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**Screening for Lipid Disorders in Adults:
Selective Update of 2001
U.S. Preventive Services Task Force Review**

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ABSTRACT

Purpose: Both the US Preventive Services Task Force (USPSTF) and the National Cholesterol Education Program (NCEP ATP III) have issued recommendations on screening for dyslipidemia in adults. To guide the USPSTF in updating its 2001 recommendations, we reviewed evidence relevant to discrepancies between these recommendations.

Data Sources: A 2001 evidence review prepared for the USPSTF, supplemented by searches of the Cochrane Library, MEDLINE, EMBASE, and reference lists of recent systematic reviews.

Study Selection: Randomized controlled trials and observational studies published between December 1999 and February 2005 that addressed screening in younger patients not at high risk; use of triglyceride levels in an initial screening panel; optimal screening intervals; selection of patients for treatment; and harms of drug therapy.

Data Extraction: We abstracted data on the design, results, and quality of each included trial. We used standard USPSTF methods to rate the internal validity of trials and epidemiologic studies.

Data Synthesis: New evidence relevant to discrepancies between USPSTF and ATP III recommendations was summarized in the context of earlier evidence.

Limitations: This document should be read in conjunction with the full systematic evidence review conducted for the USPSTF in 2001, the final report of ATP III, and the 2004 ATP III update.

Conclusions: There is no new evidence relevant to screening younger adults or to appropriate screening intervals. Evidence is conflicting regarding the additional contribution of a serum triglyceride level to the identification of individuals at short-term risk for coronary heart disease events. The balance of benefits and harms is clearly in favor of statin therapy among individuals enrolled in some, but not all, randomized trials of primary prevention. The long-term harms of statin therapy are unknown.

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INTRODUCTION

In 2001, the US Preventive Services Task Force (USPSTF)¹ recommended that all men aged 35 and older, women aged 45 and older, men aged 20 to 35, and women aged 20 to 45 who are at increased risk for coronary heart disease (CHD) be screened for total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C).¹ In 2002, the National Cholesterol Education Program (NCEP) published new guidelines (Adult Treatment Panel III [ATP III]) for the diagnosis and management of lipid disorders.^{2,3} The NCEP guidelines were updated in August 2004 to include evidence from more recent trials.⁴

Both the USPSTF and ATP III embrace the principle that, in the short term, the benefits of screening and treatment depend on reducing the risk of major CHD events; that is, sudden coronary death or myocardial infarction (MI). They agree that treatment decisions should be based on the overall risk of having an event, not on lipid levels alone, and both recommend using Framingham⁵ projections to estimate risk.

The USPSTF and ATP III guidelines agree on many essential points, but there are also important differences between them (Table 1). The USPSTF recommendations¹ address screening in asymptomatic adults who have no history of coronary heart disease. The scope of the NCEP guidelines^{2,3} is much broader. Management of patients with known heart disease, a major subject of the NCEP guidelines, is not relevant to the USPSTF. They also differ in their recommended target populations for screening, initial screening panel, frequency of screening, and criteria for initiating lipid-lowering therapy.

The purpose of this selective review was to guide the USPSTF in updating its 2001 recommendations. With input from the Agency for Healthcare Research and Quality (AHRQ), the USPSTF decided that it was critical to update only the parts of the Key Questions that pertain to discrepancies between the USPSTF recommendations and the most recent ATP III guidelines:

- 1) How frequent is elevated TC in men younger than age 35 and women younger than age 40, and what proportion have an overall 10-year risk of cardiac events of 10% or greater?
- 2) What evidence supports the use of triglyceride levels as part of an initial screening panel?
- 3) What are the optimal screening intervals in the general population and in patients at high risk for CHD events?
- 4) What risk factors should be used to select patients for lipid-modifying drug therapy?
- 5) What is the current evidence about the harms of drug therapy for lipid disorders?

METHODS

Data Sources

The 2001 systematic evidence review prepared for the USPSTF⁶ was based on searches of MEDLINE (1994 to December 1999) and the Cochrane Controlled Trials Registry through December 1, 1999. For this update, we searched the Cochrane Library (2004, Issue 4), MEDLINE (1966-February Week 1 2005), EMBASE (1980-February 4, 2005), PREMEDLINE (through February 9, 2005), and dossiers submitted by manufacturers of statins (Appendix 1). To identify key articles about the epidemiology, natural history, and detection of lipid levels and lipid disorders, we relied on the reference lists of the 2002 ATP III Final Report² and the 2004 update to ATP III⁴, as well as recent systematic reviews,⁷⁻⁹ supplemented by a title and abstract search of MEDLINE and PREMEDLINE. All searches were restricted to articles published in English.

Study Selection

We reviewed randomized trials of at least a 1-year duration that examined drug therapy with statins among patients without previously known CHD, and measured clinical end points including total mortality, CHD mortality, and nonfatal MI. To be included, the trial had to address primary prevention in the general population or in a subset of the general population identified on the basis of risk factors for CHD. We also included observational studies of the epidemiology of lipid disorders, screening to detect lipid disorders, risk factors for CHD, and the harms of statin therapy.

Data Extraction and Quality Assessment

Our methods for abstracting information about the design, results, and internal validity of each included trial are described elsewhere.¹⁰ We used text and internal validity ratings from a previous review of statins¹⁰ to summarize the results of recent statin trials and of the safety of statins. We used standard USPSTF methods to rate the internal validity of trials and epidemiologic studies included in this update but not in the statins review (See Appendix 2).

Data Synthesis and Analysis

We summarized new evidence relevant to discrepancies between USPSTF and ATP III recommendations in the context of earlier evidence from the 2001 evidence review conducted for the USPSTF, the final report of ATP III, and the 2004 ATP III update

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RESULTS

Key Question 1. How frequent is elevated total cholesterol in men younger than age 35 and women younger than age 40, and what proportion have an overall 10-year risk of cardiac events of 10% or greater?

ATP III recommends screening all men and women aged 20 and above, and points out that young adults who are in the upper quartile of cholesterol levels are at high long-term risk of cardiac mortality. The USPSTF in 2001 recommended selective screening of younger men and women who smoke, have a history of hypertension, or have diabetes mellitus. They argued that, in young adults without specific cardiovascular risk factors, the absolute reduction in risk as a result of treating dyslipidemia is small. They recommended that all patients, regardless of lipid levels, should be offered counseling about the benefits of eating a diet low in saturated fat and high in fruits and vegetables, engaging in regular physical activity, avoiding tobacco use, and maintaining a healthy weight.

A minority of men younger than 35 and women younger than 45 are candidates for lipid-lowering therapy. Based on National Health and Nutrition Examination Survey (NHANES) III data (<http://www.cdc.gov/nchs/about/major/nhanes/nh3data.htm>) in the general US population, 8.9% of men aged 18-35 and 12.3% of women aged 18-45 have a TC>240 mg/dL. Among men aged 18-35 and women younger than 40 who do not smoke, do not have a history of hypertension, and do not have diabetes mellitus, no combination of ATP-III risk factors (TC up to 310 mg/dL, HDL-c, and systolic blood pressure) would result in a predicted 10-year risk of major cardiovascular events greater than 10%. Some men younger than 35 years of age who smoke, and those who have diabetes, have a 10-year risk that exceeds 10%, but these men can be identified for lipid testing based on their history. In NHANES, among all nondiabetic women aged 40-45 years, the probability of being at intermediate risk or high risk were 1.45% and 0%, respectively; all of these women had a history of hypertension or smoking.

No new evidence examines whether targeting young adults in the upper quartile of risk is more effective than recommending a healthy diet, physical activity, avoidance of tobacco products, and maintenance of a healthy weight to all.

Key Question 2. What evidence supports the use of triglyceride levels as part of an initial screening panel?

Both the USPSTF and ATP III recommend screening with a panel that includes a TC and HDL-C, and both recommend using the average of two readings to estimate the TC and HDL-C more accurately. ATP III recommends that the initial screening lipid panel should also include a triglyceride level, while the USPSTF recommends obtaining a second lipid panel that includes a triglyceride level if the initial screening results indicate that the patient is at high risk.

The 2001 USPSTF systematic evidence review found: 1) mixed, inconclusive evidence that triglycerides are independently associated with an increased risk of CHD, and 2) insufficient evidence to conclude that treating persons with isolated increased triglycerides would reduce future CHD events.

Triglyceride level was not a consistent independent predictor of incident CHD events in prospective studies conducted in middle-aged, relatively low and moderate-risk populations. The Framingham Study⁵ and European Systematic Coronary Risk Evaluation (SCORE)¹¹ risk scoring systems do not include a measure of serum triglycerides, but a risk score derived from the Prospective Cardiovascular Munster (PROCAM) cohort does.^{12, 13} The PROCAM risk score was derived from 10-year follow-up of 5,389 German men 35 to 65 years of age. In this relatively low-risk population, triglyceride levels were an independent predictor of coronary events after adjustment for age, low-density lipoprotein cholesterol (LDL-C), HDL-C, systolic blood pressure, smoking history, family history of heart attack in a first-degree relative before age 60 years, and diabetes. In an original data meta-analysis of 26 Asian Pacific cohorts (n=96,224), triglyceride levels were associated with coronary events and with stroke after adjustment for age, sex, systolic blood pressure, smoking status, and total-to-HDL cholesterol ratio.¹⁴ However, most of the cohorts included in the Asia Pacific analysis did not have sufficient data to adjust for the other risk factors that contribute to the Framingham risk score.

Other cohort studies did not find triglycerides to be an independent predictor of coronary events or of stroke. In the CUORE study, a pooled analysis of 11 Italian cohorts (n=6,865), triglyceride levels were not an independent predictor of coronary events.¹⁵ The best proportional hazards equation included age, total cholesterol, systolic blood pressure, cigarette smoking, HDL cholesterol, diabetes mellitus, hypertension drug treatment, and family history of CHD. The coefficients of the CUORE model agreed with those of the Framingham Heart Study. However, the CUORE coefficients for triglyceride levels and for HDL-C differed from those of the PROCAM model. Forcing triglyceride level into the CUORE model reduced the influence of HDL-C and age but did not improve overall prediction. This finding was similar to that of an analysis from the Nurses Health Study that found that a fasting triglyceride level did not provide additional prediction of coronary events after adjustment for other lipid parameters, particularly HDL-C.¹⁶ In an 11-year cohort study of 12,089 black and white middle-aged individuals followed in the Atherosclerosis Risk in Communities (ARIC) population, triglyceride level was not correlated with cardiovascular events (coronary events or stroke) after adjustment for Framingham risk factors and components of the metabolic syndrome. Except for the triglyceride level, every component of the metabolic syndrome (elevated blood pressure, low HDL-C, elevated fasting glucose, and large waist circumference) was associated with a higher risk of coronary events.¹⁷

These results suggest that, although the triglyceride level is a strong univariate predictor of CHD events, its association with such events is reduced substantially by adjustment for other risk factors. ATP III argues that, if this is true, triglyceride level may be a marker for atherogenic remnant lipoproteins, other lipid risk factors (small LDL particles and low HDL), nonlipid risk factors (elevated blood pressure), and emerging risk factors (insulin resistance, glucose intolerance, prothrombotic state). That is, even if it is not an independent risk factor, if it is a marker for these non-traditional risk factors, a triglyceride level may identify individuals at high cardiovascular risk who might otherwise be missed. Specifically, elevated triglycerides (and the metabolic syndrome) might identify individuals at high long-term risk of developing cardiovascular disease who have not yet developed enough atherosclerotic disease to have a high short-term risk of events.

Would these patients benefit from treatment for elevated triglyceride levels? Older evidence on this question is inconclusive,⁶ as are recent clinical trials. Because statins, like some other classes of lipid-lowering drugs, reduce triglyceride levels as well as LDL-C levels, they cannot help determine how much of the benefit is due to lowering triglycerides. In the future, clinical trials of drugs that selectively reduce triglyceride levels may determine whether targeted therapy for hypertriglyceridemia can reduce the short-term risk of cardiovascular events in people who have already developed lesions. However, such trials do not address whether screening for high triglycerides can prevent the development of cardiovascular disease in the long-term. We identified no trials with clinical endpoints that enrolled patients with elevated triglyceride levels who would not otherwise qualify for treatment.

ATP-III also argues that initial testing should include a triglyceride level to improve the accuracy of the TC and HDL tests. Specifically, with adjustment for the triglyceride level, elevated LDL will be more frequently detected, and the HDL determination will be slightly more accurate. We did not seek new evidence on these points, which were addressed in detail in the 2001 USPSTF review.

Key Question 3. What are the optimal screening intervals in the general population and in patients at high risk for CHD events?

We did not identify new evidence relevant to the appropriate interval to screen for hyperlipidemia in the general population, or in subgroups of the general population.

Key Question 4. What risk factors should be used to select patients for drug therapy?

Treatment Decisions in Relation to Overall Risk and LDL-C Levels

Treatment decisions depend not only on the LDL-C level but also on the number and nature of other cardiac risk factors. ATP II defined three risk groups based on their history and risk status.

The three risk groups had different LDL-C goals and different intensities of LDL-lowering therapy. In 2001, the USPSTF endorsed the ATP II guidelines, which identified high LDL cholesterol as a potential target for LDL-lowering drug therapy for persons with multiple risk factors whose LDL levels are high (≥ 160 mg/dL) after dietary therapy, and for persons with 0-1 risk factors whose LDL levels are ≥ 190 mg/dL after dietary therapy.

As described in Table 1, in ATP-III the decision to treat depends on the presence of CHD or CHD equivalents, the LDL-C level, and the 10-year risk of events. The CHD group now includes persons who have a history of coronary disease as well as other persons who have an absolute 10-year risk for developing major coronary events (myocardial infarction and coronary death) $>20\%$. ATP III also expanded the concept of a “CHD risk equivalent,” which refers to persons without established CHD who should be treated in the same manner as those who have established CHD. The CHD risk equivalents are diabetes, clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease; that is, transient ischemic attacks or stroke of carotid origin or 50% obstruction of a carotid artery); or 2 or more risk factors with a 10-year risk for hard CHD events $> 20\%$. Compared with ATP-II, in ATP III many of these risk categories are assigned a lower threshold for initiating drug therapy and a lower target LDL-C level.

Table 2 describes trials of statins, conducted in outpatient or community settings, which included at least some subjects who had no history of coronary artery disease. Except for AFCAPS and WOSCOPS, all of these trials were published since the 2001 USPSTF guidelines were released. Longer-term follow-up results from WOSCOPS, published in October 2007, confirm the persistence of a beneficial decrease in coronary events over ten years after the end of the trial in men with elevated cholesterol but without a previous myocardial infarction.¹⁸ The reader is referred to the 2004 ATP III update⁴ for a more detailed description of major recent trials.

As of 1999, randomized trials of the benefits of lipid-lowering therapy in people without established CHD enrolled primarily middle-aged men of European descent.¹⁹⁻²² Many of the trials in Table 2 enrolled subjects who were under-represented in earlier trials. For example, the Heart Protection Study (HPS) targeted individuals in whom the risk and benefits of cholesterol lowering were uncertain (women, those over 70 years, diabetics, those with non-coronary vascular disease, and those with average or below-average cholesterol).^{23, 24} In ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-lowering Arm), about 24.5% of the subjects were diabetics. CARDS (Collaborative Atorvastatin Diabetes Study) was conducted in patients with type 2 diabetes without elevated cholesterol levels (LDL <107 mg/dL).²⁵ Patients had no history of cardiovascular disease but at least one of the following risk factors: retinopathy, albuminuria, current smoking, or hypertension.

In ALLHAT-LLT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack—Lipid-lowering Arm),²⁶ nearly half the subjects were women, 35% were diabetic, 15% had a history of CHD, and about 35% were black. Pravastatin did not reduce all-cause mortality or cardiovascular event rates. The reason for the lack of benefit of pravastatin in ALLHAT-LLT is unclear, but the high rate of use of statins in the control group is frequently cited as a possible explanation.

The good-quality Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial was designed to examine the benefits of statin therapy in women and in the elderly.²⁷ Overall, pravastatin reduced the composite primary endpoint (CHD death, nonfatal MI, fatal/nonfatal stroke) from 16.2% in the placebo group to 14.1%. There was also a reduction in transient ischemic attacks, but not in strokes, in the pravastatin group. There was no effect on all-cause mortality, which was 10.5% in the placebo group vs. 10.3% in the pravastatin group. The reduction in coronary heart disease deaths in the pravastatin group (absolute risk reduction 24%; 95% CI 1% to 42%) was balanced by an increase in cancer deaths (absolute risk increase 28%; 95% CI 3% to 68%).

In the recent SPARCL trial,²⁸ 4,731 patients who had had a stroke or transient ischemic attack in the past one to six months were randomized to high-dose atorvastatin (80 mg) or placebo. After a median 4.9 years of follow-up, there was a 2.2% absolute reduction in the primary endpoint of fatal or nonfatal stroke (Adjusted hazard ratio 0.84; 95% CI 0.71 to 0.99). There was also a reduction in risk of major cardiovascular events, but an increase in the incidence of hemorrhagic stroke (Adjusted hazard ratio 1.66; 95% CI 1.08 to 2.55).

The results of these recent trials support the idea that patients who have “CHD risk equivalents” benefit from lipid-lowering therapy similar to that used in individuals who have known CHD.

Treatment Decisions in Women

It is clear that lipid-lowering therapy, particularly statins, significantly reduced the risk of coronary events among women who have a history of coronary disease or diabetes.^{8, 25, 29, 30} However, data for asymptomatic women who have no known coronary disease are not conclusive.

Although only one of the first 4 primary prevention trials (AFCAPS) enrolled postmenopausal women, the USPSTF in 2001 decided that the benefits could be extrapolated to women whose risk of CHD events was similar to that of the trial participants. The USPSTF recommended screening for women beginning at age 45 years, when the average risk of CHD events is similar for that of men at 35 years of age. For the elderly, younger adults, and other groups not well represented in the trials, the USPSTF recommended treatment for patients whose risk of CHD events was 0.6% to 1.5% per year, the range observed in the first four primary prevention trials of drug therapy for hyperlipidemia available in 1999. Because recent trials enrolled only high-risk enrollees, they do not provide evidence that the low end of this range should be changed.

A 2003 systematic review conducted by the University of California San Francisco–Stanford University Evidence-based Practice Center found that 15,917 women had been included in randomized controlled-trials (RCTs) of various lipid-lowering treatments.⁷ Four of these trials^{22, 31-33} enrolled women (n=7,673) without prior CHD (primary prevention). The characteristics of these trials, their results, and the results of a meta-analysis are shown in Appendix 3. In the meta-analysis for the primary prevention studies (Appendix 3, *Results table*, right panel), “...there was insufficient evidence of reduced risk of any clinical outcome in women.” In the secondary prevention studies, women had statistically significant reductions in CHD mortality,

CHD events, nonfatal MI, and revascularization; their magnitude was similar to those for men. The risk for total mortality was not lower in women treated with lipid lowering, regardless of whether they had prior CHD or not. In a more recent meta-analysis of primary prevention trials, the pooled relative risk reduction for women was 0.87 (95% CI: 0.69 to 1.09).³⁴ Another trial, PROSPER, included a mixture of primary and secondary prevention populations. PROSPER revealed that pravastatin was more effective in men than in women.²⁷ There were 3,000 women in the study. The baseline risk in men (n=2,804) was higher; in the placebo group, almost 20% of men and 13% of women had an event (CHD death, nonfatal MI, or stroke) over the 3 years of the study. For men, there was a statistically significant reduction in the primary endpoint (Hazard ratio 0.77, CI 0.65-0.92). For women, there was no apparent effect (Hazard ratio 0.96, CI 0.79-1.18).

Treatment Decisions in Older Patients

Although evidence from primary prevention studies is lacking, recent secondary prevention trials deliberately recruited subjects 65 years and older to determine whether they benefit from lipid-lowering therapy. In the HPS, for example, simvastatin reduced major vascular events (28.7% vs. 23.6%) in subjects 70 years and older, and, in subjects aged 75 to 80 years at study entry, the benefit was even greater (32.3% vs. 23.1%; $P < .001$).²⁴

In one meta-analysis of the 6 secondary prevention trials that have reported results for subjects 65 years and older, statins reduced all-cause mortality by 15%.⁸

Treatment Decisions in Other Demographic Subgroups

Since 2001, few additional data are available from randomized trials on the effectiveness of lipid-lowering therapy in blacks and other racial and ethnic groups. In ALLHAT,²⁶ 38% of the subjects were black, but ALLHAT was a negative trial in which there was no difference between the treatment and control groups for any subgroup.

Key Question 5. What is the current evidence about the harms of drug therapy for lipid disorders?

The large randomized trials summarized above provide strong evidence about the balance of benefits and harms from drug therapy, particularly statins. Because they were analyzed on an intention-to-treat basis, the benefits in subjects who tolerated and complied with medication are diluted by the lack of benefit in subjects who discontinued medication because of side effects or did not complete the study for other reasons. Moreover, the mortality results of the trials indicate clearly that, for the enrolled subjects, and for the duration of the trials, statins are beneficial. The balance of benefits and harms of statin drugs over a longer time than the trials have observed remains unclear.

As strong as they are, these results do not ensure that the trial results are generalizable to individuals who would not meet the eligibility criteria for the trial. Some experts have voiced an additional concern, that broader use of statins and more aggressive therapy to meet lower LDL-C targets could lead to higher rates of serious harms than have been observed in trials.

Statins have rare but serious harms, especially in groups with identifiable risk factors for such events. Statin use is associated with a range of abnormalities, from mildly elevated serum creatine phosphokinase (CPK) levels, to myalgia, temporary or persistent muscle weakness, and rhabdomyolysis. Mild elevations in CPK are not well-studied because controlled trials usually record only markedly elevated levels as adverse events.

Myopathy is the best-studied harm. In placebo-controlled and direct comparison trials, rates of muscle complaints range from 1% to 4%.^{10,35} In the major clinical trials, rhabdomyolysis is uncommon. A 2003 review summarized published literature as well as data from the Food and Drug Administration (FDA) adverse event reporting system.³⁵ In 28 trials combined there were 49 cases of myositis and 7 cases of rhabdomyolysis among 42,323 patients randomized to a statin, versus 44 cases of myositis and 5 of rhabdomyolysis among 41,535 patients randomized to placebo or to usual care.³⁵ In the A to Z trial,³⁶ which enrolled post-MI patients, there was a high incidence of myopathy (9 cases, 3 with rhabdomyolysis) in patients treated with simvastatin 80 mg/d. There were no cases of myopathy with the 20 mg or 40 mg doses. The incidence of fatal rhabdomyolysis is estimated from FDA reports at 0.15 per 1,000,000 prescriptions.

Data from pre-marketing trials suggest that higher doses of statins are associated with higher rates of myopathy. These data are summarized in an FDA letter released in March 2005 (available at: http://www.fda.gov/cder/drug/infopage/rosuvastatin/crestor_CP.pdf. See Figure 1 and the following discussion).³⁷ This FDA document also estimates the frequency of voluntarily reported cases of rhabdomyolysis in the 6 months interval post-approval, ranging from 0 to 0.3 per 100,000 prescriptions (page 13).

Concomitant use of certain medications, including, for some statins, those that interact with the CYP3A4 pathway, increase the risk of rhabdomyolysis, as do other systemic lipid-lowering agents such as niacin and fibrates.

In controlled trials, among patients who have no history of liver disease, up to 2% of patients have elevation of liver enzymes (transaminases, primarily Alanine aminotransferase) > 3 times the upper limit of normal. Two meta-analyses of clinical trials^{9,38} as well as the HPS²⁴ found rates of elevated transaminases to be no higher among patients taking statins than among those receiving placebo. A review focusing on lovastatin found that rates of Alanine aminotransferase levels 3 times the upper limit of normal were dose-dependent; the rate was 2.6% at 20 mg/day and 5% at 80 mg/day.³⁹ The rate of hepatitis was 9.7 per million patient-treatment years, and the rate of liver failure (1 per 1.14 million patient-treatment years) was equivalent to the background rate of idiopathic acute liver failure. Similarly, in a trial of two doses of atorvastatin, the incidence of persistent elevations in liver aminotransferase levels was 2 per 1000 in patients taking atorvastatin 10 mg daily, versus 1.2 per 1000 in patients taking 80 mg daily.⁴⁰

LIMITATIONS AND CONCLUSIONS

In this selective update, we reviewed new evidence available since the publication of the USPSTF 2001 recommendations on screening for lipid disorders in adults. This document should be read in conjunction with the full systematic evidence review conducted for the USPSTF in 2001, the final report of ATP III, and the 2004 ATP III update. These other reports provide more detailed and thorough analysis than can be provided here. The main findings of this update, focusing on discrepancies between the USPSTF recommendations and ATP III and summarized in Table 1, should be viewed in this context.

Little new evidence directly addresses the discrepancies between ATP-III and the 2001 USPSTF recommendations. No new evidence examined whether targeting young adults at high risk is more effective than recommending healthy lifestyle behaviors to all. Another discrepancy in the recommendations concerns whether to include triglycerides in an initial screening panel. Results of recent studies are consistent with previous evidence and suggest that, although triglyceride level is a strong univariate predictor of CHD events, its association with such events is reduced substantially by adjustment for other risk factors. We did not identify new evidence relevant to the appropriate interval to screen for hyperlipidemia. The use of risk factors to select patients for treatment was not addressed in the 2001 USPSTF recommendation. Evidence from epidemiologic studies as well as from good-quality randomized controlled trials supports the idea that patients who have “CHD risk equivalents” benefit from lipid-lowering therapy similar to that used in individuals who have known CHD. New evidence demonstrates the efficacy of short-term primary prevention in high-risk individuals older than 65 and in high-risk individuals who have lower LDL-C levels than those enrolled in older trials. There is also strong evidence that lipid-lowering therapy is effective in women with coronary disease or diabetes, but there is still insufficient evidence from primary prevention trials to determine the effectiveness of lipid-lowering therapy in other low-risk and some intermediate risk groups under-represented in older trials. New evidence about harms of statin therapy comes from recent randomized controlled trials and FDA data analyses. The balance of benefits and harms is clearly in favor of statin therapy among individuals enrolled in some, but not all, randomized trials of short-term primary prevention. However, the applicability of these findings to individuals at higher risk of adverse events is unclear, and the long-term (>10 years) safety of statins is unknown.

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Table 1. Discrepancies in 2001 USPSTF and 2002/2004 ATP III Guidelines

Key Question	USPSTF	ATP-III	Eligible Evidence	Conclusions of Update
Target population				
1) How frequent is elevated total cholesterol in men younger than age 35 and women younger than age 40, and what proportion have an overall 10-year risk of cardiac events of 10% or greater?	Men aged 35 and older. Women aged 40 and older. Men aged 20-34 and women aged 20-39 who have certain risk factors.*	Adults aged 20 and older.	Observational studies (cross-sectional, prospective cohort)	We did not identify new direct evidence addressing the target population for screening. (The Task Force has also examined a review of screening for lipid disorders in children and adolescents up to 21 years of age, published in July 2007, ⁴¹ It is now examining a separate review of novel risk factors for CHD.)
Initial screening panel				
2) What evidence supports the use of triglyceride levels as part of an initial screening panel?	TC and HDL-C, or TC alone if HDL-C unavailable.	TC, HDL-C, and triglyceride level, with calculated LDL-C.	Randomized controlled trials in patients with elevated triglyceride levels who would not otherwise qualify for treatment; Observational studies	Recent evidence is conflicting regarding the additional contribution of a serum triglyceride level to the identification of individuals at short-term risk for CHD events.
Frequency of screening				
3) What are the optimal screening intervals in the general population and in patients at high risk for CHD events?	Once every 5 years. Shorter intervals for people who have lipid levels close to those warranting therapy. Longer intervals if several previous values have been reassuring.	Once every 5 years if 0-1 risk factors. Shorter intervals if --2 or more risk factors OR --0 to 1 risk factors and lipid levels close to those warranting therapy.	Observational studies	We did not identify new direct evidence from observational or experimental studies regarding follow-up testing or the frequency of screening.
Estimating Risk				
4) What risk factors should be used to select patients for lipid-modifying drug therapy?	Not defined.	Four levels of risk are defined: CHD and CHD equivalents. Multiple risk factors (2+) and 10-year risk 10-20% Multiple risk factors (2+) and 10-year risk < 10% 0 to 1 risk factor and	Observational studies	Evidence from epidemiologic studies as well as from good-quality randomized controlled trials support the idea that patients who have "CHD risk equivalents" benefit from lipid-lowering therapy similar to that used in individuals who have known CHD. For low-risk and some intermediate-risk individuals who have elevated LDL-C or decreased HDL-C, we did not identify new direct evidence relevant to the USPSTF advice to treat individuals younger than age 45 or older than age 65 if the annual incidence of coronary heart

Table 1. Discrepancies in 2001 USPSTF and 2002/2004 ATP III Guidelines, Continued

Key Question	USPSTF	ATP-III	Eligible Evidence	Conclusions of Update
		10-year risk <10%		<p>disease is at least 0.6% per year.</p> <p>There is new direct evidence demonstrating effective short-term primary prevention in high-risk individuals older than 65 and in high-risk individuals who have lower LDL-C levels than those enrolled in older trials.</p> <p>There is also strong evidence that lipid-lowering therapy is effective in women who have known coronary disease or diabetes.</p> <p>There is still insufficient <i>direct</i> evidence from primary prevention trials to determine the effectiveness of lipid-lowering therapy in other low-risk and some intermediate risk groups under-represented in older trials.</p>
Harms of drug therapy				
5) What is the current evidence about the harms of drug therapy for lipid disorders?	Not addressed in guideline. The literature review (through 1999) provided a detailed review of the adverse effects of statins and non-statin drug therapy.	Provides information about side effects and refers to 2002 NHLBI statement on safety of statins at www.nhlbi.nih.gov/guidelines/cholesterol/statins.htm	Randomized controlled trials and long-term observational studies	Statins have rare but serious harms, especially in groups with identifiable risk factors for such events. The balance of benefits and harms is clearly in favor of statin therapy among individuals enrolled in some, but not all, randomized trials of short-term primary prevention. However, the applicability of these findings to individuals at higher risk of adverse events is unclear. The long-term (>10 years) safety of statins is not known.

* Risk Factors: Diabetes; family history of cardiovascular disease before age 50 in male relatives or age 60 in female relatives; family history suggestive of familial hyperlipidemia; or multiple coronary heart disease risk factors (e.g., tobacco use, hypertension). These are not the same risk factors as those USPSTF uses for estimating the risk of cardiovascular events.

Table 2. Statin Trials that Included a Primary Prevention Group

Trial Quality	Drug/Dose	Risk Status	Baseline LDL (mg/dL)	Study length (years)	% LDL reduction	Relative risk for coronary events (95% CI)
AFCAPS ²² <i>Good</i>	Lovastatin 20mg-40mg	Average risk, no history of CAD	150	5.2	25%	0.63 (0.50–0.79)
ALLHAT-LLT ²⁶ <i>Fair-Good</i>	Pravastatin 40mg	Hypertensive moderately high LDL-C and at least one additional CHD risk factor	145	4.8	24%	0.91 (0.79–1.04)
ASCOT-LLA ^{30, 42, 43} <i>Fair-Good</i>	Atorvastatin 10mg	HTN plus CHD risk factors	133	3.3	35%	0.71 (0.59–0.86)
CARDS ²⁵ <i>Good</i>	Atorvastatin 10 mg	Type 2 diabetes, no history of CVD	117	3.9	36%	0.63 (0.48–0.83)
HPS ²⁴ <i>Good</i>	Simvastatin 40mg	History of CVD, diabetes, or non-coronary vascular disease	131	5.5	30%	0.73 (0.67–0.79)
PROSPER ²⁷ <i>Good</i>	Pravastatin 40mg	70-82 years old, history of CHD or risk factors	147	3.2	27%	0.85 (0.74–0.97)
SPARCL ²⁸ <i>Good</i>	Atorvastatin 80 mg	Stroke or TIA within 1-6 months, no history of CHD	133	4.9	53%	0.80 (0.69–0.92)
WOSCOPS ²¹ <i>Good</i>	Pravastatin 40mg	High risk, no history of CAD	192	4.9	16%	0.69 (0.57–0.85)

Screening for Lipid Disorders in Adults: Selective Update of 2001 USPSTF Review
Appendix 1. Search Strategy

- 1 exp lovastatin/ or "lovastatin".mp.
- 2 simvastatin.mp.
- 3 Pravastatin/ or "pravastatin".mp
- 4 (atorvastatin or fluvastatin or rosuvastatin).mp.
- 5 statins.mp. or exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
- 6 1 or 2 or 3 or 4 or 5
- 7 Drug Evaluation/ or drug evaluation studies.mp.
- 8 comparative study/
- 9 7 or 8
- 10 6 and 9
- 11 limit 10 to human
- 12 limit 11 to english language
- 13 11 not 12
- 14 limit 13 to abstracts
- 15 12 or 14
- 16 6
- 17 limit 16 to (human and english language and (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or meta analysis or multicenter study or randomized controlled trial))
- 18 exp clinical trials/ or clinical trial\$.tw.
- 19 exp cohort studies/
- 20 (cohort stud\$ or longitudinal stud\$ or prospective stud\$).tw. (33965)
- 21 18 or 19 or 20
- 22 6 and 21
- 23 limit 22 to (human and english language)
- 24 17 or 23
- 25 15 or 24

Appendix 2. U.S. Preventive Services Task Force Quality Rating Criteria

Diagnostic Accuracy Studies

Criteria

- Screening test relevant, available for primary care, adequately described
- Study uses a credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Handles indeterminate results in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Administration of reliable screening test

Definition of ratings based on above criteria

- Good:** Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; reliability of test assessed; has few or handles indeterminate results in a reasonable manner; includes large number (more than 100) broad-spectrum patients with and without disease.
- Fair:** Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; moderate sample size (50 to 100 subjects) and a “medium” spectrum of patients.
- Poor:** Has important limitation such as: uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; very small sample size of very narrow selected spectrum of patients.

Randomized Controlled Trials (RCTs) and Cohort Studies

Criteria

- Initial assembly of comparable groups: RCTs—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies, or intention-to-treat analysis for RCTs

Appendix 2. U.S. Preventive Services Task Force Quality Rating Criteria, Continued

Definition of ratings based on above criteria

- Good:** Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis.
- Fair:** Studies will be graded “fair” if any or all of the following problems occur, without the important limitations noted in the “poor” category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for.
- Poor:** Studies will be graded “poor” if any of the following major limitations exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention.

Case Control Studies

Criteria

- Accurate ascertainment of cases
- Nonbiased selection of cases/controls with exclusion criteria applied equally to both
- Response rate
- Diagnostic testing procedures applied equally to each group
- Measurement of exposure accurate and applied equally to each group
- Appropriate attention to potential confounding variable

Definition of ratings based on criteria above

- Good:** Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate equal to or greater than 80 percent; diagnostic procedures and measurements accurate and applied equally to cases and controls; and appropriate attention to confounding variables.
- Fair:** Recent, relevant, without major apparent selection or diagnostic work-up bias but with response rate less than 80 percent or attention to some but not all important confounding variables.
- Poor:** Major selection or diagnostic work-up biases, response rates less than 50 percent, or inattention to confounding variables.

Appendix 3. Selected Evidence from the May 2003 AHRQ Evidence Report^a on the Diagnosis and Treatment of Coronary Heart Disease in Women, Continued

LIPIDS: CHARACTERISTICS OF CLINICAL TRIALS

Study Name, Year	N Women/ Total (% Women)	Mean Age of Women	% with CHD*	Lipid Entry Criterion	Drug	Mean Follow Up (years)	Outcomes in Women	Quality Rating [†]
Scottish Society of Physicians, 1971 ¹	124/717 (17)	54	100%	None	Clofibrate	6	CHD mortality nonfatal MI	Fair
Newcastle Upon Tyne, 1971 ²	97/497 (20)	54	100%	None	Clofibrate	5	CHD mortality nonfatal MI	Fair
Colestipol Study, 1978 ³	1184/2278 (52)	57	20%	TC >250 mg/dl	Colestipol	3	total mortality CHD mortality	Fair
4S, 1994 ⁴⁻⁶	827/4444 (19)	61	100%	TC 213-309 mg/dl	Simvastatin	5.4	total mortality CHD mortality nonfatal MI revascularization CHD events [‡]	Good
ACAPS, 1994 ^{7, 8}	441/919 (48)	61	0%	LDL 130-159 mg/dl with any number of risk factors; LDL 160-189 mg/dl with no or one risk factor	Lovastatin	2.8	total mortality CHD mortality nonfatal MI	Good
PLAC II, 1994 ⁹	22/151 (15)	NA	100%	LDL in 60-90th percentile for age and gender	Pravastatin	3	total mortality CHD mortality nonfatal MI	Good
CARE, 1998 ¹⁰⁻¹²	576/4159 (14)	61	100%	TC <240 mg/dl and LDL-C 115-174 mg/dl	Pravastatin	5	total mortality CHD mortality nonfatal MI Revascularization CHD events [‡]	Good
LIPID, 1998 ¹³⁻¹⁵	1516/9014 (17)	62	100%	TC 155-271 mg/dl	Pravastatin	6.1	CHD events [‡]	Good
AFCAPS/ TEXCAPS, 1998 ^{16, 17}	997/6605 (15)	62	0%	TC 180-264 mg/dl LDL 130-190 mg/dl and HDL <47 mg/dl	Lovastatin	5.2	total mortality CHD mortality nonfatal MI revascularization CHD events [‡]	Good
HPS, 2002 ¹⁸	5082/20,536 (25)	NA	65%	TC >135 mg/dl	Simvastatin	5	CHD events [‡]	Good
ALLHAT, 2002 ¹⁹	5051/10,355 (49)	NA	14%	LDL 100-189 mg/dl	Pravastatin	4.8	total mortality CHD events [‡]	Fair

Key

Appendix 3. Selected Evidence from the May 2003 AHRQ Evidence Report^a on the Diagnosis and Treatment of Coronary Heart Disease in Women, Continued

^aGrady D, Chaput L, Kristof M. Diagnosis and Treatment of Coronary Heart Disease in Women: Systematic Reviews of Evidence on Selected Topics. Evidence Report/Technology Assessment No. 81. (Prepared by the University of California, San Francisco-Stanford Evidence-based Practice Center under Contract No 290-97-0013.) AHRQ Publication No. 03-E037. Rockville, MD: Agency for Healthcare Research and Quality. May 2003.

* CHD defined as history of myocardial infarction or angina.

[†]See Quality Assessment section in text.

[‡]CHD events in CARE, LIPID and ALLHAT defined as CHD mortality or nonfatal MI; in 4S as CHD mortality, non fatal MI or resuscitated cardiac arrest; in AFCAPS as CHD mortality, nonfatal MI or unstable angina or sudden cardiac death; in HPS as CHD mortality, nonfatal MI, stroke or revascularization.

Abbreviations

4S, Scandinavian Simvastatin Survival Study; ACAPS, Asymptomatic Carotid Artery Progression Study; AFCAPS/TEXCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent heart Attack Trial; CARE, Cholesterol and Recurrent Events trial; CHD, coronary heart disease; CVD, cardiovascular disease; ; HPS, Heart Protection Study; LDL, low density lipoprotein; LIPID, Long-term Intervention with Pravastatin in Ischemic Disease; mg/dl, milligrams per deciliter; MI, myocardial infarction; N, number; NA, not available; PLAC II, Pravastatin, Lipids and Atherosclerosis in the Carotid Arteries; TC total cholesterol.

Continued-

Appendix 3. Selected Evidence from the May 2003 AHRQ Evidence Report^a on the Diagnosis and Treatment of Coronary Heart Disease in Women, Continued

LIPIDS: OUTCOMES

Outcome	Study	RR	(95% CI)
Secondary Prevention			
Total Mortality	4S ⁴⁻⁶	1.11	(0.66, 1.5)
	PLAC II ⁹	1.18	(0.03, 54.81)
CHD Mortality	Scottish Society of Physicians ¹	0.17	(0.02, 1.34)
	Newcastle Upon Tyne ²	0.20	(0.04, 1.13)
	4S ⁴⁻⁶	0.79	(0.39, 1.6)
	PLAC II ⁹	1.18	(0.03, 54.81)
	CARE ¹⁰⁻¹²	0.80	(0.61, 1.05)
Nonfatal MI	Scottish Society of Physicians ¹	0.75	(0.42, 1.33)
	Newcastle Upon Tyne ²	0.43	(0.08, 2.25)
	4S ⁴⁻⁶	0.66	(0.48, 0.90)
	PLAC II ⁹	1.18	(0.48, 54.81)
	CARE ¹⁰⁻¹²	0.51	(0.27, 0.94)
CHD events*	4S ⁴⁻⁶	0.68	(0.51, 0.91)
	CARE ¹⁰⁻¹²	0.60	(0.37, 0.97)
	LIPID ¹³⁻¹⁵	0.87	(0.67, 1.13)
	HPS ¹⁸	0.81	(0.72, 0.92)
Revascularization	4S ⁴⁻⁶	0.52	(0.31, 0.86)
	CARE ¹⁰⁻¹²	0.82	(0.64, 1.20)
Primary Prevention			
Total Mortality	Colestipol ³	0.92	(0.51, 1.69)
	ACAPS ^{7, 8}	0.09	(0.01, 1.7)
	AFCAPS/TEXCAPS ^{16, 17}	1.53	(0.62, 3.81)
	ALLHAT ¹⁹	0.98	(0.83, 1.17)
CHD Mortality	Colestipol ³	1.08	(0.44, 2.63)
	ACAPS ^{7, 8}	0.35	(0.01, 8.47)
	AFCAPS/TEXCAPS ^{16, 17}	2.99	(0.12, 73.3)
Nonfatal MI	ACAPS ^{7, 8}	0.35	(0.04, 3.31)
	AFCAPS/TEXCAPS ^{16, 17}	0.69	(0.21, 2.28)
CHD events*	AFCAPS/TEXCAPS ^{16, 17}	0.54	(0.22, 1.34)
	ALLHAT ¹⁹	1.02	(0.81, 1.28)
Revascularization	AFCAPS/TEXCAPS ^{16, 17}	0.87	(0.33, 2.31)

Key

*CHD events in CARE, LIPID and ALLHAT defined as CHD mortality or nonfatal MI; in 4S as CHD mortality, non fatal MI or resuscitated cardiac arrest; in AFCAPS as CHD mortality, nonfatal MI, unstable angina or sudden cardiac death, and in HPS as CHD mortality, nonfatal MI, stroke or revascularization.

Abbreviations

4S, Scandinavian Simvastatin Survival Study; ACAPS, Asymptomatic Carotid Artery Progression Study; AFCAPS/TEXCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; CARE, Cholesterol and Recurrent Events trial; CHD, coronary heart disease; CI, confidence interval; HPS, Heart Protection Study; LIPID, Long-term Intervention with Pravastatin in Ischaemic Disease; MI, myocardial infarction; NA, not available; PLAC II, Pravastatin, Lipids and Atherosclerosis in the Carotid Arteries; RR, relative risk.

Continued-

Appendix 3. Selected Evidence from the May 2003 AHRQ Evidence Report^a on the Diagnosis and Treatment of Coronary Heart Disease in Women, Continued

LIPIDS: RESULTS

Outcome	Secondary Prevention		Primary Prevention	
	References	RR (95% CI)	References	RR (95% CI)
Total mortality				
All studies	4-6, 9	1.11 (0.66, 1.87)	3, 7, 8, 16, 17, 19	0.95 (0.62, 1.46)
Statin drugs	4-6, 9	1.11 (0.66, 1.87)	7, 8, 16, 17, 19	0.87 (0.37, 2.00)*
Good quality	4-6, 9	1.11 (0.66, 1.87)	7, 8, 16, 17	0.45 (0.03, 7.00)*
CHD mortality				
All studies	1, 2, 4-6, 9-12	0.74 (0.57, 0.96)	4-6, 9	1.07 (0.47, 2.40)
Statin drugs	4-6, 9-12	0.78 (0.60, 1.01)	4-6, 9	1.02 (0.11, 9.76)
Good quality	4-6, 9-12	0.78 (0.60, 1.01)	4-6, 9	1.02 (0.11, 9.76)
Nonfatal MI				
All studies	1, 2, 4-6, 9-12	0.64 (0.50, 0.82)	7, 8, 16, 17	0.61 (0.22, 1.68)
Statin drugs	4-6, 9-12	0.63 (0.48, 0.83)	7, 8, 16, 17	0.61 (0.22, 1.68)
Good quality	4-6, 9-12	0.63 (0.48, 0.83)	7, 8, 16, 17	0.61 (0.22, 1.68)
CHD events[†]				
All studies	4-6, 10-15, 18	0.79 (0.72, 0.88)	16, 17, 19	0.87 (0.50, 1.49)
Statin drugs	4-6, 10-15, 18	0.79 (0.72, 0.88)	16, 17, 19	0.87 (0.50, 1.49)
Good quality	4-6, 10-15, 18	0.79 (0.72, 0.88)	16, 17	0.54 (0.22, 1.30)
Revascularization				
All studies	4-6, 10-12	0.70 (0.42, 1.16)*	16, 17	0.87 (0.33, 2.31) [‡]
Statin drugs	4-6, 10-12	0.70 (0.42, 1.16)*	16, 17	0.87 (0.33, 2.31) [‡]
Good quality	4-6, 10-12	0.70 (0.42, 1.16)*	16, 17	0.87 (0.33, 2.31) [‡]

Key

* P-value for heterogeneity <0.10

[†]CHD events in CARE, LIPID and ALLHAT defined as CHD mortality or nonfatal MI; in 4S as CHD mortality, non fatal MI or Resuscitated cardiac arrest; in AFCAPS as CHD mortality, nonfatal MI, unstable angina or sudden cardiac death, and in HPS as CHD mortality, nonfatal MI, stroke, or revascularization. See preceding Tables for full names of studies.

[‡]Only one trial provided data on this outcome

Note: Statin drugs included lovastatin, pravastatin or simvastatin

Abbreviations

CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction; RR, relative risk.

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Appendix 3. Selected Evidence from the May 2003 AHRQ Evidence Report^a on the Diagnosis and Treatment of Coronary Heart Disease in Women, Continued

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