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# Screening and Treating Adults for Lipid Disorders

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**Context:** Screening and treatment of lipid disorders in people at high risk for future coronary heart disease (CHD) events has gained wide acceptance, especially for patients with known CHD, but the proper role in people with low to medium risk is controversial.

**Objective:** To examine the evidence about the benefits and harms of screening and treatment of lipid disorders in adults without known cardiovascular disease for the U.S. Preventive Services Task Force.

**Data Sources:** We identified English-language articles on drug therapy, diet and exercise therapy, and screening for lipid disorders from comprehensive searches of the MEDLINE database from 1994 through July 1999. We used published systematic reviews, hand searching of relevant articles, the second *Guide to Clinical Preventive Services*, and extensive peer review to identify important older articles and to ensure completeness.

**Data Synthesis:** There is strong, direct evidence that drug therapy reduces CHD events, CHD mortality, and possibly total mortality in middle-aged men (35 to 65 years) with abnormal lipids and a potential risk of CHD events greater than 1% to 2% per year. Indirect evidence suggests that drug therapy is also effective in other adults with similar levels of risk. The evidence is insufficient about benefits and harms of treating men younger than 35 years and women younger than 45 years who have abnormal lipids but no other risk factors for heart disease and low risk for CHD events (less than 1% per year). Trials of diet therapy for primary prevention have led to long-term reductions in cholesterol of 3% to 6% but have not demonstrated a reduction in CHD events overall. Exercise programs that maintain or reduce body weight can produce short-term reductions in total cholesterol of 3% to 6%, but longer-term results in unselected populations have found smaller or no effect. To identify accurately people with abnormal lipids, at least two measurements of total cholesterol and high-density lipoprotein cholesterol are required. The role of measuring triglycerides and the optimal screening interval are unclear from the available evidence.

**Conclusions:** On the basis of the effectiveness of treatment, the availability of accurate and reliable tests, and the likelihood of identifying people with abnormal lipids and increased CHD risk, screening appears to be effective in middle-aged and older adults and in young adults with additional cardiovascular risk factors.

**Medical Subject Headings (MeSH):** cardiovascular disease, cholesterol, coronary disease, hyperlipidemia, preventive health services, evidence-based medicine, MEDLINE, methods, lipids, mass screening, mortality, drug therapy (Am J Prev Med 2001;20(3S):77-89)

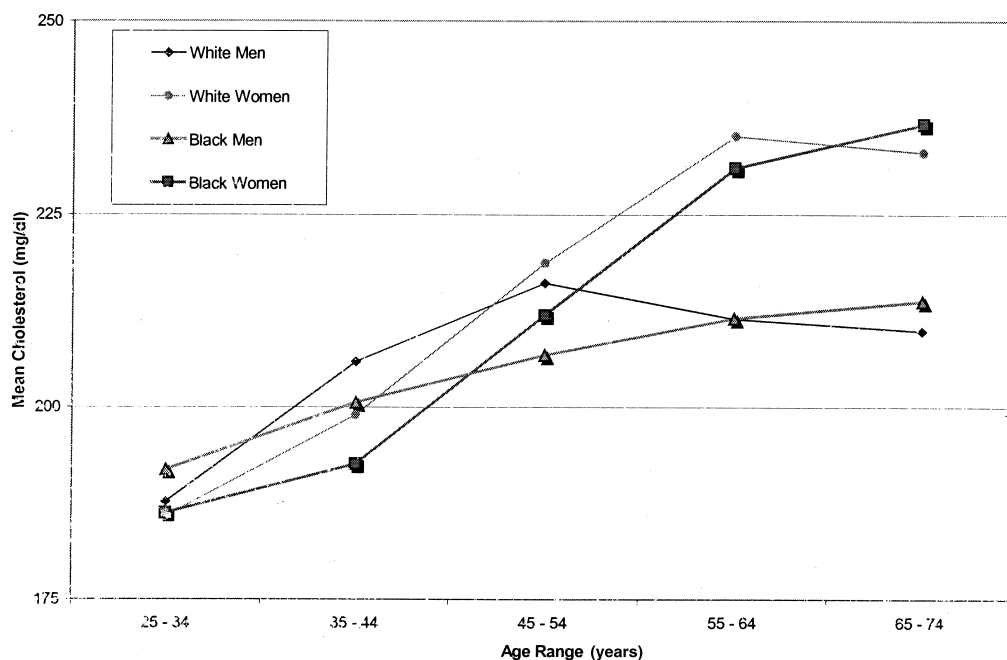
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The USPSTF recommendations based on this evidence review can be found in *Screening Adults for Lipid Disorders: Recommendations and Rationale*, available elsewhere in this supplement and from the AHRQ Web site and clearinghouse.



**Figure 1.** Mean total cholesterol (TC) values by age for white and black men and women. Data from the National Health and Nutrition Survey III, Phase 2, 1991–1994.<sup>8</sup>

## Introduction

Elevated low-density lipoprotein cholesterol (LDL-C) and low levels of high-density lipoprotein cholesterol (HDL-C) are important risk factors for coronary heart disease (CHD).<sup>1–3</sup> CHD is the leading cause of morbidity and mortality in the United States, causing nearly 500,000 deaths each year and requiring nearly 12 million hospital days of care per year. It is the leading cause of disabled life-years and is second only to injuries as a cause of life-years lost.<sup>4</sup> The lifetime risk of having a CHD event, calculated at age 40 years, is estimated to be 49% for men and 32% for women in the United States.<sup>5</sup> CHD accounted for \$78 billion in health care costs in 1995.<sup>4</sup>

## Epidemiology

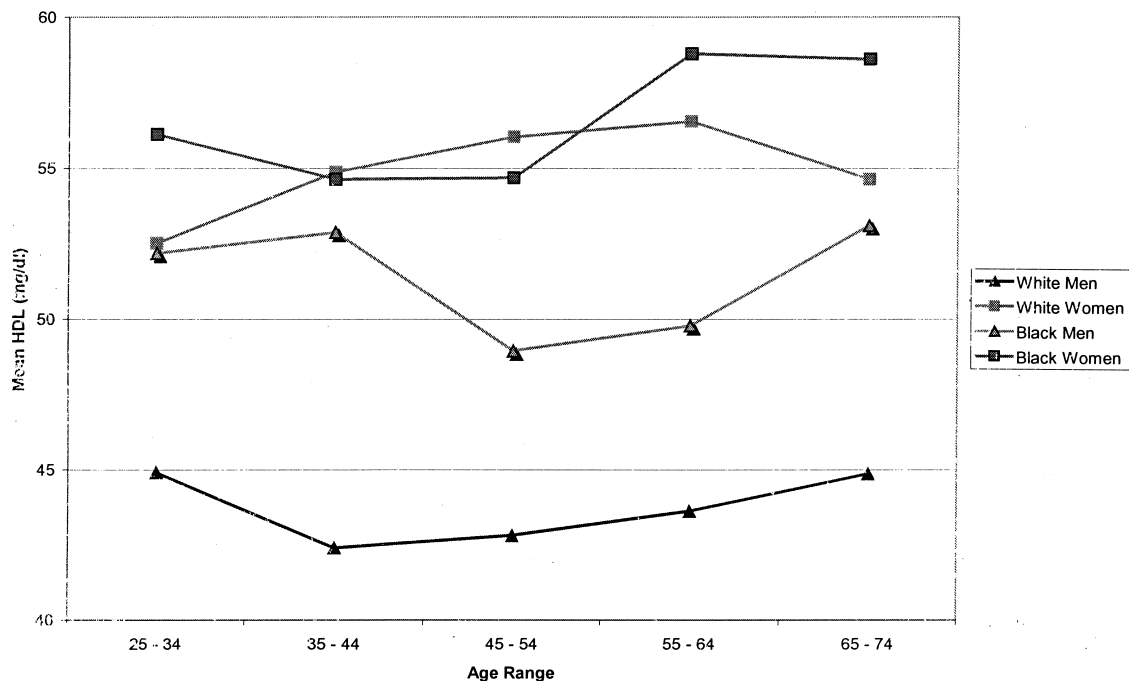
Lipid disorders are common in the United States and other Western, developed countries. Data from the National Center for Health Statistics collected from 1988 through 1994 show that 17.5% of U.S. men and 20% of U.S. women aged 20 to 74 years had total cholesterol (TC) levels greater than 240 mg/dL.<sup>6</sup> After adjusting for the effect of other risk factors, an analysis from a large U.S. cohort study estimated that 27% of CHD events in men and 34% in women were attributable to TC levels greater than 200 mg/dL.<sup>7</sup>

Figure 1 shows mean TC levels by age for men and women. In adults, mean TC increases with age for both

men and women.<sup>8</sup> In men, mean TC increases steadily from early adulthood to middle age and then reaches a plateau, falling only in men older than age 75 years. Mean TC is initially lower in premenopausal women than in men, but it rises at a similar rate. After menopause, however, women experience an additional 10- to 20-mg/dL rise, and their mean TC remains higher than for men throughout the remainder of life. HDL-C levels do not change greatly throughout adulthood and are consistently higher in women than in men.<sup>9</sup> Mean TC is similar for those identifying themselves as Caucasian or African American.<sup>10</sup> HDL-C is higher for African Americans than for Caucasians (Figure 2).

Large observational cohort studies have found a strong, graded relationship between increasing levels of LDL-C or decreasing levels of HDL-C and increasing risk of CHD events.<sup>1,2</sup> The increased risk for CHD events is continuous, linear, and graded: No clear “cut-off” value separates normal from abnormal values. A 50-year-old man with a blood pressure of 120/80 mmHg, a TC of 180 mg/dL, and an HDL-C of 40 mg/dL has a 10-year risk for CHD events of 7%. If the same man had a TC of 240 mg/dL and an HDL-C of 30 mg/dL, his 10-year risk would be 14%, a relative risk of 2.0 and an absolute risk difference of 7%.<sup>7</sup>

The total excess risk for CHD from lipid disorders depends on the presence of other risk factors. A 50-year-old man with hypertension (blood pressure of



**Figure 2.** Mean high-density lipoprotein (HDL) cholesterol values by race and gender. Data from the National Health and Nutrition Survey III, Phase 2, 1991–1994.<sup>8</sup>

160/90 mmHg) who smokes and has a TC of 180 mg/dL and an HDL-C of 40 mg/dL has a 10-year risk for CHD events of 17%. If the same man had a TC of 240 mg/dL and an HDL-C of 30 mg/dL, his risk would increase to 29%, an absolute difference of 12%.

Observational studies suggest that lipid disorders confer less relative risk of CHD events in the elderly than in other age groups. The absolute risk of CHD is higher for the elderly, however, and thus the total number of potentially preventable CHD events remains high for the elderly.<sup>11</sup>

### Prior Recommendations

The second edition of the *Guide to Clinical Preventive Services* from the U.S. Preventive Services Task Force (USPSTF) gave a “B” recommendation to “periodic” screening for high TC in men aged 35 to 65 years and women aged 45 to 65 years.<sup>12</sup> The USPSTF at that time found that the evidence was insufficient to recommend for or against TC screening in asymptomatic adults older than 65 years of age, young adults, adolescents, and children. They also found evidence to be insufficient to recommend for or against screening for other lipid abnormalities such as low HDL-C or elevated triglycerides.

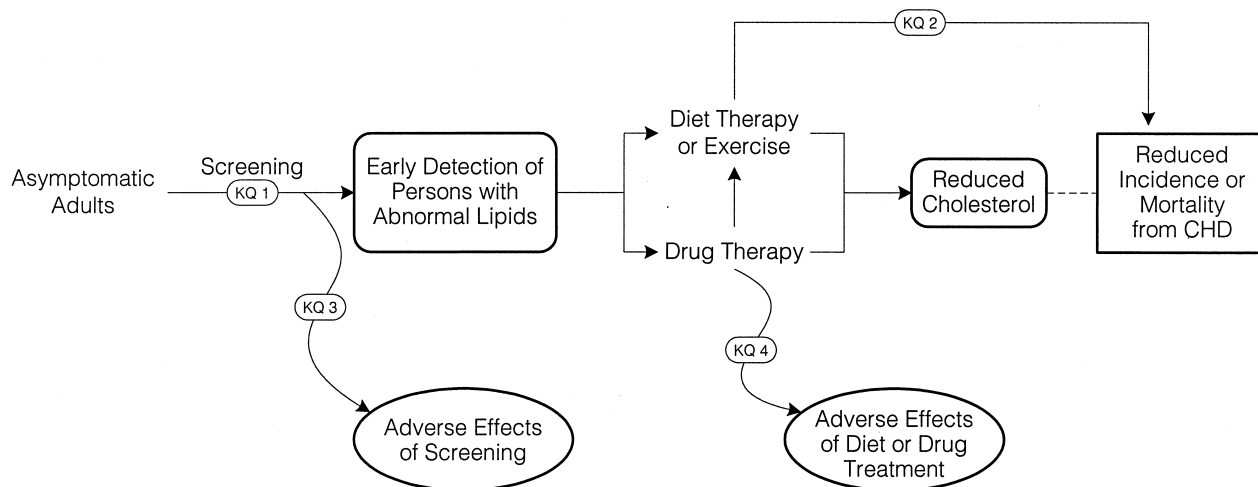
The National Cholesterol Education Program Adult Treatment Panel II (ATP II) recommended screening all adults aged 20 years and older every 5 years with

serum TC and with serum HDL-C “if accurate results are available.”<sup>3</sup> New recommendations from the ATP III are to be published in 2001. The Canadian Task Force on Preventive Health Care in 1994 recommended “case-finding” in all men aged 30 to 59 years who present to their health care providers and clinical judgment in other cases.<sup>13</sup> The American College of Physicians found “periodic” screening for men aged 35 to 65 years and women aged 45 to 65 years to be “appropriate but not mandatory”; screening young men and women was recommended only when the history or physical examination suggested a familial disorder or when the person had at least two other risk factors.<sup>14,15</sup> The American Diabetes Association recommended screening all adults with diabetes yearly with TC, LDL-C, HDL-C, and triglycerides.<sup>16</sup>

### Methods

To examine the role of practice-based screening for lipid disorders in adults without known cardiovascular disease, we first developed an analytic framework and key questions (Figure 3). The four key questions were

- What is the accuracy of screening for detecting persons at increased risk of CHD because of abnormal lipids?
- What is the effectiveness of diet therapy or exercise or drug therapy in reducing the incidence of mortality from CHD in asymptomatic people with abnormal lipids?



**Figure 3.** Screening for lipid disorders: analytic framework and key questions. Numbers refer to key questions (KQ) as follows: KQ 1. What is the accuracy of screening for detecting persons at increased risk of CHD because of abnormal lipids? KQ 2. What is the effectiveness of diet therapy or exercise or drug therapy in reducing the incidence of mortality from CHD in asymptomatic people with abnormal lipids? KQ3. What are the adverse effects of screening? KQ4. What are the adverse effects of diet or drug treatment?

- What are the adverse effects of screening?
- What are the adverse effects of diet or drug treatment?

We next identified English-language articles on drug therapy, diet and exercise therapy, and screening for lipid disorders from comprehensive searches of the MEDLINE database from 1994 through July 1999. We used published systematic reviews, hand searching of relevant articles, the second *Guide to Clinical Preventive Services*,<sup>12</sup> focused searches of MEDLINE from 1966 through 1993, and extensive peer review to identify important older articles and to ensure completeness.

We included all randomized trials of at least 1 year's duration that examined drug or diet therapy among patients without previously known CHD and that measured clinical end points, including total mortality, CHD mortality, and nonfatal myocardial infarctions (MIs), as well as randomized trials of diet or exercise therapy that measured change only in cholesterol levels. We included articles that examined the epidemiology and natural history of lipid levels and lipid disorders and ones that measured the accuracy, reliability, acceptability, and feasibility of screening. We also included any articles that examined adverse effects and harms of screening or therapy for lipid disorders.

Full details of the methods and results are available in the systematic evidence review available from the Agency for Healthcare Research and Quality ([www.ahrq.gov/clinic/uspstfix.htm](http://www.ahrq.gov/clinic/uspstfix.htm)).<sup>17</sup>

## Results

### Availability of Effective Screening Tests

Several different screening strategies have been proposed for identifying lipid disorders, including screening with TC alone, the ratio of TC to HDL-C (TC/HDL-C), and the ratio of LDL-C to HDL-C (LDL-C/HDL-C). These measures can be used alone to determine risk and the need for treatment. Alternatively, they can be

combined with information about the presence or absence of other CHD risk factors, as has been done with the ATP II guidelines.<sup>3</sup> They can also be incorporated into a quantitative risk-based screening strategy; in this approach, each person's overall risk for CHD is calculated by using a risk assessment table or computer program, and treatment is recommended for risk levels above a defined risk threshold.

### Reliability of Screening Tests

TC measurements from venous blood samples generally have good reliability. The analytic variability for TC is less than 3%; the mean total biologic variability for TC is about 6%.<sup>18</sup> Two separate measurements are required to determine a patient's TC level within 10% of the true value. TC levels do not vary substantially between fasting and nonfasting periods; hence, TC can be measured clinically at any time.

HDL-C has higher analytic (6%) and biologic (7.5%) variation than total cholesterol. Two or three values are required to estimate confidently the true level within 10% to 15%. HDL-C in the nonfasting state is lower by 5% to 10% than in the fasting state. Nonfasting measurement may, therefore, slightly overestimate CHD risk, but it is considered sufficiently accurate for use in screening.<sup>19</sup> Combined measures such as the TC/HDL-C ratio will be less reliable than each individual measure, but it can also be improved by averaging two or more individual values.

Triglycerides change by 20% to 30% between fasting and nonfasting states. Because LDL-C is routinely calculated indirectly by measuring TC, HDL-C, and triglycerides (TG) and then applying the Friedewald equa-

tion ( $TC = HDL-C + LDL-C + [TG/5]$ ), accurate calculation of the LDL cholesterol level requires a fasting sample to ensure accurate measurement of triglycerides.<sup>18</sup> The Friedewald equation produces inaccurate results when triglyceride levels exceed 400 mg/dL, so patients with very high triglyceride levels may need special techniques (e.g., ultracentrifugation) to measure LDL-C accurately.

Capillary blood samples that are used to measure total and HDL-C (so-called “point of care” testing) appear to have similar reliability under optimal conditions to venous samples but may be less reliable if proper attention is not paid to calibration and proper testing technique.<sup>20</sup>

### Lipid Levels and CHD Risk

An important objective in screening for lipid disorders is to identify accurately which patients are (or are not) at high risk of experiencing CHD events. The amount of CHD risk attributable to abnormal lipids depends on the degree of lipid abnormality and the presence of other CHD risk factors. Several means of assessing the extent of lipid abnormality are available, including measurement of individual lipid components (TC, HDL-C, LDL-C) or ratios of such components (e.g., TC/HDL-C).

Strategies that explicitly consider a person’s other CHD risk factors in addition to his or her lipid levels are more accurate than those that measure only lipid levels.<sup>7</sup> Grover et al.<sup>21</sup> found that a Framingham-based coronary risk model was the best predictor of CHD mortality. The ATP II guidelines, the LDL-C/HDL-C ratio, and the TC/HDL-C ratio performed approximately equally well. TC alone was the least accurate (Table 1).

### Acceptability of Screening to Patients or Parents

The acceptability of screening for lipid disorders in adults has been quite high. Obtaining a nonfasting sample (for measurement of TC, HDL-C, or both) at a regular health care visit is the easiest method. Obtaining a fasting sample (which may require a separate visit or change in usual eating habits) is somewhat more taxing, but apparently most patients (more than 80%) will return for such testing when requested to do so.<sup>23</sup> The acceptability to patients of the ATP II screening guidelines or an explicit risk-based approach is presumably no different than a nonfasting blood draw alone because the extra work is required of the physician, not the patient.

### Feasibility for Providers

Screening for lipid disorders by measuring cholesterol levels in adult patients is quite feasible for physicians because it involves only ordering a blood test. Providers

**Table 1.** Accuracy of different measures of coronary heart disease risk

Test	Area under ROC Curve <sup>a</sup> (± SD)
Framingham-based global risk assessment	0.85 (±0.02)
NCEP ATP II <sup>b</sup>	0.74 (±0.03)
TC/HDL ratio <sup>c</sup>	0.72 (±0.04)
TC alone	0.68 (±0.03)

<sup>a</sup>ROC indicates receiver operating characteristic; data from Grover et al.<sup>22</sup>

<sup>b</sup>National Cholesterol Education Program, Adult Treatment Panel II.

<sup>c</sup>TC indicates total cholesterol. HDL indicates high-density lipoprotein cholesterol.

appear to have achieved high levels of lipid screening based on population-based patient survey data. Data from primary care practices, however, suggest that screening may not be directed preferentially to those patients who are at highest risk and thus most likely to benefit from treatment.<sup>24</sup> The feasibility of routinely using the ATP II guidelines or a risk-based screening tool may be lower, as each requires providers to collect and integrate several pieces of health information.<sup>25</sup>

### Triglyceride Measurement

The question of whether an elevated triglyceride level is an independent risk factor for CHD remains controversial.<sup>26,27</sup> Even if elevated triglycerides are independently associated with an increased risk of CHD, the question of whether treating people with isolated increased triglycerides will reduce future CHD events is still unclear.

### Adverse Effects of Screening for Lipid Disorders

Screening for and identifying lipid disorders in adults do not appear to have important psychological sequelae or to produce important changes in indices of mental health. The research to date has not been sufficient, however, to rule out important changes in small subsets of patients or to detect subtle changes in anxiety.<sup>28–31</sup> Patients who are identified as having acceptable lipid levels may have a theoretical disincentive to follow or to adopt healthy dietary habits, which could adversely affect their risk for other illnesses not mediated through lipid levels, but this effect has not been well studied.

### Summary of Characteristics of Screening Tests

Nonfasting TC alone is the least expensive and easiest test to perform for both patient and provider, but its accuracy is lowest. The TC/HDL-C ratio alone is also easy for patients to obtain and moderately easy for providers to interpret. It performs as accurately as the ATP II guideline-based strategy. The LDL-C/HDL-C ratio or ATP II-based predictions perform no better

than the TC/HDL-C ratio and may be more difficult for patients and providers.

Risk-based algorithms, such as those based on the Framingham cohort study, that directly incorporate age, the presence and magnitude of other risk factors, and measures of TC and HDL-C are the most accurate approach to screening, but they are more difficult for providers to implement without assistance because they require them to integrate several different pieces of information.<sup>7</sup> Using a supplemental table such as the Sheffield Tables<sup>32</sup> or a simple computer program<sup>33</sup> may improve the feasibility of a risk-based strategy.

Good data directly comparing the prospective performance, costs, and marginal cost-effectiveness of the different approaches are not currently available. As initial screens, for example, we cannot say definitely whether the extra accuracy gained by universally measuring HDL-C and calculating the TC/HDL-C ratio justifies the cost difference between this measure and the use of TC alone.

### Frequency of Screening

No direct data inform the question of appropriate frequency of screening. Chiefly for that reason, previous USPSTF recommendations did not state a preferred interval.<sup>12</sup> By contrast, ATP II recommendations suggested a 5-year interval for people with previous normal results and more frequent screening for those who have borderline values.<sup>3</sup>

Several factors enter into a decision about screening frequency. These factors include the usual rates of change in cholesterol levels over time, the variability of individual cholesterol measurements, the likelihood of finding a result that would lead to a change in management (particularly values that are close to treatment thresholds), and the feasibility and costs of different frequencies of screening. A universal 5-year interval, for example, is simple to implement, but it may impose more frequent screening than is necessary on patients with few or no other risk factors and low-risk values on previous screening measurements. Using a more variable algorithm in which patients' frequency of screening would be related to their previous results could be more efficient for diagnosis, but this approach may be confusing or difficult to implement.

### Effectiveness of Drug Therapy

**Effects of drug therapy on CHD events.** We identified four trials of drug therapy for lipid disorders in the primary prevention of CHD. These include two older (pre-1995) trials: one using the bile-acid binding resin cholestyramine (Lipid Research Council [LRC] trial)<sup>34</sup> and one (Helsinki Heart Study [HHS]) using the fibric acid derivative gemfibrozil.<sup>35</sup> The other two trials were published after 1995 and used hepatic 3-methylglutaryl coenzyme A reductase inhibitors or "statin" drugs: The

West of Scotland Coronary Prevention Study (WOSCOPS) used pravastatin,<sup>36</sup> and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS-TexCAPS, hereafter AFCAPS) used lovastatin.<sup>37</sup> Table 2 describes the study design and patient characteristics for these four trials; Table 3 provides key results.

The four trials were conducted mainly among middle-aged men of European descent. The LRC, HHS, and WOSCOPS trials enrolled patients with elevated levels of TC and LDL-C, whereas the AFCAPS study included men and women with TC levels close to the U.S. average but low levels of HDL-C. Few diabetic patients were enrolled in any of the four trials. The trials lasted from 5 to 7 years. All examined the effect of drug therapy on the incidence of CHD events, including CHD mortality, using a placebo-controlled, double blind methodology. In each trial, the intervention and control groups both received low-intensity dietary interventions.

The two trials employing statin drugs (WOSCOPS and AFCAPS) had larger initial decreases in TC (20% and 18%) than the LRC or HHS (15% and 9%). The relative risk reductions for CHD events ranged from 19% to 37% and for CHD mortality from 20% to 28%. No trial was designed with sufficient power or duration to address confidently the question of whether drug therapy reduces total mortality.

WOSCOPS, which examined the highest-risk population among the four studies, demonstrated that treating middle-aged men with elevated LDL-C and a baseline risk of CHD events of about 1.5% per year decreased the relative risk of CHD events by 31% and total mortality by 22%. The absolute risk reduction for total mortality, however, was small (0.9%), suggesting that approximately 111 patients at similar risk would need to be treated for 5 years to prevent one death.<sup>36</sup>

**Meta-analysis.** The combined results of the four main trials suggest that drug therapy decreases the risk of total CHD events (defined as the sum of nonfatal MIs and deaths from CHD) by 30% (95% confidence interval [CI]=20% to 38%).<sup>38</sup> Drug therapy also reduces the risk of CHD death by 26% (95% CI=2% to 43%). Drug therapy appears to have little overall effect on total mortality for the 5 to 7 years over which these trials were conducted (odds ratio [OR]=0.91; 95% CI=0.78 to 1.07). However, the overall result may mask a total mortality benefit in higher-risk patients. The WOSCOPS trial found a 22% relative reduction in total mortality at borderline statistical significance ( $p=0.051$ ). In the other three trials, drug therapy appeared to confer no total mortality benefit. Repeat analyses, using data from the two statin trials alone, produced slightly larger estimates of effect on CHD events and CHD mortality but still no clear effect on total mortality.

**Table 2.** Screening adults for lipid disorders

Study details	LRC <sup>34</sup>	HHS <sup>35</sup>	WOSCOPS <sup>36</sup>	AFCAPS <sup>37</sup>
Year	1984	1987	1995	1998
Duration (yr)	7.4	5	4.9	5.2
Intervention (dose)	Cholestyramine (24g qd)	Gemfibrozil (600 mg bid)	Pravastatin (40 mg qd)	Lovastatin (20–40 mg qd)
Inclusion	Men with TC >265 <sup>b</sup> and LDL 190 <sup>c</sup>	Healthy Finnish men (civil service or industrial employees); non-HDL cholesterol >200	Men with “elevated LDL cholesterol”	Men and women with average TC and below-average HDL
Age range for inclusion (yr)	35–59	40–55	45–64	Men, 45–73, Women, >55
Number of subjects, intervention/control	1906/1900	2051/2030	3302/3293	3304/3301
Mean age (yr)	48	47	55	58
Male (%)	100	100	100	85
White (%)	95.5	~100	~100	89
Mean BMI (kg/m <sup>2</sup> )	26.25	26.6	26	27.05
Hypertension (%)	0	15	15	22
Mean TC start (mg/dL)	291.5	288.9	272	221
Mean LDL start (mg/dL)	215.5	NR	192	150
Mean HDL start (mg/dL)	45	47	44	Men, 36 Women, 40
Current smokers (%)	38	36	44	12.5
Angina (5)	0	0	5	0
Diabetes	0	2.65	1	2.5
ASA use (%)	NR	NR	3	17

LRC, Lipids Research Council; HHS, Helsinki Heart Study; WOSCOPS, West of Scotland Coronary Prevention Study; AFCAPS, Air Force/Texas Coronary Atherosclerosis Prevention; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BMI, body-mass index; NR, not reported; ASA, acetylsalicylic acid (aspirin).

**Effect of drug therapy on strokes.** Drug therapy reduces the incidence of total strokes in people with known CHD by about 30%.<sup>39</sup> A meta-analysis of three primary prevention studies found a 20% decrease in total stroke in incidence (OR=0.80; 95% CI=0.54 to 1.16) that did not reach statistical significance.<sup>40</sup> Another meta-analysis of statin trials conducted before the AFCAPS trial was published produced a similar result

for total strokes in primary prevention trials (OR=0.85; 95% CI=0.57 to 1.28).<sup>41</sup>

**Harms of drug therapy for lipid disorders.** On the basis of data from multiple clinical trials and 10 years of experience with adverse drug reporting, statins appear to have few important short- or medium-term (initiation to 5 years) adverse effects.<sup>17</sup> Myopathy and muscle

**Table 3.** Primary prevention trials of drug therapy: results

Study details	LRC <sup>34</sup>	Helsinki <sup>35</sup>	WOSCOPS <sup>36</sup>	AFCAPS <sup>37</sup>
Year	1984	1987	1995	1998
Main outcome	Nonfatal MI, CHD death	Nonfatal MI, CHD death	Nonfatal MI, CHD death	Nonfatal MI, CHD death, unstable angina
Cumulative event rate <sup>a</sup>	8.1/9.8	2.73/4.14	5.5/7.9	3.4/5.45
I/C	(5.5/6.6) <sup>b</sup>			1.65/2.9 <sup>c</sup>
ARR	1.7 (1.1) <sup>b</sup>	1.41	2.4	2.05 (1.25) <sup>c</sup>
NNT for 5 years <sup>c</sup>	(91) <sup>b</sup>	71	42	49 (80) <sup>c</sup>
RRR (%)	19	34	31	37
(95% CI)	(3–32) <sup>d</sup>	(8–53)	(17–43)	(21–50)

<sup>a</sup>Event rates are cumulative incidence in percentages for the event over the study; I, intervention, C, control.

<sup>b</sup>Adjusted 5-year outcomes for LRC.

<sup>c</sup>Unstable angina excluded in results.

<sup>d</sup>CI for LRC was 90%.

<sup>e</sup>NNT for 5 years to prevent 1 CHD event.

LRC, Lipids Research Council; HHS, Helsinki Heart Study; WOSCOPS, West of Scotland Coronary Prevention Study; AFCAPS, Air Force/Texas Coronary Atherosclerosis Prevention; MI, myocardial infarction; CHD, coronary heart disease; ARR, absolute risk reduction; NNT, numbers needed to treat; RRR, relative risk reduction; CI, confidence interval.

pain appear to occur infrequently (in about 1 in 500 to 1 in 1000 users). Elevations in liver enzyme levels, which some studies have noted, have not been found in recent large trials and do not seem to produce clinically important consequences.

In observational studies, hemorrhagic stroke appears to occur more frequently in patients with low TC levels, but it has not been sufficiently studied in treatment trials to conclude that it is increased in patients who have had their cholesterol levels lowered with statins or other drug therapy. Data from one recent secondary prevention study suggest that, although the incidence of total stroke is decreased by drug therapy, the rate of hemorrhagic stroke may be increased (approximate relative risk=1.7; 95% CI=0.8 to 3.2).<sup>41</sup>

The safety of statin drugs in the long run remains unclear because long-term experience is insufficient to rule out rare but serious consequences of prolonged therapy. Other agents used for lipid disorders, including gemfibrozil, niacin, and bile-acid binding resins, have some minor adverse effects (e.g., gastrointestinal upset for gemfibrozil or bile-acid binding resins; flushing for niacin) or rare major effects (e.g., liver failure for extended-release niacin). The safety experience for bile-acid binding resins and niacin, however, is based on a longer period of time than is the case for the statin drugs.

**Summary of drug therapy effects.** Drug therapy for lipid disorders reduces the relative risk for CHD events by 30%. Statin drugs have produced larger reductions in cholesterol and appear to reduce events more than the older drugs. The absolute risk reduction with drug therapy depends on the underlying risk in the person or population being treated. Drug therapy appears to have little effect on total mortality after 5 to 7 years of treatment in lower-risk patients (risk of CHD events less than 1.5% per year), but mortality may be reduced in higher-risk populations or with longer follow-up. Short- to medium-term adverse effects appear uncommon with statins, but long-term effects are unknown. Women, elderly people (older than 70 years), and people of non-European descent appear to have similar relative risk reductions for total CHD events with drug treatment, although they have been studied less than middle-aged men.

### Effectiveness of Diet Therapy

The relationships among diet, cholesterol, and heart disease have been demonstrated in numerous ecologic and observational studies. In the United States, broad changes over the past 30 years in dietary patterns, particularly the consumption of saturated fat, have been accompanied by reductions in the population's average TC levels.<sup>10</sup> In addition, individualized dietary interventions (some, but not all, of which lower TC) have been shown to reduce CHD events in patients with

known cardiovascular disease or who have been treated in institutional settings.<sup>17</sup> In this section, we examine the effectiveness of diet therapy for preventing CHD events and for reducing cholesterol levels among free-living people without previously diagnosed CHD.

**Effect of diet therapy on CHD events.** No studies in primary care settings examined the effect of dietary advice therapy on actual CHD events among patients with abnormal lipids but no previous history of CHD. Ebrahim and Smith<sup>42</sup> performed a systematic review and meta-analysis of nine multiple risk factor intervention randomized trials of at least 6 months' duration that examined the effect of diet therapy on CHD events and lipid levels. The median duration was 5 years. The interventions did not reduce total mortality (OR=0.97; 95% CI=0.92 to 1.02), CHD mortality (OR=0.96; 95% CI=0.89 to 1.04), or nonfatal MIs (OR=1.0; 95% CI=0.92 to 1.07). The net effect on serum cholesterol was a reduction of 5.4 mg/dL.

**Effect of diet therapy in reducing total cholesterol.** It is clear that alterations in diet can affect cholesterol levels. A systematic review of studies conducted on metabolic wards found that dietary therapy can produce short-term TC decreases of 10% to 20% when patients are fed a controlled low-fat diet.<sup>43</sup> However, the ability of outpatient dietary interventions to produce sustained reductions in TC is less clear.<sup>44</sup> Tang et al.<sup>45</sup> performed a meta-analysis of single intervention dietary trials conducted among free-living adults and published before 1996. Trials of patients with known CHD and trials conducted in non-primary-care settings were included; trials of specific dietary supplements (e.g., oat bran, garlic) and multiple risk factor trials were excluded. For trials of at least 6 months' duration, the mean reduction in cholesterol at 12 months was 5.3%. The subset of studies using the American Heart Association Step I diet, advocated as the first intervention for patients with no previous CHD, produced an average reduction of 3.0%. Brunner et al.<sup>46</sup> found a similar result (mean reduction of 3.7%) in their meta-analysis of 17 studies. We identified a subset of six studies that specifically examined the effect of diet therapy provided in primary care settings. They found mean TC decreases of 2% to 3%.<sup>47-54</sup>

**Effect of learning one's cholesterol level on the effectiveness of diet therapy.** A proposed rationale for screening for lipid disorders, particularly in young adults, has been that knowledge of one's cholesterol level may improve adherence to dietary advice and may increase its effect on lipid levels. Four trials published between 1992 and 1998 examined the effect of learning one's cholesterol level on the effectiveness of dietary therapy to lower TC.<sup>55-58</sup> In three studies, subjects were volunteers recruited from work sites; in the fourth, subjects were patients in a British primary care clinic. In



three trials, subjects learning their cholesterol level had no net improvement in TC with dietary therapy compared with subjects who were not given their results. In the trial by Elton et al.,<sup>55</sup> subjects with high cholesterol (mean cholesterol 277 mg/dL) on initial screening had modest TC reductions with feedback compared with controls (3.9% net reduction), but patients with more modest levels did not.

**Summary of diet therapy effects.** To date, diet therapy has not been demonstrated to reduce CHD events in free-living primary prevention populations.<sup>42</sup> Controlled studies have generally achieved only modest long-term reductions in TC (3% to 6% for trials longer than 6 months), despite relatively intensive interventions. The small cholesterol reductions in primary prevention appear to be a result of incomplete adherence.<sup>45</sup> Data are insufficient to determine in advance which patients are most likely to achieve and maintain important reductions in cholesterol. Knowledge of one's cholesterol level does not appear to affect the overall effect of dietary therapy, although people with elevated cholesterol may be slightly better able to reduce their total cholesterol.

### Effectiveness of Exercise

Observational epidemiologic studies have found that people who are physically active have lower rates of CHD than people who are inactive.<sup>58</sup> Whether these findings can be translated into successful and feasible interventions to lower CHD risk is not clear; no trials of exercise done in primary prevention settings have found decreased CHD events among those assigned to exercise.

Many studies have examined the effect of exercise on CHD risk factors, including lipid disorders. A meta-analysis of 95 studies found that subjects assigned to exercise had TC levels after intervention that were 7 mg/dL to 13 mg/dL (3% to 6%) lower than controls.<sup>59</sup> The larger reductions occurred among patients who were able to lose weight; the smaller reductions occurred among those with no weight change. Those reporting weight gain had a small (3 mg/dL), statistically nonsignificant increase in TC. HDL cholesterol levels increased by an average of 2 mg/dL and were not affected by the amount of weight loss.

Exercise interventions have not been adequately evaluated as a means of reducing CHD events in primary prevention. They do not appear to have a large effect on lipid levels, although some studies employing rigorous activity prescriptions and producing weight loss have shown changes in lipid profiles that may be clinically meaningful. These programs, however, have been difficult to implement widely.

## Discussion

### Middle-Aged Men

The evidence in favor of screening and treatment of lipid disorders is strongest for middle-aged men (aged 45 to 70 years), particularly those of European ancestry, with elevated levels of LDL-C and moderate to high short-term risk of CHD events. The populations in these studies appear similar to those found in primary care practice. The probability of finding abnormal lipids and sufficient CHD risk to warrant treatment is high in this age group.

### Postmenopausal Women

AFCAPS was the only primary prevention trial that enrolled postmenopausal women. The women in AFCAPS were older: mean age of 63 years compared with 58 years for men. These women appeared to have a relative risk reduction for first CHD events similar to that for men, but they had fewer CHD deaths. The trial was not designed with sufficient power to examine total mortality effects for either men or women.<sup>37</sup>

Evidence from secondary prevention trials suggests that women will achieve reductions in total CHD events similar to those for men if they have similar baseline levels of risk. In the short term (up to 5 years), these total reductions will take the form primarily of fewer nonfatal MIs rather than fewer CHD deaths.<sup>60-63</sup> The effect on total mortality for women remains unclear: the Scandinavian Simvastatin Survival Study of secondary prevention found a relative risk of 1.16 (95% CI=0.68 to 1.99) for total mortality.<sup>62</sup> Data on total mortality for women have not yet been published from the other major trials of secondary prevention or primary prevention, and we have insufficient long-term data to measure the longitudinal effects of CHD event reduction on total and CHD mortality.

Thus, reducing lipid levels appears to be effective in reducing CHD events in postmenopausal women with abnormal lipids, but the magnitude of that effect appears smaller than that among men, at least in part because middle-aged women with lipid disorders are at lower absolute risk than middle-aged men. Accurate global risk assessment is important, because women tend to have higher TC levels but lower CHD risk than men of similar ages.

### Elderly Men and Women

Few elderly people (older than age 70 years) have been studied in primary prevention settings. Some epidemiologic studies have found that the relative risk of elevated cholesterol is attenuated in elderly patients. However, older people generally have high levels of absolute risk of CHD events, so lipid-lowering therapy is likely to be effective in these patients, assuming that their risk of competing causes of mortality is not too

high (i.e., that their life expectancy is sufficient to allow them to realize the benefits of therapy). Data from secondary prevention trials suggest that lipid lowering is as effective, or more effective, in older patients than in younger patients.<sup>11,63,64</sup>

## Young Adults

Whether screening for and treating lipid disorders in men aged 20 to 35 years and women aged 20 to 45 years yield important benefits is controversial.<sup>65,66</sup>

**Screening to identify and treat young adults at high immediate risk of CHD.** Young adults in general are at very low absolute risk of CHD events over the short-to-medium term (5 to 10 years). Even if treatment of lipid disorders in young adults reduces risk to the same or greater extent that it does in middle-aged men, the benefits in terms of absolute risk reduction over that time period will be very small.

Screening has been considered as a means of identifying and treating the small number of patients with extreme lipid levels who would not be recognized as being at risk of CHD events on the basis of a family history of early CHD events, family history of lipid abnormalities, or the presence of two or more other CHD risk factors. If unrecognized, some patients, mainly those with extreme lipid levels from genetic lipid disorders, may have CHD events before universal screening begins at age 35 or 45 years. The actual number of people who would fit in this category has not been well quantified but appears to be small. About 10% of men aged 20 to 34 years and 7% of women aged 20 to 44 years have LDL-C levels greater than 160 mg/dL.<sup>8</sup> The proportion that would qualify for screening because of having diabetes, a family history of premature CHD or familial hyperlipidemia, or multiple other risk factors has not been reported.<sup>17</sup>

### **Treating young adults to reduce long-term CHD risk.**

The crucial issue for deciding whether to screen younger adults is the incremental effectiveness of earlier treatment compared with delayed treatment for preventing CHD events in middle age. High TC levels in young adults are clearly predictive of higher rates of future CHD events. Data from a cohort of Johns Hopkins University medical students show that the relative risk of future CHD events and CHD mortality among men aged 20 to 25 years who had cholesterol levels above the 75th percentile was two times greater than the relative risk among those at the 25th percentile.<sup>67</sup>

Ideally, we would like to have information from a randomized controlled trial that examined the effect of early screening and treatment (compared with delayed screening and treatment) on CHD events and mortality. Because such a study does not exist and is unlikely to be performed owing to the long period of follow-up

that would be required (30 years), we must use indirect data to examine the magnitude of the potential incremental benefit from early screening and treatment.

Such indirect evidence is presented in a systematic review and meta-analysis by Law et al.<sup>68</sup> These investigators estimated the magnitude of the risk attributable to lipid disorders at different ages from observational cohort data. They then examined the risk for CHD in people treated for lipid disorders. After 5 to 10 years of treatment, the CHD risk for people who had their cholesterol lowered to a given level was similar to the CHD risk for people whose cholesterol had been at that lower level throughout their lives. They concluded that the majority (about 80%) of the risk reduction from lipid therapy can be achieved after 5 to 10 years of treatment; the incremental benefit from beginning therapy earlier is, therefore, relatively small. In a similar meta-analysis and meta-regression, Fager and Wiklund<sup>69</sup> reached the same conclusion.

With the use of the Law et al.<sup>68</sup> results, one might conclude that the preferred approach is to delay screening and treatment until about 5 to 10 years before the time that the absolute risk of CHD events begins to rise to meaningful absolute levels. This approach will theoretically minimize the potential adverse effects of long-term therapy and unnecessary drug costs without reducing benefit substantially. Others have challenged this interpretation and its implications, based on data from angiographic and autopsy studies and the higher attributable risk from cholesterol in younger people.<sup>66</sup>

## Special Populations

The clinical approach to screening and treating African Americans does not appear to differ materially from the approach to Caucasian populations. Average TC levels do not differ meaningfully between African-American and Caucasian populations, although HDL-C levels are higher for African Americans. Although trial data on African Americans are scarce, there is no good reason to believe that African Americans will respond differently than European Americans at any given level of risk. Harms of drug therapy do not appear to be increased.<sup>70</sup> However, formulas to calculate CHD risk<sup>7,32</sup> have been developed mostly in patients of European descent and may not generalize well to African Americans. Fewer data exist about the prevalence of lipid disorders and the benefits of screening and treatment among Native-American, African-American, and Hispanic populations. Further research and wider recruitment in clinical trials would enable investigators to develop better estimates of the benefits of screening and treatment in people of non-European descent.

## Future Research

The effectiveness of screening to reduce CHD is well established in men of European ancestry. Data for minorities, women, and older and younger adults, however, remain scarce, and more research on the benefits of screening and treatment in these populations is warranted. Of high priority is the efficacy of lipid therapy in men of non-European descent and in all women, the elderly, and younger people with multiple risk factors or with diabetes. The effect of screening on stroke, although clear in secondary prevention trials, remains unproven in primary prevention. Strategies to improve dietary interventions and more information on the effectiveness of dietary therapy are needed. The optimal frequency of screening and the age at which screening should be initiated or discontinued are both unsettled issues, and further data on improving the accuracy and efficiency of different screening strategies are needed as well. Because clinicians require practical approaches to assessing the risk of individual patients, additional research in this arena is also called for. Although hypertriglyceridemia is a risk factor for CHD, the importance of screening for this condition and the effectiveness of interventions to control it remain to be established; the role of novel risk factors such as homocysteine or C-reactive protein also deserve attention. Finally, analysis of the optimal sequencing and combinations of different efforts to decrease CHD events (e.g., aspirin, treatment of hypertension, smoking cessation activities) would help to clarify the timing and role of lipid-lowering therapy.

## Summary: Whom to Screen and Treat

The evidence is good that identifying middle-aged men with lipid disorders and treating those with sufficient CHD risk reduces CHD events and CHD mortality. Treating those at highest risk (greater than 1.5% risk of CHD events per year) may also reduce total mortality. Screening middle-aged women, the elderly, and young adults with multiple risk factors and treating those at increased risk also appears to reduce CHD events. The balance of benefits and harms from screening and treating young adults is not clear from the available evidence but is unlikely to be large compared with starting at age 35 years in men and age 45 years in women.

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This article is based on a more comprehensive Systematic Evidence Review which is available online at [www.ahrq.gov/clinic/prevenix.htm](http://www.ahrq.gov/clinic/prevenix.htm). The systematic evidence review on which this article is based was reviewed by content experts, including Scott M. Grundy, MD, PhD, Southwestern Medical Center at Dallas; Robert Baron, MD, University of California, San Francisco; Matthew Gilman, MD, Harvard Medical School and Harvard Pilgrim Health Care; and Thomas Newman, MD, University of California, San Francisco; professional organizations, including the American Academy of Family Physicians, the American Academy of Pediatrics, the American College of Obstetricians and Gynecologists, the American College of Physicians/American Society of Internal Medicine, the American College of Preventive Medicine, and the Canadian Task Force on Preventive Health Care; and U.S. Public Health Service agencies, including the Centers for Disease Control and Prevention, National Heart, Lung and Blood Institute, the National Institutes of Health; and the Veterans' Administration. Review by these individuals and groups does not necessarily imply endorsement of this article or of the accompanying recommendations of the U.S. Preventive Services Task Force.

The authors of this article are responsible for its contents, including any clinical or treatment recommendations. No statement in this article should be construed as an official position of the Agency for Healthcare Research and Quality, the U.S. Department of Health and Human Services, the Department of Defense, or Merck and Co.

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