2. Screening for High Blood Cholesterol and Other Lipid Abnormalities

RECOMMENDATION

Periodic screening for high blood cholesterol is recommended for all men ages 35–65 and women ages 45–65. There is insufficient evidence to recommend for or against routine screening of asymptomatic persons over age 65, but recommendations to screen healthy men and women ages 65–75 may be made on other grounds (see *Clinical Intervention*). There is also insufficient evidence to recommend for or against routine screening in children, adolescents, or young adults. Recommendations for screening adolescents and young adults with risk factors for coronary disease, and against routine screening in children, may be made on other grounds (see *Clinical Intervention*). There is insufficient evidence to recommend for or against routine screening for other lipid abnormalities. All patients should receive periodic screening and counseling regarding other measures to reduce their risk of coronary disease (see Chapter 3, Screening for Hypertension; Chapter 54, Counseling to Prevent Tobacco Use; Chapter 55, Counseling to Promote Physical Activity; and Chapter 56, Counseling to Promote a Healthy Diet).

Burden of Suffering

Elevated blood cholesterol is one of the major modifiable risk factors for coronary heart disease (CHD),[1] the leading cause of death in the U.S. CHD accounts for approximately 490,000 deaths each year,[2] and angina and nonfatal myocardial infarction (MI) are a source of substantial morbidity. CHD is projected to cost over $60 billion in 1995 in the U.S. in medical expenses and lost productivity.[3] The incidence of CHD is low in men under age 35 and in premenopausal women (1–2/1,000 annually),[4] but climbs exponentially during middle age for both men and women. The onset of CHD is delayed approximately 10 years in women compared with men, probably due to effects of estrogen,[5] but women account for 49% of all CHD deaths in the U.S.[2] Clinical events are the result of a multifactorial process that begins years before the onset of symptoms. Autopsy studies detected early lesions of atherosclerosis in many adolescents and young

adults.[6–10] The onset of atherosclerosis and symptomatic CHD is earlier among persons with inherited lipid disorders such as familial hypercholesterolemia (FH)[11] and familial combined hyperlipidemia (FCH).[12]

Serum Cholesterol and Risk of Coronary Heart Disease. Epidemiologic, patho-logic, animal, genetic, and clinical studies support a causal relationship between blood lipids (usually measured as serum levels) and coronary atherosclerosis.[1,13–15] Extended follow-up of large cohorts (predominantly middle-aged men)[16–18] provides evidence that CHD risk increases in a continuous and graded fashion, beginning with cholesterol levels as low as 150–180 mg/dL;[a] this association extends to cholesterol levels measured as early as age 20 in men.[14,19] During middle age, for each 1% increase in total cholesterol, CHD risk increases by an estimated 3%.[20] High cholesterol (≥240 mg/dL) is also a risk factor in middle-aged women, but most coronary events in women occur well after menopause.[5,17,21–24] Some studies report that cholesterol alone is a weak predictor of CHD mortality in the elderly,[24a,190] but an overview of 24 cohort studies indicates that high cholesterol remains a risk factor for CHD after age 65,[23] with the strongest associations among healthier elderly populations followed over longer periods.[25–27] The association is weaker in older women than in men[23] and is not consistent for cholesterol levels measured after age 75.[28–31]

Expert panels have defined high and "borderline high" (200–239 mg/dL) cholesterol to simplify clinical decisions.[1] Because CHD is a multifactorial process, however, there is no definition of high cholesterol that discriminates well between individuals who will or will not develop CHD.[32,33] Due to nonlipid risk factors, persons with cholesterol below 240 mg/dL account for the majority of all CHD events.[34,35] Among middle-aged men, 9–12% of those with cholesterol 240 mg/dL or greater will develop symptomatic CHD over the next 7–9 years,[34,36] but most of them have multiple other risk factors for CHD.[35] The excess (i.e., absolute) risk due to high cholesterol (and the probable benefit of lowering cholesterol) increases with the underlying risk of CHD. In a 12-year study of over 316,000 men aged 35–57, the excess CHD mortality attributable to high cholesterol was greatest in men over age 45, and in those who smoked or had hypertension.[16] The increase in CHD mortality associated with a given increment in serum cholesterol was steepest at very high values (>300 mg/dL).[16] Excess risk from high cholesterol is smaller in women, who have less than half the CHD risk as do men at any given cholesterol level.[17,23,37] Although the relative risk associated with high serum choles-

[a]To convert values for serum total cholesterol, HDL-C, and LDL-C to mmol/L, multiply by 0.02586. Equivalent values for commonly used thresholds are 280 mg/dL = 7.2 mmol/L, 240 mg/dL = 6.2 mmol/L, 200 mg/dL = 5.2 mmol/L.

terol declines with age,[17,23,28] the excess risk generally does not, due to the much higher incidence of CHD in older persons.[31,38,39]

Other Lipid Constituents and Risk of Coronary Disease. The risk associated with high total cholesterol is primarily due to high levels of low-density lipoprotein cholesterol (LDL-C),[1] but there is a strong, independent, and inverse association between high-density lipoprotein cholesterol (HDL-C) levels and CHD risk.[40–42] Low HDL-C increases risk even when cholesterol is below 200 mg/dL,[41] a pattern present in up to 20% of men with confirmed CHD.[43] In many studies, measures of HDL-C or the ratio of total cholesterol to HDL-C are better predictors of CHD risk than is serum cholesterol alone.[5,22,23,24a,41,44] High total cholesterol in association with high HDL-C (≥60 mg/dL) is common in older women (especially those taking estrogen) but is not associated with an increased risk for CHD.[1,41] The importance of triglycerides as an independent risk factor for CHD remains uncertain.[40,45] Three large studies reported strong associations between triglyceride levels over 200–300 mg/dL (2.26–3.39 mmol/L) and cardiovascular mortality in women,[21,22,24] but other analyses found no association after controlling for obesity, fasting glucose, or low HDL-C.[46] The combination of high triglycerides and low HDL-C often occurs in association with other CHD risk factors such as hypertension and diabetes and is associated with a high risk of CHD.[46a]

Prevalence of High Cholesterol and Low HDL-C. Serum total cholesterol and LDL-C increase 1–2 mg/dL per year in men from ages 20–40, 2 mg/dL per year in women from ages 40–60,[47] and an average 18% during the perimenopausal period, due in part to age-related increases in weight.[48] The prevalence of serum cholesterol 240 mg/dL or higher increases from 8–9% in adults under age 35 to nearly 25% for men age 55 and nearly 40% for women over 65.[49] Approximately 11% of men and 3% of women over age 20 have low HDL-C (<35 mg/dL) with desirable or borderline-high total cholesterol.[49]

Accuracy of Screening Tests

Both total cholesterol and HDL-C can be measured in venipuncture or finger-stick specimens from fasting or nonfasting individuals. Due to normal physiologic variation and measurement error, a single measurement may not reflect the patient's true (or average) cholesterol level. Stress, minor illness, posture, and seasonal fluctuations may cause serum cholesterol to vary 4–11% within an individual.[50] Laboratory assays are subject to random errors, due to variation in sample collection, handling, and reagents, and to systematic errors (bias), due to methods that consistently overestimate or underestimate cholesterol values.[51] In a survey of 5,000 clinical laboratories, 93% of the measurements were within 9% of a reference standard.[52]

Desktop analyzers can produce reliable results, but some devices may not meet standards for accuracy.[53] Variation in training and operating technique can introduce additional error when instruments are used outside clinical laboratories.[54] Average bias for measurements based on capillary specimens compared to venous specimens was +4–7%.[55]

As a result of these considerations, a single measure of serum cholesterol could vary as much as 14% from an individual's average value under acceptable laboratory conditions.[50] For an individual with a "true" cholesterol level of 200 mg/dL, the 95% range of expected values is 172–228 mg/dL.[56] Some authorities therefore recommend advising patients of their "cholesterol range," rather than a single value.[56] Where more precise estimates are necessary, an average of at least two measurements on two occasions has been recommended, and a third if the first two values differ by more than 16%.[50]

Screening Children by Family History. Although cholesterol levels in child-hood correlate moderately well with levels in adulthood (correlation coefficient 0.4–0.6), many children with elevated serum cholesterol (defined as serum cholesterol ≥200 mg/dL or LDL-C ≥130 mg/dL, the 90–95th percentile in U.S. children under 19 years)[57] do not have high cholesterol as adults.[58–60] Furthermore, the association between childhood cholesterol levels and CHD in adults has not been studied. Because of the familial aggregation of CHD and hypercholesterolemia,[57,61,62] some experts recommend screening for family history of either premature cardiovascular disease (age 55 or younger) or parental hypercholesterolemia (≥240 mg/dL) to identify a subset of children who are more likely to be at risk from hypercholesterolemia as adults.[57] Under this definition, only 25% of all children would be screened, but the predictive value of family history is limited: 81–90% of children with such histories have normal cholesterol.[63–66] Even when parental cholesterol has been measured and found to be elevated, most children have normal cholesterol values.[57,67,68]

Parental and childhood cholesterol levels are highest in heterozygous FH (estimated prevalence 1 in 500), which is strongly associated with premature CHD. Up to 50% of men with FH develop clinical CHD by age 50.[69,70] Screening based on family history, as defined above, does not appear to be an efficient strategy for detecting FH, however. Many children would be screened, and few of those identified and treated for high cholesterol would have FH.[71] By itself, a parental history of premature CHD is likely to detect less than half of all children with FH.[70] Tracing and screening families of index cases with FH may be more cost-effective than population screening for FH.[72]

Screening for Other Lipid Abnormalities. Measurements of HDL-C and triglycerides are less reliable than measurement of total cholesterol due to greater

biologic and analytic variability.[73,74] The 95% range of expected values for an individual with HDL-C of 37 mg/dL is 29–45 mg/dL.[75] A survey of 250 laboratories found that one third of all HDL-C measurements varied more than 10% from a reference value.[76] Triglycerides must be measured on fasting specimens. Even then, intraindividual variation is greater than 20%, and a single measure is inadequate to categorize levels as high or normal.[73,74] Measurement of apolipoproteins (e.g., apoB) has been evaluated as a screening test for FH, familial coronary disease, and high LDL-C, but these assays are not yet widely available or adequately standardized.[57]

Effectiveness of Early Detection

No long-term study has compared routine cholesterol screening to alternate strategies (selective case-finding or universal dietary advice without screening) with change in cholesterol levels or CHD incidence as an outcome. The increase in cholesterol screening over the past decade in the U.S. has been accompanied by significant improvements in dietary knowledge,[77] fat consumption,[78] average cholesterol levels,[79] and CHD mortality,[14] but it is difficult to isolate the contribution of screening from other factors (e.g., public education, changes in food supply) that may account for these trends. In community- or practice-based trials, patients receiving risk-factor screening and targeted dietary advice had slightly lower average cholesterol levels (1–3%) than did unscreened controls at 1–3-year follow-up, but dietary interventions were limited.[80–82] Whether screening improves the effectiveness of routine dietary advice has been examined in two short-term studies where all subjects received counseling about diet; cholesterol screening modestly improved mean cholesterol levels in one study but had no effect in the other.[83,84] In a school-based study in which all children received similar health education, cardiovascular risk-factor screening (including cholesterol measurement) was associated with improved dietary knowledge and self-reported behavior, but changes in lipid levels were not assessed.[85]

The primary evidence to support cholesterol screening is the ability of cholesterol-lowering interventions to reduce the risk of CHD in patients with high cholesterol. These benefits are now well established for persons with preexisting atherosclerotic vascular disease. In individual trials and overviews of studies enrolling persons with angina or prior myocardial infarction (MI), cholesterol-lowering treatments slowed the progression of atherosclerosis,[86] reduced the incidence of CHD,[87,88] and reduced overall mortality.[89] In the first long-term trial of newer cholesterol-lowering drugs, treatment with simvastatin over 5.4 years reduced coronary mortality 42% and all-cause mortality 30% in 4,444 men and women with coronary disease.[90]

The absolute benefit of treating high cholesterol in persons without cardiovascular disease, however, is much smaller due to the much lower risk of death or MI (annual CHD mortality 0.1–0.3% in middle-aged men with asymptomatic high cholesterol vs. 2–10% per year in patients with symptomatic CHD).[91] The risks and benefits of lowering cholesterol in asymptomatic persons—primarily middle-aged men with very high cholesterol—have been examined in trials using medications, modified diets in institutional patients, or outpatient dietary counseling, and in overviews of these trials.

Trials of Cholesterol-Lowering Drugs in Asymptomatic Men. Three large, multicenter, placebo-controlled trials of lipid-lowering medications provide the best evidence that lowering cholesterol can reduce combined CHD incidence (fatal and nonfatal events) in asymptomatic persons. These trials enrolled hypercholesterolemic middle-aged men (age 30–59, mean cholesterol 246–289 mg/dL) and lowered total cholesterol 9–10% (and LDL-C 10–13%) over periods of 5–7 years. In the World Health Organization Cooperative Trial, treatment with clofibrate significantly reduced the incidence of nonfatal MI by 25%,[92] but this benefit was offset by significant increases in noncardiac and total mortality (40% and 30% respectively, $p = 0.01$).[93] The Lipid Research Clinics (LRC) Coronary Primary Prevention Trial reported a significant 19% reduction in cumulative incidence of MI and sudden cardiac death in patients treated with cholestyramine over 7 years (7.0% vs. 8.6%).[36] In the Helsinki Heart Study, treatment with gemfibrozil significantly reduced the 5-year cumulative incidence of cardiac events by 34% (2.7% vs. 4.1%).[94] Most of the benefit of gemfibrozil was confined to men with a high ratio of LDL-C to HDL-C (≥5) and triglycerides >200 mg/dL.[95] Effects on CHD mortality were not statistically significant in any of these trials. Two additional drug trials reported 1–3-year results in largely asymptomatic populations.[96,97] Roughly 30% of subjects had CHD at entry, however, and these patients accounted for most of the coronary events during follow-up.

Trials of Diet in Institutionalized Persons. Demonstrating a clinical benefit of modern cholesterol-lowering diets in asymptomatic persons has proven difficult. In three controlled trials in institutionalized patients, fat-modified diets reduced serum cholesterol 12–14% with generally favorable effects on CHD over periods of up to 8 years.[98–100] Each of these studies used diets high in polyunsaturated fat, which have been associated with adverse effects,[15] and none excluded patients with CHD. As a result, their findings may not be applicable to currently recommended low-fat diets in asymptomatic persons.

Trials of Dietary Advice in Outpatients. The only trials to examine the clinical benefits of a diet low in total and saturated fat in persons without CHD are

multifactorial intervention trials, which offered dietary counseling, smoking cessation advice, and/or treatment of high blood pressure to middle-aged men.[101–105] Among Norwegian smokers with very high cholesterol levels (mean 320 mg/dL) and fat consumption (44% calories), dietary advice lowered cholesterol 13% and, in conjunction with smoking cessation, reduced CHD incidence by 47%.[103] The remaining trials achieved much smaller (0–5%) reductions in cholesterol and insignificant effects on CHD; the benefits of intervention in some studies may have been limited by ineffective counseling and follow-up,[101,104] lower cholesterol levels at baseline,[101] or adverse effects of other therapies.[102,105] In the most systematic test of dietary counseling in adults, 10 weekly group sessions and periodic individual counseling were provided over 6 years to over 6,000 men (mean cholesterol 253 mg/dL).[102] Average cholesterol level declined 5% in men receiving counseling, but only 2% compared to controls. Greater changes were observed in men who lost at least 5 pounds and those with higher serum cholesterol at baseline,[106] but there was no significant reduction in CHD mortality or incidence in the intervention group.[102,107]

Short-term metabolic studies and selected trials in patients with CHD indicate that reducing dietary saturated fat and/or increasing polyunsaturated fat intake can reduce elevated total and LDL-C as much as 10–20%.[108–110] Due to variable compliance, trials of diet counseling in the primary care setting have achieved much smaller and inconsistent average reductions in serum cholesterol in asymptomatic persons (0–4%).[80–82,111–116] Although larger changes have been reported in uncontrolled follow-up studies after cholesterol screening,[117,118] these results may be biased by selective or short-term follow-up and regression to the mean in persons with high cholesterol. Ongoing studies are examining the efficacy of cholesterol screening and intervention in primary care settings in the U.S.[119] More stringent diets can produce larger reductions in cholesterol,[120] but long-term data in asymptomatic persons are limited. Two trials in women at risk for breast cancer lowered total fat intake to 20% of calories and reduced total cholesterol 6–7% over 1–2 years.[121,122]

Overviews of Cholesterol-Lowering Trials. At least 10 quantitative overviews (meta-analyses) of randomized trials have attempted to resolve uncertainties about the risks and benefits of lowering cholesterol, including effects on mortality.[18,88,89,91,123–128] Three recent overviews provide the most comprehensive analyses of long-term cholesterol-lowering trials published through 1993; 35 diet and drug trials were included in one analysis,[91] 28 in the second (excluding trials that used estrogens or thyroxine),[18,89] and 22 in the third (all trials achieving at least a 4% reduction in cholesterol for at least 3 years).[128] These overviews support a dose-response relationship between change in serum cholesterol and reduction in CHD incidence (fatal and nonfatal

events combined) comparable to that predicted from epidemiologic studies: after 2–5 years of treatment, each 1% reduction in serum cholesterol yields a 2–3% reduction in total CHD, for both diet and drug interventions, and in patients with or without CHD at entry.[18,89,128]

When only trials enrolling asymptomatic persons were analyzed, however, neither CHD mortality nor total mortality was significantly reduced by cholesterol lowering:[128] difference in total mortality among treated versus control subjects = +6%, 95% confidence interval (CI) –3% to +17%.[89] Moreover, noncardiac mortality was increased 20–24% among patients treated with lipid-lowering medications.[89,91,128] While observing similar effects of treatment, each overview offered distinct interpretations of these findings. Law et al. concluded that the increase in noncoronary mortality was most likely due to chance: the finding was of borderline statistical significance ($p = 0.02$), did not reflect any consistent cause of excess mortality among trials, and was independent of compliance with therapy.[89] Gordon attributed adverse effects to trials employing hormones or fibrate medications.[128] Davey Smith et al. concluded that lipid-lowering drugs reduced overall mortality in high-risk persons (i.e., persons with CHD), but were harmful in those at lower risk.[91] When trials were stratified by the observed CHD mortality in the control group, drug treatment was associated with a significant 20% increase in all-cause mortality in 10 trials enrolling low-risk subjects (CHD mortality <1% per year), including the WHO, LRC, and Helsinki studies.[91] A single trial (the WHO clofibrate study) accounts for nearly half of all patient-years of treatment in persons without CHD[128] and has a strong influence on results of any meta-analysis.

Due to methodologic concerns about combining results from trials employing different cholesterol-lowering drugs and diets, meta-analysis cannot prove or disprove possible harms from lipid-lowering medications.[129] These analyses, however, illustrate the importance of underlying CHD risk in determining whether expected benefits are likely to justify possible risks of treatment. Even if drugs are safe, the margin of benefit may be small for many persons with asymptomatic hypercholesterolemia. In the LRC and Helsinki trials, preventing one coronary death required treating 300–400 middle-aged men for 5–7 years.[36,94] The benefits of lipid-lowering medications on nonfatal CHD are more pronounced but must be weighed against the unpleasant and occasionally serious side effects of some drugs (see below).[92,127,130] The newest class of lipid-lowering drugs, HMG-CoA reductase inhibitors or “statins,” lowers cholesterol more effectively and appears to be well-tolerated in trials lasting up to 6 years.[90,97] These drugs are more likely to have significant effects on mortality in patients without CHD, but long-term trials of these agents in asymptomatic persons have yet to report results.[131]

Cholesterol Reduction in Women. Lipid-lowering medications and diet effectively lower cholesterol in women,[132] but no trial has specifically examined the benefits of cholesterol reduction in asymptomatic women.[133] Trials that included female subjects with CHD observed qualitatively similar benefits of cholesterol reduction on angiographic or clinical endpoints in women and men.[90,99,133] In the 4S trial, simvastatin significantly reduced CHD incidence, but not mortality, in women with CHD.[90] Two trials in women without CHD, with a cumulative enrollment of more than 6,000 women, observed no effect of drug or diet treatment on CHD incidence or mortality after 1–3 years;[96,100] the short duration of follow-up may have limited the power of these studies to detect a difference.[133] Long-term data on drug therapy in women are limited, with the exception of estrogen therapy (see Chapter 68).

Cholesterol Reduction in Older Adults. The benefit of lowering cholesterol in older persons has been questioned due to the weak association between serum cholesterol and all-cause mortality after age 60.[17,28,30] Associations between cholesterol and mortality in unselected elderly populations, however, are likely to be confounded by the increasing prevalence of chronic illnesses which increase mortality and independently lower serum cholesterol.[26,134,135] Direct evidence that cholesterol reduction is beneficial in asymptomatic older persons is not yet available, but cholesterol-lowering diets and medications reduced overall mortality 26–30% in persons over 60 with clinical CHD.[90,136,137] In two trials in patients without CHD that included older subjects, however, cholesterol reduction produced significant benefits in younger but not in older patients (over age 60 or 65).[96,98] Newer cholesterol-lowering agents are efficacious and well-tolerated in older patients.[90,138] A large multicenter trial is under way to examine the effectiveness of pravastatin and various antihypertensive medications in asymptomatic persons over age 60 with hypertension and high cholesterol.[138] There are few controlled trials of dietary counseling to lower cholesterol in older patients; no significant change in cholesterol levels was observed among rural Medicare recipients offered diet counseling[139] or older patients receiving diet counseling and placebo medication.[138]

Cholesterol Reduction in Adolescents and Young Adults. Determining the benefits of lowering cholesterol in children, adolescents, and young adults is difficult, due to their low near-term risk of clinical coronary disease. The assumption that early treatment is more effective than treatment begun later in life[57] rests on observations that early atherosclerosis is present in many adolescents and young adults, is associated with lipid levels, progresses with age,[6] and is difficult to reverse in middle age.[86] New evidence, however, suggests that much of the clinical benefit of lowering cholesterol can

be achieved within 2–5 years of initiating therapy.[18] These benefits have been attributed to stabilizing "lipid-rich" lesions[87] and improving endothelial function,[140] and they suggest that the additional benefits of early drug therapy for hypercholesterolemia (i.e., before middle age) may not justify the added expense and possible risks of longer treatment. Intensive diet or drug intervention for adolescents and young adults with FH, although never tested in a prospective trial, has become standard treatment due to the very high levels of LDL-C and dramatically increased risk of premature CHD in persons with FH.[11,71] Even in FH, however, most clinical events occur in middle age (i.e., after age 40), and risk is variable: MI was rare before age 30 in men in one study, and onset of CHD is later in women and nonsmokers with FH.[69,141]

Modified diets lower cholesterol in young adults, but the contribution of universal screening in motivating risk reduction in young persons is uncertain. Neither a multiple-intervention trial in Australian workers[142] nor a study of risk assessment in a general practice in the U.K.[116] demonstrated that screening and dietary advice led to long-term reduction in cholesterol levels in younger men (under age 35–40). The effectiveness of screening and dietary counseling has not been adequately studied in young adults and cannot be predicted reliably from studies in middle-aged men.

Cholesterol Reduction in Children. Dietary fat intake in children is associated with total cholesterol and LDL-C levels,[143,144] but controlled trials have not consistently demonstrated that individual dietary counseling is effective in children.[145–147] Results from the largest trial reported that children with elevated LDL-C who received intensive family-oriented dietary counseling (30 sessions over 3 years) experienced a significant but modest (3.2 mg/dL) reduction in mean LDL-C compared with controls.[148] Uncontrolled studies of dietician counseling for hyperlipidemic children and adolescents have reported larger short-term reductions in mean cholesterol and LDL-C,[149–153] but such studies are prone to bias from regression to the mean and selective follow-up. Physical activity and fitness are associated with higher levels of HDL-C in children and adolescents, but controlled and uncontrolled trials[154–159] have reported inconsistent effects of exercise interventions on lipids. Drug therapy effectively lowers cholesterol in children, but side effects limit compliance with bile-acid resins, the only therapy currently recommended for routine use in children.[57] In one study of 80 children with FH or FCH, only 13% were still compliant with resin therapy after 3 years.[160] Ongoing studies are examining the safety and efficacy of newer agents in children.

Potential Adverse Effects of Screening and Intervention. Measurement of serum cholesterol is safe and relatively inexpensive, but widespread screening may have some undesirable consequences. In populations in which the potential ben-

efits of early detection may be small (e.g., low-risk young persons), the possibility of harm may influence decisions about universal screening.[161] Anecdotal reports have reported decreased well-being in persons diagnosed with high cholesterol (i.e., "labeling"),[162] but a prospective study did not confirm this effect.[163] Other possible adverse effects of screening include inconvenience and expense of screening and follow-up, opportunity costs to the busy clinician, misinformation due to inaccurate results, and reduced attention to diet in persons with "desirable" cholesterol levels.[164] The importance of possible adverse effects of screening has not been systematically studied.

The safety of cholesterol-lowering interventions is especially important in children and young persons. Dietary restrictions may reduce intake of calories, calcium, vitamins, and iron in children,[165–167] and failure-to-thrive due to excessively fat-restricted diets has been reported, albeit rarely, in children.[168,169] In the most comprehensive trial of dietary intervention in children, however, no adverse effects on growth, sexual development, psychological measures, iron status, or blood micronutrients were detected at 3-year follow-up.[148] Other controlled studies also support the safety of properly performed dietary intervention in children.[147,166,170] The elderly may also be at risk from modified diets if adequate intake of calories, calcium, and essential vitamins is not maintained, but these effects have not been directly examined.

The inappropriate use of drug therapy is of greater concern, especially in young persons in whom the benefit of early drug treatment may not justify the costs and possible risks.[18,161] According to a national survey of pediatricians and family physicians, one in six regularly prescribed drugs for hypercholesterolemic children, and a substantial number did so based on inappropriate criteria, or used drugs not routinely recommended for children.[171] Persons under age 40 accounted for over 1 million prescriptions for lipid-lowering drugs in 1992;[172] gemfibrozil was the second most commonly prescribed lipid-lowering drug in the U.S. in 1992,[172] despite limited indications for its use[1] and important safety concerns. Fibrate medications (e.g., clofibrate and gemfibrozil) have been associated with an increase in gallstone disease,[92] adverse trends in CHD mortality[93,173] and cancer mortality in individual trials,[93,174] and a significant increase in noncoronary mortality in a recent overview of long-term trials.[128] HMG-CoA reductase inhibitors have not been associated with important adverse effects in trials lasting up to 6 years.[90] The safety of lifelong therapy with these agents cannot yet be determined; several medications in this class have been reported to cause liver tumors in animal studies.

Early Detection of Other Lipid Abnormalities. The importance of detecting low HDL-C or high triglycerides remains unproven, especially in persons with normal serum cholesterol. Weight loss in obese subjects,[132,175] smoking

cessation, exercise,[176,176a] and moderate alcohol consumption[177] can raise HDL-C and/or lower triglyceride levels. Some of these lifestyle interventions have only small effects, however, and most can be recommended independent of lipid levels. Most importantly, no trial has directly examined the benefit of raising HDL-C or lowering triglycerides.[40,45] Secondary analyses of several trials have attributed varying proportions of the clinical benefit of drug therapy to increases in HDL-C,[40,94,95] or reductions in triglycerides,[136] but all of the subjects had high total or LDL cholesterol. The benefit of drug treatment for low HDL-C and normal cholesterol has not been determined but is being studied in men with CHD.[43]

Recommendations of Other Groups

The National Cholesterol Education Program Adult Treatment Panel II, convened by the National Heart, Lung, and Blood Institute, recommends routine measurement of nonfasting total cholesterol and HDL-C in all adults age 20 or older at least once every 5 years.[1,178] The Canadian Task Force on the Periodic Health Examination concluded there was insufficient evidence to recommend routine cholesterol screening but endorsed case-finding in men 30–59 years old.[127] The American Academy of Family Physicians[179] recommends measurement of total cholesterol at least every 5 years in adults age 19 and older; these recommendations are under review. The American College of Obstetricians and Gynecologists recommends periodic screening of cholesterol in all women over age 20, and in selected high-risk adolescents.[180] In guidelines revised in 1995, the American College of Physicians (ACP) concluded that screening serum cholesterol was appropriate but not mandatory for asymptomatic men aged 35–65 and women aged 45–65; screening is not recommended for younger persons unless they are suspected of having a familial lipoprotein disorder or have multiple cardiac risk factors. The ACP concluded that evidence was not sufficient to recommend for or against screening asymptomatic persons between the ages of 65 and 75, but it recommends against screening after age 75.[181]

Selective screening of children and adolescents is recommended by the National Cholesterol Education Program Expert Panel on Blood Cholesterol Levels in Children and Adolescents,[57] the American Academy of Pediatrics (AAP),[182] the Bright Futures guidelines,[183] the American Medical Association Guidelines for Adolescent and Preventive Services (GAPS),[184] and the American Academy of Family Physicians.[179] Screening with nonfasting cholesterol in all children and adolescents who have a parental history of hypercholesterolemia, and with fasting lipid profile in those with a family history of premature cardiovascular disease, is recommended. These organizations recommend that children who have multiple risk fac-

tors for CHD (such as smoking or obesity) and whose family history cannot be ascertained be screened at the discretion of the physician.

Discussion

Elevated serum cholesterol is an important risk factor for CHD in men and women in the U.S., and there is now good evidence that lowering serum cholesterol can reduce the risk of CHD. Whereas measures that lower serum cholesterol and provide other health benefits (e.g., regular physical activity, reducing dietary fat, and maintaining a healthy weight) should be encouraged in all persons, cholesterol screening can identify high-risk individuals who are most likely to benefit from individualized dietary counseling or drug treatment. In addition, screening may help clinicians and patients identify priorities for risk factor modification and reinforce public awareness of the importance of a healthy diet.

Some important questions remain, however, about routine lipid screening in asymptomatic and low-risk persons, including when to begin screening and which constituents to measure. Overall, evidence is strongest for screening for high serum cholesterol in middle-aged men (ages 35–65), based on the reduction in coronary morbidity in trials enrolling asymptomatic men with very high cholesterol (mean 280 mg/dL). The epidemiology and pathophysiology of CHD is similar in men and women, suggesting that reducing high cholesterol levels will also reduce CHD in asymptomatic women. Extrapolations to premenopausal women may not be appropriate, given their low risk of CHD and the apparent protective effects of estrogen on CHD incidence. The optimal age to screen women is not known; the later onset of hypercholesterolemia and CHD suggests that routine screening should begin around age 45.

Direct evidence that screening and intervention is effective in persons over age 65 is not yet available, but epidemiologic studies indicate that the risks of high cholesterol extend up to age 75. Given the high risk of CHD in the elderly, and the benefits of lowering cholesterol in symptomatic older men and women, screening may be reasonable in older persons who do not have major comorbid illnesses. Since individual cholesterol levels usually plateau by age 65 in women (and earlier in men), continued screening is less important in patients who have had desirable cholesterol levels throughout middle age.

There is not yet evidence that routine lipid screening is effective in reducing cholesterol levels or CHD risk in younger populations. Universal screening is an inefficient way to identify the small number of hypercholesterolemic young persons at risk for premature CHD, most of whom have multiple nonlipid risk factors or a history suggestive of familial dyslipidemia. Most “high-risk” young persons (excluding young men with FH)

have a near-term risk of CHD well below that of hypercholesterolemic middle-aged men,[185] and are not appropriate candidates for early drug therapy. Screening young persons can provide information to help stimulate lifestyle changes, but promoting a healthy lifestyle (e.g., healthy diet, regular physical activity, etc.) is important for all young persons, including the majority with "desirable" cholesterol levels. International comparisons suggest that cholesterol levels explain only part of the strong association between diet and heart disease.[186a] As a result, it is uncertain whether routine cholesterol screening in low-risk younger populations is of sufficient benefit to justify the inconvenience, costs, and possible risks of screening and treatment. In a study modeling benefits of cholesterol screening, a conservative strategy of screening only middle-aged men and others with multiple CHD risk factors produced benefits comparable to screening all adults over age 20; if interventions had adverse effects on quality of life, the more conservative strategy was preferable.[186] Should future studies demonstrate that routine screening and targeted interventions are more effective in the primary care setting than universal dietary advice in young persons, this would provide some additional justification for early screening.

The benefits of screening children are even less certain. Progression of atherosclerosis in childhood is limited, many children with high cholesterol are not hypercholesterolemic as adults, and it is uncertain whether or not reducing cholesterol levels in childhood will significantly alter the risk of CHD many years later. Given the limited effectiveness of dietary counseling, poor compliance with currently recommended drug therapy, and the potential for adverse reactions in children, widespread pediatric screening might result in more harm than good.

The benefit of measuring HDL-C or triglycerides at initial screening is unproven. Measures to lower high triglycerides or raise HDL-C (e.g., weight reduction in obese persons and exercise) have relatively modest effects and should be encouraged regardless of lipid levels. Measures of HDL-C and lipoprotein analysis improve the estimation of coronary risk and should be obtained to guide treatment decisions in patients with high total cholesterol. There is, however, no evidence that they significantly improve the management of patients who do not have high total cholesterol.

While a single cholesterol test is relatively inexpensive, the cumulative costs of screening can be substantial under protocols calling for measurement of HDL-C, periodic screening, and detailed evaluation and treatment of the large population with high cholesterol. To be effective, dietary interventions require regular follow-up and reinforcement. Under optimistic assumptions, tailored dietary therapy in middle-aged men is estimated to cost more than $20,000 per year of life gained, when costs of screening and follow-up are included.[187] Drug treatment of asymptomatic

middle-aged men (assuming no important adverse effects) has been estimated to cost at least $50,000–90,000 per year of life saved.[35,188] HMG-CoA reductase inhibitors are substantially more expensive than earlier medications, but they lower LDL-C more effectively and also raise HDL-C. These agents may improve the cost-effectiveness of drug therapy for asymptomatic hypercholesterolemia, especially in high-risk men,[189] but the long-term safety and effectiveness of these agents in persons without CHD have not yet been established.

CLINICAL INTERVENTION

Periodic screening for high blood cholesterol, using specimens obtained from fasting or nonfasting individuals, is recommended for all men ages 35–65 and women ages 45–65 ("B" recommendation). There is insufficient evidence to recommend for or against routine screening in asymptomatic persons after age 65, but screening may be considered on a case-by-case basis ("C" recommendation). Older persons with major CHD risk factors (smoking, hypertension, diabetes) who are otherwise healthy may be more likely to benefit from screening, based on their high risk of CHD and the proven benefits of lowering cholesterol in older persons with symptomatic CHD. Cholesterol levels are not a reliable predictor of risk after age 75, however. There is insufficient evidence to recommend routine screening in children, adolescents, or young adults ("C" recommendation). For adolescents and young adults who have a family history of very high cholesterol, premature CHD in a first-degree relative (before age 50 in men or age 60 in women), or major risk factors for CHD screening may be recommended on other grounds: the greater absolute risk attributable to high cholesterol in such persons, and the potential long-term benefits of early lifestyle interventions in young persons with high cholesterol. Recommendations against routine screening in children may be made on other grounds, including the costs and inconvenience of screening and follow-up, greater potential for adverse effects of treatment, and the uncertain long-term benefits of small reductions in childhood cholesterol levels.

The appropriate interval for periodic screening is not known. Periodic screening is most important when cholesterol levels are increasing (e.g., middle-aged men, perimenopausal women, and persons who have gained weight). An interval of 5 years has been recommended by experts,[1] but longer intervals may be reasonable in low-risk subjects (including those with previously desirable cholesterol levels).

There is insufficient evidence to recommend for or against routine measurement of HDL-C or triglycerides at initial screening ("C" recommendation). For high-risk persons (middle-aged persons with high cholesterol or multiple nonlipid risk factors for CHD), measurement of HDL-C

or lipoprotein analysis can be recommended to help identify individuals at highest risk of CHD, in whom individual diet or drug therapy may be indicated.

Decisions about interventions for high cholesterol should be based on at least two measures of cholesterol and assessment of the absolute risk of CHD in each individual. This assessment should take into account the age of the patient (higher risk in men over 45 and women over 55), results of lipoprotein analysis (or ratio of total cholesterol to HDL-C), and the presence and severity of other risk factors for CHD (see above). [178] More specific algorithms for risk assessment have been published. [185] Initial therapy for patients with elevated cholesterol is counseling to reduce consumption of fat (especially saturated fat) and promote weight loss in overweight persons. A two-step dietary program effective in lowering serum cholesterol has been described in detail elsewhere.[1] Benefits of drug therapy are likely to justify costs and potential risks only in persons at high risk of CHD (e.g., middle-aged men and postmenopausal women with very high cholesterol or multiple risk factors). The risks and benefits of drug therapy in asymptomatic persons over 65 have not yet been determined. In postmenopausal women with high cholesterol, estrogen therapy can lower LDL-C and raise HDL-C and is associated with lower risk of CHD in epidemiologic studies (see Chapter 68). Patients should receive information on the potential benefits, costs, and risks of long-term therapy before beginning treatment on cholesterol-lowering drugs.

All adults, adolescents, and children over age 2 years, including those with normal cholesterol levels, should receive periodic counseling regarding dietary intake of fat and saturated fat (see Chapter 56) and other measures to reduce the risk of coronary disease (see Chapters 3, 54, and 55).

The draft update of this chapter was prepared for the U.S. Preventive Services Task Force by David Atkins, MD, MPH, and Carolyn DiGuiseppi, MD, MPH.

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