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REFERENCES


Correction

Error in Figure. In the Original Investigation by Jacobson et al, titled “Impact of Evidence-Based ‘Clinical Judgment’ on the Number of American Adults Requiring Lipid-Lowering Therapy Based on Updated NHANES III Data,” published in the May 8 issue of the ARCHIVES (2000;160:1361-1369), parts A and C were reversed in Figure 1 on page 1365. Figure 1 is reprinted correctly here. The journal regrets the error.

Figure 1. Distribution of low-density lipoprotein cholesterol (LDL-C) levels: A, in individuals without coronary heart disease (CHD) who had less than 2 risk factors; B, in individuals without CHD who had 2 or more risk factors; and C, in individuals with CHD. The LDL-C level was normal to mildly elevated in most individuals in each risk category. Individuals with “borderline” LDL-C levels would be considered for drug therapy using a broader application of clinical judgment as recommended in the Adult Treatment Panel II (ATP II) guidelines. Bar height indicates the number of individuals in each LDL-C range. To convert LDL-C levels from milligrams per deciliter to millimoles per liter, multiply milligrams per deciliter by 0.02586.