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Systematic Evidence Review
Number 4

Screening for Lipid Disorders

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Preface

The Agency for Healthcare Research and Quality (AHRQ) sponsors the development of Systematic Evidence Reviews (SERs) through its Evidence-based Practice Program. With guidance from the third U.S. Preventive Services Task Force* (USPSTF) and input from Federal partners and primary care specialty societies, two Evidence-based Practice Centers—one at the Oregon Health Sciences University and the other at Research Triangle Institute-University of North Carolina—systematically review the evidence of the effectiveness of a wide range of clinical preventive services, including screening, counseling, immunizations, and chemoprevention, in the primary care setting. The SERs—comprehensive reviews of the scientific evidence on the effectiveness of particular clinical preventive services--serve as the foundation for the recommendations of the third USPSTF, which provide age- and risk-factor-specific recommendations for the delivery of these services in the primary care setting. Details of the process of identifying and evaluating relevant scientific evidence are described in the "Methods" section of each SER.

The SERs document the evidence regarding the benefits, limitations, and cost-effectiveness of a broad range of clinical preventive services and will help to further awareness, delivery, and coverage of preventive care as an integral part of quality primary health care.

AHRQ also disseminates the SERs on the AHRQ Web site (http://www.ahrq.gov/uspstfix.htm) and disseminates summaries of the evidence (summaries of the SERs) and recommendations of the third USPSTF in print and on the Web. These are available through the AHRQ Web site (http://www.ahrgq.gov/uspstfix.htm), through the National Guideline Clearinghouse (http://www.ncg.gov), and in print through the AHRQ Publications Clearinghouse (1-800-358-9295).

We welcome written comments on this SER. Comments may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 6010 Executive Blvd., Suite 300, Rockville, MD 20852.

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* The USPSTF is an independent panel of experts in primary care and prevention first convened by the U.S. Public Health Service in 1984. The USPSTF systematically reviews the evidence on the effectiveness of providing clinical preventive services--including screening, counseling, immunization, and chemoprevention--in the primary care setting. AHRQ convened the third USPSTF in November 1998 to update existing Task Force recommendations and to address new topics.

Structured Abstract

Context

Lipid disorders are an important risk factor for coronary heart disease (CHD). Screening and treatment of lipid disorders in persons at high risk for future CHD events have gained wide acceptance, especially for patients with known CHD, but the proper role in persons 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, adolescents, and children for the US 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 January1994 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 ensure completeness.

Study Selection

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 endpoints, including total mortality, CHD mortality, or nonfatal myocardial infarctions. We also included randomized trials of diet or exercise therapy that measured change only in total cholesterol. To examine the question of screening, we included articles that addressed the epidemiology and natural history of lipid levels and lipid disorders or 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.

Data Extraction

We extracted the following data from the included articles: demographic details about subjects; inclusion and exclusion criteria; and study design, duration, interventions, and outcome measures. We evaluated the internal and external validity of each article and judged the overall quality of evidence by examining aggregate internal and external validity and coherence of the results.

Data Synthesis

There is strong, direct evidence that drug therapy reduces CHD events and CHD mortality in middle-aged men (35 to 70 years of age) with abnormal lipids and a potential risk of CHD events greater than 1%per year. Drug therapy may also reduce total mortality in patients at higher risk (greater than 1.5% per year). Less direct evidence suggests that drug therapy is also effective in other adults, including older men (over the age of 70 years) and middle-aged and older women (ages 45 years and older) with similar levels of risk. 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 small reductions or no effect.

Screening middle-aged and older men and women for lipid disorders can accurately identify persons at increased CHD risk who may benefit from therapy. The evidence is insufficient about benefits and harms of screening and treating persons at low absolute risk, including most men under 35 years of age, women under 45 years, and children and adolescents. To identify accurately persons with abnormal lipids, at least 2 measurements of total cholesterol and high-density lipoprotein cholesterol (HDL) are required. The role of measuring triglycerides and the optimal screening interval are unclear from the available evidence.

Conclusion

Strong evidence shows the effectiveness of therapy for lipid disorders in middle-aged men; indirect evidence shows effectiveness in older men and women of sufficient risk. Screening for lipid disorders with total cholesterol and HDL and performing a global assessment of CHD risk can accurately identify those at sufficient risk who can benefit from treatment.

Key Word: Cardiovascular diseases – cholesterol – hyperlipidemia - preventive health services - evidence-based medicine – MEDLINE – methods – lipids - mass screening – mortality - drug therapy

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Chapter 1. Introduction

Background

Burden of Suffering

Certain patterns of blood lipids —including elevated total cholesterol (TC), elevated low-density lipoprotein cholesterol (LDL), and low levels of high-density lipoprotein (HDL) cholesterol—are important risk factors for coronary heart disease (CHD).[1-3] 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.[4] The age-adjusted annual death rate for CHD is 100 per 100,000 persons overall and 140 per 100,000 persons among African Americans.[5,6] The lifetime risk of having a CHD event, calculated at age 40, is estimated to be 49 % for men and 32 % for women in the United States.[7] CHD accounted for $78 billion in health care costs in 1995.[4]

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 to 1994 show that 17.5% of US men and 20% of US women 20 to 74 years of age had TC levels greater than 240 mg/dL. The mean TC was 202 mg/dL for men and 204 mg/dL for women.[5] Approximately 6% of US men have a TC less than 200 mg/dL and an HDL cholesterol less than 35 mg/dL; 5% have a TC of 200 to –239 mg/dL and an HDL less than 35 mg/dL.[8] Lipid measurements performed in the second phase of the National Health and Nutrition Examination Survey (NHANES III) between 1991 and 1994 found that 28% of white men ages 35 to 65 years and 12% of white women ages 45 to 65 years had TC:HDL cholesterol ratios of greater than 6:1.[9] Elevated TC (greater than 200 mg/dL) was responsible for 27% of CHD events in men and 34% in women in the Framingham cohort.[10]

Data from the screening portion of the Multiple Risk Factor Intervention Trial (MRFIT),[2] the Framingham study,[1] and an overview of observational studies[9] show, for middle-aged men and women, a continuous graded relationship between TC and CHD. Elevated TC confers less relative risk in the elderly. However, the absolute risk is higher for the elderly, and thus the total number of potentially preventable CHD events remains high.[11] The relationship between lipid disorders and CHD is examined in more depth in Chapter 3.'s section on screening.

Health Care Interventions

The large burden of disease from CHD and strong epidemiologic associations between CHD and abnormal lipid levels have prompted efforts to modify or reduce the risk of CHD events by treating lipid disorders. In this report, we examine the evidence concerning the benefits and harms of drug, diet, and exercise therapy in treating lipid disorders and reducing the risk of CHD events in patients with lipid disorders. The

underlying goal of screening and therapy for lipid disorders is to reduce the burden of illness from CHD. Thus, other means of reducing CHD, such as hypertension prevention and control, smoking prevention and cessation, and possibly chemoprophylaxis with aspirin, must be considered along with treatment of lipid disorders in patients at risk for CHD.

This review focuses on interventions that are delivered to individuals or small groups. Population-level interventions, such as changes in the fat content of foods, are not within the scope of this guide; they are addressed by the Centers for Disease Control and Prevention. In some cases, however, these population-level interventions may act as the de facto comparators for individual interventions such as dietary advice therapy. Some of the interventions considered here, such as dietary advice or exercise therapy, may also have beneficial effects on CHD or other health problems that are mediated through means other than the modification of lipid disorders. The CDC Task Force is also considering these effects. Because of the important health impact of CHD and the role of lipid disorders in its development, routine universal or targeted screening for lipid disorders has been advocated.[3,12] Data from the Behavioral Risk Factor Surveillance Survey show that measurement of serum cholesterol has become a common practice: 74% of adults report that they have had their cholesterol level measured, and 66% report that they have done so within the past year. The likelihood of having had one's cholesterol measured within 5 years increases with age: 40% of adults ages 18 to 24 years have been checked, compared with 66% of those 35 to 44 years and 87% of those 65 years and older. Overall, 29% of adults report that their providers have told them that they have elevated cholesterol levels.[5]

Prior Recommendations

Currently, little controversy exists about the benefit of testing for lipid abnormalities among patients with known CHD and treating them appropriately with drug and diet therapy (secondary prevention). The Scandinavian Simvastatin Survival Study (4S), a large trial of middle-aged men and women with CHD and elevated levels of LDL cholesterol, found that treatment reduced the risk of CHD events by 34% and the risk of CHD death by 42% .[13] Total mortality was reduced in men but not in women.[14] More recent trials conducted in men and women (including older adults 65 to 75 years of age) with modest elevations in LDL cholesterol,[15-17] or low levels of HDL cholesterol,[18] have also demonstrated a benefit from drug treatment for lipid disorders after CHD is present. However, many studies have documented low rates of treatment for patients with known CHD.[19]

The decision about who should be screened and treated for lipid disorders in the absence of known CHD remains somewhat controversial, especially for those adults and children at low short-term risk of CHD events. The second edition of the *Guide to Clinical Preventive Services* from the US Preventive Services Task Force (USPSTF) gave a "B" recommendation to "periodic" screening for high TC in men 35 to 65 years of age and women 45 to 65 years of age.[12] The USPSTF at that time found insufficient evidence to recommend for or against TC screening in asymptomatic adults over 65 years of age, young adults, adolescents, and children. They also found insufficient evidence to recommend for or against screening for other lipid abnormalities such as low HDL or elevated triglycerides.

The National Cholesterol Education Program Adult Treatment Panel II (NCEP) guidelines recommended screening all adults 20 years of age and older with serum TC and with serum HDL "if accurate results are available" every 5 years.[3] The American College of Physicians found "periodic" screening for men 35 to 65 years of age and women 45 to 65

years of age to be "appropriate but not mandatory." Screening young men and women was recommended only where the history or physical exam suggested a familial disorder or there were at least 2 other CHD risk factors.[20,21] The Canadian Task Force on Preventive Health Care in 1994 recommended "case-finding" in all men ages 30 to 59 years who present to their health care providers and clinical judgment in other cases.[22] The American Diabetes Association recommends screening all adult diabetics yearly with TC, LDL, HDL, and triglycerides.[23]

The NCEP Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents[24] and the American Academy of Pediatrics Committee on Nutrition Policy Statement on Cholesterol in Children[25] recommended 2 approaches: (1) a low-fat diet in all healthy children over the age of 2 years and adolescents, equivalent to the American Heart Association Step One diet; and (2) selective screening (based on family history of elevated cholesterol or premature CHD) and treatment of children who are at highest risk for the development of accelerated atherosclerosis in early adult life.

Analytic Framework and Key Questions

The RTI-UNC Evidence-based Practice Centers, together with members of the third USPSTF and other clinical and methodologic experts, sought to clarify issues concerning screening for and treatment of lipid disorders by performing a systematic review of the relevant scientific literature on these topics. This systematic evidence review (SER) specifically updates Chapter 2. (pages 15–38) of the second *Guide to Clinical Preventive Services* produced in 1996 by the second USPSTF.[12] A shorter version of this review appeared in the *American Journal of Preventive Medicine* in early 2001.[26]

Analytic Framework

This SER examines the issue of screening for lipid disorders among patients with no previous history of recognized CHD—that is, primary prevention. Figure 1 depicts a comprehensive analytic framework for this topic.

The analytic framework begins with population(s) of persons without known CHD and moves through screening to identify persons with lipid disorders that put them at increased risk of CHD, to treatment with drugs, diet, exercise, or combinations of the three; change in abnormal lipid levels; and finally to outcomes such as reduced CHD events or deaths. Apart from the key clinical questions to be addressed (see following), this analytic framework also notes 2 points at which adverse effects or harms may arise: as sequelae to screening (eg, labeling) and as consequences of treatment (eg, direct harms from therapy or economic costs).

Key Questions

No trials have directly examined the (implied) overarching question of whether screening for lipid disorders among asymptomatic persons leads to improvement in CHD mortality or morbidity. The decision to screen for lipid disorders in such populations is, therefore, based on data that address 2 intermediate steps (ie, linkages in the analytic framework): the effectiveness of screening to detect lipid disorders and the effectiveness of

treating lipid disorders to reduce CHD events. Three key questions arise from this framework.

Key Question No. 1. Will treatment with *drug therapy* of patients (similar to those who would be identified by screening) without known CHD but with "abnormal" lipid levels improve outcomes compared with no treatment?

Key Question No. 2. Will treatment with *diet or exercise* therapy of patients (similar to those who would be identified by screening) without known CHD but with "abnormal" lipid levels improve outcomes compared with no treatment?

Key Question No. 3. Is there a reliable, accurate, acceptable, and feasible screening test (or tests) that can be used to detect lipid disorders? If so, who should be screened, and how often should screening be performed?

Apart from these core issues, we address issues relating to short-, medium-, and long-term harms of identifying patients with lipid disorders and treating them with drugs and diet therapy. In each case, the harms are considered along with the benefits to allow better judgment of the net effect of screening and therapy.

The drug therapies for Key Question No. 1 are compared with placebo pills. Clinically, the strategy of drug therapy for primary prevention can be considered to be a comparison against initiation of drug therapy only after CHD is known to be present (secondary prevention). For Key Question No. 2, most of the trials of diet and exercise therapy usually compare the intervention with a control group that receives minimal or no intervention. In some cases, these comparisons may be affected by ongoing secular trends or population-level interventions common to each group.

Organization of This Systematic Evidence Review

Chapter 2. provides an overview of our methods for producing the SER. Chapter 3. presents the results of our literature search and synthesis organized by the 3 Key Questions. These results, and their ramifications for future research and the general limitations to this literature, are discussed further in Chapter 4. Tables and figures will be found at the end of each chapter where they are first introduced. Appendices 1 and 2 provide additional information on our methods and the system for grading articles and rating the overall strength of the evidence; and Appendix 3 contains the evidence tables developed from the literature synthesis.

Chapter 2. Methods

This chapter of the systematic evidence review (SER) documents the procedures that the RTI-UNC Evidence-based Practice Center (EPC) used to develop this report on screening for lipid disorders among adults and children. We document the literature search (eg, inclusion and exclusion criteria, relevant Medical Subject Headings [MeSH terms]) and briefly describe the procedures followed in abstracting data from included articles, developing evidence tables, analyzing the literature, and subjecting the draft to a robust peer review process. The EPC followed procedures established by the USPSTF Methods Work Group.[27]

In all these steps, EPC staff collaborated with 2 members of the US Preventive Services Task Force (USPSTF) who acted as liaisons for this topic; they are coauthors of this SER. The collaboration took place chiefly by electronic mail and numerous conference calls. Steps in the development of this SER were presented at USPSTF meetings in February, May, and September 1999 and February 2000 where the EPC staff and Task Force liaisons also were able to discuss the analytic framework and key clinical questions (linkages), literature search strategy, results, and implications of the findings.

Literature Search Strategy

Inclusion/Exclusion Criteria

To identify articles relevant to the questions of screening and treatment of lipid disorders, the EPC staff searched the MEDLINE database from 1994 to December 1999. The searches focused on 4 main areas: drug therapy for lipid disorders, diet and exercise therapy for lipid disorders, screening, and harms and adverse events. Drug and diet or exercise treatments correspond to Key Question Nos. 1 and 2 in the analytic framework; screening corresponds to Key Question No. 3.

We prospectively established inclusion and exclusion criteria for all searches. Table 1 presents the overall and specific criteria for each of the 4 main searches (on drug therapy, diet therapy, screening, and harms and adverse effects). Table 2 documents the results of the 4 main literature searches.

We supplemented our searches with a check of the Cochrane database of controlled trials to identify important articles not included in MEDLINE.[28] We used the second edition of the USPSTF *Guide to Clinical Preventive Services*[12]—as well as systematic reviews, meta-analyses, and evidence-based practice guidelines that addressed screening and treatment of lipid disorders—to identify key articles that were published before 1994. We also identified and used several large, prospective observational studies to answer contextual questions about screening. Finally, we hand-searched bibliographies of included articles to detect any important articles that may have been missed in the other steps. Table 2 documents the results of the 4 main literature searches.

Literature Reviewed

Two EPC staff independently reviewed the titles and abstracts of the articles identified by the literature searches and excluded ones that they agreed clearly did not meet eligibility criteria. When the initial reviewers disagreed or were uncertain, the articles were carried forward to the next review stage, in which the EPC team members reviewed the full articles and made a final decision about inclusion or exclusion by consensus. Table 3 summarizes the results of the literature searches and reviews of abstracts. The literature searches concerning the 3 key clinical questions (linkages in the analytic framework) are described in more detail just following, as is the specific search strategy to identify adverse events.

Drug Interventions

With respect to drug therapies (Key Question No. 1), we examined randomized trials of at least 1-year duration that used pharmacologic agents and that reported coronary heart disease (CHD) outcomes. We specifically excluded estrogen, which will be considered in a separate review, and we chose not to examine dietary supplements. Neither estrogen nor dietary supplements have been studied in trials that would meet our criteria, however. We identified 475 articles from our main literature searches and added 41 other publications through supplemental searches. Of these 516 articles, we rejected 448 at the stage of reviewing abstracts and selected 68 for full article review. Of these 68, we found that 34 examined trials of secondary prevention and were thus excluded.

Two abstractors reviewed each of the 34 remaining articles and assessed them for appropriateness as defined in the eligibility criteria; we excluded 12 articles at this stage (these are documented in Appendix 1, Table 1.1).[29-41] The remaining 22 articles were then either fully abstracted for the evidence tables (4 articles) or used for supplementary information (18 articles). We collected standard information on the study design, intervention, and results; in addition, we rated the quality of the articles based on their internal and external validity. Internal validity was assessed with respect to 4 markers: adequate inclusion criteria, adequate randomization and concealment, nondifferential loss to follow-up, and use of intention-to-treat analysis (see Appendix 2).[27]

Dietary and Exercise Interventions

For Key Question No. 2 about the use of dietary and exercise therapy for lipid disorders, our initial literature searches identified 300 articles from the MEDLINE database for the years 1995 to 1999 (Table 3). We added 215 articles through supplementary searches, including 108 about the effects of exercise on lipids (based on a request from the full USPSTF). In our initial review of the abstracts, we excluded 425 articles that did not meet eligibility criteria, leaving 90 articles for full review. Two abstractors reviewed each of the remaining articles and assessed them for appropriateness as defined in the eligibility criteria; we excluded 51 articles at this stage (see Appendix 1, Table 1.2).[42-90] The final 39 articles concerning dietary interventions and lipids were then either fully abstracted (14 articles) or used to provide supplementary information (25 publications). The diet and exercise searches

included articles that measured changes in lipid levels only because these interventions are often considered for patients such as children or young adults who have low short-term risk for CHD events. We also chose not to examine the effect of particular dietary supplements such as garlic or oat bran.

In addition to the elements abstracted for drug therapy, we also rated the intensity of the dietary intervention as low, medium, or high to aid in evaluation of generalizability. Low-intensity interventions took place in 1 session less than 30 minutes in duration and did not require ongoing data collection by the patient (such as a food diary); high-intensity interventions required multiple sessions (6 or more) and considerable data collection and recordkeeping; and medium-intensity interventions fell in between. We assessed study quality in terms of internal validity according to the same criteria used for drug therapy.

Screening Literature

For Key Question No. 3, the subject headings of mass screening, diagnostic use, and sensitivity and specificity were crossed with cholesterol and hyperlipidemia, generating 177 references from 1994 to 1999. We evaluated these abstracts as well as another 40 from our supplemental searching. On the basis of review at this stage, we excluded 150 articles and retained 67 that appeared to be appropriate and useful. We then used these 67 articles to examine the accuracy, reliability, feasibility, and acceptability of screening.

Harms and Adverse Events

At the initial literature search stage, we identified a possible 133 articles specifically concerning this topic; to this set we added 140 articles from various supplemental searches. Of the 273 abstracts reviewed, we excluded 181 items, leaving 92 publications for full review of the entire article. After evaluation of the full articles, we retained 25 and used them to create sections of the results associated with drug therapy, diet therapy, and screening; information in 21 of these 25 articles appears in specific harms tables.

Literature Synthesis and Preparation of Systematic Evidence Review

Data Abstraction and Development of Evidence Tables

We entered study design and outcomes data from the articles on drug and diet treatment into an electronic database (Microsoft Access[91]); we constructed evidence tables in Microsoft Excel and Word.[92,93]

To characterize the quality of the included studies, we rated the internal and external validity for each article in the evidence tables using criteria developed by the USPSTF Methods Work Group. We then rated the aggregate internal validity and external validity as well as the coherence (agreement of the results of the individual studies) for each of the Key Questions defined in the analytic framework. The quality rating scales developed by the Methods Work Group are included in Appendix 2.[27]

Meta-analysis

To better estimate the effects of drug therapy, we performed a quantitative meta-analysis under both random and fixed effects models using RevMan software.[94] The methods and results of this analysis are briefly described here and documented more fully in a separate paper.[95] We examined the effect of drug therapy on the incidence of CHD events (nonfatal myocardial infarction and CHD deaths combined), on the incidence of CHD deaths alone, and on total mortality. We represented the results as summary odds ratios with 95% confidence intervals and examined the results for heterogeneity visually and using tests of homogeneity. We also performed subanalyses that measured the effect of the statin drugs alone, which included 4 studies that could not be clearly included or excluded based on our prospective eligibility criteria.

Peer Review Process

On completion of a draft SER, we conducted a broad-based, external review of the draft. Among the outside reviewers were representatives of key primary care professional associations that have formal liaison ties to the USPSTF, a representative of the Canadian Task Force on Preventive Health Care, representatives of other professional societies, clinical experts in the area of cardiovascular disease and lipid disorders, members of the staff of the Agency for Healthcare Research and Quality, and representatives of other relevant federal agencies. The names and affiliations of all peer reviewers are listed on page iv. We took account of all substantive comments from reviewers in developing the final version of this SER.

Chapter 3. Results

In this chapter, we present the results of our systematic evidence review (SER). The results are organized according to the Key Questions defined in our analytic framework (Chapter 1., Figure 1). The Key Questions that constitute the major headings of this chapter correspond to the major linkages of the analytic framework. We first address the questions of whether either drug therapy or diet therapy is effective in reducing the morbidity and mortality from coronary heart disease (CHD) (ie, Key Question Nos. 1 and 2). We then examine different strategies for identifying patients with lipid disorders who are amenable to treatment efforts to reduce their risk for CHD events (Key Question No. 3).

Key Question No. 1: Drug Therapy for Lipid Disorders

We identified 4 trials of drug therapy for lipid disorders in the primary prevention of CHD (see Appendix 3, Evidence Table 1). These include 2 older (pre-1995) trials: 1 using the bile-acid binding resin cholestyramine (Lipid Research Clinical trial [LRC])[96] and 1 (Helsinki Heart Study [HHS]) using the fibric acid derivative gemfibrozil.[97] The other 2 trials were published either during or after 1995 and used HMG co-A reductase inhibitors or "statin" drugs: the West of Scotland Coronary Prevention Study (WOSCOPS) used pravastatin,[98] and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS-TexCAPS, hereafter TexCAPS) used lovastatin.[99]

We identified 4 additional trials that could not be definitively included or excluded based on our eligibility criteria. The first, an older trial of clofibrate, was not included because clofibrate is not regularly used in the United States to treat patients with lipid disorders owing to concerns about its safety.[41] The 3 other articles used ultrasound measurements of carotid or femoral artery atherosclerosis to determine eligibility and as main outcomes.[100-102]

We excluded several other studies that included mixed populations of subjects with and without previously diagnosed CHD because the results for the 2 groups could not be distinguished from one another. (See Appendix 1, Table 1-1 for more details.)

Effects of Drug Therapy in Adults

CHD Events

Trial results. As documented in Evidence Table 1 (Appendix 3), the 4 included trials were conducted mainly among middle-aged men of European descent. The LRC, HHS, and WOSCOPS trials enrolled patients with elevated levels of total cholesterol (TC) and low-density lipoprotein (LDL) cholesterol, whereas the TexCAPS study included men and women with TC levels close to the United States average and low levels of high-density lipoprotein (HDL) cholesterol. The trials ranged from 5 to 7 years in duration, and 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. Few diabetics were enrolled in any of the 4 trials.

The 2 trials employing statin drugs (WOSCOPS and TexCAPS) had larger initial decreases in TC (20% and 18%) than the LRC or HHS (8.5% and 11%) (Table 4). The relative risk reductions for CHD events were larger in the statin trials, supporting the observation that reduction in events appears proportional to the magnitude of reduction in TC. The relative risk reductions for CHD events ranged from 19% to 37%. Relative risk reductions for CHD mortality ranged from 20% to 28%. None of the trials was designed with sufficient power to address the question of whether drug therapy reduces total mortality in primary prevention settings.

The results of the 2 new trials (WOSCOPS and TexCAPS) have potentially important implications for screening and therapy. We describe them in increased detail here to determine the degree to which they can be generalized to the population at large.

WOSCOPS randomized 6,600 middle-aged men (ages 45 to 64 years) with LDL cholesterol between 155 and 232 mg/dL (4-6 mmol/L) to either pravastatin 40 mg each day or placebo. Approximately 81,000 men were screened over 3 visits to identify 6,595 who met the entry criteria and agreed to participate. The randomized patients were similar to the initial 81,000-man cohort with respect to age, blood pressure, smoking status, and alcohol consumption. Mean body mass index was slightly higher in the randomized patients (26.1 versus 25.8), and the screened patients were more likely to have had a history of angina or previous myocardial infarction (MI) (11.6% versus 4.6%). The trial participants had the following CHD risk factors: 39% were smokers, 1.2% were diabetic, 5.7% had a family history of early CHD, and 11% were currently taking medication for hypertension. Few participants were taking aspirin (2.9%) or beta blockers (7.2%).[103] Unlike the other studies, patients with angina but no previous MI who had not been symptomatic or hospitalized within the past year were not excluded and accounted for 5% of the study group. Treatment with pravastatin was associated with reductions in CHD events (relative risk reduction [RRR], 31%; absolute risk reduction [ARR], 2.4%), in CHD mortality (RRR, 30%; ARR, 0.7%), and in total mortality (RRR, 22%; ARR, 0.9%.)

In the TexCAPS trial, 102,000 men and women were screened at 2 sites in Texas to identify potential participants in the trial. Potential participants underwent 4 pre-randomization visits over 14 weeks that included dietary advice using the American Heart Association Step One diet and also had to complete a 2-week placebo run-in period. Compliant, eligible subjects were then randomized to either lovastatin titrated to 20 to 40 mg per day or placebo.[104] The approximately 6,600 randomized subjects had a mean age of 58 years, 85% were men, and 89% self-reported their race as white. Few subjects were diabetic (2.5%), and only 17% were taking aspirin. Nearly 16% had a family history of early CHD, and 22% were hypertensive. Only 12.5% were current smokers.[99] No data are available to compare them with the cohort that had been screened for inclusion. Treatment with lovastatin reduced CHD events (RRR, 43%; ARR, 1.25%) but had no effect on CHD or total mortality.

Overall, the 4 included trials scored highly on our measures of aggregate internal validity, based on the strength of randomization, adequate concealment, intention-to-treat analysis, and the absence of differential dropouts or losses to follow-up. Their external validity was fair in the aggregate, based on the facts that they did not enroll sufficient women or persons of non-European descent and that 2 were conducted in Europe.

Meta-analysis

We performed meta-analyses to estimate better the effect of drug therapy on CHD events, CHD mortality, and total mortality. The full methods and results are reported in a separate publication.[95] The main results of the meta-analyses, reported as summary odds ratios (OR) with 95% confidence intervals (CI), are shown in Figures 2A-C, 3A-C, and 4A-C. We present the results here using a fixed effects model.

The combined results of the 4 main trials (Figures 2A-C) suggest that drug therapy decreases the relative risk of total CHD events (defined as the sum of nonfatal MI and deaths from CHD) by 30%. Drug therapy also reduces the relative risk of CHD death by 26%, with a 95% CI from 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 (OR, 0.91; 95% CI, 0.78, 1.07). However, the overall result may mask total mortality benefit in higher-risk patients. The WOSCOPS trial, which enrolled the patient population at highest risk (as measured by the event rate in the placebo arm), found a 22% relative reduction in total mortality with a borderline statistical significance. The absolute risk reduction, however, was modest (0.9% over 5 years). The other 3 trials clustered around the estimate of no effect for total mortality.

Hebert et al performed a meta-analysis of primary prevention trials of statin therapy before the completion of the TexCAPS trial.[105] They included WOSCOPS and 2 trials that had been designed to examine the effect of statin therapy on the size of ultrasound-measured atherosclerotic plaques in the femoral or carotid arteries; in 1 of these 2 trials, 10% of patients had a previous history of MI and thus were not included in our sample.[102] They found a 37% reduction in CHD mortality (OR, 0.63; 95% CI, 0.45, 0.89) and a significant 26% reduction in total mortality (OR, 0.74; 95% CI, 0.58, 0.95).

We recalculated the results of our meta-analysis to clarify 2 points: the effect of including the 4 articles that could not be definitively included or excluded and the effect of the statin drugs when considered alone.[41,101,102,106] Including the 4 additional studies (Figures 3A-C) did not have a large impact on the summary effect size for total CHD events (new summary OR, 0.79; 95% CI, 0.63, 1.00). This step did attenuate slightly the effect on CHD mortality (new summary OR, 0.79; 95% CI, 0.63, 1.00) but did not affect total mortality.

The statin drugs reduce cholesterol to a greater degree than older drugs. We performed another meta-analysis to determine if the effect of the statins on CHD events, CHD mortality, and total mortality was greater when they were considered alone (Figures 4A-C). For the statin trials alone, the net reduction in the odds of CHD events compared with placebo was slightly larger (35%) than for all drugs (30%), as was the reduction in CHD mortality (31% versus 26%). No significant effect on total mortality was found when the statin trials were considered alone.

These data, when combined with the findings from secondary prevention trials and systematic reviews, provide strong evidence that drug therapy reduces CHD events and CHD mortality. Further, the magnitude of that benefit appears to be closely related to the underlying risk of CHD in the population undergoing treatment.

Conclusions – CHD Events

The question of whether lipid therapy reduces total mortality in primary prevention settings remains unclear. The existing trials do not have sufficient power, even when meta-

analyzed, to confirm or exclude potentially meaningful effects, at least in part because the CHD and total mortality rates over the 5- to 7-year-long trials are low. Total mortality might be reduced for higher-risk patients (such as those in WOSCOPS) or if follow-up were continued for several more years. Improvements in secondary prevention and post-MI care, however, may increase the survival of those who are not treated before CHD becomes known and thus decrease some of the potential benefit of early therapy. A final important consideration is that most of the participants in the trials examined here were not taking aspirin. If aspirin reduces MI risk, then the CHD event and mortality rates would be even lower and the absolute benefits of lipid therapy smaller.

Strokes

Hebert et al also determined the effect of HMG co-A reductase inhibitor drugs on stroke outcomes.[107] They combined data from 14 trials of primary and secondary prevention of CHD and found that, overall, subjects assigned to statin drugs had a 29% relative risk reduction for all strokes (95% CI, 14%, 41%). When they considered 3 primary prevention studies alone (including 2 studies measuring plaque regression as their primary outcomes, but not including the TexCAPS study, which had not yet been published), they found the odds ratio for the incidence of stroke to be 0.80 (95% CI, 0.54, 1.16), which is not statistically significant. Another meta-analysis of statin trials (also pre-TexCAPS) by Warshafsky et al found a similar result for total strokes in primary prevention trials: OR, 0.85; (95% CI, 0.57, 1.28).[108]

For the primary prevention studies, the average incidence of stroke in the control group was 1.5 % for trials lasting 3 to 5 years. Thus, statin drugs appear to reduce stroke in secondary prevention settings but may not have been proven to do so in primary prevention settings. If statin therapy reduces stroke, the absolute benefit will be smaller than that for CHD events.

Effects of Drug Therapy in Children and Adolescents

We identified no trials examining the impact of drug therapy for children and adolescents that measured actual clinical endpoints such as CHD events because these events are extremely rare at young ages. Several studies have examined short- to medium-term drug treatment for children and adolescents with familial lipid disorders, but they have been too short (8 weeks to 1 year) and too small to draw definitive conclusions about harms or benefits.[109-112]

Harms and Adverse Effects

For cholesterol-lowering drug therapy to be effective in the primary prevention of CHD, the drugs must be free from serious and frequent adverse effects because the absolute benefit of treatment is lower in the primary prevention population than in secondary prevention groups. The literature on the adverse effects of lowering cholesterol is vast, and a full review is beyond the scope of this SER.

This section highlights the most important and relevant evidence regarding adverse effects of lipid-lowering drugs and how such effects influence the decision to screen patients in primary care settings and treat those who are found to have lipid disorders. We focus on

the statin drugs because they are the most commonly prescribed lipid-lowering agents (accounting for 90% of prescriptions written for cholesterol-lowering drugs in the United States in 1998)[113] and because the evidence for their benefits is also the strongest.

To examine adverse effects, we searched the literature broadly to identify all types of studies, including case series, observational data, and randomized trials. Although randomized trials are most likely to control for bias, they may have insufficient power to detect rare events. Further, they use selected, healthy patient populations and employ frequent monitoring, so their results may not be generalizable to real-world practice.

Numerous observational studies have noted the association between very low serum cholesterol levels (levels lower than usually achieved with single drug therapy) and adverse outcomes, including mortality. Much of the association, however, appears to be attributable to underlying disease processes that produce low cholesterol levels and adverse outcomes, not to the low levels themselves.[114] The risk of hemorrhagic stroke, however, does appear to be increased with low serum cholesterol in observational studies and perhaps in meta-analysis of secondary prevention trials.[108,115] Although the relative risk of hemorrhagic stroke is relatively large (RR, 1.86; 95% CI, 1.37, 2.53) for the subgroup with TC below 5 mmol/L (190 mg/dL), the absolute risk is quite small and is canceled out by the more common reductions in CHD and ischemic stroke.[108]

Any adverse effects on CHD outcomes are subsumed within the main outcome variables (CHD mortality, total CHD events) from large studies. Because CHD events are common and appear to be decreased by the main effect of lowering lipid levels, any small adverse effect on CHD outcomes due to another mechanism will produce only an attenuation of the net benefit of treatment.

Numerous studies have examined putative non-CHD adverse effects (see Tables 5 and 6).[15,16,98,99,116-137] The non-CHD adverse events can be divided into 2 groups: (1) short- to medium-term effects of therapy (initiation to 5 years of therapy); and (2) long-term effects (greater than 5 years of therapy). The remainder of this section considers these topics in turn.

Short- to Medium-term Adverse Effects for Statin Drugs

Several potential short- to medium-term adverse events have been well studied in large randomized controlled trials (RCTs) of sufficient duration and size to have adequate power to identify even small differences in their occurrence (Table 5). Commonly considered adverse effects include the following: (1) creatinine kinase (CK) elevations and myopathy, (2) liver enzyme elevations and hepatic dysfunction, (3) lens opacities and cataracts, and (4) cancer.

Elevation in CK and myopathy. Overall, myopathy related to the use of statin drugs—including muscle soreness (myalgias), weakness, or CK elevations—may occur in about 1 of 1,000 users. Patients taking higher doses, concurrently using other lipid-lowering medications (particularly gemfibrozil or niacin) or inhibitors of P-450 enzyme systems, or having complicated underlying medical problems appear to be at higher risk.[118] Cases of polymyositis- and dermatomyositis-like syndromes and of rhabdomyolysis and renal failure have been reported, but their frequency appears to be uncommon since they have not been found commonly in randomized trials.[119,121,123-125]

The large RCTs of statins also have not found significant differences in the rates of either CK elevations greater than 10 times normal levels or myopathic symptoms (Table 6).[13,15,16,98]

Liver enzyme elevation. Statin drugs have been reported to cause dose-dependent, asymptomatic liver enzyme elevations in about 1% of patients. Most of these elevations occur in the first year of therapy.[32] Cases of the development of frank cholestatic hepatitis that resolve with the discontinuation of therapy have been reported.[126] Data from the large RCTs using low to moderate medication doses do not, however, show a clear pattern of such elevations with active treatment, as the rates of elevated liver enzymes are similar in intervention and control groups.

Lens opacities. Data from 2 large RCTs in which careful ophthalmologic examinations were performed found no increase in the frequency of cataracts or other visual changes.[127,128]

Cancer. To date, large trials (Table 6) and recent meta-analyses[105] have not found increases in the frequency of cancers among those assigned to the active drug as compared to those taking placebo. These trials have an average duration of 5 years, so further surveillance is required to exclude long-term effects.

Concern was raised in the CARE study that the frequency of breast cancer was increased among women who receive active drug in their arm.[16] Further trial data from primary and secondary prevention trials have not confirmed this finding.[138]

Violence. Golomb reviewed several lines of evidence, including observational studies, older trials, and animal data, supporting the link between lower cholesterol and violence,[134] but recent large trials of the statin drugs have not shown excess violence-related morbidity and mortality among those assigned to cholesterol-lowering therapy with statin drugs.

Depression. Some small experimental studies have suggested that lowering cholesterol with drug therapy may increase scores on indices of depressed mood,[132,133] but others have not found any differences in mood or cognitive abilities.[131] One large cohort study found an increased prevalence of depression-related work absences among those taking simvastatin or following a low-fat diet, but the investigators did not control for confounding by comorbid conditions such as hypothyroidism or CHD.[139] Depression does not appear to be more common in the large randomized trials of drug therapy.[115]

Other potential adverse effects. Jeppesen et al reported 7 cases of peripheral neuropathy among patients taking statins with no other plausible explanations for their neuropathic symptoms.[117] Further evidence, however, will be required to determine if these neuropathies can be attributed to the statins. Manson et al found that adverse pregnancy outcomes were not greater than expected among women inadvertently exposed to statins during pregnancy.[136] Finally, Azzarito et al performed a before and after trial that showed no effect on testicular function in patients taking simvastatin for 1 year.[137]

Long-term Adverse Effects of Statin Therapy

Statin drugs have been extensively studied in the past decade, and they appear to be relatively safe with respect to serious short- and medium-term outcomes, as described above. We do not yet know, however, if they will have serious long-term adverse effects, as they have not been in use for a sufficient amount of time to allow such effects to arise. The announcement of a collaboration among the investigators of the large trials of drug therapy to combine and pool data to gain better sensitivity for detecting rare adverse effects is encouraging.[140]

Harms and Adverse Effects of Non-Statin Drugs for Lipid Disorders

Gemfibrozil. Gemfibrozil, a fibric acid derivative, has been reported to cause gastrointestinal (GI) disturbance (abdominal pain, nausea) in 5% of users,[141] and it may increase the likelihood of gallstones. When used with lovastatin or cirvistatin, it increases the risk of myopathy and rhabdomyolysis.[118] In the HHS, new dyspepsia or abdominal pain was reported by 20% of men taking gemfibrozil and 15% of controls. Cholecystectomies and appendectomies were more likely in intervention subjects. After 8.5 years of follow-up, total mortality was slightly higher in the gemfibrozil group than in the placebo group, but the results did not reach statistical significance (4.9% versus 4.1%, $P = 0.12$).[142] In the Veterans Administration High-Density Lipoprotein Cholesterol Intervention Trial (HIT), patients taking gemfibrozil 1,200 mg per day were more likely than controls to report dyspepsia (40% and 34%, respectively). Rates of biliary disease did not differ between groups, and total mortality was slightly lower in the treated group.[18]

Niacin. The most problematic adverse effect of niacin is dose-related flushing, which has limited long-term adherence.[139] GI symptoms (nausea, vomiting, abdominal pain) are also commonly reported, but the most worrisome adverse effect is hepatic toxicity: up to one third of patients may develop abnormal liver function tests, and fulminant hepatic failure has resulted from use, particularly with the extended-release version.[143] Exacerbations of diabetes and gout are also common.[139,144]

Bile-acid binding resins. The bile-acid binding resins seem to increase GI symptoms, including bloating and nausea, and they can affect the absorption of other drugs. Otherwise, they appear to be relatively safe and have been studied for a longer period of time than statins.[3]

Summary of Harms and Adverse Effects of Drug Therapy

Based on data from multiple clinical trials, statins appear to have few important adverse effects over the short- or medium-term (initiation to 5 years), but their long-term safety is currently unknown. Other agents, including gemfibrozil, niacin, and bile-acid binding resins, appear to have either more frequent, minor adverse effects or rare major adverse effects. 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.

Adherence to Lipid-lowering Therapy

The magnitude of the "real world" effectiveness of drug therapy for lipid disorders is related to the level of adherence to such therapy. The rates of adherence found in randomized trials of lipid-lowering drug therapy may not be generalizable to real-world settings where follow-up and monitoring are less rigorous, patients have not been preselected as being willing and able to follow protocols, and the medications are not provided free of charge. If adherence rates in ordinary practice settings are lower than those found in trials, then the potential absolute benefit of therapy may be attenuated.

In the WOSCOPS study, 15% of subjects had withdrawn after 1 year and 30% of subjects after 5 years. The rates of withdrawal were equal between intervention and placebo groups, and it is not clear what proportion left because of nonadherence or because their regular providers discontinued study medications because of potential adverse effects or a perceived lack of efficacy.[98] In TexCAPS, the investigators reported that 99% of participants took greater than 75% of their pills as determined by pill counts; 71% of subjects receiving lovastatin and 63% of subjects receiving placebo maintained adherence until the end of the trial.[99] Previous trials of statin drugs had shown rates of discontinuation of 16% at 1 year in a mixed primary and secondary trial[35] and 6% to 12% at 4 to 5 years in 3 large secondary prevention trials.[13,15,16]

The study populations from the large trials may be systematically different from the target populations for screening with respect to the likelihood of adherence. Data from real-world settings may have higher generalizability. Andrade and colleagues examined the rate of treatment discontinuation of lovastatin in a population enrolled in a health maintenance organization from 1988 to 1990 and found a 1-year rate of 15% and a 2-year rate of 25% to 30%.[145] About 50% of discontinuations were attributed to adverse effects. Avorn and colleagues examined the same question among patients older than 65 years of age, using 1990 to 1991 data from the New Jersey and Quebec drug assistance pharmacy programs.[146] Lovastatin users had the highest rate (64%) of "persistent" use. Patients with known CHD or multiple risk factors were more likely to continue their drug therapy than patients without those characteristics.

Although the Andrade et al and Avorn et al data are drawn from appropriate study populations, they are somewhat dated.[145,146] Better evidence reflecting current real-world practice and available therapies would be helpful in clarifying the actual extent of adherence to drug therapy and its relationship to the populations' expected net benefit from treatment.

Summary

Drug therapy for lipid disorders reduces the relative risk for CHD events and for CHD mortality by approximately 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. Total mortality is not reduced after 5 to 7 years of treatment in lower-risk patients (risk of CHD events less than 1.5% per year), but it 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 persons (up to age 70), and persons of non-European descent appear to have similar relative risk reductions with drug treatment, although they have been studied less than middle-aged men.

Key Question No. 2: Diet and Exercise Therapy for Lipid Disorders

We examined the following 4 subsidiary questions for the linkage (Key Question No. 2) of the effect of diet and exercise therapy on patients with lipid disorders.

1. What is the effect of dietary counseling in primary care settings on cholesterol levels?
2. What is the effect of dietary counseling on CHD events?
3. Does knowledge of one's cholesterol level increase the effectiveness of dietary therapy for lipid disorders?
4. What is the effect of exercise advice on cholesterol levels and CHD events?

In this review, we consider dietary therapy to be general dietary counseling for free-living patients without known CHD conducted by a health care provider (physician, nurse, dietitian) individually or in a group format. This report does not attempt to measure the effect of population-level interventions such as television public service announcements or changes in legislation. It is specifically focused on the effects of diet therapy on lipid levels and the risk of CHD events or mortality. The evidence for general counseling to promote a healthy diet and its effect on other health endpoints will be considered in a separate report from the USPSTF; population-level interventions are addressed by the Centers for Disease Control and Prevention's Task Force on Community Preventive Services. The effect of dietary supplements is also not considered here.

The relationships among diet, cholesterol, and heart disease have been demonstrated in numerous ecologic and observational studies. In international comparisons, rates of CHD are associated with national dietary patterns, especially saturated fat intake. 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.[7] These changes are believed to be one of a number of factors that have contributed to recent declines in mortality from CHD.

In addition, individualized dietary interventions (most, but not all, of which lower TC) have been shown to reduce CHD events in specific settings. A review for the Cochrane Collaboration examined 27 RCTs that employed reduced or modified fat diets for at least 6 months and that also collected data on mortality or cardiovascular morbidity (trials including interventions aimed at other risk factors such as smoking were not included).[147] Eight trials accounted for 99% of all cardiovascular events observed: 6 enrolled outpatients with preexisting heart disease and the remaining 2 studied institutionalized patients. Of the interventions employed, 3 trials used dietary education and counseling, 3 provided counseling plus supplements of polyunsaturated fat or fatty fish, and 2 employed institutional diets high in polyunsaturated fat. The pooled analysis showed an average reduction in total cholesterol of 11%, a statistically significant reduction in cardiovascular events (RR = 0.84; 95% CI 0.72 to 0.99), and a trend to lower cardiovascular mortality (RR = 0.91; 95% CI 0.77 to 1.07). Trials of longer duration (2 years or more) demonstrated greater effects than shorter trials.

Although these findings support the cardiovascular benefits of lowering cholesterol through specific dietary interventions, they are not easily generalized to the impact of typical outpatient diet advice provided to patients with high cholesterol. For individual dietary advice to be effective, it must produce long-term, clinically significant improvements in

lipids and coronary risk beyond those that would occur as a result of secular changes and other community-based interventions aimed at the general population. Further, the dietary advice must be able to be replicated in real-world settings. In the following sections, we will examine the effects of dietary counseling in several settings relevant to primary care practice.

Effectiveness of Dietary Advice in Primary Care Settings

Trials

Evidence Table 2 (Appendix 3) examines the 6 RCTs of dietary counseling provided in primary care settings with at least 12 months of follow-up.[144,148-153] In general, the studies were well designed and well conducted, and they had high internal validity. Their external validity was compromised only by the fact that they were all done in Europe, making their external validity fair for United States populations.

Overall, the net reductions in TC were small, with magnitudes of 2% to 3.7%. No studies in primary care settings examined the effect of dietary counseling on actual CHD events. The British Family Heart Study, a multimodal intervention designed to improve several risk factors, including serum cholesterol, examined the change in a cardiovascular risk score. In that trial, intervention subjects reduced their relative risk of CHD by 16% at 1 year, of which a 4% reduction could be attributed to changes in serum cholesterol.[153] In most cases, cholesterol reduction was largest for those with the highest initial levels.

In the Swedish Cost Effectiveness of Lipid Lowering study (CELL), Lindholm et al examined the effect of different combinations of drug and diet therapy on cholesterol levels and cardiovascular risk over 18 months.[152] Patients 30 to 59 years of age with hyperlipidemia (TC > 250 mg/dL) and at least 2 other CHD risk factors were randomized in a factorial design to usual or intensive dietary advice with or without concurrent drug therapy with pravastatin. Outcomes of interest were net changes in lipid levels, CHD risk (using a Framingham risk score), and cost-effectiveness.

Usual dietary advice consisted of brief advice from providers to reduce fat, lose weight, take exercise, and stop smoking. These messages were reinforced with a brief pamphlet. Intensive advice consisted of 6 group sessions (45 minutes each and 1 full-day meeting) with specific advice about dietary changes. Adherence over the course of the trial was high, and dropout rates were low.

Usual dietary advice alone produced no change in cholesterol levels after 18 months. Intensive advice, compared to usual advice, produced a net reduction of TC of 2.2%. The TC/HDL ratio did not improve. The combination of usual advice and drug treatment was as effective as intensive advice and drug treatment together and was more cost-effective than intensive advice alone.

An uncontrolled work place trial, The Dietary Alternatives Study, also examined the effect of fat-restricted diets on cholesterol levels. The trial randomized male industrial employees with hypercholesterolemia (LDL > 75th percentile for age) or combined hyperlipidemia (LDL and TC > 75th percentile for age) to 1 of 4 low-fat diets and followed them for 1 year. Subjects were also encouraged to eat more fiber. The hypercholesterolemia subjects reduced their mean LDL by 5% to 13%; the combined hyperlipidemia group reduced their LDL by 3% to 7%. There were small decreases in HDL for 2 of the hypercholesterolemia groups.

Meta-analysis

Tang et al conducted a meta-analysis of single intervention dietary trials conducted among free-living adults and published before 1996.[154] Trials of patients with known CHD and trials conducted in nonprimary care settings were included; trials of specific dietary supplements (eg, oat bran, garlic) and multirisk factor trials were excluded. These investigators found the mean reduction in cholesterol to be 5.3% at 12 months for trials of at least 6 months' duration. The American Heart Association Step One diet, advocated as the first intervention for patients with no previous CHD, produced an average reduction of 3.0%. Brunner and colleagues found a similar result (mean reduction of 3.7%) in their meta-analysis of 17 studies.[155]

Denke reviewed older trials of dietary advice in individuals at usual and increased risk for coronary disease.[156] She concluded that "intensive individualized counseling" in patients at usual risk for coronary disease produced 5% to 14% reductions in TC and that 4 studies in high-risk individuals produced 4% to 17% reductions. No search strategy or methods section was provided, and several published studies that were similar to the included studies were not discussed or evaluated.

The 2 studies from the Denke review that were performed in usual-risk patients were the Diet-Heart Feasibility Study and the Women's Health Trial.[156] The Diet-Heart study tested the effect of a high-intensity Step Two diet in 1,000 men with initial mean TC of 230 mg/dL. They found a 10% to 12% reduction in TC after 1 year; the control group had small (4%) reductions as well. The Women's Health Trial randomized 300 women at higher risk for breast cancer (mean TC 222 mg/dL) to a Step Two diet or control to test whether reduction in dietary fat would reduce the incidence of breast cancer. The control group did not have baseline cholesterol measurement, but the intervention group had a 7% reduction in TC at 1 year compared to baseline. The control group values at 1 year were similar to the intervention group baseline values.

The 4 studies in high-risk groups included the Oslo and Multiple Risk Factor Intervention Trial (MRFIT) trials, which are discussed in the next section of the SER. The 2 other included studies were the LRC trial and the Chicago Coronary Prevention Evaluation Program (CCPEP). The LRC was a nonrandomized 90-day study that found an 8% reduction in TC. The CCPEP was a nonrandomized, uncontrolled study of 150 men at high risk for CHD who received intensive nutritional counseling and reduced their mean TC by 10% at 4 years.

The heterogeneity of the included trials and nonsystematic nature of the Denke review make it difficult to estimate the magnitude of effect from any given level of dietary counseling. Nevertheless, it is clear that at least in some cases sustained changes in TC can be maintained in highly motivated, selected subjects undergoing intensive interventions. Whether these interventions change the risk of CHD or reduce actual CHD events is unclear: the Oslo intervention reduced CHD events, but MRFIT did not. The generalizability and feasibility of these results for primary care settings are poor.

Although individualized dietary interventions have had only a modest overall impact on TC levels (mean reduction 3% to 6%) and have not demonstrated a reduction in CHD events, the mean response may mask a smaller subgroup of individuals who are able to make significantly larger changes in cholesterol levels. It is difficult to document the size of the "exceptional responder group" from the published results of studies that we identified. One

earlier study by Henkin et al found that about 58% (42 of 73) of subjects reduced their TC by more than 10% over the initial 12 weeks of a trial using intensive Step One dietary advice. After 6 months, however, only 22 of 73 (30%) still had reductions of more than 10% from baseline. If the dropouts are considered to be nonresponders, this proportion is reduced to 21% (22/105).

Effectiveness of Dietary Advice in Large Multi-Risk Factor Trials

Trials

We identified 5 RCTs that examined the effect of a multi-risk factor intervention on the incidence of CHD events and CHD mortality.[157-161] The 5 studies ranged from 5 to 10 years in duration and enrolled a total of almost 50,000 middle-aged male subjects. Four of the studies were conducted in Europe and 1 (MRFIT) in the United States. The 5 studies were published between 1981 and 1986, and hence they consider patients that may be systematically different from patients with lipid disorders today. Initial cholesterol levels, for example, were quite high, with mean values from 240 to 330 mg/dL. The intensity of dietary advice varied among the studies. In MRFIT, the most relevant study for US populations, intervention subjects initially received 10 weekly group sessions that addressed smoking, dietary advice to reduce cholesterol, and blood pressure control. Subjects and their wives then received individualized counseling every 4 months for the remainder of the study. The dietary intervention sought to reduce weight and limit the intake of saturated fat. TC was reduced by 5% among intervention subjects and by 3% in controls.

The 5 studies generally had high internal validity but fair to poor external validity, and they achieved heterogeneous results. The Goteberg, MRFIT, and World Health Organization (WHO) studies had only small net reductions (4%, 2%, and 0.5%, respectively) in mean TC, whereas the Helsinki MRF and Oslo studies achieved substantial reductions (13% and 23%, respectively). In terms of clinical endpoints, 4 of the 5 studies had no effect or a trend toward harm; in contrast, the Oslo study produced large and statistically significant reductions in CHD events.[162]

Why did the Oslo study have such different results? The very high baseline TC levels (mean = 328 mg/dL) may be an important factor. The Oslo diet intervention mainly involved substitution of polyunsaturated fats for saturated fats. Subjects who were overweight or had elevated triglycerides were given diets that reduced caloric intake as well. Net TC was reduced by 13%, and triglycerides by 20%. HDL cholesterol increased by almost 30%. The large reduction in TC and the impressive increase in HDL cholesterol have not been repeated in other dietary intervention studies of primary prevention; moreover, these results were not seen in the MRFIT trial conducted in the United States. In addition, we cannot separate the effect of the concurrent smoking cessation advice, which may have also contributed to the reduction in CHD events.

Meta-analysis

Ebrahim and Smith performed a systematic review and meta-analysis of 14 multiple risk factor intervention randomized trials of at least 6 months' duration that included the studies described above plus several others.[163] They found, overall, that the interventions

modestly decreased blood pressure and smoking. Their net effect on serum cholesterol was a reduction of 5.4 mg/dL (0.14 mmol/L). The interventions did not reduce total mortality (OR, 0.97; 95% CI, 0.92, 1.02), CHD mortality (OR, 0.96; 95% CI, 0.88, 1.04), or nonfatal MIs (OR, 1.0; 95% CI, 0.92, 1.07).

Impact 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. As documented in Evidence Table 4 (Appendix 3), our literature review identified 4 studies published between 1992 and 1998 that examined the effect of learning one's cholesterol level on the effectiveness of dietary therapy to lower TC.[164-167] Three were randomized trials,[164,166,167] and 1 was a quasi-experimental design.[165] In 3 of the studies, subjects were volunteers recruited from work sites; the fourth was performed in a British primary care clinic. In general, the studies were of fair quality and employed low-intensity to moderate-intensity interventions.

Little overall net reduction (percentage reduction in intervention minus percentage reduction in controls) in cholesterol levels was noted with dietary therapy among those learning their cholesterol level. Robertson et al found only a 1% net reduction among those given their cholesterol levels.[164] Elton et al and Hanlon et al found, respectively, 4% and 2% net reductions in cholesterol levels.[165,166] Strychar et al found no difference in cholesterol levels between those who were or were not told their cholesterol levels.[167]

None of the trials was designed to measure important clinical endpoints such as a change in the incidence of CHD events. Relatively larger reductions in TC were observed for subjects with high cholesterol on initial screening; subjects with low starting cholesterol levels had no net change or small net increases in cholesterol levels. Both changes may be partially explained by regression to the mean. Given the (at-best) small net reductions in cholesterol among intervention subjects, feedback of cholesterol results does not appear to increase substantially the overall effectiveness of diet therapy, although the subgroup with elevated initial levels may benefit somewhat.

Special Populations: Diet Therapy in Children and Adolescents

Both the National Cholesterol Education Program (NCEP) and the American Academy of Pediatrics (AAP) have advocated adoption of a low-fat diet in childhood as a means of establishing healthy lifelong dietary habits and as a population approach to lowering blood cholesterol levels.[24,168] The population approach aims to lower the average level of blood cholesterol in all children and adolescents by encouraging the adoption of a low-saturated fat, low-cholesterol diet. The rationale is that a relatively small reduction of mean levels of TC and LDL cholesterol in children and adolescents, if continued into adulthood, could decrease the development of atherosclerosis and substantially decrease CHD incidence.

The diet recommended by the NCEP and AAP for all healthy children over the age of 2 years is the American Heart Association Step One diet. It includes the following pattern of nutrient intake: less than 10% of total calories from saturated fatty acids, an average of no more than 30% of total calories from fat, and less than 300 mg/day of cholesterol. This

contrasts with the average US diet for persons 2 months to 19 years of age as determined by the 1988 to 1991 National Health and Nutrition Examination Survey III, which found mean intakes as follows: 12% of total calories from saturated fat, 34% of total calories from fat, and approximately 270 mg/day of dietary cholesterol.[169]

Children and Adolescents

The safety, efficacy, and feasibility of low-fat diets in children and adolescents remain unsettled. To address these issues, intervention studies have been carried out in specialized clinical settings, schools, and 1 primary care setting.

The Dietary Intervention Study in Children (DISC), a 3-year, multi-center RCT, used an intensive behavioral intervention to promote adherence to a low-fat diet in children (N = 663) ages 8 to 10 years who had LDL cholesterol levels between the 80th and 98th percentiles.[170-172] Participating children were volunteers recruited from public and private elementary schools by mass mailings to members of a health maintenance organization and from pediatric practices. Participants went through a multiple-step screening process; the total number of children screened was 44,000. The intervention was carried out by highly trained nutritionists, behaviorists, and health educators who conducted group, individual, and telephone counseling sessions with intervention families over the 3-year study period. Subjects and their families participated in a combination of 18 individual and group sessions during the first year of the intervention. During each of the second and third years, intervention children and families participated in 4 to 6 individual or group sessions with monthly telephone contacts between sessions. The primary goal of the intervention was adherence to a diet providing 28% of energy from total fat, less than 8% of energy from saturated fat, and less than 150 mg/day of cholesterol; this is similar to the American Heart Association Step Two diet.

Dietary levels of total fat, saturated fat, and cholesterol decreased significantly in the intervention group, although not to study goals. DISC achieved modest lowering of LDL cholesterol levels while maintaining adequate growth, iron stores, nutritional adequacy, and psychological well-being.[170] After 3 years, the mean difference in TC between intervention and control groups was 3.23 mg/dL. The serum cholesterol level in the intervention group decreased 1.6% more than in the control group. Serum HDL levels did not differ significantly between the control and intervention groups.

The Children's Health Project evaluated the effect of nutrition education programs for hypercholesterolemic children that practicing physicians could feasibly carry out.[173] Over a 2-year period, 3,652 children between 4 and 10 years of age and followed for care in suburban pediatric practices had a screening TC. Of those screened, 997 had elevated TC greater than 176 mg/dL (75th percentile). Of the 924 eligible children, 458 agreed to participate in confirmatory testing. Of these participants, 27l had elevated LDL cholesterol levels (between 107 to 164 mg/dL for boys and 112 to 164 mg/dL for girls) and were randomized to 1 of 2 educational interventions or to an at-risk control group. One intervention was a parent-child auto-tutorial nutrition education program that could be carried out at home; the second intervention was standard nutrition counseling delivered by a registered dietitian. The interventions were carried out in a research center in a manner that was meant to replicate a pediatric practice setting. At 1 year of follow-up, children in the intervention groups reported decreased total and saturated fat intake and maintained normal

growth patterns. Baseline and 1-year follow-up values of LDL cholesterol levels did not differ among the groups.

Infants and Toddlers

The first 2 years of life are a period of rapid growth and development necessitating high energy intake. The NCEP and AAP do not recommend dietary modification in children under the age of 2 years. Dietary recommendations for children from NCEP and AAP have suggested introducing low-fat diets after the age of 2 years because of concerns that restricting fat intake in infancy could lead to inadequate intake and poor growth and development.

The Special Turku Coronary Risk Factor Intervention Project for Babies (STRIP) was a prospective RCT of the effects of a low-saturated-fat, low-cholesterol eucaloric diet on growth and serum lipid levels in infants and young children.[174] This study enrolled families of 1,062 healthy infants 7 months of age and followed them in the well-baby clinics of the city of Turku, Finland. The intervention team comprised 5 pediatricians, 3 dietitians, and a registered nurse. Intervention families were given intensive health education when the infant was 7, 8, 10, and 13 months of age; the dietitian's advice sessions lasted 20 to 45 minutes at each visit and encouraged a diet containing 30% to 35% total fat (a ratio of polyunsaturated to monounsaturated to saturated fat of 1:1:1) and dietary cholesterol of less than 100 mg/1000kcal/day.

At 13 months of age, families in the intervention group reported significantly lower daily intakes of energy and saturated fat than families of the control group. The absolute fat intake in the intervention group was lower than the researchers had expected. In addition, intervention group infants did not show the typical increase in serum lipids usually seen in this age group; in contrast, serum lipids in the control group infants did increase. Growth among these infants did not differ between the groups and was at expected rates for 13-month-old Finnish infants.[175]

The counseling team continued to see families in the intervention group at 1- to 3-month intervals until the age of 2 years and then twice yearly. At 48 months of age, the STRIP intervention children had lower intakes of saturated fat, total fat, and cholesterol than the control children. Both groups of children were reported to be growing at normal rates.[176] After adjusting for lipid levels at entry into study, mean TC concentration for children 13 and 36 months of age was significantly lower in intervention subjects than in control subjects. There was a 6.3% net difference in the change in total cholesterol (8.4% increase for intervention subjects versus 14.7% for controls). When the data were analyzed by sex, the effect of the dietary intervention was significant only in boys.[174]

In summary, although the STRIP study showed normal growth in infants on fat-restricted diets, the long-term effects of such a diet on very young children are not known. In addition, the fat intake of the infants in the STRIP study decreased below that counseled by study dietitians, suggesting that close follow-up is essential to ensure adequate growth and nutrient intake in very young children on low-fat diets. We reiterate that the NCEP and AAP do not recommend dietary modification in children under the age of 2 years.

School Health Interventions

The Child and Adolescent Trial for Cardiovascular Health (CATCH) was an RCT that evaluated an intensive 2-year school health program targeted at children between the third and fifth grades.[177] CATCH enrolled 5,106 third-grade students from 28 public schools in California, Louisiana, Minnesota, and Texas. The intervention involved modifications in school food service, enhanced physical education, and classroom health curricula.

CATCH was able to modify the fat content of school lunches, increase moderate to vigorous physical activity in physical education classes, and improve self-reported eating and physical activity habits. However, the change in blood cholesterol measures did not differ between students in the control and intervention groups.

Harms of Dietary Interventions in Children and Adolescents

Concern about the safety of low-fat diets in children has been raised because of case series that demonstrate failure to thrive or nutritional deficiencies in infants and young children on fat-restricted diets initiated by parents.[178,179] An additional concern is that substituting simple carbohydrates for fat in order to maintain eucaloric intake may lead to obesity.

In addition, the monitoring of diet and lipid levels has the potential to label the child as a patient and may lead him or her to adopt "sick role" attitudes and behaviors. Also, the increased monitoring and visits necessitated by appropriate follow-up can be difficult for busy families.

Conclusions

In summary, clinical trials of low-fat dietary interventions in children and adolescents showed maintenance of normal growth, adequate iron stores, and nutritional adequacy. However, the interventions in the DISC and STRIP trials require a significant amount of counseling and follow-up, which may not be feasible in primary care practice because of financial and resource constraints. In addition, the close monitoring of growth and nutritional status may have contributed to the lack of adverse effects.

Exercise and Lipids

Observational epidemiological studies have found that persons who are physically active have lower rates of CHD than persons who are inactive.[180] Whether these observational findings can be translated into successful and feasible interventions is not clear: no trial of exercise done in primary prevention settings has found decreased CHD events among those assigned to exercise.

Many studies have examined the impact of exercise on CHD risk factors, including lipid disorders. A meta-analysis of 95 studies found that subjects assigned to exercise had post-intervention cholesterol levels that were 7 to 13 mg/dL lower than controls.[181] The larger reductions were seen 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), 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.

Steptoe et al. evaluated whether brief behavioral counseling by practice nurses that was based on the stages of change model could reduce cardiovascular risk factors.[182] Twenty British primary care practices were randomized either to provide the intervention (2 to 3 sessions of counseling) to patients with 1 or more CHD risk factors or to act as controls. The 3 target areas were smoking cessation, dietary advice to reduce fat intake and increase fruits and vegetables (no specific percentage goal for fat intake was used), and increasing physical activity. Patients on special diets or lipid-lowering drugs were excluded. Dropout rates were high: only 54% of intervention patients and 62% of controls completed the 1-year trial.

Among trial completers, biochemically validated rates of smoking cessation, self-reported fat intake, and self-reported physical activity improved for the intervention group. The reduction in serum TC at 1 year was the same in the intervention and control groups (5.1%). The reason for the moderately large decrease in the control group is unclear, but it does not appear to be a result of diet or drug interventions in the control group. It may simply reflect regression to the mean.

Summary of Dietary and Exercise Intervention Data

Diet therapy, including diets high in fish[183] and "Mediterranean" diets,[184] have reduced CHD events in secondary prevention settings. Low-fat diets have reduced CHD events among institutionalized patients without previous CHD.[183,185] They have not, as yet, been demonstrated to reduce CHD events in free-living primary prevention populations other than the Oslo trial. Controlled studies have generally achieved only modest long-term reductions in TC (3% to 6%), despite relatively intensive interventions. The small cholesterol reductions in primary prevention are in part a result of incomplete adherence.[154]

A systematic review of studies conducted on metabolic wards found that dietary therapy can produce short-term decreases in TC of 10% to 20%[186] when patients are fed a controlled low-fat diet, but long-term change among free-living individuals is more difficult to achieve.[156] Only 20% to 40% of free-living participants in diet trials appear to achieve even short-term reductions of this magnitude. Currently, available data are insufficient to determine prospectively which patients are most likely to achieve these larger reductions.

Intensive, individualized diet therapy, such as that offered in MRFIT, appears to be relatively ineffective as a means of reducing lipid abnormalities and CHD events when compared with the secular trend toward declining average cholesterol levels that may be an effect of population-level interventions.[161]

Knowledge of one's cholesterol level does not appear to affect the overall impact of dietary therapy, although persons with elevated cholesterol may be slightly better able to reduce their TC.

Intensive educational interventions aimed at decreasing dietary saturated fat and cholesterol and serum cholesterol levels in children have had modest effects on the adoption of a low-fat diet by children and their families and very modest, if any, effects on lowering serum cholesterol. Moreover, they may be associated with harms specific to children.

Exercise interventions considered as a whole do not appear to have a large impact on lipid levels, but 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.

Key Question No. 3: Screening Strategies for Lipid Disorders

In persons without known CHD, the goal of screening for lipid disorders is to correctly identify those individuals who would benefit from special efforts to reduce the risk of future CHD events. The decision to screen for lipid disorders is based on the probability of finding lipid abnormality that would trigger specific intervention. This probability depends on the patient's age, gender, other cardiovascular risk factors, and the results of any previous lipid testing.

This section examines several areas of evidence that inform the decision about who to screen and what test or tests to use. These areas include the probability of finding an abnormal lipid level at different ages, the ability of different tests to reliably identify abnormal lipid levels, the accuracy of different measurements of lipid levels (along with other clinical information) for predicting CHD events, and the feasibility and acceptability of different screening strategies. The issues of monitoring lipid levels and drug dosages after the initiation of therapy or establishing treatment goals is beyond the scope of our work and is not considered in this report. Patients with known cardiovascular disease are at high risk for future events and should have their lipid levels measured—they will not be discussed further here otherwise.

Natural History and Epidemiology of Cholesterol Levels and Lipid Disorders

Cholesterol in Children and Adolescents

Cholesterol levels tend to follow a typical pattern during childhood and adolescence. Data from the Bogalusa Heart Study suggest that the low serum lipid levels noted during the first 2 years of life increase rapidly; lipid levels approach adult ranges by 2 to 3 years of age but are not necessarily stable.[187] The STRIP study suggests that this increase can be moderated to some extent by dietary changes.[174] Lipid levels remain fairly stable during childhood, then decrease somewhat during early puberty.[171,188,189] Adolescent boys and girls both appear to experience decreases in LDL cholesterol, whereas boys also have a decrease in HDL cholesterol.[171] As sexual maturation is completed, lipid levels increase to adult values.

Although cardiovascular disease from atherosclerosis typically becomes apparent in middle-aged and older populations, arterial lesions of atherosclerosis begin in childhood. The Pathological Determinants of Atherosclerosis in Youth (PDAY) study identified atherosclerotic lesions in persons 15 to 34 years of age who were killed by trauma.[190] In addition, these investigators demonstrated that the percentage of intimal surface involved with atherosclerotic lesions in both the aorta and right coronary artery was directly associated with postmortem serum levels of LDL cholesterol and very low-density lipoprotein (VLDL) cholesterol and negatively associated with postmortem serum high-density lipoprotein cholesterol concentrations. The prognostic significance of these lesions is unclear.

The association between childhood cholesterol levels and adult cardiovascular disease has not been determined. One indirect measure of this relationship has been to study whether

childhood cholesterol levels "track" into adulthood, ie, to determine whether childhood cholesterol levels accurately predict adult cholesterol levels.

Data from a cohort followed in the Bogalusa Heart Study indicate that about 50% of children (2.5 to 14 years of age) who had TC or LDL cholesterol levels above the 75th percentile at baseline continued to have TC or LDL cholesterol levels above the 75th percentile levels 12 years later.[189] The persistence of elevated LDL levels was greater in children 9 to 14 years of age (55%) than in those 2 to 8 years of age. The Muscatine study followed a cohort of children into adulthood.[191] Two cholesterol measurements taken during childhood, 1 at 10 years and 1 at 12 years, were compared with adult LDL cholesterol levels obtained between 20 and 30 years of age. Of the children with a screening cholesterol level above the 75th percentile at 10 and 12 years of age, only 46.8% had high LDL levels in adulthood. Increasing the childhood cut point to the 95th percentile increased the positive predictive value to 89.7%. Of note is that most adults with high cholesterol were not identified by the 95th percentile criterion during childhood.[138,168,192,193]

Cholesterol in Adults

In adults, mean TC increases with age for both men and women.[6] 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 cholesterol levels do not change greatly throughout adulthood.[194] Mean TC and the proportion with levels greater than 240 mg/dL at any age are similar for those identifying themselves as white or African American.[8]

Probability of finding an abnormal lipid level. Data from the National Health and Nutrition Examination Survey (NHANES III) can be used to estimate the likelihood of finding different lipid levels in white men and women (Figures 5 and 6). For men ages 25 to 34, the probability of finding a TC greater than 240 mg/dL is 5%; only 0.6% have a TC greater than 280 mg/dL. In men 45 to 54 years old, 27% have TC greater than 240 mg/dL and 6% greater than 280 mg/dL. Although not shown in Figure 5, men in the 55 to 64 year old cohort have a 25% probability of having TC greater than 240 mg/dL and 5% greater than 280 mg/dL. In women 25 to 34 years old, 5% have a TC greater than 240 mg/dL and 0.35% greater than 280 mg/dL. In women 45 to 54 years old, 28% have a TC greater than 240 mg/dL and 7% greater than 280 mg/dL. Although not shown in Figure 6, women in the 55 to 64 year old cohort have a 43% probability of having TC greater than 240 mg/dL and 12% greater than 280mg/dL.[6]

As shown in Figures 7 and 8 for the ratio of TC to HDL (TC/HDL), 14% of men 25 to 34 years of age have a ratio greater than 6, and 2.2% have a ratio greater than 9. In men 45 to 54 years of age, 31% have a ratio greater than 6 and 1.9% greater than 9 (Not shown in Figure 7). In women, 6.7% of those 25 to 34 years of age have a ratio greater than 6 and 0.7% greater than 9, and in women 45 to 54 years of age, 7.3% are greater than 6 and 0.9% greater than 9. In women 55 to 64 years of age, 17.5% have a ratio greater than 6 and 3.8% greater than 9 (Not shown in Figure 8).[9]

Mean 10-year risk of CHD events. Because individuals will have different combinations of nonlipid risk factors, the lipid level at which therapy would be initiated will vary. We applied the Framingham risk equations to the population of white men and women from NHANES III[9] to estimate their 10-year risk for CHD. The mean risk for men 30 to 35 years of age is 3.35% and increases steadily to 24% for men 65 to 74 years. The mean risk for women 30 to 45 years is less than 1%, rising to 11.6% for women 65 to 74 years.

Prevalence of familial hypercholesterolemia. The estimated prevalence of familial hypercholesterolemia or FH (Type II) is 0.2%, or 1 in 500 in the general US population.[195] As shown in Table 7, the risk of having a CHD event for untreated patients with familial hypercholesterolemia begins to increase at age 25 to 30 years in men and 35 to 40 years in women, and reaches 50% for men at age 50 to 60 years.[196,197] The prevalence of familial hypercholesterolemia among children with a TC of about 200 mg/dL is 0.07%, or 7 per 10 000 persons; even among children with a TC of 240 mg/dL, the prevalence is only 6%.[195]

Identifying Lipid Disorders in Young Adults and Children

In this section of the evidence review, we examine the ability of family history to identify children, adolescents, and young adults with lipid disorders.

Sensitivity of History and Examination Findings for Familial Hypercholesterolemia

In addition to the population approach of encouraging a healthy diet low in saturated fat, the NCEP and AAP recommend a "selective screening strategy" for children and adolescents. This latter strategy was adopted to identify individual children and adolescents whose elevated cholesterol levels put them at greatest risk of having high blood cholesterol as adults, thus increasing their risk of CHD. The NCEP and AAP recommend screening children and adolescents: (1) whose parents or grandparents, at 55 years of age or less, were found to have documented coronary atherosclerosis or have clinical evidence of cardiovascular, cerebrovascular, or peripheral vascular disease; (2) whose parent has an elevated blood cholesterol of 240 mg/dL or higher; or (3) whose parental or grandparental history is unobtainable or unknown, particularly those children and adolescents with other risk factors.

The data relevant to the issue of how well young persons with familial lipid disorders can be identified in the absence of universal screening depends on the sensitivity of clinical criteria in young adults. The presence of a family history of CHD events is one such criterion. The investigators in the Simon Broome study found that only 39% of men and 48% of women with FH had a paternal or maternal history of premature MI (before 55 years in men or 60 years in women). However, the investigators also found that a larger set of criteria (including the presence of other CHD risk factors or physical examination findings such as corneal arcus) would have identified 65% of the FH patients 20 to 39 years of age.

Sensitivity of Family History in Children and Adolescents

The previous NCEP and AAP guidelines for lipid screening and treatment in children recommended a selective screening approach based on family history of early CHD or

abnormal lipid levels. This approach was felt to balance sensitivity for identifying high-risk children with consideration for the harms that could result from universal screening.

The sensitivity of parental history of MI for identifying lipid disorders in children and adolescents is compromised by the fact that the parents of the patients may not have reached ages 55 or 60 years yet. Some investigators have examined using a history of other manifestations of CHD (eg, angina, bypass surgery), the history of premature CHD in grandparents, or the finding of very high cholesterol in parents (in the absence of known CHD) to increase sensitivity.

Another limitation of the existing literature is that parental and grandparental knowledge of hypercholesterolemia may be higher today than 10 to 15 years ago when lipid screening was less common in adults. Older studies' estimates of the sensitivity of elevated parental or grandparental lipid levels may underestimate their sensitivity today, because now a large majority of adults have had their cholesterol measured. Conversely, strategies using elevated parental lipid disorders will be less able to control the number of children who are asked to have blood drawn on the basis of a "positive" history, so the difference between selective and universal screening will be smaller.

Studies Using a Single Case Definition

Diller et al used a community-based cohort of white male children ages 2 to 19 years to examine the sensitivity of a combination of family history of CHD (any form of CHD in parents or grandparents before age 55 years, including "angiographically demonstrated coronary artery disease") or a parental TC greater than 240 mg/dL. They found that these criteria identified 74% of children with LDL greater than 130 mg/dL and would require obtaining cholesterol levels in 48% of subjects.[198]

Dennison et al used the Bogalusa Heart Study data to examine the sensitivity of a parental history of vascular disease (defined as previous stroke, heart attack, diabetes, or hypertension) for identifying children with LDL cholesterol above the 95th percentile. They found that the sensitivity varied by age in white children but not for African American children (Table 8).[199]

Primrose et al examined the sensitivity of a family history of a CVD event (CHD or stroke) before age 55 years for identifying Irish adolescents with TC greater than 200 mg/dL They found a sensitivity of 33%.[200]

Studies Examining Different Case Definitions

At least 3 studies have stratified their results using different cut-points to define cases of hyperlipidemia in children. Griffin et al evaluated the sensitivity of family history of CHD events or hypercholesterolemia in parents or grandparents for identifying children 2 to 13 years of age with hyperlipidemia.[201] When hyperlipidemia was defined as an LDL cholesterol above the 90th percentile for age, sensitivity was 51%. Positive histories were not more common when cases were defined as an LDL greater than the 95th percentile (greater than 160 mg/dL).

Garcia and Moodie tested white, middle-class children ages 3 to 18 years presenting at a pediatric group practice in Ohio from 1986 to 1988.[202] Of 375 children with a LDL cholesterol greater than 130 mg/dL, 299 had a family member (usually parent) who completed a family history questionnaire. Family history of a first- or second-degree relative

with an MI before age 55 years or a known history of hypercholesterolemia had a 52% sensitivity. Proportions were similar when subsets of children with LDL greater than 160 or 190 mg/dL were examined.

Steiner et al identified adolescents (ages 12 to 21, mean 15.6 years) from an urban health maintenance organization clinic with TC above 200 mg/dL.[203] Using AAP 1988 criteria, 62% of adolescents with TC above that threshold were identified. When cases were defined by a TC greater than 250 mg/dL, the 1988 criteria identified 9 of 11 patients with hyperlipidemia (82%).

Studies Examining the Performance of Parental Cholesterol Levels Alone

Resnicow and Cross examined the sensitivity of a parental self-report of elevated cholesterol (greater than 200 mg/dL) for identifying a TC above that level in elementary-age school children.[204] Sensitivity was 48.5%. Prevalence of parental cholesterol over 200 mg/dL was 34%.

Benuck et al measured the cholesterol of children ages 2 to 13 and their parents (50% had not previously known their cholesterol level).[205] They found that 98% of children with TC greater than 200 mg/dL had a parent with TC values above that level. However, the overall prevalence of parental cholesterol greater than 200 mg/dL was 72%. The proportion of children whose parents had cholesterol levels greater than 240 mg/dL was lower: 27.5%.

The NCEP performed novel data analyses for the Report of the Expert Panel on Blood Cholesterol levels in Children and Adolescents.[3] They found that parental TC greater than 260 mg/dL identified 30% of children with LDL cholesterol greater than 130 mg/dL. Using parental TC greater than 240 mg/dL increased the sensitivity to 40% and required testing 25% of children as opposed to 18% with the higher cut point.

Screening Accuracy in Children

In a cohort of families participating in an epidemiologic study, family history of premature cardiovascular disease had a positive predictive value of only 7% in identifying children with LDL cholesterol levels greater than 130 mg/dL (95th percentile).[198] Combining positive family history with parental cholesterol levels greater than 240 mg/dL increased the positive predictive value to 15.3%.

Conclusions

The performance of various criteria for identifying lipid disorders in young persons varies widely, with sensitivity values reported from 27% to 98%. The higher sensitivity values generally required more persons to have their lipid levels measured (lower specificity). Performance appeared to be higher for older subjects, although African American children in the Bogalusa study did not follow this trend. In the studies that used different case definitions, test performance did not appear to improve when "cases" were defined by more extreme lipid levels such as TC greater than 250 mg/dL. These studies were carried out in younger populations, however, which may confound the effect of case definition on sensitivity. Currently, selective screening of children seems to be able to identify about 50% of children with abnormal lipid levels (TC or LDL) and requires screening one quarter to one third of all children.

Lipid Measures: Key Attributes of Screening Measures

Several different screening strategies involving determination of serum lipid levels have been proposed for identifying lipid disorders. These strategies include screening with TC alone, the TC/HDL ratio, or the ratio of LDL to HDL (LDL/HDL). These measures can be used alone to determine the need for treatment. Alternatively, they can be combined with other information about CHD risk, as has been done with the NCEP II guidelines.[3] They can also be incorporated into an explicit risk-based screening strategy; in this approach, treatment recommendations are based on the person's overall risk for CHD, with treatment being recommended above a certain risk threshold.

This section examines the features of each of these potential screening strategies, including reliability, accuracy in predicting future CHD events, patient or parent acceptability, and feasibility for providers.

Reliability of Screening Tests

Reliability, the ability to minimize variation, is an important characteristic of screening tests. The total variability (V_t) between repeated assays is made up of analytic variability (V_a), which is the inherent variation in the test itself, and biologic variability (V_b), which is the variation that is due to natural variation in the system being measured. Analytic variability can be reduced through careful laboratory technique. The effect of biologic variability can be reduced, and reliability increased, by repeating the test at different times and averaging results.

Reliability in adults. The V_a for TC is less than 3%. Cooper et al combined data from multiple studies and found that the mean total V_b for TC was 6.3%.[206] If 2 separate specimens are obtained, V_b can be kept below 5%, which yields 95% confidence that the true value is within 10% of the mean of the 2 values. For example, a mean TC of 200 mg/dL based on 2 measures has a 95% CI of 180 to 220 mg/dL.[206] Also, TC levels do not vary substantially between fasting and nonfasting periods; hence, TC can be measured clinically at any time.

Caudill et al studied the probability of misclassification of NCEP risk category when measuring TC (defined as mistakenly calling a desirable level undesirable or vice versa, but not including misclassification into the borderline group).[207] The probability was less than 10% in laboratories meeting NCEP analytic standards.

HDL cholesterol has a V_a of 6% and a V_b of 7.5%.[168] Again, 2 or 3 values are required to estimate confidently the true risk within 10% to 13%. HDL cholesterol 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.[168] Combined measures, such as the TC/HDL ratio, will be only as reliable as the less reliable constituent measure.

Triglycerides change by 20% to 30% between fasting and nonfasting states. Because LDL is routinely calculated indirectly by measuring TC, HDL, and triglycerides and then applying the Friedewald equation (TC = HDL + LDL + [TG/5]), reliable calculation of the LDL level requires a fasting sample to ensure reliable measurement of triglycerides.[206] The Friedewald equation is inaccurate when triglyceride levels exceed 400 mg/dL.

Reliability in children. As with the adult population, 2 or 3 cholesterol values in children are necessary to assign an appropriate NCEP risk category based on TC and HDL determinations. This magnitude of within-person variability limits clinicians' ability to classify children into risk categories recommended by the NCEP with a single measurement. The need for repeated measurements may act as a significant adverse effect of screening children (see harms of screening below).[208]

Accuracy in Measuring CHD Risk

An important objective in screening for lipid disorders is to identify which patients are (or are not) at high risk of experiencing CHD events. None of the available screening strategies can differentiate perfectly between those members of a population who will and will not have a CHD event, but several studies have examined their relative performance. In general, the data suggest that risk-based strategies, which consider a person's overall CHD risk in addition to his or her lipid levels, are more accurate than those that measure only lipid levels.

Screening accuracy in adults. Grover et al used the LRC prevalence and follow-up study data for 3678 men and women 35 to 74 years of age to examine the accuracy of different screening strategies.[209] They reported 3 key findings. First, a Framingham-based coronary risk model was the best predictor of CHD mortality (area under the Receiver Operating Curve [ROC] ± standard deviation of 0.85 ± 0.02). Second, NCEP guidelines, the LDL/HDL ratio, and the TC/HDL ratio each performed approximately equally (ROCs of 0.74, 0.74, and 0.72, respectively). Third, TC alone had an ROC of 0.68.

Kinosian and colleagues also used LRC prevalence data—along with Framingham cohort data and data from the placebo group in the LRC Primary Prevention trial—to evaluate TC alone, LDL alone, TC/HDL ratio, and the LDL/HDL ratio as predictors of CHD events and CHD deaths in middle-aged adults.[210] They found the TC/HDL ratio to be the best performer. Of this study population, 52% of the men had a TC/HDL ratio less than 5 and an annual risk of CHD of about 1%; 46% of the men had a ratio between 5 and 9 and an annual risk of about 2%, and 2% had a ratio greater than 9 and an annual risk of 4.5%. For women, 71% had a ratio less than 5 and an annual risk less than 1%; 27% had a ratio between 5 and 9 and an annual risk of 2%; and 2% had a ratio greater than 9 and a risk of about 3% annually.

Avins and Browner used data from NHANES II to compare the NCEP II guidelines (a partially risk-based strategy) with a new strategy that weighted patient age more heavily.[211] They found that the new system was slightly more accurate than NCEP II for all patients 20 to 74 years of age (ROC of 0.94 to 0.96 versus 0.90 for NCEP guidelines), and it was considerably more accurate for the important subset of middle-aged men and older women (ROC of 0.94 to 0.96 versus 0.81 for NCEP guidelines).

Misclassification from measuring TC alone. We used data from Phase 2 of NHANES III to determine if using TC alone could cause significant misclassification when categorically defining risk based on lipid measurements compared with using the TC/HDL ratio.[9] If a TC greater than 240 mg/dL is labeled high risk and a TC less than 200 mg/dL is called lower risk, and if those results are compared to a criterion standard in which a TC/HDL ratio greater than 6 defines abnormally high risk and a TC/HDL ratio less than 5 defines low risk, then the following errors will be made. In men 45 to 54 years of age, 26% will be

misclassified: 13% will be "false positives" (ie, TC greater than 240 mg/dL but TC/HDL ratios less than 5) and 13% will be "false negatives" (ie, TC less than 200 mg/dL but TC/HDL ratios greater than 6).[9]

Misclassifications in younger and older men are smaller in magnitude, ranging from about 5% in 25- to 34-year-olds to 12% in those 65 to 74 years of age. In women, the misclassification is strongly directed toward false positives: 15% of women 45 to 54 years of age have TC greater than 240 mg/dL and TC/HDL ratios less than 5, increasing to 22% among those between 55 and 64 years and 18% among those 65 to 74 years old. Less than 1% of women had TC less than 200 mg/dL and TC/HDL ratios greater than 6.

Acceptability for Patients or Parents

Adults. The acceptability of screening for lipid disorders in adults has been quite high. Clearly, obtaining a nonfasting sample (for TC and/or HDL measurement) at the time of 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 it appears that most patients (more than 80%) will return for such testing when requested to do so.[212] The acceptability of the NCEP II screening guidelines or an explicit risk-based approach is presumably no different to patients than a nonfasting blood draw alone because the extra work is required of the physician, not the patient.

Children. The acceptability of pediatric cholesterol screening to children and parents is less clear. Obtaining blood from young children by finger stick or venipuncture can be challenging. A 1989 survey in a pediatric practice (done before the release of the current AAP and NCEP II guidelines) found that 136 (31%) of 439 children screened had cholesterol levels higher than the 75th percentile.[213] Only 72 children (53% of those with elevated screening) returned for the suggested follow-up test. Among the reasons given by parents for not bringing their children back for a repeat test were the following: the child was too traumatized by the screening finger stick (47%), and confirmation of an elevated cholesterol level "would make my child worry too much" (33%).

In a study of compliance with childhood cholesterol screening among members of a prepaid health plan (initiated before the NCEP guidelines for children appeared), about one third of parents whose children had positive family histories refused a screening cholesterol for their children. In addition, about one third of parents of children whose screening test results were elevated refused a confirmatory repeat test.[214]

More recent research also suggests that compliance with NCEP guidelines for screening in children has been lower than recommended. In the Children's Health Project, suburban pediatric practices identified 924 children as "at risk" because of screening TC levels greater than 176 mg/dL (75th percentile); only 458 children (about 50%) returned for the suggested confirmatory testing.

In the CATCH study, conducted at elementary schools between 1991 and 1994, parents of the 784 children with a cholesterol value greater than 200 mg/dL (95th percentile) were notified by letter of their child's elevated value and encouraged to follow up with the child's physician.[177] Only 20% of parents contacted a physician. Factors associated with physician follow-up were having a higher cholesterol value; being notified of 2 elevated screening values; having medical insurance that covered physician visits; and the parent's having his or her cholesterol tested.

Feasibility for Providers

Screening for lipid disorders by measuring cholesterol levels in adult patients is quite feasible for physicians because it involves ordering only a blood test. Providers appear to have achieved high levels of lipid screening based on population-based patient survey data.[5] Whether the impetus to screen has come primarily from the provider or from patients who want to know their cholesterol "numbers" remains unclear.

The feasibility of routinely using the NCEP guidelines or a risk-based screening tool may be lower, as each requires the collection and integration of several pieces of health information. Most providers appear to use simpler heuristics to guide their estimations of risk and decisions to treat or withhold treatment, although data suggest that patients with multiple risk factors are more likely to be screened.[215,216] British physicians have attempted to improve the feasibility of a risk-based approach by developing the Sheffield Tables.[217-219] As shown in Figure 9, the Sheffield Tables integrate the cholesterol values and other information about CHD risk and provide screening and treatment guidelines for a given threshold of risk. The absence of a defined treatment threshold means cholesterol should not be measured. Recently, the development of simple computer-based support tools has increased the potential feasibility of direct risk estimation using Framingham-based data.[220]

Lowensteyn et al studied the feasibility and impact of providing community physicians in Canada with the results of individualized CHD risk profiles for their patients.[221] They found a higher rate of appropriate return visits among those patients who had profiles performed and larger reductions in cholesterol and coronary risk. The participation rate among enrolled providers was low, however, underscoring the difficulties involved in changing physician practice

Costs

TC and HDL cholesterol can be measured in the nonfasting state, so they may be easier to perform than assessments of triglycerides and LDL. Currently, the median Medicare Part B reimbursement rates are as follows: TC alone, $8; HDL, $16; and serum triglyceride alone, $11. A lipid panel (TC, HDL, and triglyceride) is reimbursed at rates between $15 and $20.[192]

Triglyceride Measurement

The question of whether an elevated triglyceride level is an independent risk factor for CHD remains controversial. Austin et al conducted a meta-analysis of prospective cohort studies and found that an 88 mg/dL (1 mmol/L) increase in triglycerides was associated with a relative risk (RR) for CHD events of 1.32 (95% CI, 1.26, 1.39) in men and a RR of 1.76 (95% CI, 1.50, 2.07) for women in univariate analyses. After adjustment for HDL level, the effect size was attenuated, with an RR of 1.14 (95% CI, 1.05, 1.28) for men and an RR of 1.37 (95% CI, 1.13, 1.66) for women.[222] Other investigators have found that the risk associated with elevated triglycerides is not uniformly present[223]

Even if elevated triglycerides are independently associated with an increased risk of CHD, the question of whether treating persons with isolated increased triglycerides will reduce future CHD events remains unclear. Because of the uncertain benefit of therapy,

routine screening of triglycerides has not been widely endorsed.[3] Currently, triglyceride levels are not used in Framingham-based risk equations, but further research needs to be done to assess and quantify their role in risk prediction and treatment decisions.

Other Predictors of Risk of Coronary Heart Disease

The risk of CHD is independently related to several potentially modifiable risk factors besides abnormal lipids, including smoking, diabetes, hypertension, and physical inactivity. Recent epidemiologic studies and basic science research expanded knowledge about several new potential CHD risk factors.[224,225] These include lipoprotein (a), homocysteine, fibrinogen, C-reactive protein, and left ventricular hypertrophy.

Ridker recently reviewed the utility of these risk factors and concluded that each of these factors has been associated with increased risk of MI in some studies.[226] Overall, however, he found that the data for lipoprotein (a) and homocysteine as risk factors are inconsistent; understanding their utility as risk factor markers requires additional study. Fibrinogen appears to be independently associated with increased risk, but its measurement assays have not yet been sufficiently standardized for clinical use. High-sensitivity C-reactive protein has been better studied, appears to increase CHD risk independently of other risk factors, and can be reliably measured. Future research into its clinical utility is forthcoming, but it cannot be recommended currently until its role in prognosis and therapy decisions is better understood. Left ventricular hypertrophy has long been recognized as an independent predictor of CHD risk based on data from the Framingham cohort, but its role in risk assessment and therapy decisions remains unclear.

Summary of Data on Lipid Screening Strategies

Table 9 summarizes features of 5 different screening strategies for adults, indicating the relative performance of the approaches in terms of the 4 attributes discussed earlier: reliability, accuracy, acceptability, and feasibility. The testing strategies include 3 measures of lipid levels alone (TC alone, TC/HDL ratio, and LDL/HDL ratio) and 2 types of multi-factor risk assessment (NCEP and an explicit risk-based strategy) that incorporate nonfasting lipid values for TC and HDL.

Nonfasting TC alone is the least expensive and easiest to perform for both patient and provider, but its accuracy is lowest. TC/HDL ratio alone is also easy for patients to obtain and moderately easy for providers to interpret. It performs as accurately as the NCEP guideline-based strategy. LDL/HDL ratio performs no better than the TC/HDL ratio, is more difficult for patients because it requires a fasting lipid profile, and is less feasible for providers. The NCEP approach uses nonfasting total and HDL cholesterol; it stratifies treatment thresholds based on the presence of other risk factors, which are defined in a binding (yes/no) format. It is only slightly more accurate than the TC/HDL ratio and less feasible for providers.

Use of a Framingham risk-based algorithm that directly incorporates age, the presence and magnitude of other risk factors, and measures of TC and HDL is the most accurate approach. It is more difficult for providers to calculate, however, because it requires the integration of several different pieces of information. The use of a supplemental table such as the Sheffield Tables[205,217] or simple computer program[220] 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. For example, we cannot say definitely whether the extra accuracy gained by universally measuring HDL cholesterol and calculating the TC/HDL ratio justifies the cost difference between it and the use of TC alone as the initial screen.

Harms and Adverse Effects of Screening

In addition to the real and potential harms associated with the treatment of lipid disorders, the act of screening and diagnosis itself may have adverse effects. Previous research in hypertension has found, in some cases, that the diagnosis of hypertension and labeling of a person as hypertensive were associated with decrements in functional status and self-perceived level of health and with increased work absenteeism.[227] Several studies have attempted to detect and measure a similar effect from screening for lipid disorders in both adults and children.

Harms of Screening Among Adults

Brett published a case series of 6 patients who developed adverse psychological sequelae to being labeled as having high cholesterol.[228] Tijmstra found that 8% of patients who had been identified as having high cholesterol in a primary care screening effort were "shocked" at the result and had substantial anxiety about it.[229] In a large community program of cholesterol screening, Havas and colleagues administered a subset of questions from the RAND General Health Perceptions questionnaire to 867 patients before and after a cholesterol screening in which they had been identified as having high cholesterol.[230] Overall, the variables measured showed little change, but it is not clear whether the scale is sensitive to the changes associated with learning that one's cholesterol is high.

Irvine and Logan compared 287 men diagnosed with elevated cholesterol as part of a workplace screening program with 236 men from the same program found to be have normal values.[231] Questionnaires were administered at baseline and 1 year later. No adverse psychological consequences of diagnosis were detected on the RAND Mental Health Index, but one half of the men found to have high cholesterol (and informed of the diagnosis) denied having high cholesterol at follow-up. About 50% of those diagnosed with high cholesterol (compared with 20% of normal controls) were "worried" about their cholesterol.

The diagnosis of a lipid disorder in adults does not appear to cause major psychological sequelae or produce important changes in the mean values of 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. Further research using instruments that are appropriately designed and tested in patients with lipid disorders is necessary to allow definitive conclusions about the extent of harms from labeling.

Harms of Screening Among Children

Rosenberg et al administered depression, anxiety, and behavior indices to children from 2 tertiary care lipid clinics in Montreal who had recently been screened for lipid disorders.[232] Cases were significantly more likely than controls to have worse scores on the Child Behavior Checklist at 1 month (adjusted OR, 15.5; 95% CI, 2.4, 99.8) and at 12

months (adjusted OR, 15.8; 95% CI, 1.1, 223.4). Measures of depression and anxiety did not differ between cases and controls. Findings such as these, and the adverse effects of diet therapy described above, need to be confirmed but raise concern about the harm-to-benefit ratio for screening in children.

Current Use of Lipid Screening

Adults

As mentioned in Chapter 1., 73% of adults in the United States have had their cholesterol measured, and 66% have done so within the past year.[5] The 1996 National Ambulatory Medical Care Survey found 24.6 million office visits (3.4% of all visits) in which a cholesterol level was checked. Education and counseling to reduce cholesterol were provided at 16.6 million visits (2.3% of all visits).[193] In 1997, women were somewhat more likely than men to have ever been screened (75% versus 70%), and whites were slightly more likely to have been screened (71%) than African Americans (68%) and Hispanics (62%).[5] In a small study in a Wisconsin family practice residency, patients with Medicaid insurance were found to have been screened for elevated cholesterol less frequently within the past 5 years than patients with private insurance (39% versus 65%).[233]

A retrospective medical record review of 1004 subjects ages 40 to 64 years who were continuously enrolled for 5 years in a managed care organization found that, in the previous 6 years, 84% of subjects had been screened with a TC measurement and 67% had also been tested with an HDL level.[216] Screening rates did not differ between men and women, but they did increase with age. Subjects with 2 or more CHD risk factors were somewhat more likely to have been screened than those with no or fewer risk factors (95% versus 86%). Among the 210 subjects with cholesterol levels greater than 240 mg/dL, 25% had received drug and diet therapy, 57% diet therapy alone, and 5% drug therapy alone; 14% had no treatment recorded.

Data from the mid-1990s suggest that more than one half of providers screen initially with a fasting lipid panel and that treatment decisions are often based on 1 measurement, rather than the average of 2.[212] More than 85% of patients who had cholesterol screening ordered actually completed the tests. Stein and Lederman found that patients who smoke or have a tobacco-related comorbidity are less likely than those without such risk factors to be screened for hyperlipidemia, be aware of their cholesterol level, or receive drug therapy for their hyperlipidemia.[234]

The second National Heart, Lung and Blood Institute survey of primary care physicians found that cholesterol screening in children was performed by 75.7% of all physicians. Screening was highest among pediatricians (88%) and lowest among family practitioners (69%) and general practitioners (62%). A smaller proportion of physicians performed routine screening of all children and adolescents: pediatricians (22%), general practitioners (16%), and family practitioners (13%). The majority of physicians (71%) prescribed diet as the first cholesterol-lowering step, and 16% also used pharmacologic therapy.

Chapter 4. Discussion

Introduction to Key Issues

Chapter 3. and the Evidence Tables in Appendix 3 have systematically reviewed the evidence about drug, diet, and exercise therapy for lipid disorders and examined the performance of various strategies for screening. Table 10 presents a qualitative summary of our findings. This chapter summarizes the evidence about benefits and harms of treatment and screening for different demographic groups. We begin with the group in which the evidence is strongest (middle-aged men) and then consider postmenopausal middle-aged women, elderly men and women (more than 70 years of age), young adult men and premenopausal adult women, and finally adolescents and children.

The most important reason for screening is to identify patients with a lipid disorder who will benefit from treatment, whether such treatment is pharmacologic therapy or more intensive diet and exercise therapy (ie, more than the general population recommendations of a healthy diet low in saturated fat diet and moderate physical activity). The available screening tests appear to identify reliably abnormal lipid levels across the spectrums of age, gender, ethnicity, and risk for coronary heart disease (CHD). Several means exist to identify accurately those patients with increased risk of CHD events because of lipid abnormalities, age, or the presence of other risk factors.

Data from lipid treatment studies in primary and secondary prevention settings suggest that the relative reduction in risk for CHD events for a given amount of cholesterol reduction is similar for patient populations with different underlying levels of risk for CHD events. Because the relative risk reduction is similar, the absolute benefit of treatment is related to the underlying absolute risk of CHD in the group being treated.

Areas of Controversy in Screening Policy

The decision to screen for lipid disorders is based on the balance between the potential benefits and the potential harms of screening and treatment. Among many other factors, this balance is affected by the probability of finding an abnormal lipid profile and the short-term and long-term risks of CHD in the population being considered. The harms of screening and treatment have not been as well studied but are generally independent of underlying CHD risk. Controversy continues, however, about how far to extrapolate the data beyond the populations studied in the large trials of treatment, how to value potential benefits and harms, and how much weight to put on surrogate measures of benefit and harm such as changes in serum total cholesterol (TC) or changes in serum creatinine kinase.

Extrapolation to Other Populations

The currently available lipid treatment studies have enrolled primarily middle-aged men (up to age 70 years) of European descent. We have less evidence to inform fully the decision about screening and treatment of asymptomatic persons in other demographic groups. Some trial data are available for middle-aged women, but men and women who are young (younger than 45 years), elderly (older than 70 years), or of non-European descent

have not been studied extensively in trials. Little data are available for children and adolescents. In such cases, we must consider whether to utilize indirect evidence, which includes extrapolating the results from primary prevention trials in middle-aged men and secondary prevention trials in women and the elderly and also using surrogate endpoints and observational data about potential benefits and harms. We currently have no evidence to suggest that such extrapolations are inappropriate for persons with levels of CHD risk similar to those in the primary prevention trials.

Weighing Benefits and Harms and the Use of Surrogate Outcomes

Differences in the relative weights assigned to the various potential benefits and harms are another important issue. At least three benefits other than the short-term prevention of CHD events and mortality are possible: identifying persons at early and high risk for CHD because of severe lipid disorders; providing motivation and feedback to encourage behavioral change among young adults and children in order to modify the development of atherosclerosis and prevent future CHD events; and providing a better estimate of CHD risk for prognostication and to guide decisions about other interventions such as the intensity of blood pressure control, advice to avoid tobacco, or the use of aspirin chemoprophylaxis.

Screening and treatment are also associated with possible harms, such as the labeling effect and the identification of persons as being at high risk who will not actually go on to have CHD events (false-positives). These effects become especially important when considering screening among low-risk patient groups in whom the magnitude of benefit is small and may be canceled out or exceeded by the adverse consequences of screening and treatment. In each of these areas, we have only indirect evidence available to help guide decision-making. The way in which these potential outcomes are valued has important ramifications for screening policy.

Similarly, experts do not fully agree about which outcome variables are sufficient to demonstrate efficacy and effectiveness. Some argue that the ability to lower cholesterol is sufficient proof of efficacy, whereas others would require that changes in CHD mortality or even total mortality be demonstrated in trials.

Costs

Because the relative risk reduction with drug therapy appears to be approximately the same over a wide spectrum of baseline risks, the decision about whom to treat requires consideration of cost-effectiveness and the proportion of all CHD events that can be prevented. Treating at a higher threshold of absolute risk increases cost-effectiveness at the expense of failing to prevent the large total number of CHD events that occur in lower-risk individuals. Conversely, treating at a lower threshold will prevent a greater proportion of total events but is less cost-effective. Strategies that employ global CHD risk assessment to determine whom to treat are more accurate and efficient but may also be less acceptable or feasible and thus more difficult to implement.

Findings for Specific Population Groups

Middle-aged Men

The evidence in favor of screening and treatment of lipid disorders is strongest for middle-aged men with elevated levels of low-density lipoprotein (LDL) cholesterol and moderate to high short-term risk of CHD events. The West of Scotland Coronary Prevention Study (WOSCOPS) study demonstrated that treating middle-aged men with elevated LDL cholesterol and a baseline risk of CHD events of about 1.5% per year decreases the relative risk of CHD events by 33% and total mortality by 22%.[98] The Air Force/Texas Coronary Atherosclerorsis Prevention Study (TexCAPS) showed that treating middle-aged men at increased risk because of low levels of high-density lipoprotein (HDL) decreased CHD events, although the absolute benefit was low and total mortality was not affected.[99] The populations in these studies appear similar to those found in primary care practice. The probability of finding abnormal lipids and sufficient CHD risk is high in this age group.

Postmenopausal Women

TexCAPS was the only trial in our final set of primary prevention studies that enrolled postmenopausal women. In general, the women in TexCAPS appeared to have a relative risk reduction for first CHD events similar to that for men, but they had fewer CHD deaths relative to total CHD events and the trial was not powerful enough to examine total mortality effects in this lower-risk population.[99]

Evidence from secondary prevention trials suggests that women will achieve reductions in total CHD events similar to those for men at a given level of risk. In the short term (up to 5 years), these total reductions take the form primarily of fewer nonfatal myocardial infarctions (MI) rather than fewer CHD deaths.[14,15,88,235] The effect on total mortality for women remains unclear: the Scandinavian Simvastatin Survival Study (4S) study found a relative risk of 1.16 (95% confidence interval [CI], 0.68, 1.99) with drug therapy.[14] Data on total mortality for women have not yet been published in the other major trials of secondary prevention or primary prevention, and we have insufficient longitudinal data to measure the long-term effects of 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, 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. Ongoing trials such as the Women's Health Initiative will help to better define the effectiveness of lipid-lowering therapy in women.

Elderly Men and Women

Few elderly persons (older than 70 years of age) have been studied in primary prevention trials, and some epidemiological studies have questioned the strength of the association between cholesterol and CHD among elderly patients (see Chapter 1.). However, data from the TexCAPS, Cholesterol and Recurrent Events Study, and Long-Term Intervention with Pravastatin in Ischemic Disease trials suggest that lipid lowering is as

effective, or more effective, in older patients.[11,15,17] Older persons are otherwise at high levels of absolute risk of CHD events, so lipid-lowering therapy is likely to be effective, assuming that their risk of competing causes of mortality is not too high (ie, that their life expectancy is sufficient to allow them to realize the benefits of therapy).

Young Men and Premenopausal Women

The benefits of screening for and treating lipid disorders in young adult men (ages 20 to 35 years) and premenopausal women (ages 20 to 45 years) are controversial.[236,237] The 2 main potential reasons for screening and treating lipid disorders in these populations are (1) identifying and treating with diet or drug therapy the small proportion of persons at immediate risk for CHD and (2) identifying persons at future risk for CHD events and treating them now to modify (ie, reduce) their future risk.

Rationales for Screening and Treating Young Adults

Identifying and treating those at risk of CHD events at an early age. With regard to the first rationale for screening and treatment (reduction of immediate risk), young adults in general are at very low absolute risk of CHD events. Even if we assume that lipid-lowering therapy in these groups reduces risk to the same or greater extent that it does in middle-aged adults, the benefits in terms of absolute risk reduction are low.

Universal screening of young adults has also been considered as a means of identifying and treating the small number of patients with severe, often genetic, lipid disorders who are at risk for premature CHD and who would not be recognized on the basis of either a family history of early CHD events or lipid abnormalities or the personal presence of multiple other CHD risk factors. If unrecognized, some patients with severe lipid disorders may have CHD events before universal screening at age 35 or 45 years. As we described in Chapter 3., familial hypercholesterolemia (FH) occurs in about 1 in 500 persons. Estimates of the gender-specific percentages of persons with this disorder who would have CHD events in the absence of recognition and treatment before ages 35 and 45 years, respectively, are 5% and 15% for men and 10% and 15% for women.[196,197] The proportion of young adults with severe lipid disorders and with no family history of early CHD events or personal history of multiple CHD risk factors appears to be 50% or less.[238] The proportion who also have no family history of extreme cholesterol levels may be even smaller.

Treating to prevent future CHD risk. The burden of CHD events occurring in men who are 20 to 35 years of age and women who are 20 to 45 years of age is small. Thus, the decision to screen at those ages depends on whether identifying and treating young adults will reduce *future* CHD events more effectively than waiting until age 35 years in men and age 45 years in women. The crucial issue is whether beginning treatment of those persons with lipid abnormalities at a young age is more effective than waiting until later.

High TC levels in young adults are clearly predictive of higher rates of future CHD events in middle age. Data from a cohort of Johns Hopkins University medical students show that the relative risk of future CHD events and CHD mortality among those men with TC at the 75th percentile was 2 times greater than the relative risk among those at the 25th percentile.[239] The crucial issue for deciding whether to screen younger adults, however, is

the incremental effectiveness of earlier treatment compared with delayed treatment for those patients with lipid disorders.

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 follow-up period (30 years) that would be required, we must rely on indirect data to examine the arguments in favor of and against early screening and treatment.

Four main arguments can be offered for beginning screening and treatment earlier. First, earlier treatment with drugs and diet may prevent the development of atherosclerotic lesions that may increase the risk of future CHD events. Second, earlier identification of lipid disorders and treatment with diet therapy may be more effective because dietary patterns are easier to change at an earlier age. Third, knowledge of one's lipid disorder may make dietary therapy more effective. Fourth, early screening and treatment may reduce sudden death as the first presentation of CHD.

Four main arguments can be made against earlier universal screening. First, identification and treatment of lipid abnormalities at the later age thresholds (35 years in men and 45 years in women) may still allow enough time to prevent the majority of CHD events that would occur. Second, earlier treatment could expose many persons to years of unnecessary drug therapy, which may have unrecognized adverse effects. Third, a healthy diet low in saturated fat (eg, American Heart Association Step One**)** is now recommended universally. If the currently available evidence does not suggest that intensive individualized dietary advice is more effective in reducing future CHD events than general population advice to eat a low-fat diet (see Key Question No. 2), then early identification of persons with abnormal lipids is not warranted. Fourth, in light of the potentially small incremental benefit from screening and treating earlier, the marginal cost-effectiveness of early universal screening is low; the resources that would be devoted to screening and treating at earlier ages might be better spent on different health and nonhealth needs.

In the next section, we will examine and integrate the evidence for or against screening in young adults.

Evidence about Screening Young Adults

Atherosclerosis. Atherosclerotic plaques can be detected in autopsy studies of adolescents and young adults,[190] and these plaques are risk factors for CHD events. The exact strength of the relationship between atherosclerotic plaques and the incidence of future CHD events, including angina and acute MI, is not clear, because not all persons with these plaques will develop clinically evident CHD. Although the argument that early treatment would reduce these plaques and the possibility of future events is intuitively appealing. How much, if any, additional benefit is possible has not been established.

Knowledge of cholesterol levels. Data reviewed for Key Question No. 2 suggest that knowledge of one's cholesterol does not appear to increase the effectiveness of diet therapy overall, but may improve cholesterol reduction in those with initially high levels. The idea that early dietary change is more sustainable than changes made in later life has intuitive and logical appeal, although we were not able to identify any supporting evidence in our literature search.

The sustainability of such changes may also be facilitated by population changes in food fat content, school meals, and familial eating patterns. Such changes could make it more difficult for individualized therapy to show additional effectiveness.

Sudden death. Another rationale that has been proposed to support screening for lipid disorders in young adults is that a large proportion of persons, including many with occult lipid disorders, will present with sudden death as the first and only manifestation of CHD.[240] This assertion is often coupled with a statement that 25% of CHD presents as sudden death, which is referenced to a 1985 paper by Kannel and Schatzkin.[241]

The question that is germane to the issue of screening young adults, however, is the following: What proportion of CHD in young adults presents as sudden death, and how often does it occur? Further, what proportion of those in whom it does occur would not have been screened for lipid disorders (or even screened 5 years earlier) under a strategy of delayed screening? This group would include only those victims of early sudden death without previous evidence of CHD, a family history of CHD, or multiple other risk factors for CHD.

The Kannel and Schatzkin data show that for the entire Framingham cohort (including patients 35 to 84 years of age) sudden death accounts for 11.5% of all coronary events in men and 7.6% in women.[241] When angina is excluded as a presentation of CHD, sudden death accounts for 18.0% of CHD events in men and 24.3% in women; these data appear to be the basis for the 25% figure. However, the presence of angina should always prompt lipid screening, and in many cases we are here concerned with *sudden death* in young adults, so these data appear to be less useful for addressing the screening question than previously believed.

The relevant data show that for men 35 to 44 years, sudden death accounts for 8.1% of CHD presentations. Too few events occurred in women in that age range to measure the frequency of sudden death. For adults 45 to 54 years, sudden death accounts for 9.5% of events in men (although regular screening would have occurred 10 years earlier in the "delayed" screening strategy) and for 7.1% in women. The incidence of sudden death in men 45 to 54 years without known CHD was 2.4 per 1,000 persons and in women was so small as to be not measurable in Framingham. Even in women 55 to 64 years of age, the rate was only 1.2 per 1,000 women without CHD. These numbers probably would be even smaller if persons with other CHD risk factors (such as family history of CHD, diabetes, hypertension, or smoking) were excluded.

In summary, the incidence of CHD presenting as sudden death in adults 35 to 44 years of age is quite low, and it would be even lower if persons with multiple other CHD risk factors were excluded. In the absence of multiple CHD risk factors or a strong family history of early CHD, early screening to detect and treat hyperlipidemia will not prevent a large proportion of the few sudden deaths expected in young adults.

Adverse effects and diet issues. To date, concerns about the long-term adverse effects associated with lipid-lowering statin drugs remain only theoretical. The drugs appear to have few short-term or medium-term adverse effects that would compromise quality of life or increase morbidity. Screening to improve the effectiveness of dieting therapy does not appear to be effective overall.

Incremental benefit of earlier screening and treatment. The strategy of delayed screening is based on the arguments that the majority of the CHD events that would occur

without treatment in a given cohort of persons can be prevented by screening and subsequent treatment at age 35 years in men and 45 years in women and that earlier identification and treatment adds little incremental benefit. This rationale is generally based on a systematic review and meta-analysis by Law et al.[242] Their work suggests that the majority (about 80%) of the potential benefit from lipid therapy, as predicted by cohort data, can be achieved after 5 to 10 years of treatment. By this argument, the preferred approach is to delay screening and treatment until about 5 to 10 years before the time that the absolute risk of events begins to rise to meaningful absolute levels. This approach will theoretically minimize potential adverse effects of long-term therapy and unnecessary drug costs without reducing benefit substantially.[242] Others have challenged this interpretation and its implications.[237]

Children and Adolescents

As with the discussion for young adults, little evidence supports the contention that the net benefits of screening and individualized treatment of children for lipid disorders are greater than the net benefits of simply providing general population advice to follow a healthy diet low in saturated fat after age 2 years and performing other recommended interventions to reduce future CHD risk. Compared with other population subgroups, children face more potential harms including labeling, the trauma of venipuncture, parental worry, and the costs associated with long-term therapy. Actual evidence about these outcomes is minimal, however.

Special Populations

The evidence about cholesterol lowering in children, adolescents, women, and the elderly is previously discussed. Differences in the clinical approach to screening and treating African Americans do not appear to be large. Average cholesterol levels do not differ meaningfully between the 2 groups, and although trial data on African Americans are scarce, there is no good reason to believe that African Americans will respond differently than European American subjects at any given level of risk. Harms of drug therapy do not appear to be increased.[243] However, formulae to calculate CHD risk[10,218] have been developed mostly in patients of European descent and may not generalize well to African Americans. Few direct data exist about the prevalence of lipid disorders or evidence for the benefits of screening and treatment among Native American, Asian American, and Hispanic populations. Further research and wider recruitment in clinical trials would enable better estimates of the benefits of screening and treatment in persons of non-European descent.

Final Conclusions – Whom To Screen

Table 10 summarizes the evidence on the question of whom to screen and indicates our evaluation of the overall quality of that evidence. The explanation of these grades can be found in Appendix 2.

The evidence is good that treating lipid disorders in middle-aged men of European descent reduces CHD events, CHD mortality, and perhaps total mortality in patients with sufficient CHD risk. Screening and treatment in middle-aged women and the elderly with sufficient CHD risk may also be effective, although the effect on total mortality for women is

unclear. The balance of benefits and harms from screening and treating young adults or children is not clear from the available evidence**,** but screening to implement more aggressive dietary therapy does not appear to produce large improvements in CHD risk profiles above and beyond the improvements from general population advice to follow a healthy diet.

Final Conclusions – Frequency of Screening

No direct data inform the question of appropriate frequency of screening. Chiefly for that reason, previous recommendations of the US Preventive Services Task Force (USPSTF) did not state a preferred interval.[12,21] By contrast, the recommendations of the National Cholesterol Education Program suggested a 5-year interval for persons with previous normal results and more frequent screening for those who have borderline values.[3]

Several factors enter into a decision about screening frequency. These 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, 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 in diagnosis, but this approach may be confusing or difficult to implement. Again, computer reminders and decision support tools are promising—but not fully tested—means of increasing feasibility and accuracy.

Future Research Needs

As noted throughout the report, several important issues related to screening for lipid disorders have not been well studied. Foremost, the efficacy of lipid therapy in men of non-European descent and in all women, the elderly, and younger persons with multiple risk factors or diabetes should be examined more rigorously. The effectiveness of novel methods of diet therapy, including "Mediterranean" diets, should be examined in primary prevention populations. Further data on the real-world use of lipid screening and means of improving the accuracy and efficiency of different screening strategies are warranted as well. Better information about the effect of treating isolated abnormal triglycerides will help define the role of screening with triglyceride measurement, as will further research on the role of novel risk factors such as homocysteine or C-reactive protein. Finally, analysis of the optimal sequencing and combinations of different efforts to decrease CHD events (aspirin, treatment of hypertension, smoking cessation therapy)[211] would help better clarify the timing and role of lipid-lowering therapy.

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APPENDIX 1

Methods

Table 1.1. Trials Excluded From Drug Therapy Literature Search*

Reason for Exclusion	Study
Mixed primary/secondary prevention (unable to sort out results for primary prevention population)	Dorr et al, 1978[29]; McCaughan, 1981[30]; Bradford et al, 1991[31]; Bradford et al, 1994[32]; Pravastatin Multinational Study Group, 1993[33]; Athyros et al, 1997[34]
Study does not measure clinical endpoints	Ives et al, 1993[35]; Lansberg et al, 1995[36]; Bredie et al, 1996[37]; Eriksson et al, 1998[38]
Nonrandomized study	Kyushu Lipid Intervention Study Group, 1996[39]; Itoh et al, 1997[40]
Drug no longer used in United States	WHO Investigators, 1978[41]

*Thirty-four other studies (not listed) were excluded because they examined only secondary prevention.

Table 1. 2. Trials Excluded From Diet Therapy Literature Search

Reason for Exclusion	Study
Inadequate (<1 year) follow-up	Luepker et al, 1978[42]; Jones et al, 1979[44]; Cunningham et al, 1987[45]; Gemson et al, 1990[46]; Kuehl et al, 1993[47]; Heller et al, 1994[48]; Rivellese et al, 1994[49]; Johnston et al, 1995[50]; Walden et al, 1997[51]; Stefanick et al, 1998[52]
Secondary prevention study	Andrews et al, 1997[53]; Schlierf et al, 1995[54]; La Rosa et al, 1982[55]; Kromhout, 1986[56]; Levy, 1987[57]; Heller et al, 1989[58]; Brown et al, 1990[59]; Singh et al, 1991[60]; Waters et al, 1995[61]; Niebauer et al, 1997[62]
No clinical endpoints	Gorder et al, 1986[63]; Lovibond et al, 1986[64]; Laitinen et al, 1993[65]; Laitinen et al, 1994[66]; Schmidt et al, 1994[67]; Bovbjerg et al, 1995[68]
Nonclinical setting	Cambien et al, 1981[69]; Rose et al, 1980[70]; Walter et al, 1988[71]; Schectman et al, 1994[72]; Byers et al, 1995[73]; Garcia et al, 1996[74]
Nonrandomized design	Murray et al, 1990[75]; Kinlay and Heller, 1990[76]; van Beurden et al, 1990[43]; Milne et al, 1994[77]; Elmer et al, 1995[78]
Special population	Turpeinen et al, 1979[79]; Lee-Han et al, 1988[80]; Boyd et al, 1990[81]; Insull et al., 1990[82]
Wrong topic/misclassified	Parker et al, 1986[83]; Johannesson et al, 1996[84]; Davidson et al, 1997[85]
Diet supplement trial	Anderson et al, 1992[86]; Neil et al, 1996[87]
Nonsystematic review or no primary data	Walsh and Grady, 1995[88]; Corr and Oliver, 1997[89]
Other	Dayton, 1969[90]

APPENDIX 2

Grading System

Criteria for Grading the Internal Validity of Individual Studies

Introduction

The Methods Work Group for the US Preventive Services Task Force (USPSTF) developed a set of criteria by which the quality of individual studies could be evaluated for both internal validity and external validity. At its September 1999 quarterly meeting, the USPSTF accepted the criteria (and the associated definitions of quality categories) that relate to internal validity..

This document describes the criteria relating to internal validity and the procedures that topic teams will follow for all updates and new assessments in making these judgments. The overall evaluation for each study is recorded in the Evidence Tables in Appendix 3.

All topic teams will use initial "filters" to select studies for review that deal most directly with the question at issue and that are applicable to the population at issue. Thus, studies of any design that use outdated technology or that use technology that is not feasible for primary care practice may be filtered out before the abstraction stage, depending on the topic and the decisions of the topic team. The teams will justify such exclusion decisions if there could be reasonable disagreement about this step. The criteria below are meant for those studies that pass this initial filter.

Design-Specific Criteria and Quality Category Definitions

Presented below are a set of minimal criteria for each study design and then a general definition of 3 categories—"good," "fair," and "poor"—based on those criteria. These specifications are not meant to be rigid rules but general guidelines, and individual exceptions—when explicitly explained and justified—can be made. In general, a "good" study is one that meets all criteria well. A "fair" study is one that does not meet (or it is not clear that it meets) at least 1 criterion but has no known "fatal flaw." "Poor" studies have at least 1 fatal flaw.

Systematic Reviews

Criteria:

X Comprehensiveness of sources considered/search strategy used

X Standard appraisal of included studies

X Validity of conclusions

X Recency and relevance are especially important for systematic reviews

Definition of ratings from above criteria:

Good: Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions.

Fair: Recent, relevant review that is not clearly biased but lacks comprehensive sources and search strategies.

Poor: Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies.

Case-Control Studies

Criteria:

X Accurate ascertainment of cases

X Nonbiased selection of cases/controls with exclusion criteria applied equally to both

X Response rate

X Diagnostic testing procedures applied equally to each group

X Measurement of exposure accurate and applied equally to each group

X Appropriate attention to potential confounding variables

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%; 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% or attention to some but not all important confounding variables.

Poor: Major selection or diagnostic work-up biases, response rates less than 50%, or inattention to confounding variables.

Randomized Controlled Trials and Cohort Studies

Criteria:

X Initial assembly of comparable groups

□ for randomized controlled trials (RCTs): adequate randomization, including first concealment and whether potential confounders were distributed equally among groups

□ for cohort studies: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts

X Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)

X Important differential loss to follow-up or overall high loss to follow-up

X Measurements: equal, reliable, and valid (includes masking of outcome assessment)

X Clear definition of interventions

X All important outcomes considered

X Analysis: adjustment for potential confounders for cohort studies, or intention to treat analysis for RCTs

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%); reliable and valid measurement instruments are used

and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for RCTs, intention to treat analysis is used.

Fair: If any or all of the following problems occur, without the fatal flaws noted in the following "poor" category: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with 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. Intention to treat analysis is done for RCTs.

Poor: If any of the following fatal flaws 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. For RCTs, intention to treat analysis is lacking.

Diagnostic Accuracy Studies

Criteria:

X Screening test relevant, available for primary care, adequately described

X Credible reference standard, performed regardless of test results

X Reference standard interpreted independently of screening test

X Handles indeterminate results in a reasonable manner

X Spectrum of patients included

X Sample size

X 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 fatal flaw, such as uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; very small sample size or very narrow selected spectrum of patients.

Criteria for Grading Linkages in the Analytic Framework

Introduction

As noted in the previous document in this Appendix, the Methods Work Group for the USPSTF developed a set of criteria by which the quality of individual studies could be evaluated

for both internal and external validity. The Methods Work Group also developed definitions and criteria for judging the strength or quality of evidence for key questions—ie, linkages in the analytic frameworks—for the topics of systematic evidence reviews. These quality criteria were discussed at the May 1999 quarterly meeting and were essentially adopted for use by the Evidence-based Practice Centers in developing their first set of systematic evidence reviews. This document describes the criteria relating specifically to linkages in the analytic framework.[1]

Linkage Category Definitions

The rating scheme for grading the evidence for a linkage in the analytic framework rests on 3 classes of criteria: aggregate internal validity, aggregate external validity, and consistency or coherence. The Methods Work Group did not establish set formulae for arriving at any linkage score for these criteria sets. As with the criteria for quality of individual articles, they are intended to be applied as general guidelines, and the judgments are made implicitly. Judgments can be made about evidence of benefits and evidence of harms. In addition, a summative grade—ie, an overall rating—combining the evaluations of the 3 categories defined below can be given.

Also, as with the criteria for individual studies, these 3 categories can be labeled as "good," "fair," or "poor." That is, the linkages can be understood to be supported by good

[1] **The USPSTF is developing a separate set of criteria for rating its recommendations about an entire preventive service, including policies for appropriate extrapolation to populations or settings not reflected in the reviewed literature. But, because the SERs do not contain USPSTF recommendations, those ways of grading recommendations are not dealt with here.**

evidence, fair evidence, or poor evidence. The summative, overall rating can also range from good to poor.

Aggregate Internal Validity:

This category refers to the overall extent to which data are valid for conditions addressed within studies. It would be rated according to quality grading information about individual studies.

Aggregate External Validity:

This category concerns the generalizability of evidence to questions addressed by the linkage. This would include the concordance between populations, interventions and outcomes in the studies reviewed, and those to which the linkage pertains. In short, this category reflects the applicability of the evidence to real-world conditions.

It is expected that differences between conditions examined in studies and those addressed by the linkages should be considered if they could potentially influence outcomes. These might include (but not necessarily be limited to): (a) biologic or pathologic characteristics; (b) incidence and prevalence of clinical conditions; (c) distribution of comorbid conditions that might affect outcomes; and (d) likelihood of acceptability and adherence on the part of patients or providers (or both).

Consistency:

This category relates to the overall "coherence" of the body of evidence relating to the linkage. Specifically, it includes the number of studies, the homogeneity of those studies (in

terms of clinical conditions, populations, settings, and the like), the level of precision of findings in the studies, and the direction of results. In addition, it can include dose-response relationships.

Table 1. Screening for Lipid Disorders: Inclusion and Exclusion Criteria

Category	Inclusion	Exclusion
General Inclusion and Exclusion Criteria		
Databases	MEDLINE	Other databases
Languages	English only	Other languages
Populations	Humans only	Animal studies
Study Design	Cost-effectiveness, systematic reviews, meta-analyses to be reviewed and analyzed separately	Letters, editorials, and non-systematic reviews that have no original data
Drug Therapy Inclusion and Exclusion Criteria		
Publication Date	1994-June 1999	
Study Design	Randomized controlled trials	
Outcomes of Interest	Total mortality, CHD mortality, CHD events, CHD procedures required	Outcome of ischemic changes on exercise tests; angiographic outcomes
Study Duration	At least 1 year	
Study Population	Outpatients without known CHD	Patients with known CHD
Diet Therapy Inclusion and Exclusion Criteria		
Publication Date	1994-June 1999	
Study Design	Randomized controlled trials	
Outcomes of Interest	As for drug therapy above, plus change in total, HDL, LDL cholesterol	
Study Duration	At least 1 year	
Study Population	Ambulatory patients	Institutionalized patients or metabolic ward/inpatient studies
Screening Search Inclusion and Exclusion Criteria		
Publication Date	1994-December 1998	
Study Design	All	
Outcomes of Interest	Prevalence measures	
	Precision and accuracy measures (reliability, sensitivity, specificity)	
	Natural history studies of cholesterol levels	
Study Population	Outpatients with or without CHD	
Harms and Adverse Effects Search Inclusion and Exclusion Criteria		
Publication Date	1994-December 1998	
Study Design	All	
Outcomes of Interest	Any report of harms	
Study Population	Any	

Note: CHD = coronary heart disease; HDL = high-density lipoproteins; LDL = low-density lipoproteins.

Table 2. Screening for Lipid Disorders: Search Strategy Results

Search Strategy for Drug Therapy		
1	Explode cholesterol or cholesterol, dietary	72 453
2	Explode hyperlipidemia	26 922
3	Explode anticholesteremic agents, or explode simvastatin, or explode lovastatin, or explode pravastatin	11 958
4	atorvastatin or fluvastatin or gemfibrozil or cholestyramine or colestipol or niacin	5696
5	1 or 2	88 404
6	3 or 4	14 759
7	5 and 6	7116
8	Limit 7 to (human and English language and year=1994-1999)	1274
9	Randomized controlled trial, or controlled clinical trial for randomized controlled trials or random allocation, or double-blind method, or single-blind method	203 709
10	8 and 9	475
Search Strategy for Diet Therapy		
1	Explode cholesterol, or cholesterol dietary, or explode hyperlipidemia	88 404
2	Limit 1 to (human and English language and year=1994-1999)	11 754
3	Explode diet, or diet therapy	96 021
4	Dietary advice	406
5	3 or 4	96 279
6	2 and 5	1113
7	Randomized controlled trial or controlled clinical trial, or randomized controlled trials or random allocation, or double-blind method, or single-blind method	203 709
8	6 and 7	300
Search Strategy for Screening		
1	Explode cholesterol, or cholesterol dietary	70 738
2	Explode hypercholesterolemia	9872
3	1 or 2	75 724
4	Limit 3 to (human and English language and year=1994-1998)	8684
5	Explode mass screening	37 906
6	4 and 5	177
Search Strategy for Adverse Events		
1	Explode cholesterol or cholesterol, dietary	70 738
2	Explode hypercholesterolemia	9872
3	1 or 2	75 724
4	Explode anticholesterolemic agents (adverse effects)	1173
5	3 and 4	133

Table 3. Summary Results from Literature Searches and Reviews

Search and Review Results	Key Questions			Adverse Events	All Searches
	Drug Therapy	Diet Therapy	Screening		
Number of Abstracts					
From literature search	475	300	177	133	1085
From supplemental search	41	215	40	140	436
Reviewed	516	515	217	273	1521
Excluded at abstract review phase	448	425	150	181	1204
Included for full article review	68	90	67	92	317
Number of Articles					
Excluded after full review	46	51	0	67	164
Included in SER	22	39	67	25	153
Included in Evidence Tables	4	14	N/A	21	39

Note: N/A = not applicable; SER = systematic evidence review.

Table 4: Main Results from Trials of Drug Therapy

Trial /Year	Drug /Dose	Percent Change in TC	RRR CHD Events (95% CI)	ARR CHD Events (5 years)
LRC, 1984[96]	Cholestyramine 24g qd*	8.5	19% (3-32%)	1.1%
HHS, 1987[97]	Gemfibrozil 600 mg bid†	11	34% (8-53%)	1.4%
WOSCOPS, 1995[98]	Pravastatin 40 mg qd	20 ‡	31%§ (17-43%)	2.4%
TexCAPS, 1998[99]	Lovastatin 20-40 mg qd	18	37% (21-50%)	1.25% ‖

NOTE: LRC = Lipid Research Clinics; HHS = Helsinki Heart Study;TexCAPS = Texas Coronary Atherosclerosis Prevention Study; WOSCOPS = West of Scotland Coronary Prevention Study.

* qd indicates once daily
† bid indicates twice daily
‡Percentage based on actual use, not intention to treat.
§ The RRR when unstable angina is excluded is 43%.
‖Percentage absolute risk reduction for nonfatal MI and CHD deaths only.

Table 5. Frequency of Important Adverse Effects From Large Trials of HMG Co-A Reductase Inhibitors (Statin Drugs)

Study	Adverse Event	Cumulative Incidence Intervention/Control
Scandinavian Simvastatin Survival Study (4S)[116]	Elevated CK (>10 x nml)	0.3% / 0.05%
	Myalgias	3.7% / 3.2%
	Elevated AST (>3 x nml)	1.0% / 1.1%
	Elevated ALT (>3 x nml)	2.2% / 1.6%
	Depression	2.2% / 2.5%
	Cancer *	4.0% / 4.3%
CARE[16]	Elevated CK (>10 x nml)	0.6% / 0.3%
	Elevated liver enzymes (AST or ALT)	3.2% / 3.5%
	Cancer*	8.3% / 7.7%
WOSCOPS[98]	Elevated CK (>10 x nml)	0.09% / 0.03%
	Myalgias / muscle aches	3.5% / 3.7%
	Elevated ALT (>3 x nml)	0.48% / 0.36%
	Cancer*	3.5% / 3.2%
TexCAPS[99]	Elevated CK (>10 x nml)	0.6% / 0.6%
	Elevated AST or ALT (>3 x nml)	0.6% / 0.3%
	Cancer*	7.6% / 7.8%
LIPID[15]	Elevated CK (>10 x nml)	No difference
	Elevated ALT (>3 x nml)	2.1% / 1.9%
	Serious hepatic disease	No difference
	Cancer*	8.9% / 9.3%

NOTE: ALT = alanine amino transferase; AST = aspartate aminotransferase; CK = creatinine kinase; nml = normal; CARE = Cholesterol and Recurrent Events Study; LIPID = Long-Term Intervention with Pravastatin in Ischemic Disease; TexCAPS = Texas Coronary Atherosclerosis Prevention Study; WOSCOPS = West of Scotland Coronary Prevention Study.

*Incidence of new primary cancers (excluding nonmelanoma skin cancers).

Table 6. Adverse Effects of HMG Co-A Reductase Inhibitors (Statin Drugs), by Type of Harm

Source	Study Design	Findings
Myopathy, Elevated Creatinine Kinase, Rhabdomyolysis, and/or Renal Failure		
Pierce et al, 1990[118]	Case series (FDA)	12 case reports of elevated CK levels for patients taking lovastatin and gemfibrozil concurrently; 5 patients had associated, reversible ARF
Wallace and Mueller, 1992[119]	Case report	Rhabdomyolysis and ARF in patient who had been taking lovastatin for 14 months
Contermans et al, 1995[120]	RCT (24 subjects)	No difference between patients on simvastatin or pravastatin in exercise-induced CK release or muscle histology
Hill et al, 1995[121]	Letter/Case report	Dermatomyositis developing in a 76 yo woman taking simvastatin x 18 months – patient died of respiratory failure
Scalvini et al, 1995[122]	Case report	Myopathy and inflammatory changes on muscle biopsy in patient taking pravastatin x 5 months
Chu et al, 1997[123]	Case report	Rhabdomyolysis, renal failure requiring dialysis for 3 weeks after 4 weeks of lovastatin monotherapy
Giordano et al, 1997[124]	Case report	42 yo with elevated CK and polymyositis developing 3 months after starting simvastatin
Wicher-Muniak et al, 1997[125]	Case report	Elevated CK, muscle pain and weakness 2 months after starting simvastatin. Resolved off drug
Elevation of Liver Enzymes		
Hartleb et al, 1999[126]	Case report	57 yo man (taking 20 mg pravastatin/day x 2 months) found to have intrahepatic nonobstructive jaundice on biopsy; resolved off drug
Lens Opacities and Cataracts		
Laties et al, 1991[127]	RCT	No difference in lens opacities between lovastatin and placebo at 48 weeks (8245 patients enrolled)
Harris et al, 1995[128]	RCT	No evidence of differences in lens opacity between simvastatin and placebo at 18 months (621 patients)
Cancer		
Newman and Hulley, 1996[129]	Animal studies	Statin drugs and fibric acid derivatives have caused tumors (malignant and benign) in laboratory animals

Table 6. Adverse Effects of HMG Co-A Reductase Inhibitors (Statin Drugs), by Type of Harm (continued)

Source	Study Design	Findings
Depression or Decreased Cognition		
Boumendil and Tubert-Bitter, 1995[130]	Cohort study	Diet (PR = 1.83) and simvastatin (PR=2.18) associated with increased work absenteeism from depression
Cutler et al, 1995[131]	Cross-over trial	No differences in cognitive measures after 4 weeks among those taking simvastatin or pravastatin compared with controls
Davidson et al, 1996[132]	Before/after uncontrolled trial	Increased scores on CES-D scale screener after 6 weeks of therapy; 2 patients met criteria for depressed mood
Delva et al, 1996[133]	Nonrandomized experiment	Beck depression mean score lower (worse) in patients treated for high cholesterol (5.4) than in healthy controls (age and sex matched) (2.3)
Golomb 1998[134]	Systematic review	Several lines of evidence, including cohort data, animal studies, and some meta-analyses, support the link between low cholesterol and violence. Large RCTs have not found increased risk
Lupus-like Reaction		
Sridhar and Abdulla, 1998[135]	Case report	Case of woman who developed lupus reaction and ARDS (and later died) 1 week after starting fluvastatin
Peripheral Neuropathy		
Jeppesen et al, 1999[117]	Case reports	7 cases of peripheral neuropathy in patients where other potential causes had been excluded
Teratogenesis		
Manson et al, 1996[136]	Descriptive study	Rates of adverse pregnancy outcomes were not increased over expected in data from inadvertent exposures to lovastatin or simvastatin
Testicular Function		
Azzarito et al, 1996[137]	Before/after trial	8 patients had no changes in testicular function over 12 months of treatment with simvastatin

NOTE: ARDS = Acute Respiratory Distress Syndrome; ARF = acute renal failure; CES-D = Center for Epidemiological Studies-Depression; CK = creatinine kinase; PR = prevalence ratio; RCT = randomized controlled trial; yo = year old.

Table 7. Cumulative Incidence of Coronary Heart Disease Events in Men and Women With Type II Familial Hypercholesterolemia

Cumulative Risk of a CHD Event at Age:	Men		Women	
	Slack, 1969[196]	Stone et al, 1974[197]	Slack, 1969[196]	Stone et al, 1974[197]
30 years	5%	8%	0%	N/R
40 years	N/R	16%	N/R	9%
50 years	51%	N/R	12%	19%
60 years	85%	52%	58%	32%

NOTE: N/R = not reported.

Table 8. Sensitivity of Family History in Identifying Children and Young Adults With Lipid Disorders

Study/ Population	Lipid Level Used to Define Cases	Diagnostic Criteria	Sensitivity	Percentage Requiring Lipids Measured
NCEP/ LRC, 1992[96] Children 0-19	LDL > 130	Parental TC > 260 Parental TC > 240	29.7% 40.5%	18.3% 25.1%
Primrose et al, 1994[200] Children 12-15	TC > 200	1st or 2nd degree relative with CVD event < age 55	33%	N/A
Diller et al, 1995[198] Children < 20	LDL > 130	Family history (parents or grandparents) of CHD at age < 56	73.9%	47.8%
Simon Broome Register Group, 1991[238] British FH patients	N/A - FH cases age 20-39	MI in father < 55 or mother < 60	Men 39% Women 48%	N/A
Steiner et al, 1991[203] Urban HMO teen clinic- ages 12-21	TC > 250 TC > 200	Hyperlipidemia in parent or sibling; CHD in 1st or 2nd degree relative before age 65	82% 62%	N/A N/A
Garcia and Moodie, 1989[202]	LDL > 130*	1st or 2nd degree relative with MI < age 55 or known lipid disorder	52%	N/A
Dennison et al, 1989[199] Bogalusa Children 4-17	TC > 95th percentile for age	Parental history of heart attack, stroke, diabetes, or hypertension	White 4-10 years, 38% White 11-17 years, 59% African American 4-10 years, 27% African American 11-17 years, 25%	N/A
Resnicow and Cross, 1993[204]	TC > 200 mg/dL	Parental self-report of TC > 200 mg/dL	48.5%	34%
Benuck et al, 1992[205] Children 2-13 and parents	TC > 200 mg/dL	A parent with TC > 240 mg/dL A parent with TC > 200 mg/dL	27.5% 98%	52% 72%
Griffin et al, 1991[201] Children 2-13	> 90th percentile	Any family history of CHD or hyperlipidemia	51% 46%	N/A N/A

* Sensitivity did not improve when cases defined as LDL > 160 or 190 mg/dL

NOTE: FH = familial hypercholesterolemia; N/A = not available; CVD = cardiovascular disease; TC = total cholesterol; CHD = coronary heart disease; LDL = low-density hypoprotein; MI = myocardial infarction.

Table 9. Features of Different Screening Strategies for Adults

Test	Reliability	Accuracy	Patient Acceptability	Feasibility for Providers
Nonfasting TC	Intermediate	Lower	Higher	Higher
Nonfasting TC/HDL	Lower	Intermediate	Higher	Intermediate
LDL/HDL ratio requires fasting TC, HDL, triglycerides	Higher	Intermediate	Lower	Intermediate
Nonfasting TC + HDL and NCEP guidelines	Intermediate	Intermediate	Intermediate	Lower
Nonfasting TC + HDL with calculation of Framingham risk	Intermediate	Higher	Intermediate	Lower

NOTE: TC = total cholesterol; HDL = high-density lipoproteins; LDL = low-density lipoproteins; NCEP = National Cholesterol Educational Panel.

Table 10. Ratings of Aggregate Internal Validity, Aggregate External Validity, Coherence, and Overall Rating for Three Key Questions

Subsidiary Questions	Aggregate Internal Validity	Aggregate External Validity	Coherence	Overall Rating
Key Question No. 1. Drug Therapy				
Benefits	Good	Fair	Good	Good
Harms	Good (short term) Poor (long term)	Fair	Fair	Fair
Key Question No. 2. Diet Therapy				
Benefits (overall)	Good	Fair	Fair	Fair
Primary care studies	Good	Good	Fair	Good
Large MRF trials of diet	Good	Fair	Poor	Fair
Trials of effect of learning cholesterol	Fair	Fair	Fair	Fair
Harms (overall)	Poor	Fair	Poor	Poor
Key Question No. 3. Screening				
Reliability	Good	Good	Good	Good
Accuracy	Good	Fair	Good	Good
Acceptability	Poor	Poor	Poor	Poor
Feasibility	Poor	Fair	Poor	Poor
Harms	Fair	Fair	Poor	Poor

NOTE: See Appendix C for explanation of ratings.
MRF = multiple risk factor.

Evidence Table 1. Studies of Cholesterol Reduction with Drug Therapy in Primary Care

Source: Author, Year	Study Population	Size of Intervention & Control Groups	Study Population Diagnosis/Condition	Study Design & Characteristics
Lipid Research Clinics Program, 1984[96] *	Mean Age: 48 y % Female: 0 % White: 95.5 Mean BMI: 26.25 % HTN: 0 Mean SBP (mm Hg): Total: 119.6 Mean DBP (mm Hg): Total: 78.2 % Smokers: Total: 38 Initial TC (mg/dl) Interven: 291.5 Control: 291.8	Start Interven: 1,906 Control: 1,900 End Interven: NR Control: NR Total: NR	Inclusion: men ages 35-59 with TC > 265 and LDL > 190 Exclusion: history of MI or angina; angina on ETT; CHF; abnormal EKG; diabetes; hypothyroidism; liver disease; nephrotic syndrome; hyperuricemia; hypertension; cancer	Duration: 7.4 y Study Design: Placebo controlled, double-blind, multi-site clinical trial
Helsinki (HHS): Frick et al., 1987[97]	Mean Age: 47 y % Female: 0 % White: ~100 Mean BMI: 26.6 % HTN: 15 Mean SBP (mm Hg): Total: 141.7 Mean DBP: (mm Hg): Total: 91.25 % Smokers: Total: 36 Initial TC (mg/dl) Total: 288.9	Start Interven: 2,051 Control: 2,030 End Interven: NR Control: NR Total: 2,859 (no diff between grps)	Inclusion: healthy Finnish men ages 40-55 (civil service or industrial employees) with non-HDL chol > 200 Exclusion: clinical evidence of heart disease (angina or MI); CHF; abnormal EKG	Duration: 5 y Study Design: Random sampling, placebo controlled, double-blind, multi-site clinical trial

Note: Event rates are cumulative percentages with event over the study. Absolute Risk Reduction, Number Needed to Treat and Relative Risk Reduction are for the main outcome.

*Numbers in parentheses are 5-year outcomes for LRC

†Without unstable angina and numbers in parentheses are for nonfatal MI & CHD death

‡5% of patients had angina

Evidence Table 1. Studies of Cholesterol Reduction with Drug Therapy in Primary Care (cont'd)

	Results			
Interventions	**Lipids**	**Total & CHD Events**	**Main Outcome & Relative Risk for Main Outcome**	**Quality Considerations**
Interven: cholestyramine (24g qd) Control: placebo Both Grps: moderate cholesterol-lowering diet	% Net Reduction TC: 8.5%	Total Mortality % Interven: 3.6 Control: 3.7 CHD Mortality Rate Interven: 1.6 Control: 2	Definition: Total CHD Events Interven: 8.1 (5.5)† Control: 9.8 (6.6)† RRR Interven: 19% 95% CI for RRR 3 - 32% p value NR ARR Interven: 1.7 (1.1)† NNT 59 (91)†	Internal Validity good External Validity fair Quality Grade fair
Interven: gemfibrozil (600 mg bid) Control: placebo Both Grps: cholesterol-lowering diet	% Net Reduction TC: 11%	Total Mortality % Interven: 2.19 Control: 2.07 CHD Mortality Rate Interven: 0.68 Control: 0.94	Definition: Total CHD Events Interven: 5.5 Control: 7.9 RRR Interven: 34% 95% CI = 8 - 53% p < 0.02 ARR Interven: 1.4% NNT Interven: 71	Internal Validity good External Validity fair Quality Grade fair

Note: Event rates are cumulative percentages with event over the study. Absolute Risk Reduction, Number Needed to Treat and Relative Risk Reduction are for the main outcome.

*Numbers in parentheses are 5-year outcomes for LRC

†5% of patients had angina

‡Without unstable angina and numbers in parentheses are for nonfatal MI & CHD death

Evidence Table 1. Studies of Cholesterol Reduction with Drug Therapy in Primary Care(cont'd)

Source: Author, Year	Study Population	Size of Intervention & Control Groups	Study Population Diagnosis/Condition	Study Design & Characteristics
WOSCOPS: Shepherd et al., 1995[98] ‡	Mean Age: 55 y % Female: 0 % White: ~100 Mean BMI: 26 % HTN: 15 Mean SBP (mm Hg): Total: 135.5 Mean DBP: (mm Hg): Total: 84 Control: NR % Smokers Interven: 44 Control: 34 Initial TC (mg/dl) Total: 272	Start Interven: 3,302 Control: 3,293 End Interven: ~2,278 Control: ~2,305	Inclusion: men ages 45-64 with "elevated LDL cholesterol" Exclusion: history of MI; pathologic q waves on EKG; atrial fibrillation on EKG	Duration: 4.9 y Study Design: Random sampling, placebo controlled, double-blind, multi-site clinical trial
TexCAPS: Downs et al., 1998[99]	Mean Age: 58 y % Female: 15 % White: 89 Mean BMI: 27.05 % HTN: 22 Mean SBP (mm Hg): Total: 138 Mean DBP (mm Hg): Total: 78 % Smokers: Total: NR Initial TC (mg/dl) Total: 221	Start Interven: 3,304 Control: 3,301 End Interven: 2,335 Control: 2,081	Inclusion: men and women ages 45-73 for men and > 55 for women with "average TC and below average HDL" Exclusion: History of MI, or angina, claudication, CVA, or TIA; nephrotic syndrome; DM (on insulin); uncontrolled HTN	Duration: 5.2 y Study Design: Random sampling, placebo controlled, double-blind, multi-site clinical trial

Note: Event rates are cumulative percentages with event over the study. Absolute Risk Reduction, Number Needed to Treat and Relative Risk Reduction are for the main outcome.

*Numbers in parentheses are 5-year outcomes for LRC

†Without unstable angina and numbers in parentheses are for nonfatal MI & CHD death

‡5% of patients had angina

Evidence Table 1. Studies of Cholesterol Reduction with Drug Therapy in Primary Care (cont'd)

	Results			
Interventions	**Lipids**	**Total & CHD Events**	**Main Outcome & Relative Risk for Main Outcome**	**Quality Considerations**
Interven: pravastatin (40 mg qd) Control: placebo Both Grps: diet advice	% Net Reduction TC: 20% (based on actual use, not intention to treat)	Total Mortality % Interven: 3.2 Control: 4.1 CHD Mortality Rate Interven: 1.6 Control: 2.3	Definition: Total CHD Events Interven: 5.5 Control: 7.9 RRR Interven: 31% 95% CI = 17 - 43% p < 0.001 ARR Interven: 2.4 NNT Interven: 42	Internal Validity good External Validity fair-good Quality Grade good
Interven: lovastatin titrated(20-40 mg qd) Control: placebo (dummy-titrated) Both Grps: Step One Diet	% Net Reduction TC: 18% (at 1 y)	Total Mortality % Interven: 4.6 Control: 4.4 CHD Mortality Rate Interven: 0.5 Control: 0.7	Definition: Total CHD Events Interven: 3.4 (1.65)† Control: 5.45 (2.9)† RRR Interven: 37% (43)† 95% CI = 21 - 50% p < 0.001 ARR Interven: 2.05 (1.25)† NNT Interven: 49 (80)†	Internal Validity good External Validity good Quality Grade good

Note: Event rates are cumulative percentages with event over the study. Absolute Risk Reduction, Number Needed to Treat and Relative Risk Reduction are for the main outcome.

*Numbers in parentheses are 5 year outcomes for LRC

†Without unstable angina and numbers in parentheses are for nonfatal MI & CHD death

‡5% of patients had angina

Evidence Table 2. Studies of Cholesterol Reduction with Diet Therapy in Primary Care

Source: Author, Year	Study Population		Size of Intervention & Control Groups	Study Population Diagnosis/Condition
Roderick et al., 1997[144]	Mean Age: 47.3 y % Female: 50 % Racial Groups: NR Setting: Primary care clinic Mean BMI Interven: NR Control: NR Total: 26.1 HTN Interven: NR Control: NR	Mean SBP (mm Hg) Interven: 124 Control: 125 Mean DBP (mm Hg) Interven: 78 Control: 77 % Smokers Interven: 26 Control: 30 Initial TC (mg/dl) Interven: 241 Control: 244	Start Interven: 473 Control: 483 End Interven: 407 Control: 357	Inclusion: adults ages 35-59 from general practices in four geographic areas Exclusion: severe psychiatric disease, pregnancy, terminal illness
Bakx et al., 1997[148]	Mean Age: NR % Female: NR % Racial Groups: NR Setting: Primary care clinic Mean BMI Interven: NR Control: NR Total: 25.4 HTN Interven: NR Control: NR	Mean SBP (mm Hg) Interven: 144 Control: 150 Mean DBP (mm Hg) Interven: 88 Control: 92 % Smokers Interven: 60 Control: 54 Initial Total Chol (mg/dl) Interven: 244 Control: 237	Start Interven: NR Control: NR End Interven: 360 Control: 112	Inclusion: Finnish family practice patients with high risk of CHD Exclusion: NR
OXCHECK: (no author), 1994[149] and 1995[150]	Mean Age: 49.3 y % Female: NR % Racial Groups: NR Setting: Primary care clinic Mean BMI Interven: NR Control: NR Total: NR HTN Interven: NR Control: NR	Mean SBP (mm Hg) Interven: NR Control: NR Mean DBP (mm Hg) Interven: NR Control: NR % Smokers Interven: NR Control: NR Initial Total Chol (mg/dl) Interven: NR Control: NR	Start Interven: 2776 Control: 2783 End Interven: 1660 Control: 1916	Inclusion: adults ages 35-64 who were members of 1 of 5 general practices in Bedfordshire Exclusion: NR

Evidence Table 2. Studies of Cholesterol Reduction with Diet Therapy in Primary Care (cont'd)

Study Design & Characteristics	Interventions	Results: Lipids	Quality Considerations
Random sampling Duration: 1 y	Interven: Dietary advice from a specially trained nurse; medium intensity Control: Usual care (written booklets)	Final TC (mg/dl) Interven: 232 Control: 244 % Change in TC Interven: -3.7% Control: 0% Net Diff in mg/dl -7.8 (-15.5, 5.0) Net % Change -3.7% p value NS	Internal Validity Fair External Validity Fair Quality Grade Fair
Consecutive patients Duration: 17 y	Interven: 1 year of bimonthly diet advice (given 1978); medium intensity Control: Usual care	Final TC (mg/dl) Interven: 252 Control: 252 % Change in TC Interven: 3.3% Control: 6.3% Net Diff in mg/dl -7.8 (CI not reported) Net % Change -3.0% p value NS	Internal Validity Poor External Validity Fair Quality Grade Fair
Random sampling Duration: 4 y	Interven: Health check in 1989; (diet therapy, low intensity) Control: No health check in 1989	Final TC (mg/dl) Interven: 232 Control: 243 % Change in TC Interven: NR Control: NR Net Diff in mg/dl -7.37 (-4.66, -10.1) Net % Change -3.1% p value NR	Internal Validity Good External Validity Fair Quality Grade Fair

Evidence Table 2. Studies of Cholesterol Reduction with Diet Therapy in Primary Care

Source: Author, Year	Study Population		Size of Intervention & Control Groups	Study Population Diagnosis/Condition
Baron et al., 1990[151] [Results for men only]	Mean Age: 42 y % Female: 0 % Racial Groups: NR Setting: Primary care clinic Mean BMI Interven: 25.1 Control: 24.4 Total: NR HTN Interven: 12% Control: 14%	Mean SBP (mm Hg) Interven: NR Control: NR Mean DBP (mm Hg) Interven: NR Control: NR % Smokers Interven: 32 Control: 48 Initial Total Chol (mg/dl) Interven: 191 Control: 187	Start Interven: 97 Control: 92 End Interven: 77 Control: 79	Inclusion: members of a geographically defined general practice Exclusion: severe psychosis, debilitating chronic illness, chronic GI disease
Lindholm et al., 1995[152]	Mean Age: 48.7 y % Female: 15 % Racial Groups: NR Setting: Primary care clinic Mean BMI Interven: NR Control: NR Total: 27.1 HTN Interven: NR Control: NR	Mean SBP (mm Hg) Interven: 132 Control: 131 Mean DBP (mm Hg) Interven: 82 Control: 82 % Smokers Interven: 52 Control: 49 Initial Total Chol (mg/dl) Interven: 264 Control: 264	Start Interven: 339 Control: 342 End Interven: 306 Control: 320	Inclusion: adults ages 30-59 with 2 or more CV risk factors; cholesterol 6.5-7.79 mmol/L Exclusion: NR
Family Heart Study: Pyke et al., 1997[153] [Results for men only]	Mean Age: 51.5 y % Female: 0 % Racial Groups: NR Setting: Primary care clinics Mean BMI Interven: NR Control: NR Total: NR HTN Interven: NR Control: NR	Mean SBP (mm Hg) Interven: NR Control: NR Mean DBP (mm Hg) Interven: NR Control: NR % Smokers Interven: 24 Control: 24 Initial TC (mg/dl) Interven: NR Control: NR	Start Interven: 2,011 Control: 2,174 End Interven: 1,767 Control: 2,174	Inclusion: Britiol general practice patients Exclusion: NR

Evidence Table 2. Studies of Cholesterol Reduction with Diet Therapy in Primary Care (cont'd)

Study Design & Characteristics	Interventions	Results: Lipids	Quality Considerations
Random sampling Duration: 1 y	Interven: Dietary advice; medium intensity Control: No advice	Final TC (mg/dl) Interven: 175 Control: 175 % Change in TC Interven: -8.4% Control: -6.4% Net Diff in mg/dl NR Net % Change -2.0% p value NS	Internal Validity Good External Validity Fair Quality Grade Fair
Volunteers Duration: 1.5 y	Interven: Dietary advice; high intensity Control: Usual dietary advice	Final TC (mg/dl) Interven: NR Control: NR % Change in TC Interven: NR Control: NR Net Diff in mg/dl 5.82 (1.6, 10.0) Net % Change -2.2% p value NR	Internal Validity Good External Validity Fair Quality Grade Fair
Duration: 1 y	Interven: Nurse-led health check with targeted dietary advice Control: None	Final TC (mg/dl) Interven: 5.58 Control: 5.72 % Change in TC Interven: NR Control: NR Net Diff in mg/dl -0.13 Net % Change 2.3% p value NR	Internal Validity Good External Validity Fair Quality Grade Fair

Evidence Table 3. Study Characteristics of Multiple Risk Factor Interventions Including Diet

Source: Author, Year	Study Population	Size of Intervention & Control Groups	Study Population Diagnosis/Condition	Study Design & Characteristics
MRFIT: Neaton et al., 1992[2]	Mean Age: 46 y % Female: 0 % HTN: 62 Setting: Other Initial TC mg/dl Interven: 240 Control: 240 Initial HDL mg/dl Interven: 42 Control: 42	Start Interven: 6,428 Control: 5,438 End Interven: NR Control: NR	Inclusion: men ages 35-57 at increased risk of death from CHD Exclusion: known CHD, angina, diabetes (on meds or symptoms), Chol > 350 mg/dl, DBP > 115 mm Hg, > 150% IBW	Volunteers Duration: 6 y
WHO: (no author), 1986[158]	Mean Age: 48.5 % Female: 0 % HTN: N/A Setting: 66 factories in Europe Initial TC mg/dl Interven: NR Control: NR Initial HDL mg/dl Interven: NR Control: NR Mean BMI: 25.5 kg/m^2 % Smokers: 16%	Start Interven: 30,489 Control: 26,971 End Interven: NR Control: NR	Inclusion: factory workers ages 40-59 from 4 European countries Exclusion: NR	Random Sampling Duration: 6 y

Evidence Table 3. Study Characteristics of Multiple Risk Factor Interventions Including Diet (cont'd)

	Results			
Interventions	**Lipids**	**CHD Events and Mortality**	**Main Outcome & Relative Risk for Main Outcome**	**Quality Considerations**
Interven 1: Diet therapy Interven 2: Individual counseling including intensive treatment of HTN and smoking cessation Control: Usual care	Final TC Interven: 228 mg/dl Control: 233 mg/dl % Change in TC Interven: 5.0% Control: -2.9% Net % Change -2.0% p = < 0.01 Final HDL Interven: 41.7 Control: 41.9	Total CHD Events Interven: NR Control: NR % Diff (Adj) NR CHD Mortality Interven: 1.79 Control: 1.93 p value NS Nonfatal MI Interven: NR Control: NR Total Mortality Interven: 4.12 Control: 4.04 Diff in Total Mortality .8 p value NS	Definition: CHD mortality RRR Main Outcome: 7.2% ARR Main Outcome: 0.14% NNT: 714	Internal Validity Good External Validity Fair Quality Grade Good
Interven 1: Diet therapy Control: No tx	Net % Diff in TC -0.5%	Total CHD Events Interven: 3.08 Control: 3.27 % Diff (Adj) -10.2% p = 0.07 CHD Mortality Interven: 1.41 Control: 1.50 Nonfatal MI Interven: 1.93 Control: 2.11 Total Mortality Interven: 4.34 Control: 4.40 % Change in Total Mortality (adjusted for clustering) Interven: -5.3% p = 0.4	Definition: CHD mortality RRR Main Outcome: 6.9% (-19, 7) p value NS ARR Main Outcome: 0.09% NNT: 1,111	Internal Validity Good External Validity Poor Quality Grade Fair

Evidence Table 3. Study Characteristics of Multiple Risk Factor Interventions Including Diet (cont'd)

Source: Author, Year	Study Population	Size of Intervention & Control Groups	Study Population Diagnosis/Condition	Study Design & Characteristics
Oslo: Hjermann et al., 1981[159]	Mean Age: 45 y % Female: 0 % HTN: 22% Setting: Community Population Initial TC mg/dl Interven: 328 Control: 329 Initial HDL mg/dl Interven: 28.5 Control: 28.7 Mean BMI: NR % Smokers: NR	Start Interven: 604 Control: 628 End Interven: 590 Control: 625	Inclusion: men ages 20-49 at high risk of CHD Exclusion: known CHD, angina, diabetes, cancer, "disabling disease," alcoholism, psychiatric disease	Volunteers Duration: 5 y

Evidence Table 3. Study Characteristics of Multiple Risk Factor Interventions Including Diet (cont'd)

	Results			
Interventions	**Lipids**	**CHD Events and Mortality**	**Main Outcome & Relative Risk for Main Outcome**	**Quality Considerations**
Interven 1: Diet therapy Interven 2: Smoking cessation advice Control: No tx	Final TC Interven: 263 mg/dl Control: 341 mg/dl % Change in TC Interven: -19.8% Control: 3.6% Net % Change -23.4% p = < 0.01 Final HDL Interven: 50.1 mg/dl Control: 42.2 mg/dl % Change in HDL Interven: 76% Control: 47% Net % Change 29% p value NR	Total CHD Events Interven: 3.1 Control: 5.7 % Diff (Adj) NR CHD Mortality Interven: 1.0 Control: 2.2 Change in CHD Mortality Interven: 54.5 Nonfatal MI Interven: 2.2 Control: 3.5 Total Mortality Interven: 2.6 Control: 3.8 Change in Total Mortality Interven: -31.6 p = 0.246	Definition: Total CHD events RRR Main Outcome: 45.6% p = 0.038 ARR Main Outcome: 2.6% NNT: 38	Internal Validity Good External Validity Poor Quality Grade Fair

Evidence Table 3. Study Characteristics of Multiple Risk Factor Interventions Including Diet (cont'd)

Source: Author, Year	Study Population	Size of Intervention & Control Groups	Study Population Diagnosis/Condition	Study Design & Characteristics
Goteberg MRF: Wilhelmsen et al., 1986[160]	Mean Age: 51 y % Female: 0 % HTN: NR Setting: Community Population Initial Total Chol mg/dl Interven: 250 Control: 250 Initial HDL mg/dl Interven: NR Control: NR Mean BMI: NR % Smokers: NR	Start Interven: 7,455 Control: 2,501 End Interven: NR Control: NR	Inclusion: all men born 1915-1922 or 1924-1925 in Goteberg, Sweden Exclusion: None	Random sampling Duration: 10 y

Evidence Table 3. Study Characteristics of Multiple Risk Factor Interventions Including Diet (cont'd)

	Results			
Interventions	**Lipids**	**CHD Events and Mortality**	**Main Outcome & Relative Risk for Main Outcome**	**Quality Considerations**
Interven 1: Diet therapy Interven 2: Treatment of HTN and smoking Interven 3: Drug therapy if chol remained over 300 Control: No Tx	Final TC Interven: 234 mg/dl Control: 235 mg/dl % Change in TC Interven: -6.5% Control: -6.3% Net % Change -0.2% p value NS	Total CHD Events Interven: 8.4% Control: 8.4% % Diff (Adj) NR CHD Mortality Interven: 4.6% Control: 4.5% Nonfatal MI Interven: 5.0% Control: 4.9% Total Mortality Interven: 12.9% Control: 13.0% Change in Total Mortality Interven: 0.8% Change in CHD Mortality Interven: 0 Cumulative incidence over trial	Definition: Total CHD events RRR Main Outcome: 0 ARR Main Outcome: 0 NNT: N/A	Internal Validity Good External Validity Poor Quality Grade Fair

Evidence Table 3. Study Characteristics of Multiple Risk Factor Interventions

Source: Author, Year	Study Population	Size of Intervention & Control Groups	Study Population Diagnosis/Condition	Study Design & Characteristics
Helsinki MRF: Miettinen et al., 1985[161]	Mean Age: 48 y % Female: 0 % HTN: 33% Setting: Other Initial Total Chol Interven: 275 Control: 275	Start Interven: 612 Control: 610 End Interven: 575 Control: 580	Inclusion: businessmen born 1919-1934 in Helsinki, having at least 1 CV risk factor Exclusion: known CHD, angina, diabetes (glucose > 180 or req. drugs), SBP > 200, DBP > 115, EKG abn., malignancy, psychiatric disease	Volunteers Duration: 5 y

Evidence Table 3. Study Characteristics of Multiple Risk Factor Interventions

	Results			
Interventions	**Lipids**	**CHD Events and Mortality**	**Main Outcome & Relative Risk for Main Outcome**	**Quality Considerations**
Interven 1: Diet therapy and exercise program Interven 2: Smoking cessation advice Interven 3: Drug therapy for HTN and lipids Control: Given test results and referred to their own physician	Final TC Interven: 260 mg/dl Control: 295 mg/dl % Change in TC Interven: -5.5% Control: 7.3% Net % Change -12.8% p = < .01	Total CHD Events Interven: 3.1 Control: 1.5 P value NR CHD Mortality Interven: 0.7 Control: 0.2 Nonfatal MI Interven: 2.5 Control: 1.3 Total Mortality Interven: 1.6 Control: 0.8 Change in Total Mortality Interven: NR Change in CHD Mortality Interven: NR Nonfatal stroke Interven: 0 Control: 1.3%	Definition: Total CHD events RRR Main Outcome: NR ARR Main Outcome: -1.6% NNT: -62	Internal Validity Good External Validity Poor Quality Grade Fair

Evidence Table 4. Impact of Learning One's Cholesterol Level

Source: Author, Year	Study Population	Size of Intervention & Control Groups	Study Population Diagnosis/Condition	Study Design & Characteristics
Robertson et al., 1992[164]	Mean Age: N/A % Female: Interven: 54 Control: 63 Setting: Primary care/Community clinic % Smokers: 25 Initial TC mg/dl Interven: 223 Control: 215	Start Interven: 297 Control: 281 End Interven: N/A Control: N/A	Inclusion: patients attending their general practice office ages 25-64 Exclusion: chol > 380	Consecutive Duration: 3 mos
Elton et al., 1994[165] *	Mean Age: 38 % Female: Interven: 40 Control: 44 Setting: Other % Smokers: 18 Initial TC mg/dl Interven: 277 Control: 276	Start Interven: 239 Control: 256 End Interven: 229 Control: 240	Inclusion: employees of an industrial company in Manchester, UK Exclusion: age < 20 or > 65, previous knowledge of one's chol level	Volunteers from industrial company Duration: 13 wks Quasi-experimental design
Hanlon et al., 1995[166]	Mean Age: N/A % Female: 12 Setting: Other % Smokers: 36 Initial TC mg/dl Interven: 227 Control: 225	Start Interven: 263 Control: 233 End Interven: 211 Control: 193	Inclusion: employees at two engineering factories in Glasgow ages 20 - 65 Exclusion: taking lipid-lowering agents	Volunteers Duration: 5 mos F/U visit at 1 y
Strychar et al., 1998[167]	Mean Age: 50 y % Female: 34 Setting: Other % Smokers: 37 Initial TC mg/dl Interven: 198 Control: 210	Start Interven: ~250 Control: ~250 End Interven: 216 Control: 213	Inclusion: employees at 6 hospitals Exclusion: using medication for chol, HTN, CHD, pregnant women, diabetes, initial chol > 300	Volunteers Duration: 16 - 20 wks

*Quasi-experimental design. Results presented here only for subects with initial cholesterol > 250. Subjects with lower initial cholesterol levels showed no effect or had small increases compared with controls.

Evidence Table 4. Impact of Learning One's Cholesterol Level (cont'd)

	Results	
Interventions	**Lipids**	**Quality Considerations**
Interven: immediate feedback by means of fingerstick chol check; low intensity Control: no immediate feedback on chol check	Final TC Interven: 219 mg/dl Control: 213 mg/dl Change in TC mg/dl Interven: -4 Control: -2 Net % Change: .09% p value NS	Internal Validity good External Validity fair Quality Grade fair
Interven: told if their chol was "high, not so high, or below average"; medium intensity diet intervention Control: received diet advice without knowledge of chol level	Final TC Interven: 265 mg/dl Control: 276 mg/dl Change in TC mg/dl Interven: -11 Control: 0 Net % Change: 4% p = .024	Internal Validity fair External Validity fair Quality Grade fair
Interven: received health education and feedback on chol level; low intensity Control: internal control = subjects from a site who received neither health education nor feedback on their chol levels	Final TC Interven: 221 mg/dl Control: 224 mg/dl Change in TC mg/dl Interven: -6 Control: -1 Net % Change: 2% p = .02	Internal Validity good External Validity fair Quality Grade fiar
Interven: received their initial chol results at the beginning of the study; medium intensity Control: received initial and final chol results at the end of the study	Final TC Interven: 186 mg/dl Control: 198 mg/dl Change in TC mg/dl Interven: -12 Control: -12 Net % Change: 0 p value NR	Internal Validity good External Validity fair Quality Grade fair

Evidence Table 5. Dietary Interventions for Children

Source: Author, Year	Study Population	Size of Intervention & Control Groups	Study Population Diagnosis/Condition	Study Design & Characteristics
CATCH Study[177]	Mean age: 8.76 years % F = 48.2 Setting: 3rd–5th grade elementary schools Initial TC (mg/dL): I: 169.9 (0.4) C: 170.7 (0.8) ***Total Cholesterol measured in mg/dL	Start: 5106 (total) End: 4019	Schools were chosen based on geographic location, ethnic diversity, food service potential for intervention, commitment to offering at least 90 min/wk PE Students in 3rd grade at schools agreed to provide a blood sample at baseline	Fall 1991 – Spring 1994
CHP/NCEP Study[240]	I_1: mean age (SD): 6.3 (0.2) %F: 51 TC 125.8 (1.54) I_2: mean age (SD): 6.2 (0.2) %F: 50 TC 127.4 (1.54) C_1: mean age (SD): 6.3 (0.2) %F: 51 TC 125.8 (1.54) C_2: mean age (SD): 6.3 (0.2) %F: 51 TC 125.8 (1.54) Setting: 9 suburban pediatric practices	Start: 342 I_1: 88 I_2: 86 C_1: 87 C_2: 81 End: 292 I_1: 66 I_2: 73 C_1: 78 C_2: 75	3652 children between 3.3 and 9.9 years of age screened to identify those with plasma TC > 75th percentile who agreed to randomization normal controls randomly selected from children with TC < 60th percentile Exclusion: no secondary causes of increased cholesterol, body weight >85% but <130% of ideal	Oct. 1990 – Dec. 1992 RCT with 2 nutrition education interventions and 2 control groups (1 at-risk and 1 not at-risk) Assessed at baseline, 3, 6, 12 months

Evidence Table 5. Dietary Interventions for Children (cont'd)

Interventions	Lipids	Main Outcome & Relative Risk for Main Outcome	Quality Considerations
I_1: School-based program (food service modifications, PE interventions, and classroom health curricula) I_2: School-based program plus family-based program Control: usual health curricula, PE, and food service programs	Final TC (mg/dL): I: 168.7 C: 169.5 net % change=0	Fat content of school lunches significant decrease Intensity of physical activity in PE class significant increase No change in blood pressure, body size, or serum TC No harmful effects of low-fat diet on growth or development	Good Internal validity: good for school level; on student level, no data on individual participation in school lunch program No mention of interaction by site; good external validity No mention of blinded assessment
I_1: parent child autotutorial (PCAT), based on social-cognitive theory. Included 10 lessons (tapes and activities) for a 10-week period I_2: child and at least one parent attended 45-60 min session with dietitian C_1 & C_2: usual care, no educational materials	I_1: LDL decreased 4.6% - 7.9% from baseline, but not significantly different from C_1	I_1 had significant increase in knowledge I_1 & I_2 had significant decrease in total and saturated fat intake No significant time-related differences in height, weight, or weight for height median by quintile of fat as a percentage of energy	Good/Fair Internal validity: differential dropout (15% dropout, more among intervention than control); children with and without increased TC were combined for growth analysis External validity: children with increased cholesterol, predominately white, higher SES, 89% living with both biologic parents

Evidence Table 5. Dietary Interventions for Children (cont'd)

Source: Author, Year	Study Population	Size of Intervention & Control Groups	Study Population Diagnosis/Condition	Study Design & Characteristics
DISC study[170,171]	Mean age: 9.7 M 9.0 F % F: 45 Setting: children recruited from schools, HMOs, and pediatric practices Initial TC I: 200 (14.6) C: 200 (14.6) Initial HDL I: 57.1 (10.7) C: 57.0 (11.0)	Start I: 334 C:329 End I: 320 C: 303	44,000 children, 8–10 years of age at baseline prescreened to identify children with age & sex specific TC >75th percentile and < 99th percentile Pre-pubertal, normal psychosocial and cognitive development Exclusion: medical conditions, on medications affecting growth and/or blood lipids, family history of premature heart disease	6-center RCT starting in 1987, running three years, with blinded assessment at baseline, year 1 & year 3

Evidence Table 5. Dietary Interventions for Children (cont'd)

Interventions	Lipids	Main Outcome & Relative Risk for Main Outcome	Quality Considerations
Adherence to a diet with 28% energy from total fat, <8% saturated fat, 9% polyunsaturated fat, and <150 mg/day cholesterol Strategy based on social learning theory and social action theory: Yr1: 15 group and 4 individual meetings Yrs2 & 3: 4-6 group and individual meetings/yr with monthly phone calls Control: Usual care, given educational material available to public about heart-healthy diet. Told of increased cholesterol, no specific recommendations to see MD	Final TC I: 183.3 (21.5) C: 186.4 (22.3) % change I: 8.4% C: 6.8% Net % change 1.6%, p=0.04 Final HDL I: 52.7 (10.0) C: 52.6 (10.3)	Significant decrease in LDL in I Growth was comparable in both groups Serum ferritin decreased in both groups I (18.5%)>C (13%), but in both groups mean levels were above 75th percentile for age & sex No effect of low fat diet on puberty	Good Internal validity: Fair. Twice as many controls (8%) dropped out as intervention subjects (4%) and the two papers have opposite findings for ferritin External validity: Applies to pre-pubertal children with increased cholesterol

Evidence Table 5. Dietary Interventions for Children (cont'd)

Source: Author, Year	Study Population	Size of Intervention & Control Groups	Study Population Diagnosis/Condition	Study Design & Characteristics
STRIP Study [174,176]	Age – 5 months at enrollment %F: 49 Setting: Families recruited in well-baby clinics in Turku, Finland, at the routine 5-month visit. 56.5% of the eligible age cohort agreed to participate Initial TC: M I: 146.6 C: 149.7 F I: 162.1 C: 157.8 HDL: M I: 34.8 C: 35.2 F I: 35.2 C: 34.8	Start: 1062 End: 816	Healthy 5-month-old infants No discussion of exclusions	Infants enrolled between March 1990 and May 1992 at the age of 5 months; followed to age 4 years. Blood drawn at 7, 13, 24, 36 months

Evidence Table 5. Dietary Interventions for Children (cont'd)

Interventions	Lipids	Main Outcome & Relative Risk for Main Outcome	Quality Considerations
Counseling by nutritionist so that fat intake = 30-35% of total energy to age 3, then not exceed 30%. Tried to achieve polysaturated/monosaturated/saturated fat ratio of 1:1:1. Three or four day food records taken at 8, 13, 24, 36 months. Visits at 1-3 month intervals to age 2, then 2/yr to age 4 Controls: seen twice/year, received basic health education. Counseled to use cow's milk with a minimum of 1.9% fat Both groups advised to use supplemental Vitamin A (400*u*) and Vitamin D (10*u*)	Final TC: M I: 159.0 C: 171.4 F I: 171.8 C: 173.3 Final HDL M I: 40.5 C: 43.2 F I: 40.5 C: 41.7 % change in TC: + 8.4% intervention + 14.7% controls 6.3% net difference	Intervention group had significant decrease in intake of fat as percentage of total energy (31.2% versus 33.1%, p<0.001) and cholesterol from age 13 months through 4 years compared to control group. Results significant only in M No adverse affects on growth in either group Both groups had low intakes of Vitamin D and iron after age 2	Fair Internal validity: 23% dropout rate may affect internal validity. Also, the assessments were not blinded External validity: Healthy northern European infants and young children (exclusions not discussed)

Glossary of Evidence Tables Abbreviations

Abbr.	Definition
ARR	absolute risk reduction
abn	abnormal
adj	adjusted
bid	twice a day
BMI	body mass index
C	control
CHD	coronary heart disease
CHF	congestive heart failure
Chol	cholesterol
CI	confidence interval
cond	condition
CV	cardiovascular
CVA	cerebro-vascular accident
DBP	diastolic blood pressure
Diff	Difference
dL	deciliter
DM	diabetes mellitus
Dx	diagnosis
EKG	electrocardiogram
ETT	exercise treadmill test
F	female
g	grams
GI	gastrointestinal
Grps	groups
HDL	high density lipoprotein
Hg	hemoglobin
HTN	hypertension
Hx	history
I	intervention
IBW	ideal body weight
LDL	low density lipoprotein
M	male
MD	medical doctor
Meds	medications
mg	milligrams
MI	myocardial infarction
min	minute

Glossary of Evidence Tables Abbreviations (cont'd)

Abbr.	Definition
mm	millimeter
N/A	not applicable
NNT	numbers needed to treat
NR	not reported
NS	not significant
P	probability
PE	physical education
q.d.	every day
req	required
RRR	relative risk reduction
SBP	systolic blood pressure
SD	standard deviation
SES	socioeconomic status
TC	total cholesterol
TIA	transient ischemic attack
tx	treatment
wk	week
y, yr	years

Glossary of Evidence Tables Abbreviations (cont'd)

Study Names	Preferred Abbreviations
Helsinki Heart Study	HHS
Air Force / Texas Coronary Prevention Study	AFCAPS/TexCAPS or TexCAPS
Children's Health Project/National Cholesterol Education Program	CHP/NCEP
Cholesterol and Recurrent Events Study	CARE
Dietary Intervention Study in Children	DISC
Lipid Research Clinics Coronary Primary Prevention Trial	LRC
Long-term Intervention with Pravastatin in Ischemic Disease	LIPID
Multi-factor Primary Prevention Trial	MRF
Multiple Risk Factor Intervention Trial Research Group	MRFIT
Oslo Study Group	Oslo
Scandivanian Simvastatin Survival Study	4S
Special Turku Corony Risk Factor Intervention Project	STRIP
Veterans Administration High Density Lipoprotein Intervention Trial	VA HIT
West of Scotland Coronary Prevention Study	WOSCOPS
World Health Organization- European Collaborative Group	WHO