Eligibility for Lipid-Lowering Drug Therapy in Primary Prevention

How Do the Adult Treatment Panel II and Adult Treatment Panel III Guidelines Compare?

Antonio M. Gotto, Jr, MD, DPhil; Lewis H. Kuller, MD, DrPH

In May 2001, the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program issued revised guidelines for diagnosing and treating high blood cholesterol.1 These guidelines represent a major advance in risk assessment. They were preceded by the ATP I guidelines (1988), which focused on primary prevention of coronary heart disease (CHD), and by the ATP II guidelines (1993),2 which discussed primary and secondary prevention. In the ATP II and ATP III guidelines, low-density lipoprotein cholesterol (LDL-C) is the primary target of risk-reduction therapy.

See p 152

The ATP II recommendations were based on epidemiological, preclinical, and incomplete clinical trial evidence. Within a few years after their publication, the results of 5 large-scale trials of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (ie, “statins”) were reported. Two of these (West of Scotland Coronary Prevention Study [WOSCOPS] and Air Force/Texas Coronary Atherosclerosis Prevention Study [AFCAPS/TexCAPS]) were primary-prevention trials.3,4 The remaining 3 focused on secondary prevention.5-7 Based on these epic trials and other laboratory, epidemiological, and clinical evidence, the ATP III guidelines were developed (Tables 1 and 2).

Clinical Trial Evidence

The major statin trials and resulting meta-analyses provided a firm foundation for a truly evidence-based approach to guideline revision. Involving 5 different populations with widely varying absolute risk levels and using 3 different statins (simvastatin, pravastatin, lovastatin), they produced remarkably consistent reductions of 24% to 37% in relative risk for major CHD events. In WOSCOPS, 6595 men with moderate hypercholesterolemia (LDL-C=192 mg/dL±SD) received pravastatin 40 mg/day for up to 4.9 years. Results indicated a 31% relative decrease in major CHD events, with a 26% reduction in LDL-C levels. AFCAPS/TexCAPS evaluated lovastatin 20 to 40 mg/day for up to 5.2 years in 6605 generally healthy men and women with average LDL-C levels (150 mg/dL±SD) and below-average levels of high-density lipoprotein cholesterol (HDL-C) (<36 mg/dL in men, <40 mg/dL in women, ±SD). There was a 37% relative reduction in major CHD events and a 25% decrease in LDL-C levels. Just 17% of participants would have qualified for drug therapy under the ATP II criteria then guiding clinical practice. This indicates the merit of reducing LDL-C levels to targets below those recommended for primary prevention.

ATP III Guidelines: Patients Eligible for Intensive Primary Prevention

To estimate the effect of the new guidelines on the number of primary-prevention patients eligible for LDL-C–lowering drug therapy, Donald O. Fedder and colleagues8 applied the ATP II and ATP III criteria to a population sample (n=13 589) from the 1988–1994 National Health and Nutrition Examination Survey III (NHANES III). They concluded that 36 266 650 people are eligible under the 2001 recommendations versus 15 166 776 under those issued in 1993. The ATP III guidelines produce a substantial increase in the number of eligible women in each age group. However, the overall percentage of eligible women declines from 49% to 45%. The number of women exceeds the number of men in only 2 age groups (20 to 29 and 70 to 79 years of age).

When the investigators applied both sets of guidelines to a “liberal” (ie, lifestyle changes fail) and a “conservative” (ie, lifestyle changes succeed) scenario, they found that 36 266 650 versus 24 199 701 patients would be eligible for drug therapy, respectively. The differential, which suggests that diet and exercise may adequately reduce LDL-C levels in approximately 50% of primary-prevention patients, reinforces the ATP III endorsement of therapeutic lifestyle changes as the foundation of primary prevention.

Discussion

In this study, the overall increase in eligibility is encouraging and consistent with our expectations. However, we should consider that the sample was selected largely on the basis of self-reported information, which the authors note, and that neither the methods for estimating population size nor the significance of the data is discussed.

“Primary prevention” was defined as a negative response to the question “has a doctor ever told you that you had a
heart attack?” However, we do not know if the authors have adjusted for confounding factors. For example, CHD may not be diagnosed in women and in middle-aged patients presenting with chest pain.10 Because 4 out of 5 women may be unaware that CHD is the greatest threat to their health,10 their symptoms may be underreported. In addition, myocardial infarction (MI) in the diabetic elderly may be silent, painless, or atypical in presentation, which can lead to misdiagnosis.11 Finally, the sample may include patients with other forms of cardiovascular disease (CVD) or with subclinical CVD, which was shown to be the primary determinant of clinical CVD in older patients with diabetes enrolled in the Cardiovascular Health Study.12

According to the authors, the smaller number of eligible women versus men runs counter to current opinion regarding an equivalent CVD risk in both sexes. Unfortunately, however, data on CVD in women are not consistent. Although recent figures show more CVD deaths per year in women than in men,13 NHANES III data reveal a lower annual incidence of CVD in women versus men up through the age of 64.14 Furthermore, the Cardiovascular Health Study reported a higher incidence of CVD in men compared with women ≥65 years of age.15 Within all age groups, the extent of coronary atherosclerosis is lower in women than in men.16 In the present study, the finding that more older women than men are eligible for primary-prevention drug treatment may reflect the greater longevity of women and the higher probability that men will have developed clinical CHD by the age of 70 to 79. The reasons for the surprising outcome that more women than men aged 20 to 29 are eligible for primary-prevention drug treatment require clarification.

When Fedder et al8 applied the ATP III guidelines to a liberal scenario, they judged most patients to be eligible for drug treatment solely on the basis of LDL-C levels. However, a 1991 study using the ATP I guidelines found that primary-prevention patients deemed eligible for drug treatment based on lipid levels alone were at less risk than age-matched subjects with lower lipid levels and other risk factors.17 This was particularly true for women in the study. Applying the guidelines to a conservative scenario, Fedder et al8 attributed eligibility to absolute risk as calculated by the Framingham system, which uses just 5 risk factors: age, total cholesterol, smoking status, HDL-C, and systolic blood pressure. Neither scenario involves global risk assessment, an essential feature of the new guidelines (Table 2).

Particularly in the elderly, LDL-C levels may not be the most accurate predictor of risk.18 Reasons for this may include the long-term progression of atherosclerotic disease, which suggests that CHD risk is a function both of LDL-C elevation and duration of exposure; the decrease in LDL-C levels that occurs in some older individuals, despite a high prevalence of atherosclerosis in the elderly; and the recent finding that the primary determinants of MI in the elderly, in addition to age and sex, are fasting glucose level, systolic hypertension, and the extent of subclinical atherosclerosis.18

Subclinical atherosclerosis can be identified by noninvasive imaging techniques such as electron beam computed tomography (EBCT) for coronary artery calcification, brachial artery reactivity for endothelial dysfunction, and carotid ultrasound for carotid intima-media thickening.19 In the Healthy Women Study, LDL-C levels and 3 features of the metabolic syndrome (HDL-C and triglyceride levels; waist circumference) were significantly related to coronary calcification as measured by EBCT.20 Advances in assessing subclinical atherosclerosis will improve individual CHD risk prediction and lower the number needed to treat in order to reduce the incidence of CHD events by one.

Recent evidence indicates that LDL particle size and number may predict CHD risk independently of lipid lev-

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**TABLE 1. ATP III Guidelines: New Features**

- Classify certain conditions as “CHD risk equivalents”: peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease, diabetes, ≥2 major risk factors with a 10-year CHD risk >20%.
- Assign patients to 1 of 3 risk categories instead of primary or secondary prevention: high (CHD or CHD risk equivalent); intermediate (≥2 major risk factors with a 10-year CHD risk ≤20%); and low (0–1 major risk factor with a 10-year CHD risk <10%). Within these categories, there is further stratification.
- Calculate 10-year risk using a modified version of the Framingham risk scoring system.
- Reclassify diabetes from a major risk factor to a CHD risk equivalent.
- Change the LDL-C goal for patients with CHD (or CHD risk equivalents) from ≤100 mg/dL to <100 mg/dL, signifying that an LDL-C goal below 100 mg/dL may be beneficial.

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**TABLE 2. ATP III Guidelines: Global Risk Assessment**

<table>
<thead>
<tr>
<th>Risk factors</th>
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<tbody>
<tr>
<td><strong>Major</strong></td>
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<tr>
<td>Cigarette smoking</td>
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<tr>
<td>Hypertension (≥140/90 mm Hg)</td>
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<tr>
<td>HDL-C level &lt;40 mg/dL</td>
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<tr>
<td>Premature CHD (First-degree family member)</td>
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<tr>
<td>Age (men ≥45 years, women ≥55 years)</td>
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<tr>
<td><strong>Life-habit</strong></td>
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<tr>
<td>Obesity</td>
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<tr>
<td>Physical inactivity</td>
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<tr>
<td>Atherogenic diet</td>
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<tr>
<td><strong>Emerging</strong></td>
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<tr>
<td>Lipoprotein(a)</td>
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<tr>
<td>Homocysteine</td>
</tr>
<tr>
<td>Prothrombotic/proinflammatory factors</td>
</tr>
<tr>
<td>Impaired fasting glucose</td>
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<tr>
<td>Subclinical atherosclerotic disease</td>
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The metabolic syndrome*  
A constellation of lipid and nonlipid risk factors with 3 or more of the following clinical characteristics†:

- Waist circumference >40 in (men), >35 in (women)
- Triglycerides ≥150 mg/dL
- HDL-C <40 mg/dL (men), <50 mg/dL (women)
- Blood pressure ≥130/85 mm Hg
- Fasting glucose ≥110 mg/dL
- Triglycerides ≥200 mg/dL

* A secondary therapeutic target after the lowering of LDL-C levels. † Small, dense LDL particles are also characteristic.
elderly, statin therapy to reduce LDL-C levels is extremely efficacious in CHD risk reduction, as reinforced by data from the Heart Protection Study announced at the 2001 Scientific Sessions of the American Heart Association.  

Conclusions

Fedder et al have preliminarily shown that the ATP III guidelines substantially increase the number of primary-prevention patients eligible for LDL-C-lowering drug treatment in all age groups. However, future studies must evaluate the effect of the guidelines by more selectively identifying primary-prevention patients and applying all lipid and non-lipid risk factors.

One important feature of the new guidelines is the reclassification of diabetes from a major CHD risk factor to a CHD risk equivalent, thereby increasing the number of primary-prevention patients eligible for drug therapy. This may help explain why substantially more patients in all age groups were found eligible for primary-prevention drug treatment under the ATP III guidelines. According to the authors, the increase in the number of eligible patients ≥65 years of age may also be explained by the linear relationship between increasing age and increased risk in the Framingham scoring system.

The ATP III guidelines represent a giant step forward in diagnosing and treating CVD. One important reason for this is the emphasis on global risk assessment. Although LDL-C is the primary target of risk-reduction therapy, an elevated level may not always be the most appropriate indication for initiating drug treatment. In the elderly, for example, active life expectancy may be a better determinant. Furthermore, patients with diabetes and those who smoke or have recently stopped smoking are likely to have subclinical atherosclerosis and be at high risk. Therefore, they are appropriate candidates for global risk assessment and therapeutic interventions.

Because CVD is a risk function both of LDL-C level and duration of exposure, physicians must measure their patients’ LDL-C and other lipoprotein levels at regular intervals, beginning in young adulthood, in order to make rational therapeutic decisions. As the patents for certain lipid-lowering drugs begin to expire, price reductions can be expected, making primary-prevention drug therapy more cost-effective.

Without implementation, the potential of these guidelines for reducing CHD risk will not be realized. Both the primary-care physician and the entire health-care team are essential to risk assessment. If possible a “champion” of the guidelines should be identified in each practice setting to insure that every effort is made to apply them. Reasons for not implementing the guidelines include the perception that they are complicated. While the Framingham risk scoring system is quite straightforward, simple tables and electronic hand-held devices, including Palm Pilots, are available to facilitate its use.

Certain political and societal changes are also needed. This will require a tremendous educational effort involving cooperation between the public and private sectors. The ATP III members have rendered a wonderful service in preparing these extraordinarily valuable guidelines. Now it is up to the public to implement them. We must use the fruits of our successful research to achieve substantial reductions in CHD morbidity and mortality, thereby realizing the enormous potential of these guidelines.

Acknowledgments

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References


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Editor’s Clarification of Statement of Conflict of Interest by Dr Antonio M. Gotto, Jr (Circulation. 2002;105:136–139)

In the Editorial titled, “Eligibility for Lipid-Lowering Drug Therapy in Primary Prevention,” (Circulation. 2002;105:136–139), written by Drs Antonio M. Gotto and Lewis H. Kuller, Dr Gotto indicated in the published Acknowledgment that he had received support from Merck & Co, Inc, for his contribution to the Editorial. In response to a question about this financial disclosure, the Editor wishes to clarify it for Dr Gotto. Dr Gotto was indicating that he receives an honorarium from Merck & Co, Inc, in support of his research, writing, lecturing, and scholarly activities. He received no direct financial support for writing the Editorial in Circulation.