



Screening and Management of Lipids

Lipid Therapy Guideline Team

Team Leader

William E. Barrie, MD
General Medicine

Team Members

R. Van Harrison, PhD
Medical Education

Ujjaini B. Khanderia,
PharmD
Pharmacy

Robert B. Kiningham, MD
Family Medicine

Robert S. Rosenson, MD
Cardiology

Updated

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UMHS Guidelines Oversight Team

William E. Chavey, MD
R. Van Harrison, PhD
Connie J. Standiford, MD

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These guidelines should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific clinical procedure or treatment must be made by the physician in light of the circumstances presented by the patient.

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. This guideline focuses on lipids – other measures of CHD risk (e.g., C-reactive protein, apolipoprotein A-I/B, coronary calcium score) are not addressed.

Key Points

■ Primary Prevention

Screening. Screen men age 35 and older and age 20 to 35 if at increased risk for CHD. Screen women only if at increased risk for CHD. [IC*] Repeat screening in 5 years in patients with normal lipids [IID*]. Screening with fasting lipid profile is advised. If screened non-fasting for patient convenience, follow-up on abnormal non-fasting lipids with a fasting lipid profile.

Risk. See Table 3 for risk factors. Determination of risk can be facilitated by using the [Framingham based Global Risk Score](#), which predicts 10 year risk of a coronary event [C].

Treatment.

- Initial treatment: lifestyle modification - smoking cessation, diet, exercise, and weight reduction [IA]. Evaluate LDL-C response in 6 weeks to 6 months based on patient's cardiovascular risk. [ID]
- Drug therapy. Consider if LDL-C remains above threshold: patients with low risk ≥ 190 mg/dl, moderate risk ≥ 160 mg/dl, moderately high risk ≥ 130 [option ≤ 100] mg/dl [IIA].
- Evidence is insufficient to recommend drug therapy for low HDL-C or high triglycerides for primary prevention.

■ Secondary Prevention

Screening. Screen with a full lipid panel all patients with CHD, other atherosclerotic cardiovascular disease (ASCVD), diabetes mellitus (DM), or Framingham 10 year risk $>20\%$ [IA].

Risk. Determine whether patient risk for cardiovascular events is:

- High: CHD without major risk factors or other risks associated with “very high” risk.
- Very high: CHD or other atherosclerotic vascular disease plus one or more of: major risk factors (e.g. diabetes, metabolic syndrome, active cigarette smoking), or acute coronary syndrome.

Treatment.

- All patients: Lifestyle modification [IA]
- Drug therapy: statin therapy should be considered for all patients. Statins reduce mortality and CHD/ASCVD endpoints, including if LDL-C < 100 mg/dl [A]. High potency statins (atorvastatin, rosuvastatin) at high doses reduce events more than low potency statins or high potency statins at low doses. [A]
 - Prescribe moderate potency statin (e.g. simvastatin 40 mg/daily) even if low LDL-C [IA] (Note: in DM patients age <40 with no other CHD risk, statin is only marginally cost-effective.)
 - LDL-C goals: high risk ≤ 100 mg/dl, very high risk substantially < 100 (option ≤ 70) mg/dl [IIA]
 - Non statin lipid agents (fibrates, niacin, resins, ezetimibe) have less or no evidence for improved outcomes compared to statins. [A]
 - Combination therapy (statin + any other lipid agent) improves lipids, but may increase myopathy risk, and has not yet been shown to improve outcomes compared to statins. [IIC]

■ Cost effectiveness

- Simvastatin is currently the most cost-effective agent per mg/dl lowering in LDL-C, and lowers LDL-C up to 46% at the 80 mg dosage. Lovastatin and pravastatin are also generic.

* Strength of recommendation:

I = generally should be performed; II = may be reasonable to perform; III = generally should not be performed.

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.

Table 1. Overview of Primary Prevention *

<p>1. Candidates. Confirm appropriate for primary prevention.</p> <ul style="list-style-type: none">• Men age 35 and older; age 20–35 if increased risk for CHD• Women age 20 and older if increased risk for CHD <p>For candidates, go to next step.</p> <p>2. Laboratory testing. Obtain lipid/CHD profile – fasting advised. If screened non-fasting and lipids abnormal, perform fasting lipid panel.</p> <p>3. Abnormal levels? Is: HDL-C \leq 40 mg/dl or TC \geq 240 mg/dl or TC . 200 mg/dl with 2 or more CHD risks (Table 3)? If normal levels: reinforce lifestyle education (as appropriate: smoking cessation, diet, exercise, weight loss) and repeat screen in 5 years. If abnormal levels, go to next step.</p> <p>4. Secondary causes? Consider and treat any secondary causes (Table 4).</p> <p>5. Lifestyle modifications. As appropriate, address smoking cessation, diet, exercise, weight loss, reduce excessive alcohol.</p> <p>6. Lipid profile. Obtain a lipid profile periodically (6 weeks to 6 months) to assess efficacy of lifestyle / lipid lowering therapy.</p> <p>7. Triglycerides elevated? If triglycerides > 400 mg/dl, see text for triglyceride management. If triglycerides \geq200 mg/dL, calculate non-HDL cholesterol. Non-HDL cholesterol = total cholesterol – HDL cholesterol. If triglycerides \leq 400 mg/dl go to next step.</p> <p>8. Risks sufficient to start drug therapy? See Table 5 for risks levels to initiate drug therapy. (Step 8 continues on next column.)</p>	<p>(Step 8 continued) If not starting drug therapy:</p> <ul style="list-style-type: none">• Reinforce lifestyle modifications (as appropriate: smoking cessation, diet, exercise, weight loss, reduce excessive alcohol)• Follow-up lipids in 1 to 2 years. <p>If risk sufficient to start drug therapy, go to next step.</p> <p>9. Initiate drug therapy.</p> <ul style="list-style-type: none">• Check baseline ALT.**• Treat with statin (see Tables 6 and 7) <p>10. Initial follow-up. Check lipids in 6–12 weeks. Check ALT as indicated.** Check creatinine kinase (CK) only if patient has symptomatic muscle aches and weakness.</p> <p>11. Lipid goal met? See Table 5 for lipid goals. If lipid goal not met:</p> <ul style="list-style-type: none">• Address adherence• Reinforce lifestyle modifications• Modify drug treatment, e.g., increase statin. See Table 8 for statin intolerance.• Consider referral to specialist in lipid management.• Follow-up in 6–12 weeks and reassess whether lipid goal met (repeat step 11). <p>If lipid goal met or no further reduction likely, go to next step.</p> <p>12. Longer term follow-up. Follow-up lipids at least annually.</p>
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* Assumes candidate does not already have a disease that requires lipid measurement for secondary prevention, e.g., CHD, atherosclerotic cardiovascular disease, and diabetes mellitus.

** Careful follow-up of liver tests is indicated for those with known liver disease or risk factors for liver disease, or in patients who are on other potentially hepatotoxic medications. No evidence suggests that routine testing is beneficial in normal risk patients, but it can be done at physician discretion.

Table 2. Overview of Secondary Prevention *

<p>1. Lifestyle. Lifestyle counseling</p> <p>2. Nutrition. Consider nutrition consult</p> <p>3. Secondary causes. Treat secondary causes of lipid disorder (see Table 4).</p> <p>4. Statin. See Table 5 for statin goals, Table 6 for statins, Table 7 for common interactions, and Table 8 for statin intolerance.</p> <ul style="list-style-type: none">• <u>Start.</u> Start at least a moderate dose/high potency statin (e.g., simvastatin 40 mg) in all patients, even if low lipids (no recommendation if baseline TC is <135 mg/dl or LDL-C <50 mg/dl unless the patient is a candidate for empiric statin therapy in the setting of an acute coronary syndrome). Lower doses in special situations (elderly, renal insufficiency, cytochrome 3A4 inhibitors, etc.)• <u>Titrate up.</u> Titrate up statin dose as tolerated to target an LDL-C <100 mg/dl.• <u>High risk.</u> Consider further titration of statin (higher dose/potency) in high risk patients with CHD, including recent acute coronary syndrome (ACS), metabolic syndrome, or poorly controlled risks (diabetes, tobacco). <p>5. Consider triglycerides. After reaching statin target dose, consider treatment of high triglycerides and low HDL-C. However, there is no randomized controlled trial showing event reductions with combination therapy. Avoid statin/gemfibrozil combination to reduce risk of myopathy.</p> <p>6. Longer term follow-up. Follow-up lipids at least annually.</p>
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* Target group: Patients with coronary artery disease (CHD), atherosclerotic cardiovascular disease (ASCVD), diabetes mellitus (DM), Framingham risk score >20%, or chronic renal insufficiency.

Table 3. Major CHD Risk Factors other than LDL-C *

Cigarette smoking
 Hypertension (blood pressure $\geq 140/90$ mm Hg or on antihypertensive medication)
 Low HDL cholesterol (< 40 mg/dl) ** ADA recognizes low HDL cholesterol < 50 mg/dL in women.
 Family history of premature CHD (CHD in first-degree relative: male < 55 years or female < 65 years).
 Age (men ≥ 45 years: women ≥ 55 years)

Note: [Framingham 10-Year Risk Score](http://hp2010.nhlbi.nih.net/atpiii/calculator.asp?usertype=prof) can be calculated at: <http://hp2010.nhlbi.nih.net/atpiii/calculator.asp?usertype=prof>

* Diabetes is regarded as a CHD risk equivalent. See Table 5, footnote “d” for other medical conditions that are CHD risk equivalents.

** HDL cholesterol ≥ 60 mg/dl counts as a “negative” risk factor; its presence removes 1 risk factor from the total count.

Table 4. Secondary Causes of Lipid Disorders

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

Adopted from VA/DOD lipid guidelines

Table 5. Risk Categories for Initiating Lifestyle Change, Considering Drug Therapy, and LDL-C Goals

Risk Category	LDL-C to Initiate Lifestyle Changes ^a	LDL-C to Consider Drug Therapy	LDL-C Goal
Primary Prevention			
Low risk: 0–1 risk factors ^b	≥ 130 mg/dl	≥ 190 mg/dl	< 160 mg/dl
Moderate risk: 2+ risk factors & 10-year risk $< 10\%$ ^c	≥ 130 mg/dl	≥ 160 mg/dl	< 130 mg/dl
Moderately high risk: 2+ risk factors & 10-year risk 10 to 20% ^c	All	≥ 130 mg/dl (option: ≥ 100 mg/dl)	< 100 mg/dl
Secondary Prevention			
CHD or CHD risk equivalent ^d without risk factors that are major or severe/poorly controlled ^e	All	All – at least moderate statin	< 100 mg/dl
CHD or CHD risk equivalent ^d with risk factors that are major or severe/poorly controlled ^e	All	All – at least moderate statin	Substantially < 100 mg/dl (option: < 70 mg/dl)

Note: This table was modified from ATP, based on HPS.

^a As appropriate, address smoking cessation, diet, exercise, weight loss, reduce excessive alcohol.

^b Almost all people with 0–1 risk factor have a 10-year risk $\leq 10\%$; thus 10-year risk assessment is not necessary.

^c Major risk factors are listed in Table 3. Electronic 10-year risk calculators are available at “www.nhlbi.nih.gov/guidelines/cholesterol”.

^d CHD includes history of myocardial infarction, unstable angina. Stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia. CHD risk equivalents include diabetes and clinical manifestations of noncoronary forms of atherosclerotic cardiovascular disease (ASCVD) such as peripheral arterial disease, abdominal aortic aneurysm, carotid artery disease, or Framingham score $\geq 20\%$.

^e Very high risk is established CHD (see above) plus one or more of: major risk factors (e.g. diabetes, metabolic syndrome – especially triglycerides ≥ 200 plus non-HDL-C ≥ 130 plus HDL-C < 40), current cigarette smoking or acute coronary syndrome.

Table 6. Drug Therapy Summary [Agents available as generics in **Bold**]

	Dose Range	\$/Mo gen ^a	\$/Mo br ^a	LDL-C	HDL-C	TG	General Cautions about Drug Class
HMG-CoA reductase inhibitors (Statins)							
<u>High Potency</u>							
Atorvastatin (Lipitor®) 10, 20, 40, 80 mg	10-80 mg/d	N/A	\$86-123	30 - 60% ↓	7 - 10% ↑	25 - 46% ↓	Statins are contraindicated in pregnancy. LFT's ↑ in 0.1-1.9%; monitor ALT. Careful f/u is indicated for those with known liver disease or risk factors for liver disease, or who are on other potentially hepatotoxic meds. There is no evidence that routine LFT testing is beneficial in normal risk patients, but can be done at physician discretion.
Rosuvastatin (Crestor) * 5, 10, 20, 40 mg	5-40 mg/d	N/A	\$102	45-63 % ↓	8-14 % ↑	10-35% ↓	
<u>Moderate Potency</u>							
Simvastatin (Zocor®) 5, 10, 20, 40, 80 mg	5-80 mg/d	\$6-9	\$63-148	24 - 46% ↓	5 - 21% ↑	1 - 46% ↓	Myopathy risk very low as monotherapy, increased with gemfibrozil and many other drugs (see table) that inhibit CYP3A4. Routine CPK screening not proven beneficial. Avoid in combination with gemfibrozil.
<u>Low Potency</u>							
Fluvastatin (Lescol®) 20, 40 mg, Lescol® XL 80 mg	20-80 mg/d ^b	N/A	\$77-154	19 - 32% ↓	3 - 8% ↑	0 - 11% ↓	Caution in severe renal impairment. Use low dose in moderate renal impairment & monitor. No dosage adjustment necessary for atorvastatin or fluvastatin. Doubling a statin dose reduces LDL-C by about 6%.
Lovastatin (Mevacor®) 10, 20, 40 mg	10-80 mg/d ^b	\$12-40	\$36-256	24 - 40% ↓	5 - 19% ↑	3 - 22% ↓	
Pravastatin (Pravachol®) 10, 20, 40, 80 mg	10-40 mg/d	\$13-90	\$113-168	18 - 35% ↓	4 - 16% ↑	1 - 25% ↓	* Rosuvastatin drug levels are two fold higher in Asian patients, use with caution.
Vytorin (ezetimibe-simvastatin) 10 mg-10 mg, 10 mg-20 mg, 10 mg-40 mg, 10 mg-80 mg	10/10–10/80 (ezetimibe/ simvastatin) mg/d	N/A	\$97	45-60%↓	6-10 % ↑	23-31% ↓	* Combination therapy (statin + other lipid agent) improves lipids, but may increase myopathy risk, and has not yet been shown to improve outcomes compared to statins.
Absorption Inhibitors							
Bile Acid Resins: Cholestyramine (Questran®) 4 g powder/LIGHT	4-12 gm bid	\$40-80	\$200-460	11 - 31% ↓	3 - 5% ↑	May ↑ TG	<ul style="list-style-type: none"> ▪ Effective and safe with statins. ▪ Take other meds 1 hr prior or 4 hr after; or take with dinner. ▪ May cause constipation, bloating, altered fat absorption. ▪ May decrease absorption of vitamins.
Colesevelam tab (Welchol®)	1.875 gm bid	N/A	\$192	10 – 15%↓	NC	NC	
Colestipol (Colestid®) 5 g powder/1g tab	5-15 gm bid	N/A	\$87-323	16 - 29% ↓	3 - 5% ↑	May ↑ TG	
Ezetimibe (Zetia®)	10 mg daily	N/A	\$95	18%↓	1%↑	8%↓	----- ▪ Effective and safe with statins

Table 6. Drug Therapy Summary, continued [Agents available as generics in **Bold**]

Drug & Strength	Dose Range	\$/Mo gen ^a	\$/Mo br ^a	LDL-C	HDL-C	TG	General Cautions about Drug Class
Niacin ^{c,d} Niacin Immediate release (IR) 100, 250, 500 mg Niacor®	500-1500 mg tid	\$6-10	\$23-46	13 - 21% ↓	10 - 24% ↑	19 - 24% ↓	<ul style="list-style-type: none"> ▪ Take w/ meals to avoid flushing or GI upset. ▪ With Niaspan SR follow titration schedule: week 1-4: 500 mg qhs; week 5-8: 1000 mg qhs; may titrate to 1500 mg/day then 2000 mg/day, as needed. Women may respond at lower doses than men. Take at bedtime after a low-fat snack. Do not crush tablets. 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/ hx of complicated active PUD. ▪ Decreases urinary secretion of uric acid, caution with gout. ▪ Contraindicated in hepatic disease. ▪ If CrCl = 10-50 mL/min give 50% dose; if < 10 mL/min give 25%.
Niacin Extended release (ER) 500 mg, 750 mg, 1 g Niaspan® Advicor® (extended-release niacin / lovastatin)	1-2 gm/d	\$6-10	\$128-227	13% ↓	19% ↑	10% ↓	
	500 mg/20 mg- 2000 mg /40 mg/d	N/A	\$89-204	30-42% ↓	20-30% ↑	15-35% ↓	
Fibrates Gemfibrozil 600 mg tab, Lopid®	600 mg bid	\$14	\$132	± 10%	10% ↑	43% ↓	<ul style="list-style-type: none"> ▪ Obtain baseline ALT, monitor at physician discretion, unless at increased risk (see text). ▪ Contraindicated in hepatic disease or severe renal disease. ▪ Risk of myopathy with statins. ▪ Dosage should be reduced with renal insufficiency.
Fenofibrates (Lofibra®) 54 mg, 160 mg tab; 67 mg, 134 mg, 200 mg capsules (Antara®) 43 mg, 130 mg capsules (Lipofen®) 50 mg, 150 mg capsules (Tricor®) 48 mg, 145 mg tab (Triglide®) 50 mg, 160 mg tab	48-145 mg/d	\$22-86 N/A N/A N/A N/A	\$22-86 \$39-116 \$32-69 \$37-112 \$38-115	17 - 35% ↓	2 - 34% ↑	32 - 53% ↓	<ul style="list-style-type: none"> ▪ Initial dose 48 mg in elderly and patients with renal dysfunction. Increases effect of warfarin. ▪ Dosage should be reduced with renal insufficiency.

^a Cost = Average wholesale price based -10% for brand products and Maximum Allowable Cost (MAC) + \$3 for generics on 30-day supply, *Amerisource Bergen item Catalog 5/08* & Michigan Department of Community Health M.A.C. Manager, 5/08.

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

^c Generic niacin (IR and SR) is inexpensive but not federally regulated and much less tolerated than extended release niacin (DIRECT COMPARISON STUDIES). Some OTC niacin SR formulations have been associated with hepatitis, fulminant hepatitis and death.

^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 7. Common 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 (<1%)
Resins	Fat soluble vitamins	Impaired absorption (though vitamin supplement not routinely necessary)
	All other drugs	Impaired absorption. Take all other meds 1 hour before or 4 hours after resins
Fibrates	Statins	Increased risk of myopathy
	Warfarin	Increased INR
	Glyburide	May increase risk of hypoglycemia

^a Pravastatin, fluvastatin, and rosuvastatin have lower risk of drug interactions with other medications metabolized through the CYP3A4 system than other statins.

^b Grapefruit juice increases risk of myopathy for statins that are metabolized by the cytochrome P450 3A4 system (atorvastatin, lovastatin, simvastatin).

Table 8. Management of Statin Intolerant (muscle aches/myopathy) Patients

- 1. Reversible causes.** Check for reversible causes of muscle aches/myopathy while on statin (hypothyroidism, cytochrome 3A4 inhibitors). Consider drug interactions (cyclosporine and concomitant use of certain statins (atorvastatin, lovastatin, simvastatin) and other agents that are metabolized by the cytochrome P450 3A4 system.
- 2. Alternative statin.** Trial alternative low dose statin, and titrate up slowly.
- 3. Alternate day dosing.** If failing a second statin, consider a trial of alternate day dosed long acting statin (atorvastatin/rosuvastatin).
- 4. Non-statin agents.** If failing alternate day statin, consider one or more non-statin lipid lowering agents, including niacin, bile acid sequestrants, fibrates (if low HDL-C, high triglycerides), that have some evidence of CHD event reduction.
- 5. Consider ezetimibe.** If intolerant to second line agents, consider ezetimibe (LDL-C reduction but no data showing event reduction).

Clinical Background

Clinical Problem

Incidence. Coronary heart disease (CHD) and stroke are the two most important causes of death and disability in developed countries. 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) > 240 mg/dl, and another 30% have

borderline TC (200-240 mg/dl). NHANES data sets show that overall prevalence of high cholesterol have not changed in recent years, but recognition, treatment and control of high cholesterol has improved dramatically. CHD and atherosclerotic cardiovascular disease (ASCVD) have declined in the past two decades, likely due to improvements in blood pressure and cholesterol control, and decline in smoking.

Issues. Many studies have shown that CHD patients are not adequately treated. The situation is likely worse for secondary prevention groups without CHD. Why do we fail to screen and adequately lower cholesterol? Costs may

be an issue for some patients and patient compliance despite insurance is another. Patient education about the benefits and general need for lifelong treatment may help improve compliance. Polypharmacy is an issue in secondary prevention. Patients may be hesitant to take another pill, especially one that may cause muscle aches. Health providers need to provide patients with information on the indications, proven benefit, long term use, and small but real risks.

Rationale for Recommendations

Scope of This Guideline

This guideline makes recommendations on lipid screening and treatment for prevention of cardiovascular events and mortality. Primary prevention refers to lower risk groups, people without prior CHD, other atherosclerotic cardiovascular disease (ASCVD), DM, or Framingham risk score indicating 10 year risk for cardiovascular event at >20%. Secondary prevention includes people with prior CHD, ASCVD, DM, or Framingham risk score >20%. Not all patients with DM are high risk; this is reviewed further in the University of Michigan guideline [Management of Type 2 Diabetes Mellitus](#). The guideline does not address severe or familial dyslipidemias.

This guideline reviews lipid targets and treatment strategies in the context of cardiovascular risk. It also reviews major classes of medications and their place in therapy. Statins remain our primary treatment modality, particularly in secondary prevention. We make reference to the National Cholesterol Education (NCEP), Adult Treatment Program (ATP) guidelines throughout the guideline. They are a national work group/expert panel that has provided regular updates on lipid assessment and treatment since 1988.

Etiology

Many studies support 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. Increasing evidence indicates that the triglyceride rich VLDL remnant and IDL particles are atherogenic, suggesting the need for secondarily targeting the non-HDL, non-LDL cholesterol fractions.

It is important to evaluate for secondary causes of hyperlipidemia by history and selected laboratory tests (see Table 4). 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

Treatment options include diet, lifestyle changes, and medication, with many patients also using complementary and alternative therapies. Of these, trial evidence has shown most benefit with medications. Statins proved the greatest cholesterol/LDL-C reduction, and most dramatic reduction in CHD events. In secondary prevention trials, statins have reduced CHD and total mortality, as well. Non-statin medications, including niacin, fibrates and resins, have shown smaller reductions in CHD events.

Primary Prevention

Primary prevention studies have shown consistent reduction in CHD, ASCVD (stroke), and revascularization events. Meta-analysis has shown a nonsignificant (22.6%) reduction in CHD mortality and no change in total mortality. A recent large RCT (JUPITER study) looking at rosuvastatin in patients with low LDL-C and elevated C-reactive protein was terminated early due to dramatic CHD event reduction in the statin arm. The primary endpoint was reduced 44% (P<0.00001). All subgroups benefited. However, early termination may have overestimated treatment benefit. (This was a trial of statin therapy, not CRP screening, and should not be used as evidence to screen all prevention patients with CRP.)

Interpreting treatment benefit in primary prevention requires looking at absolute versus relative risk reduction (RR). As a group, the primary prevention trials showed a 29% relative RR. However, primary prevention populations have low CHD risk, translating into low absolute RR. A meta-analysis looking at low (10 year risk <6%), intermediate (10 year risk 6-20%, and high (10 year risk >20%, i.e., secondary prevention), found that 4.3 years of statin therapy would reduce CHD events by 0.75%, 1.63%, and 2.51%, respectively, with NNT's of 133, 61, and 40. Statins may not be considered cost effective in the low risk group, but may be cost-effective in the intermediate risk group. Prior cost-effectiveness studies were done prior to generic simvastatin and reduced statin pricing. Even if medication were free, however, the low absolute benefit in low risk primary prevention makes drug therapy (with potential side effects) unattractive.

Secondary Prevention

Secondary prevention trials have shown consistent reduction in CHD events, CHD and total mortality. Event reduction is related to LDL-C reduction in a log-linear pattern, i.e. CHD risk rises more steeply with increasing LDL-C. Each 30 mg/dl decrease in LDL-C reduces the relative risk by about 24%. Therefore, when two patients, one with high and one with low LDL-C, start a statin that reduces LDL-C 40%, the patient with high LDL-C will obtain a higher absolute RR.

Statins have shown reduction in different secondary prevention groups, including CHD, acute coronary syndromes, ASCVD, and DM. All subgroups, including elderly and females, have benefited. Older trials used statins that lowered LDL-C 30-40% with approximately 30% event reduction. In recent years, new trials have convincingly shown that high potency/high dose statins (e.g., atorvastatin 80 mg/d), are more effective in reducing events than low potency/low dose statins. A meta-analysis of high versus lower dose statins, including PROVE IT-TIMI 22, TNT, IDEAL (Incremental Decrease in End Points Through Aggressive Lipid-Lowering) and A-Z (Aggrastat-to-Zocor), yielded a significant 16% reduction in CHD events. There was no difference in mortality, but a trend toward decreased CHD mortality (OR 12%, p=0.054).

The HPS trial randomized 20,536 secondary prevention patients with normal cholesterol to simvastatin 40 mg or placebo. These were patients with healthy cholesterol, i.e. their doctors had not recommended drug treatment. Treatment resulted in a 24% relative RR for CHD events and a 12% reduction in total mortality. All subgroups benefited, including women and the elderly (age >70 years). Notably, patients at all levels of baseline LDL-C benefited to a similar degree. Treatment of 1,000 patients with simvastatin would prevent 70-100 patients from having a major vascular event. Even those patients with a baseline LDL-C <100 mg/dl (about 3,500 patients) had a similar benefit.

Screening

Primary prevention. See the overview of primary prevention in Table 1.

Target population. The age group for screening for primary prevention remains an area of controversy. National organizations have different age recommendations for screening (see Table 8). 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.

Table 8. National Screening Guidelines by Age

National Group	Men	Women
U.S. Preventive Services Task Force (2008)	≥ 35	(if CHD risk)
American Academy of Family Physicians (2007)	≥ 35	≥ 45
American College of Physicians (1996)	35 - 65	45 - 65
National Cholesterol Education Program (NCEP) (2004)	≥ 20	≥ 20
Canadian Task Force on Periodic Health Examination (1994)	Men age 30-59	

Most guidelines have agreed there is good evidence for screening men aged 35 to 65. The optimal age for screening women is unknown, but relative to men they generally have a lower overall risk and a 10-year delay in relative risk. Epidemiologic studies indicate the risks of high cholesterol extend to age 75, though little trial data exist for this older age group. AFCAPS/TexCAPS showed benefit in older adults (aged 65-73). PROSPER looked at older adults (age 70-82), but the primary prevention group (3,239 patients) did not have a significant reduction in CHD events. Screening for lipid disorders, like other primary prevention efforts, may not be appropriate in individual patients with reduced life expectancy.

USPSTF performed the most recent evidence review and this guideline incorporates its assessment that for screening and treating lipid disorders:

- benefits substantially outweigh potential harms for all men age 35 and older and for women age 45 and older at increased risk for CHD.
- benefits moderately outweigh potential harms for younger adults (men age 20 to 35 and women age 20 to 45) at increased risk for CHD.

Lipid measures. When ordering screening lipids, which tests should be requested?

A fasting lipid panel is advised. For patient convenience a non-fasting screen may be initially performed, but abnormal non-fasting screening lipids (i.e. TC > 200 mg/dl, or an HDL-C < 40 mg/dl) should go on to have a fasting lipid panel. LDL-C is typically measured indirectly in a lipid panel. The indirect measure is less accurate if TG > 400 mg/dl, so most laboratories also perform a direct LDL-C if TG > 400 mg/dl.

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.

Non-HDL-C is a secondary measure in patients with elevated triglycerides. It is the sum of LDL-C and VLDL-C, or TC minus HDL-C. Non-HDL-C goals are 30 mg/dl higher than LDL-C goals, and have been shown to be a better predictor of CHD risk than LDL-C. This would be expected, because it includes LDL-C and other atherogenic lipoproteins. In a cohort study (Ingelsson E et al, 2007), non-HDL-C did not perform better than TC:HDL-C at predicting CHD risk.

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. Table 5 lists ATP III recommended LDL-C levels at which dietary and drug therapy should be initiated taking into account other risks. (These targets are based on expert opinion.) No changes in the literature suggest changing prior ATP III recommendations. Drug therapy is likely cost-effective in high risk primary prevention groups. It is unclear if recent declines in costs for generic statins

will make treating lower risk primary prevention groups cost-effective.

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 when TG remains above 400 mg/dl. Options include measurement after treating the TG, or direct LDL-C measurement.

Persons with a LDL-C >190 mg/dl should be considered to have a genetic disorder such as polygenic or familial hypercholesterolemia. When combined with a family history of premature coronary disease or stroke, consideration should be given to treatment at a younger age. Evidence is insufficient to recommend drug therapy for low HDL-C or high triglycerides for primary prevention.

Secondary prevention. See Table 2 for an overview of secondary prevention.

Target population. Secondary prevention includes all CHD, ASCVD, diabetes, and Framingham risk score > 20%.

Lipid measures. Patients should have a lipid profile (TC, LDL-C, HDL-C, and TG). Patients with an acute coronary syndrome without a recent fasting lipid profile should have one drawn by the morning following the event, and treatment with a statin should be initiated early and prior to discharge. The cholesterol may be artificially low at the time of an acute MI, returning to baseline in four weeks.

Lipid targets. Lipid guidelines have historically used LDL-C targets as a guide to therapy, and are still recommended by NCEP/ATP. An alternative approach in secondary prevention is moderate-to-high dose/high potency statins for all patients, acknowledging that more is better, but without a specific lower threshold LDL-C target.

The target LDL-C for secondary prevention used to be <100 mg/dl. However, recent studies have shown that patients with lower baseline LDL-C obtain similar benefit from statins, and high dose/high potency statins result in reduced CHD events relative to low dose/low potency statins (see treatment benefit section). A recent ATP III update recommended LDL-C <70 mg/dl as an optional goal for high risk patients, a broad group including those with multiple risk factors (especially diabetes), poorly controlled risk factors, multiple risk factors for metabolic syndrome, and acute coronary syndromes. Achieving these low LDL-C targets will be difficult, and may require adding other medications to high dose/high potency statins.

Some patients will have a metabolic syndrome picture, with low HDL-C/high triglycerides. The American Heart Association/American College of Cardiology (AHA/ACC) guidelines for secondary prevention of CAD recommend consideration for additional medication directed at these abnormal lipids, including niacin and fibrates. However, the role of combination therapy is controversial. No studies show combination therapy to reduce CHD events or mortality. Combination simvastatin/niacin was shown to

reduce angiographic stenosis in one trial. Other options to further reduce triglycerides or LDL-C would be to add omega-3 fatty acids and cholesterol absorption blockers (resins and ezetimibe), respectively. Unfortunately, the ENHANCE study, a 2 year surrogate endpoint trial using carotid intima-media thickness (IMT), showed no benefit.

We recommend that all CHD or equivalents be treated with at least a moderate dose high potency statin (i.e. simvastatin 40 mg/d or equivalent), and consider higher doses as tolerated. For patients with diabetes and no other CHD risk factors, statin therapy may reasonably be delayed until age 40 since statin use in this population is only marginally cost-effective. (See UMHS clinical care guideline [Management of Type 2 Diabetes Mellitus.](#))

Data are insufficient to make general treatment recommendations on patients with baseline TC <135 mg/dl or LDL-C <50 mg/dl.

Treatment through 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 9. Patients vary widely 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. However, the reductions in total and LDL-C induced by dietary therapy and pharmacologic therapy are generally greater than for either therapy alone. A trial of diet should not delay statin therapy in secondary prevention patients.

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. Consumption should increase for fruits and vegetables rich in fiber, fish (omega-3 fatty acids), and linolenic acid (canola oil, soy, flax seed). Whole grain should be substituted 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. 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.

Table 9. 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%

Fish oil supplements. Omega-3 polyunsaturated fatty acids (PUFAs) found in dietary fish oil, have been shown to reduce atherosclerosis in animal models. Increased dietary omega-3 PUFAs via dietary change or supplements have been shown to improve CHD and CHD mortality in some, but not all studies. They reduce hepatic production of triglycerides and VLDL-C, and lower serum triglycerides by 20-50%. They may have other anti-thrombotic and anti-inflammatory properties as well. Most studies have shown benefit; though a recent meta-analysis did not show benefit.

Lovaza is the only FDA approved fish oil supplement, available by prescription. Many OTC brands are available at a much lower price, but are not regulated, and require more capsules to achieve the same effect. Lovaza is dosed at 4 grams per day.

Fish oil supplements are a reasonable adjunct to secondary prevention populations with high triglycerides. Unlike gemfibrozil, they do not increase myopathy risk when added to statins.

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. However, nicotine replacement therapy is contraindicated in unstable angina or acute MI. For more information, see the [UMHS Smoking Cessation guideline](#).

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. Moderate intensity exercise, including walking at a moderately brisk pace, done regularly (30 minutes 3-5 times a week) raises HDL-C by an average of approximately 5%. The increase of HDL with exercise training is inversely related to the pre-training HDL level. Exercise training less consistently lowers TC, TG and LDL-

C. However, exercise training increases the effect of reduced dietary fat intake on reducing TC, LDL-C, and TG.

Decreased dietary fat intake alone causes reduced LDL-C and HDL-C. However, the addition of exercise training counteracts the HDL-C lowering effect of reduced dietary fat, and HDL-C levels are maintained or even increased.

Age and gender do not appear to influence the effect of exercise training on increasing HDL-C. Resistance exercise (e.g., weight lifting) has also been shown to increase HDL-C in young and older adults.

For patients with known CHD, exercise must be tailored to the degree of disease. Aerobic exercises (walking, cycling, swimming) should be done at levels that do not precipitate cardiac ischemia and 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.

Choice of drug. Statins are generally used as first-line agents. Statins have the advantage of potency, tolerability, safety, and strong clinical trial data supporting benefit. Bile acid resins are generally more expensive per LDL-C reduction, and have much higher rates of side effects. Fibrates are well tolerated, but have minimal impact on LDL-C and have not shown dramatic results in terms of event reduction. Niacin is effective at improving metabolic syndrome profiles, i.e. low HDL-C/high triglycerides, but is not well tolerated by many patients. Ezetimibe is well tolerated, but with limited power to lower LDL-C, and no trial evidence to support its use (i.e. reduction of CHD events).

Statin patients should have baseline ALT. Careful follow up is indicated for those known liver disease or risk factors for liver disease or who are on other potentially hepatotoxic medications. No evidence shows that routine testing is beneficial in normal risk patients, but further testing can be done at physician discretion.

Niacin patients should have baseline ALT, glucose and uric acid, with follow up ALT at 3 months or at dose escalations, and periodically thereafter.

Fibrates significantly increase risk of myopathy and rhabdomyolysis in combination with statins.

Table 6 presents a summary of information regarding commonly used lipid lowering drugs. Table 7 presents information regarding common interactions with them. Table 8 outlines management of the statin intolerant patient. 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 clinical event trials have included lovastatin, pravastatin, simvastatin atorvastatin, and rosuvastatin. Statins are considered to have a class effect. Evidence is now convincing that high potency/high dose statins reduce clinical events more than low potency/low dose statins in secondary prevention populations. Rosuvastatin is the most potent agent. Pravastatin is not metabolized by CYP450 (liver), and has less drug interactions. Lovastatin, pravastatin, and simvastatin are now available as generics. Choice of statin should be dictated by desired LDL-C reduction and cost (see Table 6).

We recommend using doses that target LDL-C reduction in the 30-40% range for most patients. Patients with very high LDL-C will not necessarily reach low (<100 mg/dl) levels despite maximal doses. No literature addresses combination therapy resulting in reduced clinical events over full dose statin monotherapy. However, combination therapy (particularly with gemfibrozil), may increase risk of adverse drug events. Patients at risk for myopathy (see below) should start at lower doses, and may not reach doses used in the trials. Doubling the dose of the statins from the starting dose results in only 6-7% additional LDL-C reduction.

The most common adverse effect from statins is muscle aches, which have resulted in dropouts in 5% of trial patients. No evidence indicates that myalgias are more common with one statin than another. Myopathy is uncommon. Peripheral neuropathy is another uncommon complication. Rhabdomyolysis is a life threatening complication of statin therapy, with a 10% mortality rate. The average incidence per 10,000 person-years for monotherapy is 0.44. However, this incidence rises to 5.98 when combined with a fibrate. Other drugs that increase risks are inhibitors of cytochrome P450 enzymes

(lovastatin/simvastatin/atorvastatin use CYP3A4, while fluvastatin uses CYP2C9), including cyclosporine, azoles, macrolides, protease inhibitors, verapamil, diltiazem, amiodarone and others. Grapefruit juice also increases the blood level (AUC) of statins that are metabolized by the cytochrome P450 3A4 system e.g. atorvastatin, lovastatin, simvastatin.

Myopathy risk is also increased in obstructive liver disease or renal dysfunction, hypothyroidism, serious infections, and advanced age. Routine CK monitoring is not recommended, and moderate CK elevations (<800 IU) do not necessarily indicate toxicity or increased risk of myopathy. No evidence indicates that routine LFT testing is beneficial in normal risk patients, but can be done at physician discretion. Careful follow up of liver tests is indicated for those with known liver disease or risk factors for liver disease, or in patients who are on other potentially hepatotoxic medications. If ALT is >2 times upper laboratory norm, stop medication or reduce dose. The increase in liver enzymes is dose related, but serious liver disease is almost unheard of.

Statins are contraindicated in pregnancy.

Statin intolerance is a common problem in primary and specialty care, generally due to myalgia. No studies support a particular strategy. A suggested strategy for managing statin intolerance is presented in Table 8.

Bile Acid Resins. Cholestyramine, colestipol, and colesevelam have been shown to reduce LDL-C cholesterol 10-20%, depending on dose. They are available in powder and pill 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 may increase triglycerides and should be used cautiously in patients with hypertriglyceridemia.

Adverse effects are common 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. With the exception of colesevelam, they should be taken 1 hour before or 4 hours after other medications. Side effects can be reduced somewhat by titrating up slowly. Colesevelam has been shown to have a lower incidence of GI side effects, similar to placebo, and does not interfere with absorption of statins, digoxin, metoprolol, quinidine, valproic acid, or warfarin. Colesevelam improves glycemic control in type 2 diabetes.

Ezetimibe. Ezetimibe inhibits intestinal absorption of cholesterol via blocking cholesterol transport at the intestinal brush border. It lowers LDL-C by 15-20% alone and provide significant incremental reduction with the statins but without the side effects of resins. It may be added to statins when they do not achieve lipid-lowering goals. Data on ezetimibe's effect on morbidity and

mortality are not yet available. However, a recent surrogate endpoint (carotid artery disease progression) trial showed no benefit of Vytorin over simvastatin. Ezetimibe should only be considered for patients intolerant to statin, niacin, fibrates, and resins, all of which have better evidence supporting their use.

Niacin. Niacin improves all aspects of the lipid profile (HDL-C increases 15-35%, triglycerides decreases 20-35%, LDL-C decreases 5-25%). The mechanism is not known. Niacin has been shown to reduce coronary events and total mortality, though results are less dramatic than statins. LDL-C reductions are minimal compared to the statins, and many patients are unable to tolerate the side effects. Their greatest benefit would be alone or in combination with statins in patients with a low HDL-C and moderate elevation of triglycerides, and those intolerant to the statins. 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 Niacor (IR) and Niaspan (SR), the product taken at bedtime, which is associated with improved compliance. 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 of niacin include flushing, pruritus, GI disturbances, fatigue, glucose intolerance, and gout. 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. Niacin should be avoided in patients with underlying liver disease or uncontrolled diabetes. Niacin ER has been shown to have lower side effects than IR niacin. Niacin ER 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, and bezafibrate (not available in US). Clofibrate is no longer used, as it is associated with increased total mortality in large randomized controlled trials. Fibrates are generally used to lower triglycerides and raise HDL-C. Fibrates activate the nuclear transcription factor peroxisome proliferator-activated receptor-alpha (PPAR-alpha), which regulates genes that control lipid metabolism. Gemfibrozil has no significant effect on LDL-C. Fenofibrate has been shown to lower LDL-C by 20% in hypercholesterolemia patients and 12% in combined hyperlipidemia metabolic syndrome, type 2 diabetes patients. Angiographic studies have shown benefit. Fibrates have been shown to reduce CHD events in primary and secondary prevention trials, but have had no effect on mortality, and in some instances have been associated with increased adverse events. For this reason, they are considered second line medications for CHD prevention. The VA-HIT trial (secondary prevention) did result in significant event reduction relative to placebo,

in a high risk group with low HDL-C and mild triglyceride elevation. However, the FIELD study did not show significant event reduction with fenofibrate in a diabetic population with established CHD, but a significant reduction in cardiovascular events in the primary population. The secondary prevention group was contaminated by unequal numbers of statin drop-ins in the two treatment groups.

Adverse effects are generally GI, including nausea, dyspepsia, and change in bowel habits. The risk of cholestasis and cholecystectomy is increased. Fibrates carry a small risk of myopathy as monotherapy, but the risk is increased markedly when gemfibrozil is combined with statins. Gemfibrozil interferes with metabolism of statins, whereas this interaction has not been observed in pharmacokinetic studies with fenofibrate. Fenofibrate is preferred when using combination therapy with statins. Fibrates may cause a small reversible increase in creatinine, and dose adjustment in renal insufficiency. Contraindications include severe renal or liver disease, pregnancy, or preexisting gallbladder disease.

Triglycerides and non-HDL cholesterol. The sum of LDL-C+VLDL cholesterol is clinically estimated as non-HDL cholesterol. No prospective trials of treatment specifically target non-HDL cholesterol, but expert opinion recommendations suggest using non-HDL cholesterol as a secondary treatment target for CHD and CHD equivalent patients, in order to reduce the coronary events attributable to VLDL remnant particles.

Triglycerides have been associated with an increase in coronary events in population studies, and event rate and mortality in CHD secondary prevention independent of statin treatment. Current evidence is insufficient to support drug therapy for elevated triglycerides in primary prevention. The focus for primary prevention patients should be on lifestyle changes and treating secondary causes of elevated triglycerides. For secondary prevention patients, based on expert opinion, ACC/AHA guidelines for secondary prevention of CHD recommend drug therapy for elevated triglycerides, regardless of HDL-C and LDL-C, in addition to aggressive lifestyle management.

Patients with severe triglyceride elevation (> 500 mg/dl) despite lifestyle change should be considered for drug therapy to prevent pancreatitis.

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 and red yeast rice. Their effects are noted below.

Estrogen and progestins. 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) by up to 25%. Hormone replacement therapy may increase triglycerides by 10-15%. However, two large trials assessed combined estrogen and progestin therapy in post-menopausal women with and without coronary disease, finding that combination therapy increased coronary disease and stroke. Combination therapy has no role in coronary disease prevention. The role of estrogens alone in women who have undergone a previous hysterectomy is not yet known. Hormone therapy should be based on direct indications for that therapy, e.g., hot flashes, not for lipid management.

Red yeast rice. Red yeast rice, a Chinese remedy (*Hong Ou*) developed over 1000 years ago for indigestion, diarrhea, and abdominal pain, has been marketed for cholesterol lowering in several capsule forms including *Cholestin*. It contains several naturally occurring substances related to the statins; the predominant is mevinolin, the major component of lovastatin. Use in patients already on statins may increase risk of myopathy. Lack of standardization and regulation in manufacturing increase the risk of toxicity relative to prescription statins. The FDA has determined it to be an unapproved drug not a dietary supplement, and it has been removed from the market.

Plant stanols/sterols. Plant stanols/sterols are available as spreads or capsules. These are the most effective OTC formulations available for LDL-C lowering.

Others. Even less proof exists regarding efficacy or safety in cholesterol lowering for several other products that are widely available in health food stores and pharmacies. These include guggulipid (an Asian Indian extract of bark from the *Mukul myrrh* tree), L-carnitine, and lecithin. They should be avoided.

Special Populations for Preventive Therapy

Women. Studies have shown significant treatment benefit in women. A meta-analysis on the effect of statins on risk of CHD found a 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.

Ischemic cardiomyopathy. The CORONA study looked at rosuvastatin in this population, and did not find significant cardiovascular disease event reduction (primary endpoint) but there were fewer hospitalizations for cardiovascular causes (pre-specified endpoint). Rosuvastatin was well tolerated. The findings were unexpected, and further studies in heart failure/cardiomyopathy are expected.

End Stage Renal Disease. A large RCT comparing atorvastatin (20 mg/d) to placebo in a diabetic dialysis population did not find a significant reduction in

cardiovascular events with statin therapy. Atorvastatin was well tolerated, however.

Strategy for Literature Search

The literature search for this update began with results of the literature search performed in 1999 to develop the initial guideline published in 2000. For this update a search of more recent literature was conducted on Medline prospectively using the overall keywords of: *cholesterol (including hyperlipidemia, lipoproteins, HDL cholesterol), 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 from 1/1/2000 to 7/31/2007*. In addition to the overall terms, for primary prevention a major search term was primary prevention of coronary artery disease with specific topic searches for: screening, pharmacotherapy, diet, exercise, alternative or complementary medicines, and other treatment. In addition to the overall terms, for secondary prevention a major search term was secondary prevention (treatment only) of coronary artery disease, peripheral vascular disease, or cerebral vascular disease/stroke with specific topic searches for pharmacotherapy, diet, exercise, alternative or complementary treatment, and other treatment.

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 8 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 screening
 - NCEP guidelines on primary and secondary prevention.

Disclosures

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Team Member	Company	Relationship
William E. Barrie, MD	(none)	
R. Van Harrison, PhD	(none)	
Ujjaini B. Khanderia, PharmD	Pfizer	Speakers Bureau Research Support
Robert B. Kinningham, MD	(none)	
Robert S. Rosenson MD	Abbott	Consultant, Speaker's Bureau, Research Support
	Astra Zenica	Consultant, Speaker's Bureau, Research Support
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	Roche	Consultant
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Annotated References

Cannon CP, Braunwald E, McCabe CH. Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes (PROVE-IT). *NEJM* 2004;350: 1495-504.

RCT comparing pravastatin 20 mg/d and atorvastatin 80 mg/d after acute coronary syndrome, with a RRR 16% favoring intensive therapy (atorvastatin).

Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on

Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001; 285; 2486-2497

Third version of US lipid guidelines prepared by representatives from involved medical specialties and organizations. Addresses screening, evaluation, and treatment of various lipid disorders. Gives firm recommendations/cut-offs for different treatment options.

The FIELD Study Investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus: randomized controlled trial. *Lancet* 2005;366:1849-61.

RCT of fibrate in a diabetic population. It did not show a significant reduction in the primary outcome (CHD events).

Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004 Jul 13;110(2):227-239.

An update on ATP III, with recommendations for more aggressive LDL-C reduction in high risk secondary prevention populations.

Hayward RA, Hofer TP, Vijan S. Narrative Review: Lack of Evidence for Recommended Low- Density Lipoprotein Treatment Targets: A solvable Problem. *Ann Intern Med* 2006; 145:520-530.

A review of trials/studies that examined the independent relationship of LDL-C and CHD outcomes in patients with LDL-C <130 mg/d. They did not find sufficient evidence to recommend titrating statin to achieve proposed LDL-C goals.

Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. *Lancet*. 360(9326):7-22, 2002 Jul 6.

RCT in secondary prevention patients with low cholesterol. Simvastatin lowered CHD events dramatically, independent of baseline LDL-C. Patients with baseline LDL-C <100 mg/dl had similar benefit.

Ingelsson E, Schaefer EJ, Controls JH, et al. Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. *JAMA*, 2007; 298(7):776-785.

A cohort study found that in clinical practice measures of apo B or apo A-I did not offer incremental utility over total cholesterol and HDL-C

LaRosa JC, Grundy SM, Waters DD. Intensive Lipid Lowering with Atorvastatin in Patients with stable Coronary Disease (treating to new targets (TNT)). *NEJM* 2005; 352: 1425-35

RCT comparing low/high dose statin in stable CHD patients. High dose statin resulted in a 22% RRR, and 2.2% absolute RR for CHD events.

Ridker PM, Danielson E, Fonseca F. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein (JUPITER). *NEJM* 2008;359:2195-207.
RCT comparing statin to placebo in primary prevention population with low LDL-C and elevated high-sensitivity C-reactive protein. Stopped early due to dramatic benefit in statin arm.

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). *N Engl J Med.* 1999;341:410-8.

A fibrate RCT in secondary prevention with low HDL-C, showing significant reduction in CHD composite events

Smith C et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update. *Journal of the American College of Cardiology* 2006; 47(10):2130-9

An expert panel guideline of recommendations on secondary prevention of CHD/ASCVD, including treatment of lipids with diet and pharmacotherapy.

Vijan S, Choe HM, Funnell MM, Bernstein SJ, Harrison RV, Herman WH, Campbell-Scherer D, Lash RW. Management of Type 2 Diabetes Mellitus [update 2008]. Ann Arbor, Michigan: University of Michigan Health System, 2008. Available at: www.med.umich.edu/1info/fhp/practiceguides/ccg.html and at www.guideline.gov

Overview for care of patients with diabetes.