Screening and Management of Lipids

Lipid Therapy Guideline Team

Team Leader

William Barrie, MD
General Medicine

Team Members

Van Harrison, PhD
Medical Education

Ujjaini Khanderia, PharmD
Pharmacy

Robert Kiningham, MD
Family Medicine

Shawna Nesbitt, MD
Hypertension

Melvyn Rubenfire, MD
Cardiology

Developed
May, 2000
(Next Update, May 2002)

UMHS Guidelines Oversight Team

Connie Standiford, MD
Lee Green, MD, MPH
Van Harrison, PhD
Renée Stiles, PhD

Literature search service
Taubman Medical Library

For more information call
GUIDES: 936-9771

Patient population: Adults 20-75 years of age without familial or severe dyslipidemias.

Objective: Primary and secondary prevention of coronary heart disease (CHD) and stroke by outlining strategies for lipid screening, identifying patients who would benefit from treatment, and recommending appropriate treatment regimens.

Key Points

■ **Primary Prevention**

Screening. Screen men age 35-65, and women age 45-65. Screening is optional for men age 20-34 and women age 20-44. Screening should be considered in both men and women ages 65-75 based on life expectancy. Repeat screening in 5 years in patients with normal lipids *[D*]*. Screen with fasting or non-fasting total cholesterol (TC) and HDL cholesterol *[D*]*.

Treatment.

- Initial treatment: lifestyle modification - smoking cessation, diet, exercise, and weight reduction *[A*]*.
- Drug therapy. Consider after 6 or more months if LDL-C remains elevated in those at high risk for CHD *[A*]*.

■ **Secondary Prevention**

Screening. Screen all patients with CHD or other atherosclerotic cardiovascular disease (ASCVD), including stroke and peripheral vascular disease *[A*]*. Screen annually *[D*]*.

Treatment. Treat patients with LDL-C >100 mg/dl *[A*]*.

- Initial treatment: lifestyle modification (described above) *[A*]* and dietary consultation *[D*]*.
- Drug therapy. After a 6-12 week trial of lifestyle modification, initiate drug therapy for patients with LDL-C > 125 mg/dl *[A*]*. For elevated LDL-C after acute CHD event, consider immediate drug therapy *[D*]*.
  - Statins reduce mortality and CHD/ASCVD endpoints *[A*]*.
  - Consider treating isolated low HDL-C, which has been shown to reduce CHD events, but not total mortality *[A*]*.

■ **Cost effectiveness**

- Currently, cerivastatin (lowers LDL-C ≤ 42%) and atorvastatin (lowers LDL-C 30-60%) are the most cost-effective agents.

■ **Special Populations**

Diabetes mellitus (DM) patients have a marked increased risk for CHD. Those without CHD should have annual lipid profile. Treatment goals are those for secondary prevention *[D*]*.

*** Levels of evidence reflect the best available literature in support of an intervention or test:**
A=randomized controlled trials; B=controlled trials, no randomization; C=observational trials; D=opinion of expert panel.

Clinical Background

Clinical Problem

Incidence. Coronary heart disease (CHD) and stroke are the two most important causes of death and disability in developed countries. While there has been a significant reduction in cardiovascular events in the past decade, in 1998 about 1.5 million people in the US suffered a myocardial infarction with 500,000 deaths at a cost over $95 billion.

It is estimated that over 50% of first CHD events and 75% of CHD deaths are preventable with use of evidence-based strategies, including diet, exercise, weight and BP control, aspirin, and lowering lipids. Roughly 20% of the US adult population has total cholesterol (TC) > 240mg/dl, and another 30% have borderline TC (200-240mg/dl).

(continued on page 6)

Figure 1. Primary Prevention

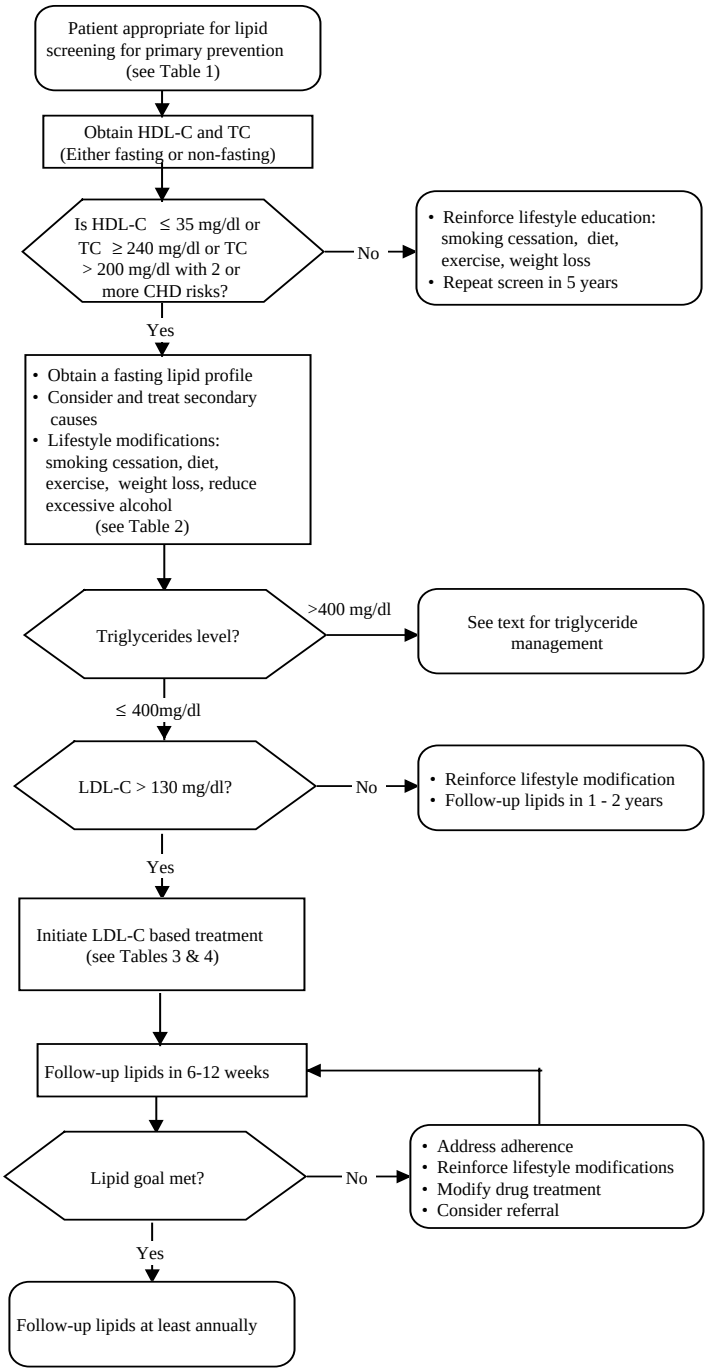


Table 1. Candidates for Lipid Screening for Primary Prevention *

Recommended for:
Men age 35 - 65
Women age 45 - 65

Optional for:
Men age 20 - 34
Women age 20 - 44
Anyone age 65-75 based on life expectancy

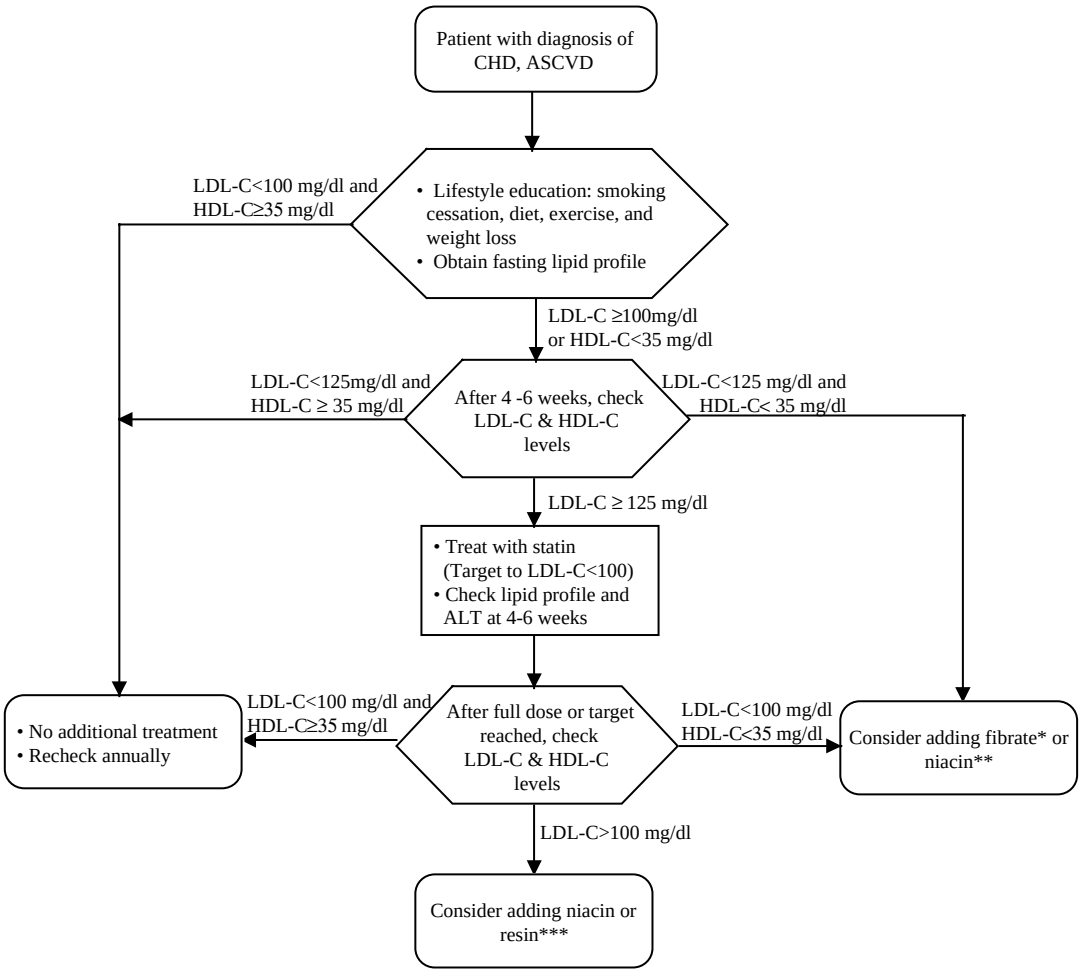
* Assumes candidate does not already have a disease that requires lipid measurement, e.g., CHD, ASCVD, DM.

Table 2. Secondary Causes of Lipid Disorders

Disorder / Patient Characteristic	Effect on Lipids	Lab Test for Diagnosis
Nephrotic Syndrome	TC ↑, TG ↑	Urinalysis, serum albumin
Diabetes Mellitus	TG ↑, TC ↑, HDL-C ↓	Fasting glucose
Obstructive Liver Disease	TC ↑	Liver function tests (LFT's)
Hypothyroidism	TC ↑, TG ↑	Thyroid stimulating hormone (TSH)
Chronic Renal Failure (CRF)	TC ↑, TG ↑	Creatinine (Scr)
Obesity	TG ↑, HDL-C ↓	
Ethanol	TG ↑, HDL-C ↑	
Inactivity	HDL-C ↓	
Smoking	HDL-C ↓	

Adopted from VA/DOD lipid guidelines

Figure 2. Secondary Prevention



* Fibrates have been shown to reduce coronary events, not all-cause mortality
** No randomized controlled trials showing additional benefits beyond statin treatment as of yet
*** Failure to reach LDL-C goal is discussed on page 8.

Treatment Strategy: Assess factors in Table 3, then treat to goals in Table 4.

Table 3. CHD Risk Factors other than LDL-C

Positive Risk Factors

Age, years (male ≥ 45, female ≥ 55 or premature menopause without estrogen replacement therapy)

Family history of premature CHD (definite MI or sudden death in male before 55 years, or female before 65 years)

Current smoker

Hypertension (BP ≥ 140/90 mmHg or on medication)

Low HDL-C (< 35 mg/dl)

Diabetes Mellitus

Negative Risk Factors

High HDL-C (≥ 60 mg/dl)

Note: Total the number of risks to determine the Patient Category value in Table 4.

Adopted from NCEP II

Table 4. Treatment Thresholds (based on patient category and LDL-C mg/dl)

Patient Category	LDL-C for Dietary Rx	LDL-C for Drug Rx	Goal
≤ 1 CHD risks *	≥ 160	≥ 190**	< 160
≥ 2 CHD risks	≥ 130	≥ 160	< 130
CHD or ASCVD	≥ 100	≥ 130	< 100
DM Type 2	≥ 100	≥ 130	< 100

* Total of the number of risks present from Table 3.

Adopted from NCEP II and ADA guidelines

** Men < 35 years old and premenopausal women are at extremely low short-term risk, and medication may be held unless LDL-C > 220 mg/dl

Table 5. Drug Therapy Summary

Drug & Strength	Dose Range	Cost/Mo [a]	LDL-C	HDL-C	TG	General Cautions about Drug Class
HMG-CoA reductase inhibitors (Statins)						• LFT's ↑ in 0.1-1.9%; monitor ALT within 6 to 12 weeks after initiation or dosage increase, then about annually. • Myopathy < 0.2%, 5% in combination w/ gemfibrozil, 2% in combination w/ niacin. (CPK screening not necessary.) • Caution in hepatic disease. • Caution in severe renal impairment, use lowest does in moderate renal impairment & monitor. • Doubling a statin dose reduces LDL-C by about 6%.
Atorvastatin 10, 20, 40 mg	10-80 mg/d	$59-210	30 - 60% ↓	7 - 10% ↑	25 - 46% ↓	
Cerivastatin 0.2, 0.3, 0.4, 0.8 mg	0.2-0.8 mg/d	$48-69	15 - 42% ↓	5 - 10% ↑	12 - 22% ↓	
Fluvastatin 20, 40 mg	20-80 mg/d [b]	$40-80	19 - 32% ↓	3 - 8% ↑	0 - 11% ↓	
Lovastatin 10, 20, 40 mg	10-80 mg/d [b]	$41-261	24 - 40% ↓	5 - 19% ↑	3 - 22% ↓	
Pravastatin 10, 20, 40 mg	10-40 mg/d	$68-118	18 - 35% ↓	4 - 16% ↑	1 - 25% ↓	
Simvastatin 5, 10, 20, 40, 80 mg	5-80 mg/d	$53-119	24 - 48% ↓	5 - 21% ↑	1 - 46% ↓	
Bile Acid Resins						• Take other meds 1 hr prior or 4 hr after; or take with dinner. • May cause constipation, bloating. • May decrease absorption of vitamins.
Cholestyramine 4 g powder/LIGHT	4-12 gm bid	$56-170 generic	11 - 31% ↓	3 - 5% ↑	May ↑ TG.	
Colestipol 5 g powder/1g tab	5-15 gm bid	$48-145 Light $100-300	16 - 29% ↓	3 - 5% ↑	May ↑ TG.	
Niacin [c, d]						• Take w/ meals to avoid flushing or GI upset • LFT's baseline, 6 wks after start or dosage change: monitor every 6-12 months thereafter • Causes glucose intolerance-caution in established or borderline DM • May cause GI intolerance, caution w/ history of complicated active PUD • Decreases urinary secretion of uric acid, caution with gout • Contraindicated in hepatic disease • If CrCl is 10-50 mL/min give 50% 0f dose; if < 10 mL/min give 25%
Immediate release (IR) 100, 250, 500 mg Niacor®	500-1500 mg tid	$25-76	13 - 21% ↓	10 - 24% ↑	19 - 24% ↓	
Sustained release (SR) 500 mg, 750 mg, 1 g Niaspan®	1-2 gm/d	$30-60	13% ↓	19% ↑	10% ↓	
Fibrates						• Monitor LFT's about annually. • Contraindicated in hepatic disease or severe renal disease. • Risk of myopathy with statins • Increases effect of warfarin.
Gemfibrozil 600 mg tab	600 mg bid	$11 generic $88 Lopid	± 10%	10% ↑	43% ↓	
Fenofibrate 200 mg capsule	200 mg/d	$72	17 - 35% ↓	2 - 34% ↑	32 - 53% ↓	

[a] Cost for 30 days treatment based on price listings (AWP and HCFA) in *Drug Topic Red Book 2000 and June Update*

[b] Dose given as 40 mg bid when total is 80 mg/d

[c] Generic niacin (IR and SR) are inexpensive but not federally regulated.

[d] Start IR 50-100 mg bid-tid & ↑ dose by 300 mg/day per week; use titration pack. Usual maximum daily dose IR 3 g/day.

Table 6. Required Percent LDL-C Reductions to Meet NCEP Goals

	Goal LDL-Cholesterol		
Baseline LDL-C (mg/dl)	**< 2 Risk Factors 160mg/dl**	**≥ 2 Risk Factors 130mg/dl**	**Secondary Prevention 100mg/dl**
240	33%	46%	58%
230	30%	43%	57%
220	27%	41%	55%
210	24%	38%	52%
200	20%	35%	50%
190	16%	32%	47%
180	11%	28%	44%
170	6%	24%	41%
160	XXX	19%	38%
150	XXX	13%	33%
140	XXX	7%	29%
130	XXX	XXX	23%
120	XXX	XXX	17%
110	XXX	XXX	9%

For recommendation of drug and strength necessary to reach NCEP goal, refer to following table.

Table 7. Statin Dose Equivalency Chart*

% LDL-C Reduction Needed	***HMG-CoA Reductase Inhibitor***					
	Atorvastatin	***Simvastatin***	***Cerivastatin***	***Lovastatin***	***Fluvastatin***	***Pravastatin***
18	10 mg ($59)	5 mg ($53)	0.2 mg ($46)	10 mg ($41)	20 mg ($40)	10 mg ($68)
20						
22						20 mg ($73)
24		10 mg ($68)		20 mg ($72)	40 mg ($40)	
26						
28			0.3 mg ($46)	40 mg ($130)	80 mg ($80)	40 mg ($118)
30			0.4 mg ($46)			
32		20 mg ($114)				
34				80 mg ($261)		
36	20 mg ($87)	40 mg ($119)	0.8 mg ($69)			
38						
40						
42		80 mg ($119)				
44	40 mg ($105)					
46						
48						
50						
52	80mg ($210)					
54						
56						
58						

* *Pooled data from randomized clinical trials and/or the product package insert were used to calculate the mean LDL-C reductions. Mean LDL-C values were weighted based on the number of subjects in each included study.*

Cost = Average wholesale price based on 30-day supply, *Redbook, 2000*

Table 8. Drug Interactions

	Interactive Agent(s)	Clinical Manifestations
Statins [a,b]	Fluconazole, Itraconazole, ketoconazole	Increased risk of myopathy
	Cyclosporin, tacrolimus	Increased risk of myopathy
	Clarithromycin, erythromycin	Increased risk of myopathy
	Verapamil, diltiazem	Increased risk of myopathy
	Ritonavir	Increased risk of myopathy
	Nefazodone	Increased risk of myopathy
	Niacin, fibrates	Increased risk of myopathy
Niacin	Statins	Increased risk of myopathy (2%)
Resins	Fat soluble vitamins	Impaired absorption (through vitamin supplement not routinely received)
	All other drugs	Impaired absorption. Take all other meds 1 hour before or 4 hours after BAR
Fibrates	Statins	Increased risk of myopathy (5%)
	Warfarin	Increased INR
	Glyburide	May increase risk of hypoglycemia

[a] Pravastatin and fluvastatin has lower risk of drug interaction than other statins.
[b] Grapefruit juice increases risk of myopathy

Clinical Background: Clinical Issues

Issues. Many studies have shown that CHD patients are not being treated. Those that are treated are often not achieving LDL-C < 100 mg/dl. The situation is likely worse for those with atherosclerotic cardiovascular disease (ASCVD) without CHD. Even with aggressive cardiac rehabilitation programs, the percentage of patients achieving LDL-C target is low (39% in one study). Why do we fail to screen and reach LDL-C targets? Costs may be an issue for some patients. Patient education about the benefits, and general need for lifelong treatment may help improve compliance. Despite a wealth of safety data with statins, clinicians are still anxious over monitoring/transaminase issues. Health providers need to provide patients with information on the indications, proven benefit, long term use, and small but real risks.

Rationale for Recommendations Primary and Secondary Prevention:

Etiology

There is now a wealth of literature supporting the causal relationship of cholesterol and CHD. Large cohort studies had previously shown that each 1% increase in LDL-C cholesterol is associated with a 1-2% increase in CHD, and each 1% increase in HDL-C associated with a 2-3% drop in CHD event rates.

Approximately 60% of CHD patients will have LDL-C > 130 mg/dl. Most of those with normal LDL-C will have low HDL-C, another independent risk factor for CHD. Triglycerides have been shown in some, but not all studies, to be an independent risk factor for CHD events.

It is important to evaluate for secondary causes of hyperlipidemia by history and selected laboratory tests (see Table 2). It is particularly important to identify patients with familial dyslipidemias, who often have premature CHD and a strong family history. These patients may not achieve lipid goals with standard treatment, and may benefit from referral to a lipid specialist.

Treatment Benefit

LDL-C based drug therapy for primary prevention has been shown to reduce total mortality in high-risk populations. Prior to statins, many primary prevention trials had been shown to reduce CHD events, but not total mortality. Clofibrate was found to increase total mortality. Two recent major lipid trials, both with statins, have shown dramatic reductions in CHD events. The AFCAPS/TEXCAPS study looked at 5608 men and 997 women with average total cholesterol and LDL-C, and below average HDL-C. Patients randomized to lovastatin had 37% fewer first CHD events. The number needed to treat (NNT) over 5 years to prevent 1 CHD event was 86. This was a relatively low risk population. The West of Scotland Study looked at a higher risk population, and also found dramatic benefits from statin (pravastatin) treatment. Over 5 years, CHD events were 31% lower, with significant reductions in CHD (32%) and

total (22%) mortality. The NNT to prevent one nonfatal MI or CHD death was 42. Although less dramatic than secondary prevention, these benefits are similar to that received in a large anti-hypertensive trial.

Lowering cholesterol has been shown to reduce the incidence of CHD, with each 10% reduction dropping the incidence by 20%. Angiographic trials have shown statins and other agents to slow the progression of atherosclerosis on quantitative coronary arteriography. In the past 5 years, large randomized controlled trials have provided final evidence that lipid lowering reduces CHD and total mortality. These trials have used statins, which have now replaced older agents as first line therapy for elevated LDL-C. In the 4S study, simvastatin reduced CHD events by 34% ($p< 0.0001$), and total mortality by 30% ($p=0.003$). The CARE and LIPID trials confirmed these benefits in CHD patients with lower LDL-C levels. CARE showed no benefit treating patients with baseline LDL-C < 125 mg/dl. Benefit in these trials became apparent within 1-2 years. The number needed to treat (NNT) in the LIPID trial to prevent one non-fatal MI or CHD death was 28. Patients enrolled in these lipid trials, like other randomized controlled trials, are a select group. The generalizability of those results to unselected patients in the community is less clear (i.e., results may not be as dramatic).

Table 4 presents the NCEP recommendation for LDL-C levels at which to initiate dietary and drug treatment for patients with CHD or ASCVD (i.e. for secondary prevention).

There are no large randomized control trials on lipid therapy in secondary prevention for ASCVD. Subgroup analysis from CHD trials have shown that statin therapy reduces the incidence of stroke. A systematic review found that cholesterol-lowering therapy reduces the progression of peripheral vascular disease.

Statins are considered to have a class effect. There is no evidence that any one statin is better, though potency varies with the different agents. Statins in primary prevention are cost-effective only in high-risk groups. In secondary prevention, they are cost-effective in all CHD patients. Though not yet studied in elderly CHD patients (>74 years old), cost-effectiveness analyses have recently found statins cost-effective in this group as well. At current pricing, atorvastatin and cerivastatin are the most cost-effective agents. Lovastatin will soon be generic. Cost can be reduced by pill splitting. However, statins are generally not scored tablets, making pill splitting more difficult.

Screening

Whom to screen – primary prevention. Controversy surrounds who is appropriate for screening. The effects of treatment depend on the underlying risk. While low risk individuals may have the same relative risk reduction with cholesterol lowering therapy, their absolute risk reduction may be quite small. The incidence of CHD in men under age 35 and premenopausal women is low (1-2/1000 annual risk). However, autopsy studies have shown that atherosclerosis begins at adolescence or young adulthood.

Table 9. National Screening Guidelines by Age

National Group	Men	Women
U.S. Preventive Services Task Force	35 - 65	45 - 65
American Academy of Family Physicians	≥ 35	≥ 45
American College of Physicians	35 - 65	45 - 65
National Cholesterol Education Program (NCEP)	≥ 20	≥ 20
Canadian Task Force on Periodic Health Examination	Insufficient evidence for universal screening	

The age group for screening for primary prevention remains an area of controversy. National organizations have differing age recommendations for screening (see Table 9). Some groups have argued for screening at age 20, because atherosclerosis begins long before clinical manifestations. Others have argued that there is no evidence that screening or treating young adults has not shown to be of benefit, and given their low absolute risk, would not be cost effective.

Most guidelines have agreed there is good evidence for screening men aged 35 to 65. The optimal age for screening women is unknown, but they generally have a 10-year delay in risk relative to men. Epidemiologic studies indicate the risks of high cholesterol extend to age 75, though there is little trial data in this older age group. AFCAPS/TEXCAPS showed benefit in older adults (aged 65-73). There is no evidence of benefit in screening patients > 75 years. Screening for lipid disorders, like other primary prevention efforts, may not be appropriate in individual patients with reduced life expectancy.

Which lipids to screen, how often – primary prevention. When ordering screening lipids, which tests should be requested? There is consensus that non-fasting lipids are adequate for screening. NCEP recommends TC and HDL-C, fasting or non-fasting. HDL-C is an important cardiac risk factor. However, there is no evidence that treating HDL-C in patients with normal TC lowers their risk of CHD or mortality. Patients with abnormal screening lipids should go on to have a fasting lipid panel. This would include patients with TC > 240 mg/dl, HDL-C < 35 mg/dl, and TC 200-240 with 2 or more CHD risks. Patients with normal screening lipids are generally rechecked at 5-year intervals, as lipids may gradually worsen over time and they may develop secondary causes later in life. Patients with borderline values, not requiring therapy, may be rechecked at 1-2 year intervals.

Whom to screen, how often – secondary prevention. Patients with known CHD or ASCVD should have a lipid profile (TC, LDL-C, HDL-C, and TG). For patients with a normal lipid profile, screen annually. Patients with abnormal lipids should be treated and evaluated every 4-8 weeks until target lipid levels are met. Patients with acute MI should have lipid profile reassessed within 60 days after the acute event. Total cholesterol may be artificially low at the time of an acute MI.

A new HEDIS measure for lipid therapy in CHD will measure the proportion of patients with LDL-C < 130mg/dl at some time between 2-12 months after acute CHD event.

Whom to treat and Lipid Targets

Patients with elevated LDL-C should have treatment tailored to CHD risks, with lower levels of LDL-C initiating treatment and lower LDL-C targets for those at increased risk. CHD risks are listed in Table 3. Table 4 lists LDL-C levels at which dietary and drug therapy should be initiated taking into account other risks. Since laboratory and biologic variability is considerable (up to 10% for LDL-C, 20-25% TG, and 3-5% HDL-C), at least 2 sets of lipids should be obtained before initiating therapy. LDL-C cannot be estimated in when TG remains above 400mg/dl. Options include measurement after treating the TG, or direct LDL-C measurement.

Primary Prevention. As is indicated in Table 4, the National Cholesterol Education Project (NCEP) recommends lowering LDL-C to < 130 mg/dl in those with 2 or more CHD risks. Thresholds for initiating diet and drug therapy in those with one or no CHD risks are ≥160 mg/dl and ≥190 mg/dl, respectively. If 2 or more CHD risks are present, these thresholds are ≥130 mg/dl and ≥ 160 mg/dl, respectively. Young adults (men < 35 and premenopausal women) with one or no CHD risks have extremely low short-term risk, and have higher LDL-C thresholds at which drug therapy is started (220 mg/dl). There is insufficient evidence to recommend drug therapy for low HDL-C or high triglycerides. Triglycerides > 1000 mg/dl are generally treated to reduce the risk of pancreatitis.

Secondary Prevention. The NCEP recommends lowering LDL-C < 100 mg/dl for secondary prevention. Could further lowering reduce risks lower? Trials are now underway to answer this question. A recent angiographic trial in CABG patients showed that patients given lower doses of statin (target LDL-C < 140 mg/dl) had worse outcomes than those given full doses (target LDL-C < 85 mg/dl). After 4 years, angiographic progression for the moderate and aggressive groups was 39% and 27%, respectively. Revascularization was reduced by 29% in the lower LDL-C group. This study supports current NCEP recommendations, but it is still not clear if lowering LDL-C further would provide more benefit.

Some experts argue it is the percentage drop in LDL-C, not the absolute LDL-C achieved, that is important in achieving benefit. Analysis of the WOSCOPS data shows that maximal CHD reduction occurred with LDL-C lowering of about 24%. Subgroup analysis of the 4S results supports this as well, with each quartile of LDL-C (< 170, 170-187, 188-206, and > 206) having similar reductions in LDL-C (32% to 37%), and similar decreases for CHD. The CARE results also supported the importance of baseline LDL-C, as no clinical benefit was seen for patients with baseline LDL-C < 125 mg/dl (again, supporting NCEP recommendations). Treating to New Targets (TNT) is a 5-year randomized controlled trial currently under way looking at lowering LDL-C below targets in patients with CHD, who will be randomized to atorvastatin 10 mg vs. 80 mg per day.

Treatment

Three approaches to treatment are available: lifestyle changes, drug therapy aimed at lipid control, and complementary and alternative therapies that may affect lipid levels.

Lifestyle Changes

Lifestyle changes are the first mode of treatment in primary and secondary prevention. These include dietary changes, smoking cessation, weight loss (if overweight), and exercise. In addition, these changes reduce cardiovascular disease risk independent of their influence on lipids.

Diet and Food Supplements. The first treatment of hyperlipidemia is reduction in total dietary fat, primarily through reduction in saturated fat. Dietary recommendations with expected change in LDL-C are listed in Table 10. There is wide variation between patients in their response to low fat diets, with 10-25% showing no change in serum lipids with dietary therapy. For primary prevention, 40-50% of patients with a high risk level of LDL-C will reduce their LDL-C to borderline or low risk with 6 months of the NCEP Step II diet. It is much less likely that patients with known CHD will be able to reduce LDL-C to less than 100 mg/dl (as recommended) with dietary therapy alone. However, the reductions in total and LDL-C induced by dietary therapy and pharmacologic therapy are generally greater than for either therapy alone. Many clinicians chose to start dietary and pharmecologic therapy simultaneously in patients after an acute coronary event.

The degree of response to various dietary interventions including soluble fiber, soy, and plant stanols correlates highly with the amount consumed and baseline LDL-C levels. Prescribed diets should not be restrictive, but instead emphasize what should be eaten rather than what should not be eaten. There should be an increase in fruits and vegetables rich in fiber, an increase in fish (omega-3 fatty acids) and linolenic acid (canola oil, soy, flax seed)

Table 10. Low Fat Diets and Effect on Serum Lipids

Diet	Total Fat % of Cal	Sat Fat % of Cal	Chol mg/dl	Decrease in LDL-C
NCEP Step I	< 30%	≤ 10%	< 300	9 - 12%
NCEP Step II	< 30%	< 7%	< 200	15%
AHA very Low Fat	≤ 15%	5%	< 200	15 - 24%
Ornish	< 10%	< 5%	< 5	35%

and a substitution of whole grain for processed flours and simple sugars. This diet is comparable to the Mediterranean diet, which has been shown to reduce CHD events beyond its impact on serum lipids. The plant stanols (sitostanol and sitostanol esters) are available in soft margarine and can be used as a spread on bread products and vegetables. They will also be available soon in salad dressings and snacks foods. Hard stick and tub vegetable margarine should be avoided. They are derived by hydrogenation to trans-fatty acids and can increase LDL-C. Many patients with hyperlipidemia will benefit from a consultation with a dietitian to help them make appropriate food choices.

Smoking cessation. In persons with CHD smoking cessation reduces coronary event rate by about 50% within one to two years of stopping. Among the benefits of smoking cessation is a 5-10% increase in HDL-C. CHD is not a contraindication to pharmacotherapy for smoking cessation (see UMHS smoking cessation guideline). However, nicotine replacement therapy is contraindicated in unstable angina or acute MI.

Weight loss. Excess body weight is associated with higher triglycerides, lower HDL-C, and higher TC. The more overweight the patient, the less responsive he or she is to dietary therapy if weight loss does not also occur. Low fat diets not associated with weight loss or exercise can raise triglycerides and lower HDL-C. Even modest weight loss counteracts the HDL-C lowering effect of the diet alone, lowers triglycerides, and causes further reduction in TC and LDL-C.

Exercise. Regular physical exercise raises HDL-C and lowers triglycerides. Exercise alone has little effect on LDL-C. Exercise in combination with a low fat diet induces greater reduction in TC, LDL-C, and weight loss than dietary therapy alone. Even mild exercise (walking) done regularly (30 minutes, 4-5 times a week) has been shown to be beneficial. Weight training has also been shown to increase HDL-C. exercise must be tailored to the degree of CHD, with aerobic exercises (walking, cycling, swimming) at levels that do not precipitate angina.

Alcohol. Population studies suggest a coronary protective effect of moderate alcohol (1-3 oz/day) intake in men and women including the elderly. Alcohol of all types is associated with a modest (5 – 15%) increase in HDL-C. In some there is a modest increase in triglycerides, which may be profound in diabetics and hypertriglyceridemia. The coronary protective effects of alcohol are off set by increased mortality from other causes. Reduction in excessive alcohol intake is recommended.

Pharmacologic Treatment

Drug therapy should be reserved for those with known CHD/ASCVD and those patients at increased CHD risk failing to reach LDL-C targets with lifestyle modifications. Statins have been shown to be cost-effective in both these populations. Some groups have recommended restricting drug therapy to those whose 5-year risk for CHD event is 10% or more. This can be easily calculated (Circulation.1998; 97:1837-47).

Choice of drug. Statins are generally used as first-line agents. However, a meta-analysis of lipid trials found that the lowering of LDL-C was important, not the particular drug class. Realistically, statins have the advantage of potency, ease of use, and tolerability. Bile acid resins are generally more expensive per LDL-C reduction, and have much higher rates of side effects. Niacin may certainly be considered for primary prevention patients, given its low cost and powerful effect on the LDL-C/HDL-C ratio. Niaspan, a new slow release niacin product, offers convenient dosing, lower side effects, but at a cost comparable to statins.

Cost becomes an issue with lower risk patients, as it is unlikely that drug therapy with statins can be cost-effective at current prices. Statins should be considered first-line in particularly high-risk patients, such as those seen in WOSCOPS, in whom therapy was shown to reduce total mortality.

Statin patients should have baseline ALT, with follow-up once they have reached target doses, and periodically thereafter. Niacin patients should have baseline ALT, glucose and uric acid, with follow up ALT at 3 months or at dose escalations, and periodically thereafter. Extended release niacin products carry a significant risk of hepatitis at doses beyond 2 gm/day. The risk of hepatitis and rhabdomyolysis increase significantly with dual therapy, and requires more frequent follow-up.

Table 5 presents a summary of information regarding commonly used lipid lowering drugs and Table 8 presents

information regarding interactions with them. The commonly used drugs are considered individually below.

HMG-CoA Reductase Inhibitors (statins). The statins are the best studied and show most benefit, in terms of absolute LDL-C reduction and patient outcome. Large statin-based trials have included lovastatin, pravastatin, and simvastatin. Statins are considered to have a class effect. There is no convincing evidence that one statin is better than another. Atorvastatin is the most potent agent. Pravastatin is not metabolized by CYP450 (liver), and has less drug interactions. Cerivastatin and fluvastatin also carry a lower risk of drug interactions. Lovastatin is the oldest, and will be generic in the near future. Consider initial dose based on desired LDL-C reduction. Choice of statin should be dictated by cost and desired LDL-C reduction (see Tables 6 & 7).

Adverse effects include mild GI disturbances, muscle aches, rash and headache. Rhabdomyolysis occurs in < 0.5%, but is increased in patients with niacin, fibrates, cyclosporin, azoles, macrolides, and grapefruit juice. The risk is also increased in hepatic or renal dysfunction, hypothyroidism, serious infections, and advanced age. Routine CPK monitoring is not indicated, and moderate CPK elevations (<800 IU) do not necessarily indicate toxicity or increased risk of myopathy. Statins are contraindicated in pregnancy.

Failure to reach LDL-C goal with statins. Prior studies of niacin/resins have shown some evidence of reduction in CHD events, and niacin has been shown to reduce total mortality at 15-year follow-up in one study. Therefore, until further evidence is available, it is reasonable to add niacin or resin to patients on full dose statins not achieving LDL-C target. Caution is advised with niacin and fibrates, as combination with statins increases the risk of hepatitis and rhabdomyolysis. However, these medications will give the added benefit of improving HDL-C and triglycerides.

Bile Acid Resins. Cholestyramine and colestipol have been shown to reduce LDL-C cholesterol 10-20%, depending on dose. They are available in powder and pill (colestipol) form. Resins work by binding cholesterol in the gut and interfering with absorption. These drugs are generally considered second line because of their high side effect rate and cost. They raise triglycerides, and should be avoided in patients with hypertriglyceridemia.

Adverse effects are universal with resins, and are dose dependent. The most common side effects are bloating, nausea, constipation, and abdominal pain. Non-GI side effects are uncommon. Resins interfere with absorption of fat-soluble vitamins and many drugs. They should be taken 1 hour before or 4 hours after other medications. Side effects can be reduced somewhat by titrating up slowly.

Niacin. Niacin improves all aspects of the lipid profile. The mechanism is not known. It also decreases lipoprotein *(a)*. Niacin has been shown in one secondary prevention study to reduce cardiac events, and nine years later, total mortality as well. LDL-C reductions are less dramatic than statins, and many patients are unable to tolerate the side effects. Niacin is available over the counter (OTC) as a dietary supplement in both immediate release (IR) and sustained release (SR) formulations. Prescription niacin products include Naicor (RI) and Niaspan (SR). Dietary supplements are not subject to the same FDA regulations as prescription products, therefore OTC niacin products may not be therapeutically equivalent to the prescription only products.

Adverse effects include flushing, pruritus, GI disturbances, fatigue, glucose intolerance, gout, and peptic ulcer. The vasoactive symptoms are reduced by using aspirin, slow titration, or use of sustained release formulations. GI disturbances are more common among patients on SR formulations. Hepatic toxicity has been reported, particularly with SR products at doses > 2 gm/day. It should be avoided in patients with underlying liver disease or uncontrolled diabetes. Niaspan, a new SR agent, has been shown to have lower side effects than IR niacin (it has not been studied against other SR agents). SR niacin is generally considered twice as potent. When switching from IR to SR, the dose should be reduced in half, and no more than 2 gm/day.

Fibrates. Fibrates include gemfibrozil, fenofibrate, benzafibrate (not available in US), and clofibrate. Clofibrate is no longer used, as it is associated with increased total mortality in large randomized controlled trials. Gemfibrozil has been associated with reduced cardiac events, but increased non-cardiac events, and no effect on total mortality.

The mechanism of action is unclear. Fibrates are generally used to lower triglycerides and raise HDL-C. Gemfibrozil has no significant effect on LDL-C. Fenofibrate has been shown to lower LDL-C. Whether this will translate into better cardiac and mortality outcomes is unknown. Angiographic studies have shown benefit from both agents.

Adverse effects are generally GI, including nausea, dyspepsia, and change in bowel habits. The risk of cholestasis and cholecystectomy is increased. When used in conjunction with statins, the risk of hepatitis and rhabdomyolysis is increased. Prior trials, particularly with clofibrate, noted increased number of deaths due to violence and accidents. Contraindications include severe renal or liver disease, pregnancy, or preexisting gallbladder disease.

Treatment of HDL-C and triglycerides. HDL-C is an independent predictor for CHD, with each 1% increase resulting in about a 3% lower risk of CHD. Triglycerides have been associated with an increase in mortality in CHD patients, but have not universally been found to be an independent risk factor. There is insufficient evidence to

support drug therapy in primary prevention. Focus should be on lifestyle changes and treating secondary causes in this group. Triglycerides > 1000 mg/dl are generally treated to prevent pancreatitis.

The VA-HIT trial recently reported results of CHD patients with low HDL-C, randomized to gemfibrozil or placebo for 5 years. Patients had HDL-C < 40 mg/dl, LDL-C < 140 mg/dl, and triglycerides < 301 mg/dl. The primary outcome, combined CHD death and nonfatal MI, was reduced 22% in the treatment group (95%CI, 7-35%, p=0.006). There were no differences in cardiac or non-cardiac mortality (study wasn't powered to detect mortality benefit). The NNT to prevent one cardiac death or nonfatal MI was 23.

These results are supported by recent angiographic trials of fibrates, which have shown slowing of progression of atherosclerosis. However, these recent encouraging results cannot erase the decades of prior dismal results with fibrates in primary and secondary prevention efforts. These prior studies reduced CHD events, but either failed to lower total mortality, or in the case of clofibrate, increased total mortality. The newer fibrates may offer better results in long-term studies, but this remains to be seen.

The American College of Cardiology (ACC) and American Heart Association (AHA) guidelines for post-MI treatment recommend drug treatment if HDL-C < 35 mg/dl. There is insufficient data on the treatment of high levels of triglycerides, but based on expert opinion, ACC and AHA recommend niacin or gemfibrozil for elevated triglycerides, regardless of HDL-C and LDL-C.

In summary, lifestyle changes and treatment of secondary causes should be the major intervention. In patients with established CHD, consider drug therapy if HDL-C remains low despite conservative measures. Whether to advise 1-2 drinks of alcohol per day to improve HDL-C remains controversial, for various concerns, despite the clear association with alcohol and reduced mortality. Hormone replacement therapy in women improves HDL-C, but its place in secondary prevention is now in question given the recent Heart and Estrogen Replacement Study (HERS) trial.

Complementary and Alternative Treatment

Complementary and alternative therapies may affect lipid levels, although most are untested. Some of the therapies for which evidence of the effect on lipids is known include estrogen replacement therapy, yogic lifestyle, garlic, and red yeast rice. Their effects are noted below.

Estrogen and progestins. While the role of estrogen replacement therapy (ERT) in postmenopausal women without coronary disease is not established, there is a considerable potential benefit of ERT on serum lipids. The benefits to the lipid profile attributable to oral estrogens include a 10-15% reduction in LDL-C, a 10-20% increase in HDL-C, and a decrease in lipoprotein (a) [Lp (a)] by up to 25%. ERT may increase triglycerides by 10-15%. The addition of progestins reduces the increase in HDL-C with minimal impact on LDL-C lowering. Since the publication of the HERS demonstrating an adverse effect of estrogens (with progestins) during the first year of treatment in women with coronary disease, this treatment should be avoided. However, for those women with coronary disease already on ERT for a year there appears to be a benefit.

Yogic lifestyle. The Ornish program of a vegetarian diet, regular exercise, meditation, and yoga has been shown to reduce LDL-C by 37%, reduce coronary atherosclerosis progression, and need for revascularization in coronary disease. In a small study of Asian-Indian coronary patients, yoga alone resulted in a modest reduction in total and LDL-C, triglycerides, and weight.

Garlic. Garlic has been used as a food and medicinal substance since biblical times. In relatively small trials, one gram of garlic (powder or tablets but not oil) generally lowers serum cholesterol levels by 7 to 10%. However, in hypercholesterolemic patients on a low fat diet there is no benefit of garlic over a placebo.

Red yeast rice. Red yeast rice, a Chinese remedy (*Hong Ou)* developed over 1000 years ago for indigestion, diarrhea, and abdominal pain, is marketed for cholesterol lowering in several capsule forms including *Cholestin*. It is made by fermenting a yeast over rice. In a study comparing 2.4 gm of *Cholestin* to a placebo in men and women on an AHA step I diet, *Cholestin* lowered the cholesterol by 17% and LDL-C by 22.4% with no change in HDL-C. Red yeast rice contains several naturally occurring substances related to the statins, the predominant is mevinolin, the major component of lovastatin.. The average recommended dose of 600 mg twice daily contains about 5 mg of statin. Lack of standardization and regulation in manufacturing increase the risk of toxicity relative to prescription statins.

Others. There is even less proof of efficacy or safety in cholesterol lowering for several other products that are widely available in health food stores and pharmacies. These include gugulipid an Asian Indian extract of bark from the Mukul myrrh tree, L-carnitine, and lecithin.

Special Populations for Preventive Therapy

Women. AFCAPS showed significant treatment benefit in women. A recent meta-analysis on the effect of statins on risk of CHD found similar benefit in women. Surrogate endpoints, such as atherosclerotic progression, have shown benefit from statins in women. Premenopausal women are at low CHD risk, with approximately a 10-year delay in risk on their male counterparts. For this reason, ACP and USPSTF recommend starting screening at age 45 for women and age 35 for men.

Diabetes mellitus. Patients with DM type 2 have a 2-4 fold increased risk of CHD. One recent study found similar CHD event rates for diabetics and non-diabetics with known CHD. The American Diabetes Association (ADA) recommends drug therapy if LDL-C remains > 130 mg/dl despite lifestyle changes, with a target LDL-C < 100mg/dl. While there are no large randomized controlled trials of lipid therapy in this population, diabetic subgroups in primary (AFCAPS/TEXCAPS) and secondary (4S) trials have similar benefit to non-DM patients. These patients often have type 4 hyperlipidemia (low HDL-C and high Trig). Niacin must be used with caution as it may worsen insulin resistance and glycemic control.

Strategy for Literature Search

The literature search for this project was conducted prospectively using the major keywords of: *cholesterol, hyperlipidemia, lipoproteins hdl cholesterol, lipoproteins ldl cholesterol, triglycerides; consensus development conferences, practice guidelines, guidelines, outcomes and process assessment (health care); clinical trials, controlled clinical trials, multicenter studies, randomized controlled trials, cohort studies; adults; English language; and published in 1955-1999* on Medline. Terms used for specific topic searches within the major key words included: *mass screening, screening; drug therapy, statins, hydroxymethylglutaryl-CoA reductase inhibitors, antilipemic agents, niacin, bile acid sequesterant; and [diet, exercise, alternative/complementary medicine] each within [coronary arteriosclerosis, coronary disease, coronary thrombosis, peripheral vascular diseases, cerebrovascular disorders]*. The search was conducted in components each keyed to a specific causal link in a formal problem structure (available upon request). The search was supplemented with very recent clinical trials known to expert members of the panel. Negative trials were specifically sought. The search was a single cycle. Conclusions were based on prospective randomized clinical trials if available, to the exclusion of other data; if randomized controlled trials were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was used to estimate effect size.

Related National Guidelines

The UMHS Clinical Guideline on Lipid Therapy addresses screening and treatment.

- Screening for primary prevention: see Table 9 for relevant national guidelines and their recommendations. The UMHS guideline recommends screening for the age groups that are common to the recommendations of most national guidelines. The UMHS guidelines state that screening is optional in younger age groups that are also included in recommendations of a few national guidelines.
- Treatment: The UMHS guidelines are consistent with
  - USPSTF guidelines on secondary prevention
  - NCEP guidelines on primary and secondary prevention.

Disclosures

The University of Michigan Health System endorses the Guidelines of the Association of American Medical Colleges and the Standards of the Accreditation Council for Continuing Medical Education that the individuals who present educational activities disclose significant relationships with commercial companies whose products or services are discussed. Disclosure of a relationship is not intended to suggest bias in the information presented, but is made to provide readers with information that might be of potential importance to their evaluation of the information.

Team Member	Company	Relationship
William Barrie, MD		(None)
Van Harrison, PhD		(None)
Ujjaini Khanderia, PharmD	Bristol Meyers, Novartis, Merck, Pfizer	Speakers Bureau
Robert Kiningham, MD		(None)
Shawna Nesbitt, MD	Astra-Zeneca	Research Support
	Astra-Zeneca, Novartis, Pfizer-Parke-Davis, SmithKline Beecham	Speakers Bureau
Melvyn Rubenfire, MD	Bristol Meyers Squibb, Parke-Davis, Pfizer	Research Support
	Bristol Meyers Squibb, Merck, Parke-Davis	Speakers Bureau

Annotated References

Anonymous. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study(4S). Lancet. Nov 19, 1994. 344. 1383-89.

Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels (AFCAPS/TexCAPS). JAMA 1998;279:1615-1622.

Expert Panel on Detection, Evaluation, and Treatment of

High Blood Cholesterol in Adults. Summary of the Second Report of the National Cholesterol Education Program(NCEP) Expert panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). JAMA. June 16,1993.269:23;3015-23.

Landmark lipid guideline most referenced. Addresses screening, evaluation, and treatment of various lipid disorders. Gives firm recommendations/cut-offs for different treatment options. Provides dietary recommendations.

Guide to Clinical Preventive Services (second edition). Report of the USPSTF. Section one: screening for high blood cholesterol and other lipid abnormalities. Williams & Wilkens. 1996. pp 15-38.

An evidence-based review of issues pertaining to lipid screening in young and older adults. Finds insufficient evidence to recommend for or against HDL-C screening.

Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol (VA HIT). NEJM 1999;341:410-8.

Sacks FM, Pfeffer MA, Moye LA, et al. The effect o f pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels(CARE). NEJM 1996;335:1001-9.

Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia (WOSCOPS). NEJM 1995;333:1301-7.