Screening and Management of Lipids

Lipid Therapy Guideline Team

Team Leader
Audrey L Fan, MD
General Medicine

Team Members
Jill N Fenske, MD
Family Medicine

R Van Harrison, PhD
Medical Education

Elizabeth A Jackson, MD
Cardiology

Marie A Marcelino, PharmD
Pharmacy

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Grant Greenberg, MD, MA, MHSA
R. Van Harrison, PhD

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Patient population: Adults 20-79 years of age without familial or severe dyslipidemias or chronic kidney disease (CKD). *(For lipid management in patients with CKD, see UMHS CKD guideline.)*

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

Key Points

Screening / baseline lipid profile

Patients. All men age ≥ 35 and women age > 45 and also men age 20-35 and women age 20-45 if at increased risk for ASCVD *[IC*]*. Can also consider checking baseline lipid profile in adults ≥ 20 who are free from ASCVD for assessment of traditional ASCVD risk factors (age, sex, total and HDL-C, systolic BP, use of antihypertensive therapy, diabetes, and current smoker) *[IIC*]*.

Fasting/non-fasting. Screening test can be obtained fasting or non-fasting to facilitate obtaining data.

Assess ASCVD risk factors

- Clinical atherosclerotic cardiovascular disease (ASCVD includes stroke; peripheral arterial disease; coronary heart disease).
- LDL-C ≥ 190 mg/dL and age ≥ 21,not caused by drugs or underlying medical condition (Table 1).
- Diabetes mellitus type 1 or 2, age 40-75 years of age with LDL-C 70-189 mg/dL.
- 10-year ASCVD risk ≥ 7.5% for ages 40-75years (see Table 2 for calculation information).
- CKD.*(If CKD, see the UMHS CKD guideline for managing lipids in CKD patients.)*
- For additional risk factors to consider, see Table 3.

If no ASCVD or none of the above risk factors

Reinforce healthy lifestyle. Education as appropriate: smoking cessation, diet-exercise-weight loss, reduce excessive alcohol *[IA*]*.

Follow-up. Repeat screening/risk assessment in 4-6 years*[IID*]*. If borderline, consider repeat in 1-2 years.

If ASCVD or above risk factors other than CKD

Treatment through lifestyle changes. Education as appropriate: smoking cessation (reduces coronary event rate by ~ 50% within 1-2 years), diet-exercise-weight loss, reduce excessive alcohol *[IA*]*.

Initiate statin therapy. (Non-statin medications should be considered only in statin-intolerant patients.)

- Discuss with patient: risk reduction benefits, adverse effects, drug interactions, patient preferences.
- Check baseline ALT. (See Table 4 for monitoring if liver function tests are abnormal.)
- Dosing for LDL-C reduction: high-intensity statin (≥ 50%), moderate-intensity statin (30%-50%). See Table 5-8 for "intensity" levels, effects, interactions, and contraindications.
- Four main treatment benefit groups and their dosing intensity:
  - Clinical ASCVD: age ≤ 75 years = high-intensity*[IA*]*; age > 75 years = moderate-intensity*[IID*]*
  - LDL-C ≥ 190 mg/dL, age ≥ 21 = high-intensity*[IA*]*
  - Diabetes (type 1 or 2) and age 40-75 years with LDL-C 70-189 mg/dL =moderate-intensity*[IA*]*; can consider high-intensity if 10-year ASCVD risk ≥ 7.5%*[IID*]*
  - 10-year ASCVD risk ≥ 7.5% and age 40-75 years = moderate-to-high intensity*[IA*]*
  - If other risks (see Table 3), consider statin therapy based on individual benefit and harm.
- In 6-12 weeks:
  - Check lipids to evaluate adherence. Check ALT only if baseline abnormal, known liver disease, risk factors for liver disease, or on other potentially hepatotoxic medications. Check creatine kinase (CK) only if symptomatic muscle aches/weakness. If statin-intolerance, address (Table 9).
  - If lipids do not decrease as expected: address adherence, reinforce lifestyle modifications, and consider referral to specialist in lipid management.

Triglycerides. After initiating statin therapy, if fasting triglycerides ≥ 500 mg/dL, consider treating.

Longer term follow-up. Check lipids annually to assess adherence.

*** 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. Secondary Causes of Hyperlipidemia

Secondary Cause	Elevated LDL-C	Elevated Triglycerides
Diet	Saturated or trans fats, weight gain, anorexia	Weight gain, very low-fat diets, high intake of refined carbohydrates, excessive alcohol intake
Drugs	Diuretics, cyclosporine, glucocorticoids, amiodarone	Oral estrogens, glucocorticoids, bile acid sequestrants, protease inhibitors, retinoic acid, anabolic steroids, sirolimus, raloxifene, tamoxifen, beta blockers (not carvedilol), thiazides
Diseases	Biliary obstruction, nephrotic syndrome	Nephrotic syndrome, chronic renal failure, lipodystrophies, Cushing's syndrome
Disorders and altered states of metabolism	Hypothyroidism, obesity, pregnancy*	Diabetes (poorly controlled), hypothyroidism, obesity, inactivity; pregnancy*

* Cholesterol and triglycerides rise progressively throughout pregnancy; treatment with statins, niacin, and ezetimibe are contraindicated during pregnancy and lactation.

Adapted from 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol

Table 2. 10-Year Risk Assessment for ASCVD

Ten-year risk is defined as the risk of developing a first ASCVD event (nonfatal MI, CHD death, fatal or non fatal stroke) over a 10-year period among people free from ASCVD at the beginning of the period

Pooled Cohort Equations estimate 10-year ASCVD risk in individuals age 40 to 79 years with and without diabetes. A downloadable spreadsheet enabling estimation of 10-year and lifetime risk for ASCVD and a web-based calculator are available at http://my.americanheart.org/cvriskcalculator and http://www.cardiosource.org/science-and-quality/practice-guidelines-and-quality-standards/2013-prevention-guideline-tools.aspx .

Risk is calculated based on: gender, age (40-79 years), race (African American or whites/others), total cholesterol, HDL-cholesterol, systolic blood pressure, treatment for high blood pressure (Y/N), diabetes (Y/N), and smoker (Y/N).

The Pooled Cohort Equation may be revised in the near future due to concerns of over-estimating risk, however a 10-yr risk score cut off of ≥7.5% may be reasonable to initiate a conversation between clinician and patient regarding ASCVD risk reduction (see text on Assessing ASCVD Risk Factors)

When compared with non-Hispanic Whites, estimated 10-year risk for ASCVD is generally lower in Hispanic-American and Asian-American populations and higher in American-Indian populations. If using equations for non-Hispanic Whites for other race/ethnic groups, the estimated risks may be over-estimates, especially for Hispanic- and Asian-Americans.

Table 3. Other Patient Risk Factors that May Benefit from Statin Therapy

In selected individuals who are not in the four main statin benefit groups (see page 1), and for whom a decision to initiate statin therapy is otherwise unclear, additional factors may be considered to inform treatment decision making:

- Primary LDL-C ≥ 160 mg/dL or other evidence of genetic hyperlipidemias
- Family history of premature ASCVD with onset <55 years of age in a first degree male relative or <65 years of age in a first degree female relative
- High-sensitivity C-reactive protein ≥2mg/L
- Coronary artery calcium score ≥ 300 Agatston units or ≥ 75 percentile for age, sex and ethnicity
- Ankle-brachial index <0.9
- Metabolic syndrome. The NCEP ATP III defines the metabolic syndrome as a diagnosis of 3 or more of the following risks:
  - Waist circumference > 40 inches for men or > 35 inches for women
  - HDL-C < 40 mg/dL for men or < 50 mg/dL for women
  - Impaired fasting glucose ≥ 110 mg/dL (American Diabetes Association defines impaired fasting glucose as ≥100 mg/dL.)
  - Triglycerides ≥ 150 mg/dL or higher
  - Blood pressure of 130/85 mm Hg or higher
- Elevated lifetime risk of ASCVD
- HIV (Human immunodeficiency virus)
- Rheumatologic or inflammatory diseases
- Solid organ transplant
- Current tobacco user

Table 4. Monitoring Abnormal Baseline ALT

Careful follow-up of liver tests is indicated for those with known liver disease, risk factors for liver disease, or in patients who are on other potentially hepatotoxic medications. For other patients:

- If baseline liver function tests (LFTs) are normal, no further monitoring is required.
- If baseline LFTs are mildly abnormal (over upper limit of normal but < 5 X upper limit of normal): reassess LFTs after 6-12 weeks of statin treatment for stability. Consider monitoring annually for stability if baseline LFTs are abnormal.

Abnormal baseline liver biochemistries can frequently improve with statin therapy.

Table 5. Statin Dose Intensity and Equivalency Chart*

Statin Intensity	%LDL-C Reduction	HMG-CoA Reductase Inhibitor						
		Rosuvastatin	Atorvastatin	Pitavastatin	Simvastatin	Lovastatin	Pravastatin	Fluvastatin
High-Intensity (lowers LDL-C ≥ 50%)	63	40 mg ($196)						
	62							
	61							
	60		80mg ($9 gen, $236 br)					
	59							
	58							
	56	20 mg ($196)						
	54							
	52	10 mg ($196)						
	50		40mg ($9 gen, $236 br)					
Moderate-Intensity (lowers LDL-C 30% to < 50%)	48							
	46							
	44	5 mg ($196)						
	42		20mg ($9 gen, $236 br)	4 mg ($81)	40 mg ($4 g, $202 br)	80mg ($4 gen, $306 br)	80 mg ($25 g, 173 br)	80mg ($95 gen, $300 br)
	40							
	38		10mg ($7 gen, $165 br)					
	36				20 mg ($4 g, $202 br)			
	34						40 mg ($25gen, 173 br)	
	32			2 mg ($81)				
	30			1 mg ($81)	10 mg ($4 g, $116 br)	40mg ($4 gen, $153)	20mg ($17 gen, 117 br)	
Low-Intensity (lowers LDL-C < 30%)	28							
	26				5 mg ($4 g, $82 br)	20 mg ($4 gen, $43 br)		40mg ($95 gen, 150 br)
	24							
	22							
	20					10 mg ($4 gen, $43 br)	10mg ($19 gen, 58 br)	20mg ($95 gen, 150 br)
	18							

Note: The shading reflects doses listed in the ACC/AHA Guideline on Treatment of Blood Cholesterol (2013) as reflecting high-intensity therapy (≥ 50% reduction in LDL-C, darker shading) and moderate-intensity therapy (30% to 50% reduction in LDL-C, lighter shading).

* In one trial atorvastatin 40 mg was used for down-titration if unable to tolerate 80 mg.

Table 6. Drug Therapy Summary

	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	$8-9	$165-236	39−60% ↓	5−9% ↑	19−37% ↓	▪ Statins are contraindicated in pregnancy ▪ Liver function tests (LFTs)↑ in 0.1-1.9%. Careful follow-up is indicated for those with known liver disease, risk factors for liver disease, or who are on other potentially hepatotoxic meds. For other patients, if baseline LFTs are normal, no further monitoring is required. If baseline LFTs are mildly abnormal (over ULN, but < 5 times ULN): monitor LFTs during first 6 months of statin treatment for stability ▪ Myopathy risk very low as monotherapy, but is increased with drugs that inhibit CYP3A4 (see Table 8). Routine creatine kinase (CK) screening not proven beneficial ▪ Avoid in combination with gemfibrozil ▪ Dose adjustments are recommended for patients with eGRF < 60 ml/min/1.73m2. No dose adjustment necessary for atorvastatin. See UMHS CKD guideline for dose recommendations in CKD ▪ Doubling a statin dose reduces LDL-C by about 6-7% <u>Specific statin cautions:</u> * Rosuvastatin drug levels are two fold higher in patients of Asian descent; use with caution **Simvastatin 80 mg dose is available, but is associated with increased risk of muscle injury and should not be started in new patients. Only patients taking simvastatin 80 mg for ≥ 12 months without evidence of muscle injury should continue this dose ***Strong CYP3A4 inhibitors can increase atorvastatin, lovastatin, and simvastatin exposure increasing risk for muscle injury. See Table 8 for dose limitations with interaction drugs
Rosuvastatin (Crestor®)* 5, 10, 20, 40 mg	5−40 mg/d	N/A	$196 all	45−63 % ↓	8−14 % ↑	10−35% ↓	
<u>Moderate Potency</u> Pitavastatin (Lovalo®) 1, 2, 4 mg	1−4 mg/d	N/A	$81	32−43% ↓	5−8 ↑	15−18%↓	
Simvastatin (Zocor®)** 5, 10, 20, 40 mg	5−40 mg/d	$4-6	$86−202	26−47% ↓	8−16% ↑	12−33% ↓	
<u>Low Potency</u> Fluvastatin (Lescol®, Lescol® XL) 20, 40 mg capsule 80 mg ER tablet	20−80 mg/d [b]	$95	$150-300 $201 (80 mg ER)	19−32% ↓	3−8% ↑	0−11% ↓	
Lovastatin (Mevacor®)*** 10, 20, 40 mg	10−80 mg/d [b]	$4-6	$43−306	24−40% ↓	5−19% ↑	3−22% ↓	
Pravastatin (Pravachol®) 10, 20, 40, 80 mg	10−40 mg/d	$19-25	$60−173	18−35% ↓	4−16% ↑	1−25% ↓	
Absorption Inhibitors							
<u>Bile Acid Resins:</u> Cholestyramine (Questran®, Questran® Light) 4 g resin/variable g powder	4−12 g BID	$18-52	$19-57	15−30% ↓	3−5% ↑	0–20% ↑	▪ Effective and safe with statins ▪ Take other meds 1 hour prior or 4 hours after; or take with dinner ▪ May cause constipation, bloating, altered fat absorption ▪ May decrease absorption of vitamins
Colesevelam (Welchol®) 3.75 g/packet 625 mg tablet	3.75 g/d or 1.875 g BID	N/A	$362	15−18% ↓	3% ↑	9−10% ↑	
Colestipol (Colestid®) 5 g powder/1g tab	5-15 g BID	$42-125	$185−550	15−30% ↓	3−5% ↑	0–20% ↑	
Ezetimibe (Zetia®)	10 mg/d	N/A	$200	15−20% ↓	1−4% ↑	5−8% ↓	▪ Effective and safe with statins

Table 6. Drug Therapy Summary, continued

Drug & Strength	Dose Range	$/Mo gen [a]	$/Mo br [a]	LDL-C	HDL-C	TG	General Cautions about Drug Class
Fibric Acid Derivatives							
Fibrates Gemfibrozil (Lopid®) 600 mg tablet	600 mg BID	$11	$222	± 10%	10% ↑	43% ↓	▪ Obtain baseline ALT, monitor at physician discretion, unless at increased risk (see text) ▪ Contraindicated in hepatic disease or severe renal disease with GFR < 10 mL/min ▪ Risk of myopathy with statins ▪ Dosage should be reduced with renal insufficiency ▪ Use lowest initial starting dose of fenofibrate dosage form in elderly ▪ Increases effect of warfarin ▪ Dosage should be reduced with renal insufficiency
Fenofibrates Antara® (micronized) 43, 130 mg capsules	43−130 mg/d	N/A	$70−208	17−35% ↓	2−34% ↑	32−53% ↓	
Fenoglide® 40, 120 mg tablets	40−120 mg/d	N/A	$96-287				
Lipofen® 50, 150 mg capsules	50−150 mg/d	N/A	$72−157				
Lofibra® 54, 160 mg tablets	54−160 mg/d	$44-131	$44-131				
Lofibra® (micronized) 67, 134, 200 mg capsules	67−200 mg/d	$44-131	$44−131				
Tricor® 48, 145 mg tablets	48−145 mg/d	$36-90	$69−208				
Triglide® 50, 160 mg tablets	50−160 mg/d	N/A	$216				
Fenofibric Acid Fibricor® 35, 105 mg tablet	35-105 mg/d	N/A	$37-111				
TriLipix® 45, 135 mg delayed release capsule	45-135 mg/d	N/A	$66-198				
Niacin [c, d]							
Niacin Immediate Release (IR) (Niacor®) 50, 100, 250, 500 mg	500−1500 mg TID	$10	$31−92	5−25% ↓	15−35% ↑	20−50% ↓	▪ Take with meals to avoid flushing or GI upset; take Niaspan ER at bedtime with a low-fat snack ▪ With Niaspan ER follow titration schedule – week 1-4: 500 mg at bedtime; week 5-8: 1000 mg at bedtime; may increase dose by 500 mg/d every 4 weeks to a max dose of 2 g/d. Do not crush tablets. LFTs baseline, 6 weeks after start or dosage change: monitor every 6-12 months thereafter ▪ Causes glucose intolerance; caution in established or borderline diabetes ▪ May cause GI intolerance; caution with history of complicated active peptic ulcer disease ▪ Urinary secretion of uric acid, caution with gout ▪ Contraindicated in hepatic disease ▪ Caution in renal impairment
Niacin Extended Release (ER) (Niaspan®) 500, 750, 1000 mg	1000−2000 mg/d	$8-12	$225−449	7−16% ↓	14−22% ↑	16−38% ↓	

Table 6. Drug Therapy Summary, continued

Drug & Strength	Dose Range	$/Mo gen [a]	$/Mo br [a]	LDL-C	HDL-C	TG	General Cautions about Drug Class
Combination Products							
Ezetimibe and simvastatin (Vytorin®) 10/10, 10/20, 10/40, 10/80 mg	10/10–10/80 (ezetimibe/ simvastatin) mg/d	N/A	$198 all	45-60% ↓	6-10 % ↑	23-31% ↓	Combination therapy (statin + other lipid agent) improves lipids, but may increase myopathy risk, and has not been shown to improve outcomes compared to statin monotherapy
Niacin ER and lovastatin (Advicor®) 500/20, 750/20, 1000/20, 1000/40 mg	500/20–2000/40 (niacin/ lovastatin) mg/d	N/A	$182-209	30-42% ↓	20-30% ↑	32-53% ↓	
Niacin ER and simvastatin (Simcor®) 500/20, 500/40, 750/20, 1000/20, 1000/40 mg	500/20–2000/40 (niacin/ simvastatin) mg/d	N/A	$127-225	5–14%↓	15–29% ↑	23–38%↓	

[a] Cost = Average wholesale price based -10% for brand products and Maximum Allowable Cost (MAC) + $3 for generics for average 30-day supply, from Red Book Online, 2/2014, and Michigan Department of Community Health M.A.C. Manager, 1/2014. Some commonly used generic drugs are available at commercial pharmacies at discounted prices (e.g., $4 or $5)

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

[c] Generic niacin immediate release (IR) and sustained release (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 and ↑ 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, posaconazole	Increased risk of myopathy
	Cyclosporin, tacrolimus	Increased risk of myopathy [c]
	Clarithromycin, erythromycin, telithromycin	Increased risk of myopathy [c]
	Verapamil, diltiazem, amlodipine	Increased risk of myopathy [c]
	HIV protease inhibitors (e.g., ritonavir)	Increased risk of myopathy [c]
	Nefazodone	Increased risk of myopathy [c]
	Niacin, fibrates	Increased risk of myopathy [c]
	Danazol	Increased risk of myopathy [c]
	Ranolazine	Increased risk of myopathy [c]
Niacin	Statins	Increased risk of myopathy (<1%) [c]
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
	Sulfonylureas	May increase risk of hypoglycemia

[a] Pravastatin, fluvastatin, rosuvastatin, and pitavastatin have lower risk of drug interactions with other medications metabolized through the CYP3A4 system than other statins. Simvastatin has higher risk of myopathy compared to other statins.

[b] Grapefruit juice increases risk of myopathy for statins that are metabolized by the cytochrome P450 3A4 system (atorvastatin, lovastatin, simvastatin).Avoid large quantities of grapefruit juice (> 1 quart daily).

[c] Consider non-CYP3A4 statins such as pravastatin, fluvastatin, rosuvastatin, and pitavastatin.

Table 8. Simvastatin and Lovastatin Updated Contraindications and Dose Limitations

Simvastatin	Lovastatin
Contraindicated with simvastatin: ▪ Itraconazole ▪ Ketoconazole ▪ Posaconazole ▪ Erythromycin ▪ Clarithromycin ▪ Telithromycin ▪ HIV protease inhibitors ▪ Nefazodone ▪ Gemfibrozil ▪ Danazol	Contraindicated with lovastatin: ▪ Itraconazole ▪ Ketoconazole ▪ Posaconazole ▪ Erythromycin ▪ Clarithromycin ▪ Telithromycin ▪ HIV protease inhibitors ▪ Nefazodone ▪ Boceprevir ▪ Telaprevir
	Avoid with lovastatin: ▪ Cyclosporine ▪ Gemfibrozil
Do not exceed 10 mg simvastatin daily with: ▪ Verapamil* ▪ Diltiazem*	Do not exceed 20 mg lovastatin daily with: ▪ Danazol ▪ Diltiazem ▪ Verapamil
Do not exceed 20 mg simvastatin daily with: ▪ Amiodarone ▪ Amlodipine ▪ Ranolazine	Do not exceed 40 mg lovastatin daily with: ▪ Amiodarone

*Contraindicated with Simcor® (simvastatin/niacin ER) as Simcor® is only available with 20 mg or 40 mg of simvastatin

Table 9. Management of Statin Intolerant Patients

1. **Discontinue statin.** For patients with mild to moderate muscle symptoms that develop during statin therapy discontinue the statin until the symptoms can be evaluated. If rhabdomyolysis is a concern, consider excluding rhabdomyolysis by evaluating with CK, creatinine and checking a urinalysis for myoglobinuria.

2. **Secondary causes/conditions.** Consider other conditions that may increase the risk for muscle aches/myopathy (e.g., hypothyroidism, reduced renal or hepatic function, rheumatologic disorders, steroid myopathy, vitamin D deficiency or primary muscle diseases). Consider drug interactions [concomitant use of certain statins (atorvastatin, lovastatin, simvastatin) and other agents that are metabolized by the cytochrome P450 3A4 system].

3. **Trial without statin**. If, after 2 months without statin treatment, muscle symptoms or elevated CK do not resolve completely, consider other causes of muscle symptoms listed above. If persistent muscle symptoms are determined to arise from a condition unrelated to statin therapy, resume statin therapy at the original dose

4. **Consider lower dose statin retrial.** If muscle symptoms resolve with 2 months, and no contraindications exists, consider retrial of the original or a lower dose of the same statin to establish a causal relationship.

5. **Alternative statin.** If a causal relationship exists, discontinue original statin and once muscle symptoms resolve, trial an alternative low dose statin, and titrate up slowly to maximum tolerable dose.

6. **Intermittent statin dosing.** If failing a second statin, consider a trial of twice weekly or alternate day dosed long-acting statin (atorvastatin or rosuvastatin).

7. **Consider referral to lipid specialist.** If failing both a second statin and alternate day statin dosing, consider referring patient to a lipid specialist for further evaluation and treatment.

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 blood pressure control, aspirin, tobacco cessation, and lowering lipids. NHANES data show that roughly 33.5% of the US adult population has high LDL-C (>130 mg/dl). Over the past decade, the percentage of American adults with high total cholesterol decreased from 18.3% to 13.4%. This reduction reflects the increased percentage of adults with high LDL-C who are being treated: the percentage increased from 28.4% in 1999-2002 to 48.1% in 2005-2008. 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. Less than half of adults with high LDL-C get treatment. The situation is likely worse for secondary prevention groups without CHD. Why do we fail to screen and adequately treat cholesterol? Cost 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 in patients age 20-79 years. Primary prevention refers to patients without prior CHD or other clinical atherosclerotic cardiovascular disease (ASCVD). Primary prevention includes patient with diabetes mellitus (DM),chronic kidney disease(CKD stage 1-5),or patients with Pooled Cohort Equation 10 year ASCVD risk >=7.5%.Secondary prevention includes people with known ASCVD including prior CHD, stroke, and clinical peripheral arterial disease (PAD).

This guideline addresses groups that would most benefit from statin treatment in terms of ASCVD risk reduction and treatment strategies in the context of cardiovascular risk. It also addresses major classes of medications and

their place in therapy. **Statins remain the primary treatment of choice.**

In CKD patients lipid management depends on stage, dialysis treatment, and prior kidney transplant. Lipid management for CKD patients is addressed in the UMHS clinical care guideline for CKD.

The guideline does not address severe or familial dyslipidemias, which typically involve specialists in management.

Etiology, Treatment Benefit, and Strategy

Etiology. Many studies support the causal relationship of cholesterol and CHD. People with high total cholesterol (>240 mg/dL) have approximately twice the risk of heart disease as people with optimal levels (<200 mg/dL). 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. Predictive modeling in one study suggested that every 10% increase in the prevalence of treatment among adults with high LDL-C could prevent approximately 8,000 deaths per year in those ages <80 years.

It is important to evaluate for secondary causes of hyperlipidemia by history and selected laboratory tests (see Table 1). 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. These medications are to be considered only in statin intolerant patients who are candidates for statin treatment, particularly in secondary prevention.

Benefit of secondary prevention**.** Secondary prevention trials have shown consistent reduction in ASCVD events, CHD mortality and total mortality. Statins have shown reduction in different secondary prevention groups, including CHD, acute coronary syndromes, and cerebrovascular disease. 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 who had cholesterol levels for which 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.

Benefit of primary prevention**.** Primary prevention studies have shown consistent reduction in ASCVD 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 are not considered cost effective in the low risk group, but may be cost-effective in the intermediate risk group.

For patients with diabetes and no other ASCVD 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.)

Statins may not be appropriate in all patients with diabetes. Relatively young patients with a recent diagnosis of Type 1

diabetes, patients with diabetes from pancreatic insufficiency, especially in the setting of severe malnutrition, and patients with a limited life expectancy are possible examples. When deciding on whether to start a statin, consider the patient's 10 year ASCVD risk, nutritional status, and life expectancy.

Evidence is insufficient to recommend drug therapy for low HDL-C or high triglycerides for primary prevention.

Treatment strategy. Treatment strategy is changing from a "treat-to-target" approach with lipid level goals to risk-based treatment.

Risk-based treatment. The 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults provides a new perspective on LDL-C treatment benefit and strategy to achieve it. Rather than focusing on targets for LDL-C levels, the new recommendations reflect using the appropriate intensity of statin therapy to reduce ASCVD risk in those patient populations most likely to benefit.

Even though LDL-C levels are independently associated with risk for atherosclerotic events, the clinical benefits of statin treatment (including reduction in ASCVD fatal and non-fatal events) are proportional to total baseline ASCVD risk rather than baseline LDL-C. In order to maximize the ratio of benefits to harms and costs, statin therapy is recommended for individuals at increased ASCVD risk who are most likely to experience a net benefit in terms of the potential for ASCVD risk reduction and the potential for adverse effects. Focusing on ASCVD risk of patient groups facilitates risk assessment and treatment in the clinical setting.

Main risk groups. The 2013 ACC/AHA guideline identifies four main patient risk groups (one for secondary prevention and three for primary prevention) and subgroups within them. The risk groups are:

Secondary prevention

- Clinical ASCVD (coronary heart disease, stroke and peripheral arterial disease)
  - Age ≤ 75 years
  - Age > 75 years

Primary prevention

- LDL-C ≥ 190 mg/dL (age ≥ 21)
- Diabetes mellitus Type 1 or 2 and age 40-75 years with LDL-C 70-189 mg/dL
  - ≥ 7.5% estimated 10-year ASCVD risk
  - < 7.5% estimated 10-year ASCVD risk
- ≥ 7.5% estimated 10-year ASCVD risk, age 40-75 years with LDL-C 70-189 mg/dL, without DM, without clinical ASCVD

For each of these risk groups the 2013 ACC/AHA guideline has a recommendation for either high-intensity or moderate-intensity statin treatment, based on potential risk, benefit, and harm.

This University of Michigan guideline for lipid management follows the risk-based approach recommended by ACC/AHA.

Other approaches. Some national and international groups have not yet changed their recommended approach to lipid management. For example, the American Diabetes Association's (ADA) current guideline for lipid management uses a "treat-to-target" approach. Revisions by ADA taking into consideration the new ACC/AHA guideline will not be available until 2015.

Recent updates to the European Society of Cardiology (ESC) Guidelines use LDL-C targets with a LDL-C goal of < 115 mg/dL for adults who are low to moderate risk (class 1a)and a LDL-C goal of < 100 mg/dL for those with high risk for CVD events including those with one or more 'markedly elevated' risk factors or a SCORE level of 5 to 9%. It should also be noted that different risk scores are used in the AHA/ACC and ESC guidelines.

Screening / Baseline Lipid Profile

Target population. Patients with clinical ASCVD should have a baseline and annual lipid profile. This secondary prevention group includes those with acute coronary syndromes, history of MI, stable and unstable angina, coronary or other arterial revascularization, stroke, TIA and peripheral arterial disease, all of presumed atherosclerotic origin.

For primary prevention (no clinical ASCVD) the age group for screening remains an area of controversy. National organizations have different age recommendations for screening. 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 been 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 years. 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.

This guideline incorporates 2008 USPSTF recommendations in assessment for screening and treating lipid disorders:

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

2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk states it is reasonable to assess traditional ASCVD risk factors (age, gender, total and HDL-C, systolic BP, use of antihypertensive therapy, diabetes, and current smoking) every 4-6 years starting at age 20 years.

Lipid measures. Obtain a baseline screening lipid profile (TC, LDL-C, HDL-C, and TG). Ideally this should be obtained when the patient is fasting for a more accurate evaluation of potential dyslipidemias, including hypertriglyceridemia. However, if patient convenience or compliance is an issue, a non-fasting lipid profile is adequate to assess cardiovascular risk and to monitor statin compliance. Only total cholesterol and HDL-C are needed for cardiovascular risk calculators. While non-fasting LDL-C is less accurate than fasting LDL-C, non-fasting values are sufficient for monitoring general statin compliance. If lipids are obtained non-fasting and are abnormal (i.e. TC >200 mg/dL, HDL-C <40 mg/dL, or triglycerides >500 mg/dL), consider obtaining a follow up fasting lipid panel to better evaluate for dyslipidemias.

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. At the University of Michigan, the lab automatically measures the direct LDL-C when TG > 400 mg/dL. If a local laboratory does not measure LDL-C directly, when non-fasting TG > 400 mg/dL, obtain a fasting lipid panel.

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.

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.

Results other than high LDL-C. 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 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 comparing simvastatin with or without the addition of ezetimibe.

For elevated fasting triglyceride levels (>500 mg/dL), please see Triglycerides section.

Data are insufficient to make general treatment recommendations on patients with baseline TC <135 mg/dl, LDL-C <40 mg/dl, or HDL-C <40.

Assess ASCVD Risk Factors

Assess level of ASCVD risk using the four categories of risk groups likely to benefit and consider assessment of other risk factors as clinically indicated.

- Clinical ASCVD present (secondary prevention)
- LDL-C ≥ 190 mg/dL not caused by drugs or underlying medical condition, age ≥ 21 years. See Table 1 for common secondary causes of lipid disorders and treat as appropriate.
- Diabetes mellitus type 1 or 2 for ages 40-75 years, LDL-C 70-189 mg/dL
- Calculate 10-year ASCVD risk for ages 40-79 years. See Table 2 for calculation.
- CKD. If CKD, refer to the UMHS clinical care guideline for CKD for lipid management information for this population.
- Other risk factors. See Table 3 for other patient risk factors to consider in selected individuals who are not in the above statin benefit groups, and for whom a decision to initiate statin therapy is otherwise unclear.

Controversy currently exists concerning the ACC/AHA Pooled Cohort Equation to calculate 10-year risk of ASCVD (see Table 2). It may over-estimate risk, and there is concern regarding the 10-year ASCVD risk score cut off of ≥ 7.5% resulting in over-treating the primary prevention patient population. Using the 7.5% cut off score is reasonable for providing an opportunity to initiate a conversation between clinician and patient regarding potential ASCVD risk reduction benefits, adverse effects, drug interactions, and patient preferences.

Due to the larger diversity of patient population included in the Pooled Cohort Equation, we recommend using the Pooled Cohort Equation rather than calculating the Framingham score, as the Framingham score is based upon a population that is largely composed of middle aged, non-Hispanic Whites, and calculates out CHD risk rather than ASCVD risk (which includes CVA).

Checking ahs-CRP is currently *not* recommended as a cardiovascular disease screening test for average-risk adults without symptoms.

Coronary Artery Calcium score (CAC score) can be helpful only in intermediate risk patients to further stratify their risk level. Consider CAC scoring for patients age > 40 years with metabolic syndrome or a family history of premature CHD who are not already classified at high 10-year risk.

Carotid Intima-Media Thickness (CIMT) testing as an additional tool for risk stratification is not clinically useful at this time due to lack of standardization.

Treatment if No ASCVD or Risk Factors

Reinforce lifestyle. Educate and reinforce lifestyle activities shown to reduce cardiovascular disease risk independent of their influence on lipids. Activities include smoking cessation, dietary changes, weight loss (if overweight), and exercise. These activities are discussed in more detail below as the initial treatment that also applies to patients with ASCVD or risk factors.

Follow-up. Patients with normal screening lipids are generally rechecked at 4-6-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.

Treatment through Lifestyle Changes

Lifestyle changes are a critical component of health promotion and ASCVD risk reduction in both primary and secondary prevention, both prior to and in addition to use of cholesterol lowering drug therapies. The reductions in total and LDL-C induced by a combination of dietary therapy and pharmacologic therapy are generally greater than for either therapy alone. These include smoking cessation, dietary changes, smoking cessation, weight loss (if overweight), and exercise. In addition, these changes reduce cardiovascular disease risk independent of their influence on lipids.

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. A recent meta-analysis found no increase risk in major adverse events with nicotine therapy - but overall events increased. Nicotine replacement therapy is contraindicated in unstable angina or acute MI. For more information, see the UMHS Tobacco Treatment clinical care guideline.

Diet and food supplements. AHA/ACC Guidelines on Lifestyle Management to Reduce Cardiovascular Risk, published in2013, recommends a dietary platter which is high in fruits, vegetables and whole grains. Dairy products should be low fat. Dietary patterns should be adapted to the caloric needs of the patients. The DASH or Mediterranean dietary pattern and USDA food pattern were cited as examples of dietary patterns which are in line with current recommendations. 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, and linolenic acid (canola oil, soy, flax seed). Whole grain should be substituted for processed flours and simple sugars. This diet pattern is comparable to the Mediterranean diet, which has been shown to reduce CHD events beyond its impact on serum lipids. A large RCT published in 2013 demonstrated that adults at high risk for CVD events, randomized to a Mediterranean diet supplemented with olive oil or mixed nuts had significantly less major cardiovascular events including myocardial infarction, stroke, or CVD death when compared to those assigned to the control group.

The plant stanols (sitostanol and sitostanol esters) can lower LDL cholesterol by approximately 10%, are available in soft margarine and can be used as a spread on bread products and vegetables. However outcome data (i.e. evidence in the reduction of CVD events) has not been demonstrated with plant stanols. 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.

Fish oil supplements. Omega-3 fatty acids eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), found in dietary fish oil, have been shown to reduce atherosclerosis in animal models. Increased dietary omega-3 fatty acidsvia dietary change or supplements have been shown to improve CHD and CHD mortality in some, but not all studies. A recent meta-analysis suggests that supplementation with omega-3 fatty acids does not reduce risk for CVD events. 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. Thus omega-3 fatty acids may be useful in the treatment of elevated triglycerides.

Two to four grams of EPA and DHA per day can lower triglycerides 20% to 40%. Lovaza and Vascepa are FDA approved fish oil supplement, available by prescription. Vascepa contains only EPA versus Lovaza which contains both DHA and EPA. In clinical trials evaluating patients with severe hypertriglyceridemia, Vascepa did not increase LDL-C levels, whereas an increase in LDL-C was seen in Lovaza trials. Many OTC brands are available at a much

lower price, but are not regulated, and require more capsules to achieve the same effect.

Fish oil supplements are a reasonable adjunct to secondary prevention populations with high triglycerides. Unlike fibrates, they do not increase myopathy risk when added to statins. Fish oil supplements are generally well tolerated with gastrointestinal upset and fishy aftertaste as possible side effects. Clinical significant bleeding has been reported at higher doses and caution should be used in patients on concomitant antiplatelet or anticoagulant therapy.

Weight loss. Excess body weight is associated with higher triglycerides, lower HDL-C, and higher TC. The more overweight the patient, the less responsive lipid parameters are 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 aerobic physical exercise raises HDL-C and lowers triglycerides. Exercise alone has little effect on LDL-C. The Look Ahead Study, which included over 5,000 overweight or obese diabetic adults, observed improvements in glycosylated hemoglobin, but no reductions in LDL cholesterol. The primary goal of the intervention was weight loss – CVD events were similar in the intervention and control groups. 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 reducing dietary fat intake on lowering 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 may be offset by increased mortality from other causes. If alcohol intake is more than moderate (1 serving of alcohol daily for women, and 1-2 servings of alcohol daily for men), reduction is recommended.

Pharmacologic Treatment: Statins

Statins the first-line agents. Statins are the first-line agents for lipid management. 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).

Individual statins. Statins are the best studied lipid-lowering drugs 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. Atorvastatin, lovastatin, pravastatin, and simvastatin are now available as generics.

Table 5 present dosing equivalents across statins for "high-intensity" dosing (≥ 50% LDL-C reduction) and "moderate-intensity" dosing (30%-50% LCL-C reduction). Table 6 presents a summary of information regarding commonly used lipid lowering drugs.

Adverse effects. The most common adverse effect from statins is myalgia (i.e., muscle pain or soreness), weakness, and/or cramping without CK elevations, which have resulted in dropouts in 5% of trial patients. No evidence confirms that myalgias are more common with one statin than another. Peripheral neuropathy is another uncommon complication. Rhabdomyolysis (CK > 10,000 IU/L or CK > 10 times ULN plus elevation in serum creatinine) 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.

Observed rates of new onset diabetes varies with statin intensity, with approximately 0.1 and 0.3 excess cases of diabetes per 100 statin treated individuals per year observed for moderate and high-intensity statins respectively. Limited evidence associates statin use with reversible

cognitive impairment (e.g., memory loss, confusion, forgetfulness, amnesia, memory impairment) and with incidental cases of new-onset diabetes. Statin labeling has been updated to reflect these potential risks, however, this evidence remains controversial. For patients at high risk of cardiovascular events, the cardiovascular benefits of statins outweigh these increased risks.

Contraindications and dose limitations for simvastatin and lovastatin are presented in Table 8. High dose simvastatin and lovastatin (i.e., 80 mg) have a greater risk of muscle injury compared to lower doses of these two drugs or with other statins. For simvastatin this risk is greatest during the first year of treatment and declines afterward. Therefore, only patients who have been on simvastatin 80 mg for at least twelve months without evidence of myopathy should continue to be treated at this dosage. Statin naïve patients should not be started on simvastatin 80 mg.

Characteristics predisposing individuals to statin adverse effects include multiple and serious co-morbidities including impaired renal or hepatic function, history of previous statin intolerance or muscle disorders, unexplained ALT elevations > 3X ULN, or concomitant use of drugs affecting statin metabolism, and age > 75 years. If any of these predisposing characteristics are present, moderate-intensity statin therapy is recommended in individuals whom high-intensity statin therapy would otherwise be recommended. High-intensity statin therapy should also be used cautiously in patients of Asian ancestry or with a history of hemorrhagic stroke.

Statin interactions. Statins interact with several other medications (see Table 7), primarily increasing the risk of myopathy. For example adding a fibrate increases the risk of rhabdomyolysis to 5.98 per 10,000 person-years. Other drugs that increase risks are inhibitors of cytochrome P450 enzymes (lovastatin/simvastatin/atorvastatin use CYP3A4, while fluvastatin uses CYP2C9), including cyclosporine, azoles antifungals, macrolide antibiotics, protease inhibitors, verapamil, diltiazem, amiodarone and others. Given the increased risk of muscle injury with simvastatin and lovastatin, labeling has been updated to reflect contraindications and dose limitations with concomitant use of these statins and specific interaction drugs (see Table 8). A large amount of grapefruit juice (> 1 quart) also increases the blood level (AUC) of statins that are metabolized by the CYP450 3A4 system.

Whenever possible, avoid using the interacting drug rather than modifying the patient's statin therapy. If an interacting drug cannot be avoided, these statins should be adjusted or an alternative with less potential for drug-drug interactions should be considered. If a patient experiences myopathy on any statin, the medication should be discontinued immediately.

Intolerance. Statin intolerance is a common problem in primary and specialty care, generally due to myalgia. Prior to initiation of statin therapy, a history of prior or current muscle symptoms should be obtained to avoid unnecessary discontinuation of statins. No studies support a particular strategy for management of statin intolerance. A suggested strategy for managing patients with statin intolerance is presented in Table 9.

Pregnancy. Statins are FDA Pregnancy Category X and contraindicated in pregnancy.

Initiating statin therapy. Once patient risk category has been assessed, initiating therapy involves discussing statin therapy with the patient, determining intensity of statin dosing, and .following up on response to statin therapy in terms of patient tolerance, lipid profile response, and ALT in those with known liver disease, risk factors for liver disease, or in patients who are on other potentially hepatotoxic medications.

Discussing drug therapy. Before initiating statin therapy, clinicians and patients should discuss:

- Benefits for ASCVD risk reduction
- Potential adverse effects
- Drug-drug interactions
- Patient preferences

When discussing benefits for ASCVD risk reduction in the primary prevention population (without clinical ASCVD), the ACC/AHA Guideline on the Treatment of Blood Cholesterol suggests using the estimated 10-year ASCVD risk and the relative risk reduction of ~30% for moderate-intensity statin or ~45% for high-intensity statin therapy in order to estimate the absolute risk reduction from moderate- or high-intensity statin therapy. Benefit is less clear in patients outside of the four main target groups identified in the ACC/AHA guideline. For individuals outside those groups, clinicians will need to consider other risk factors (see Table 3) when discussing potential benefit.

The ACC/AHA guideline notes that the main adverse consideration is the excess risk of diabetes – about 0.1 excess case per 100 individuals treated with a moderate-intensity statin for 1 year and about 0.3 excess cases per 100 individuals treated with a high-intensity statin for 1 year. Both statin-treated and placebo-treated participants experienced the same rate of muscle symptoms. The actual rate of statin-related muscle symptoms in the clinical population is unclear. (See other adverse effects above.)

Statins interact with several other drugs (see Table 7). If potential interactions are a concern, the usual approach is to avoid using the interacting drug rather than modifying statin therapy. The discussion should address the importance of other medical conditions and potential changes in drug therapy for the overall clinical benefit of the patient. (See more complete discussion of interactions above.)

Patient preferences regarding medications, life-time therapy, and ability to pay costs should also be addressed.

Check baseline ALT. Baseline measurement of ALT should be performed before initiating statin therapy. See Table 4 for monitoring if liver function tests are abnormal.

Statin dosing based on risk group for non-pregnant patients. The ACC/AHA guidelines for dosing (see Table 5 for Statin Dose Equivalency Chart) based on risk group are:

- Clinical ASCVD
  - Age ≤ 75 years = high-intensity
  - Age > 75 years = moderate-intensity
- LDL-C ≥ 190 mg/dL and age ≥ 21 years = high-intensity
- Diabetes Mellitus Type 1 or 2 and age 40-75 years with LDL-C 70-189 mg/dL
  - moderate-intensity
  - can consider high-intensity if estimated 10-year ASCVD risk ≥ 7.5% [expert opinion]
- ≥ 7.5% estimated 10-year ASCVD risk, age 40-75 years, LDL-C 70-189 mg/dL without DM, without clinical ASCVD = moderate-to-high-intensity

For those patients who are already on statin therapy at lower doses, and LDL-C had been at previously recommended goal values, we recommend clinicians and patients engage in a discussion which considers the potential for ASCVD risk reduction benefits and for adverse effects, as well as patient preferences for intensifying statin therapy.

Check in 6-12 weeks. Careful follow-up of liver function tests is indicated only for those with abnormal baseline ALT, known liver disease, risk factors for liver disease, or in patients who are on other potentially hepatotoxic medications. Liver function tests (LFTs) should also be measured if symptoms suggesting hepatotoxicity arise (e.g., unusual fatigue or weakness, loss of appetite, abdominal pain, dark-colored urine or yellowing of the skin or sclera).For other patients with abnormal baseline LFTs, see Table 4 for monitoring based on level of abnormality. If no concerns over liver function and normal LFTs, no further monitoring is required.

Routine CK monitoring is not recommended in individuals receiving statin therapy, and moderate CK elevations (<800 IU) do not necessarily indicate toxicity or increased risk of myopathy. Baseline CK measurement is reasonable for individuals believed to be at increased risk of adverse events and during statin therapy for individuals experiencing muscle symptoms.

Check for:

- Adverse effects of statin treatment and address as appropriate.
- Expected reduction in LDL-C based on intensity of statin treatment. If expected reduction does not occur, address statin and lifestyle adherence and consider referral to specialist in lipid management

Reinforce lifestyle modifications.

Longer term follow-up. Monitor LFTs if indicated. Check lipids annually to assess adherence. Reinforce lifestyle modifications.

An annual lipid profile is recommended to check on statin adherence and to provide an opportunity to reinforce lifestyle modifications ¬ the cornerstone of ASCVD risk reduction. A study of statin adherence in 2001 found that on average, patients did not take their statin medication 20% of the time. Fifty percent of patients discontinued statin treatment by one year if copayment was > $20/month and by 3.9 years if copayment was < $10/month. Insurance records of statin dispensing are becoming more unreliable indicators of statin adherence because statin medications are increasingly being filled without an insurance claim, e.g., statins obtained through $4 generic programs or free (atorvastatin) through local pharmacies. An annual lipid profile is a relatively non-invasive test to monitor adherence.

Non-Statin Pharmacologic Treatment

Treatment with statin and non-statin combinations. Limited evidence exists to support the routine use of non-statin drugs in combination with statin therapy to further reduce ASCVD events. Addition of non-statin therapy may be considered in high-risk patients who are completely statin intolerant, who have an inadequate response to statins (high-intensity therapy should show ≥ 50% reduction in LDL-C, moderate-intensity therapy should show 30% to 50% reduction in LDL-C), who are not able to tolerate the recommended statin intensity, or who have severe triglyceridemia (>500 mg/dl) necessitating the use of fibrates to prevent pancreatitis. Adherence to statin therapy and lifestyle should be reassessed and re-emphasized before addition of a nonstatin drug. Combination therapy of statins with fibrates significantly increases risk of myopathy and rhabdomyolysis.

Bile acid resins. Cholestyramine, colestipol, and colesevelam are generally considered second line because of poor patient tolerability to side effects and difficult dosing/administration time. These drugs have been shown to reduce LDL-C cholesterol 15-30%, depending on dose. They are available in powder and tablet form. Resins work by binding cholesterol in the gut and interfering with absorption. They may increase triglycerides and should not be initiated in individuals with baseline fasting triglyceride ≥ 300 mg/dL or type III hyperlipoproteinemia. If triglycerides exceed 400 mg/dL, resin therapy should be discontinued.

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 and lower LDL-C by 15-20% alone. Data on ezetimbe's effect on morbidity and mortality are not available. However, a recent surrogate endpoint (carotid artery disease progression) trial showed no benefit of simvastatin plus ezetimibe (Vytorin®) over simvastatin alone. Ezetimibe should only be considered for patients intolerant to statin, niacin, fibrates, and resins, all of which have better evidence supporting their use and are more cost effective. Please see the UMHS CKD guideline for role of ezetimibe in patients with CKD. Baseline ALT should be measured prior to initiation of therapy and as clinically indicated. Ezetimbe should be discontinued if persistent ALT elevations > 3X ULN occur.

Fibrates. Fibratesavailable in the US include gemfibrozil and fenofibrate. Clofibrate is no longer used, as it is associated with increased total mortality in large randomized controlled trials. Safety and efficacy of fenofibric acid (Fibricor® and TriLipix®), the active metabolite of fenofibrate, has not been extensively studied in clinical trials and approval was largely based off the fenofibrate studies.

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 and are primarily reserved for patients with severe triglyceride elevation (> 500 mg/dl) despite lifestyle changes to prevent pancreatitis.

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 is recommended. Contraindications include severe renal or liver disease, pregnancy, or preexisting gallbladder disease.

Niacin. Niacin improves all aspects of the lipid profile (HDL-C increases 15-35%, triglycerides decreases 20-50%, 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. Rare cases of rhabdomyolysis have been associated with concomitant use of statins and niacin in doses > 1 g. Careful monitoring during initiation of niacin therapy or dose escalation is warranted with patients on concurrent statins.

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

Niacin is available over the counter (OTC) as a dietary supplement in both immediate release (IR) and sustained release (SR) formulations. "Flush-free" and "no flush" preparations are also marketed OTC, but contain very little to no active niacin and should not be used. Prescription niacin products include Niacor® (IR) and Niaspan ®, the extended-release formulation taken at bedtime, which is associated with improved side-effect tolerance and 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 pre-medicating with aspirin, 325 mg 30 minutes prior, slow titration, or use of extended release formulations. Hepatotoxicity has been reported, particularly with SR products at doses > 2 g/day. Niacin should not be used if ALT is > 2-3X ULN. Niacin should also be discontinued in patients experiencing persistent severe cutaneous symptoms, persistent hyperglycemia, acute gout, unexplained abdominal pain or GI symptoms, or if new-onset atrial fibrillation or weight loss occurs. 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 ER, the dose should be reduced in half, and no more than 2 gm/day.

Triglycerides

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 (see Table 1 for secondary causes).

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 fasting triglyceride elevation (> 500 mg/dl) despite lifestyle modifications can be considered for drug therapy to prevent acute pancreatitis. Fenofibrate is the preferred fibrate for triglyceride lowering and can be used concomitantly with low- or moderate-intensity statin therapy. Fish oil supplements containing DHA and/or EPA can alternatively be used for triglyceride lowering. Gemfibrozil should not be initiated for triglyceride lowering on patients taking statins due to the increased risk for muscle symptoms and rhabdomyolysis.

Complementary and Alternative Treatment

Complementary and alternative therapies may affect lipid levels, although testing is limited. Some of the therapies for which evidence is available are reviewed 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 hormone replacement therapy in post-menopausal women with and without coronary disease, finding an increased risk of coronary disease, thromboembolism, and stroke. Hormone replacement is not indicated for primary or secondary prevention of cardiovascular disease. Therapy should be based on direct indications, e.g., hot flashes, not for lipid management.

Red yeast rice. Red yeast rice products contain several naturally occurring substances related to the statins; the predominant is mevinolin, the major component of lovastatin. Potential side effects are the same as statins, including a risk of myopathy and hepatotoxicity. The FDA considers red yeast rice products containing mevinolin to be unapproved drugs, and illegal. However, the products are still available in stores and on the internet. Many manufacturers do not list the amount of mevinolin contained in the products. Other products labeled as red yeast rice may contain alternative ingredients such as policosanol (a sugar cane derivative), flavonoids, EPA or DHA. Commercial preparations vary substantially and one study found supplements containing nephrotoxic toxins. Patients should be advised not to use red yeast rice products due to the lack of manufacturing standards leading to concerns for safety and lack of effectiveness.

Plant stanols/sterols. Plant stanols/sterols are available as spreads or capsules. They work by helping to prevent cholesterol absorption and can reduce LDL by 5-17%. There is no evidence that stanols or sterols reduce the risk of cardiovascular disease. Long term safety has not been established.

Artichoke extract. Artichoke extract contains cynaroside and its derivative luteolin, which may function similar to statins. Preliminary evidence suggests some effectiveness. No serious adverse events have been reported. The recommended dose is 1800 mg/day divided into 2-3 doses. It can cause flatulence, and should be avoided by those with ragweed allergy since artichoke is in the same plant family as ragweed.

Garlic. Many patients use garlic for hyperlipidemia, but recent evidence suggests that it is less effective than initially thought. Natural Medicine Comprehensive Database recently downgraded garlic to a rating of "Possibly ineffective". Garlic can also cause drug interactions and increased risk of bleeding.

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 includepolicosanol, chitosan, gugulipid (extract from resin of Indian thorny tree). 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, USPSTF recommends starting screening in those women age 45 and older who are at increased risk for CHD and all men age 35 and older. The ACP has a somewhat similar age difference, recommending screening women age 45-65 years and men age 35-65 years.

End Stage Renal Disease. Evidence is insufficient to make recommendations regarding statin therapy for patients with end stage renal disease. For these patients, an individualized approach is recommended taking into consideration possible risk reduction, adverse effects, and contraindications. For lipid management in patients with ESRD, see UMHS CKD guideline.

Individuals >75 Years of Age. Randomized controlled trials support the continuation of statins beyond 75 years of age in persons who are already taking and tolerating these drugs, as well as the use of moderate-intensity statin therapy for secondary prevention in individuals with clinical ASCVD >75 years of age. However few data are available regarding primary prevention among individuals

>75 years of age. Initiation of statins for primary prevention in individuals >75 years of age requires consideration of additional factors, including increasing comorbidities, safety considerations, and priorities of care. Discussion of the potential ASCVD risk reduction benefits, risk of adverse effects, drug-drug interaction and patient preferences should precede the initiation of statin therapy for primary prevention in older individuals. In patients with increasing co-morbidities, or those patients with a limited life expectancy, it is reasonable to consider discontinuation of statin.

Related National Guidelines

The UMHS Clinical Guideline on Lipid Therapy is consistent with the following national guidelines concerning lipid screening and treatment.

American Association of Clinical Endocrinologists: Guidelines for management of dyslipidemia and prevention of atherosclerosis (2012)

American College of Cardiology/American Heart Association:
- Guideline on the Assessment of Cardiovascular Risk (2013)
- Guideline on Lifestyle Management to Reduce Cardiovascular Risk (2013)
- Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (2013)

American College of Cardiology Foundation:
- Cardiovascular disease prevention in women (2011)
- Guideline for secondary prevention for patients with coronary and other atherosclerotic vascular disease (2011)

American Diabetes Association: Standards of medical care for diabetes (2014)

US Preventive Services Task Force: Screening for lipid disorders in adults (2008)

Measures of Clinical Performance

National programs that have clinical performance measures for lipid screening and management include the following.

Centers for Medicare & Medicaid Services:
- Physician Quality Reporting Measures for Group Practice Reporting Option (GPRO)
- Clinical Quality Measures for financial incentives for Meaningful Use of certified Electronic Health Record technology (MU)
- Quality measures for Accountable Care Organizations (ACO)

Regional programs that have clinical performance measures for lipid screening and management include the following.
- Blue Cross Blue Shield of Michigan: Physician Group Incentive Program clinical performance measures (PGIP)
- Blue Care Network [HMO]: clinical performance measures (BCN)

These programs' clinical performance measures for lipid screening and management are summarized below. When programs have measures, the measures are generally similar, although specific details vary (e.g., population inclusions and exclusions).

Preventive care and screening: fasting LDL-C test. The percentage of patients aged 20-79 years whose risk factors have been assessed and a fasting LDL-C test performed for those at risk. High risk = CHD or CHD risk equivalent; test performed in preceding year. Moderate risk = 2 or more of cigarette smoking, hypertension, low HDL-C, family history of premature CHD, men age ≥ 45, women age ≥ 55; test performed in preceding year. Low risk = 0 or one of: cigarette smoking, hypertension, low HDL-C, family history or premature CHD, men age ≥ 45, women age ≥ 55; test performed in preceding 5 years (MU).

Preventive care and screening: risk stratified fasting LDL-C control. The percentage of patients aged 20-79 years who had a fasting LDL-C test performed and whose risk-stratified fasting LDL-C is at or below the recommended goal: high risk < 100 mg/dL, moderate risk < 130 mg/dL, low risk < 160 mg/dL (see preceding measure for risk definitions) (MU).

CAD and lipid screening. The percentage of patients aged 18-75 years with coronary artery disease who had an LDL-C test during the measurement year (BCN, PGIP).

CAD and lipid lowering drug. The percentage of patients aged 18 years or older with a diagnosis of coronary artery disease who were prescribed lipid lowering therapy. (MU, ACO, PGIP)

Diabetes and lipid profile. The percentage of patients aged 18-75 years with diabetes who received at least one lipid profile within 12 months (MU, GPRO, PGIP aged 40-75 years).

Diabetes and LDL-C control. The percentage of patients aged 18-75 years with diabetes mellitus who had most recent LDL-C in control (less than 100 mg/dL) (MU, ACO composite, GRPO, BCN, PGIP).

Heart failure and LDL-C screening. The percentage of patients aged 18-75 years with congestive heart failure who had an LDL-C test in the measurement year (PGIP).

IVD and lipid profile and LDL-C control. The percentage of patients aged 18 years and older discharged with acute myocardial infarction, coronary artery bypass graft, or percutaneous transluminal coronary angioplasty in the year before the most recent year or who had a diagnosis of

ischemic vascular disease during the past two years who had a complete lipid profile performed during the past year and whose LDL-C was less than 100 mg/dL (MU, ACO)

Strategy for Literature Search

The literature search for this update began with results of the literature searches performed in 1999 for the 2000version of this guideline and in 2007 for the 2009 update of this guideline. Since that time the American Association of Clinical Endocrinologists performed a search of relevant literature through early 2011 in developing its guidelines for management of dyslipidemia and prevention of atherosclerosis (see references). Those results were used for the literature through 12/31/10. For more recent literature, a search similar to those previously performed for this guideline 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 1/1/2011 to 4/30/2013*. 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. An additional search using the overall terms was performed for statins and drug interactions and for individual differences and class effects of statins.

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 controlled 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.

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	Relationship	Company
Audrey L Fan, MD	(none)	
Jill N Fenske, MD	(none)	
R. Van Harrison, PhD	(none)	
Elizabeth A Jackson, MD	Consultant	Pfizer
Marie A Marcelino, PharmD	(none)	

Review and Endorsement

Drafts of this guideline were reviewed in clinical conferences and by distribution for comment within departments and divisions of the University of Michigan Medical School to which the content is most relevant: Family Medicine, General Medicine, and Cardiology. The final version was endorsed by the Clinical Practice Committee of the University of Michigan Faculty Group Practice and the Executive Committee for Clinical Affairs of the University of Michigan Hospitals and Health Centers.

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2000 (May): William E Barrie, MD, R. Van Harrison, PhD, Ujjaini B. Khanderia, PharmD, Robert B. Kiningham, MD, Shawna D. Nesbitt, MD, Melvyn Rubenfire, MD.

2003 (April): William E Barrie, MD, R. Van Harrison, PhD, Ujjaini B. Khanderia, PharmD, Robert B. Kiningham, MD, Melvyn Rubenfire, MD.

2009 (February): William E Barrie, MD, R. Van Harrison, PhD, Ujjaini B. Khanderia, PharmD, Robert B. Kiningham, MD, Robert S. Rosenson, MD

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