Screening and Management of Lipids

Lipid Therapy Guideline Team

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Patient population: Adults age 20–79 years without familial or severe dyslipidemias or chronic kidney disease (CKD). *(In patients with CKD, see* UMHS Management of Chronic Kidney Disease.)

Objective: Primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD) through lipid screening, determining treatment benefit and risk, and providing appropriate treatment.

Key Points

Obtain a screening / baseline lipid profile

Patients. Men age ≥ 35 and women age ≥ 45 years. Also men age 20–35 and women age 20–45 who are at increased risk for ASCVD *[IC*]*. Can also consider a screening or baseline lipid profile in adults age ≥ 20 when assessing traditional ASCVD risk factors (age, sex, total cholesterol, HDL-C, systolic BP, use of antihypertensive therapy, diabetes, and smoking) *[IIC*]*.

Fasting/non-fasting. Screening lipid profile can be obtained fasting or non-fasting.

Prior to considering drug treatment for dyslipidemias at any age exclude secondary causes (Table 1).

Assess ASCVD risk. Does the patient have any of the following risk factors?

Clinical ASCVD. This includes stroke/TIA, carotid and peripheral arterial disease, and clinical evidence of coronary heart disease.

LDL-C ≥ 190 mg/dL and age ≥ 20, not caused by drugs or an underlying medical condition (Table 1).

Diabetes mellitus type 1 or 2, and age 40–75 years, with LDL-C 70–189 mg/dL.

10-year ASCVD risk ≥ 7.5% and age 40–75 years (see Table 2 for calculation information).

Chronic kidney disease. *(See the UMHS CKD guideline for managing lipids in CKD patients.)*

For additional risk factors (risk enhancers), see Table 3.

If no ASCVD and none of the above risk factors

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

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

If the patient has ASCVD or any of the above risk factors other than CKD

Treat with lifestyle changes. Educate as appropriate: smoking cessation (reduces coronary event rate by ~ 50% within 1-2 years), healthy diet, regular 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.)
- Choose dosing for % LDL-C reduction: high-intensity statin (≥ 50%), moderate-intensity statin (30–49%). See Table 6-9 for statin "intensity" levels, effects, interactions, and contraindications.
- Four main treatment benefit groups and their dosing intensity (Tables 5 and 6).

  Clinical ASCVD: If age ≤ 75 years, use high-intensity *[IA*]*; if age > 75 years, use moderate-intensity *[IIA*]*. If at very high-risk for ASCVD, on maximally tolerated statin, and LDL-C is ≥ 70 mg/dL, consider adding ezetimibe *[IIA*]*. If LDL-C remains ≥ 70 mg/dL, consider adding a PCSK9 inhibitor *[IIA*]*.

  LDL-C ≥ 190 mg/dL, age ≥ 20, use high-intensity *[IA*]*.

  Diabetes (type 1 or 2) and age 40–75 years with LDL-C 70–189 mg/dL, use moderate-intensity *[IA*]*; consider high-intensity with risk assessment *[IID*]*.

  10-year ASCVD risk ≥ 7.5% and age 40–75 years, use moderate-to-high intensity *[IA*]*.

  If other risks (see Table 3), consider statin therapy or increasing statin intensity based on individual benefit and harm; including younger persons and those with 10-yr ASCVD risk <7.5%, lifetime risk 39% or greater, and particularly an elevated coronary artery calcium score by CT.
- In 6–12 weeks:
  - Check lipids to evaluate adherence. Recheck ALT only if baseline was abnormal, or if patient has known liver disease, risk factors for liver disease, or is on other potentially hepatotoxic medications. Check creatine kinase (CK) only if muscle aches/weakness. If statin-intolerance, address (Table 10).
  - If lipids do not decrease as expected: address adherence, reinforce lifestyle modifications, and consider referral to a specialist in lipid management.

Triglycerides: Important risk enhancer. After excluding secondary causes and initiating healthy lifestyle, for persons on a statin with TG > 350 mg/dL consider 2 g twice daily of OTC EPA or EPA+DHA. If fasting TG ≥ 500 mg/dL or if there is a history of pancreatitis, consider referral to a lipid specialist. Recent evidence demonstrates triglycerides are a marker of risk for ASCVD.

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

Note: For cholesterol, total = TC, high-density lipoprotein = HDL-C, low-density lipoprotein = LDL-C. Triglycerides = TG
*** Strength of recommendation:** I = generally should perform; II = reasonable to perform; III = generally should not perform.
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 nervosa	Weight gain, very low-fat diets, high intake of refined carbohydrates, excessive alcohol intake
Drugs	Diuretics, cyclosporine, glucocorticoids, amiodarone	Oral contraceptives, estrogens, glucocorticoids, bile acid sequestrants, protease inhibitors, retinoic acid, anabolic steroids, sirolimus, raloxifene, tamoxifen, beta blockers (not carvedilol), thiazides
Diseases	Biliary obstruction, nephrotic syndrome, chronic kidney disease	Nephrotic syndrome, chronic kidney disease, lipodystrophies, Cushing syndrome
Disorders and altered states of metabolism	Hypothyroidism, obesity, pregnancy*	Diabetes (poorly controlled), hypothyroidism, obesity, inactivity; pregnancy*

* Cholesterol and triglycerides rise progressively throughout pregnancy. Note that 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 nonfatal 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 40–79 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

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 particularly in those with a healthy lifestyle, well educated, and higher socioeconomic status. However, a 10-yr risk score cutoff 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, the 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. Patient Factors that May Enhance Risk for ASCVD or Increase Benefit from Statin Therapy

In selected individuals who are not in the four main statin benefit groups (see Table 5), and for whom a decision to initiate statin therapy is otherwise unclear, additional factors may be considered to inform treatment decision making:

Risk enhancers include:

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

Primary hypercholesterolemia, including LDL-C ≥ 160–189 mg/dL, or non-HDL-C 190–219 mg/dL

Metabolic syndrome. The NCEP ATP III defines metabolic syndrome as a diagnosis of 3 or more of the following risks:

- Waist circumference > 40 inches (102 cm) for men or > 35 inches (88 cm) for women
- HDL-C < 40 mg/dL for men or < 50 mg/dL for women
- Impaired fasting glucose ≥ 100 mg/dL*
- Triglycerides ≥ 150 mg/dL
- Blood pressure ≥ 130/85 mm Hg

Chronic kidney disease (eGFR < 60 mL/min/1.73m^2)

Chronic inflammatory conditions, such as psoriasis, SLE, rheumatoid arthritis, human immunodeficiency virus (HIV)

History of preeclampsia

History of premature menopause (age < 40 years)

High-risk ethnic groups (eg, South Asian)

Current tobacco user

Factors associated with increased ASCVD risk:

- Persistent elevations of triglycerides ≥ 175 mg/dL
- High-sensitivity C-reactive protein ≥ 2 mg/L
- Apolipoprotein B ≥ 130 mg/dL
- Lipoprotein (a) > 50 mg/dL or 125 nmol/L, especially at higher values of lipoprotein (a)
- Ankle-brachial index < 0.9
- Coronary artery calcium (CAC) score ≥ 100, or ≥ 75th percentile for age, sex and ethnicity

*The American Diabetes Association defines impaired fasting glucose as ≥ 100 mg/dL. SLE = Systemic lupus erythematosus.

Adapted from: 2018 Guideline on the Management of Blood Cholesterol: Guidelines Made Simple (updated June 2019). Washington, DC: American College of Cardiology, 2019.

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 who are on other potentially hepatotoxic medications. When ALT is elevated and TG > 200 mg/dL in patients with diabetes, pre-diabetes, or the metabolic syndrome, consider hepatic ultrasound for NAFLD/NASH/cirrhosis. 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 [ULN] but < 2 times the ULN): reassess LFTs after 6–12 weeks of statin treatment for stability. If ALT > 2 ULN, consider screening for liver disease to clarify the cause of the elevated ALT, so as not to have to stop statins. Consider monitoring annually for stability if baseline LFTs are abnormal.

Abnormal baseline liver biochemistries can frequently improve with statin therapy.

Table 5. Main Groups Likely to Benefit from Lipid Treatment

Risk Group	Treatment
Secondary Prevention	
Patients with clinical ASCVD (angina, ACS, PCI, CABG, PVD, stroke/TIA, evidence of ischemia on stress testing, carotid plaque, aortic aneurysm)	
If very high-risk ASCVD [a]	High-intensity or maximal statin
If on maximal statin and LDL-C ≥ 70 mg/dL	Consider adding ezetimibe
If LDL-C still ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL	Consider adding a PCSK9 inhibitor
If not very high-risk ASCVD	
If age > 75	Consider initiating/continuing high-intensity statin
If age ≤ 75	High-intensity statin to reduce LDL-C ≥ 50%
If high-intensity statin not tolerated	Moderate-intensity statin
If on maximal statin and LDL-C ≥ 70 mg/dL	May consider adding ezetimibe
Primary Prevention (assess ASCVD risk)	
LDL-C ≥ 190 mg/dL	High-intensity statin
Diabetes mellitus and age 40–75 and LDL-C ≥ 70 mg/dL	Moderate-intensity statin
If multiple risk factors	Consider high-intensity statin to reduce LDL-C ≥ 50%
If 10-year ASCVD risk of ≥ 20%	Consider adding ezetimibe to max tolerated statin to reduce LDL-C ≥ 50%
Other patients	
If Age 40–75 and LDL-C is 70–189 and ASCVD risk is:	
≥ 20% (high risk)	Statin to reduce LDL-C ≥ 50%
7.5–19.9% (intermediate risk)	
If risk enhancers (see Table 3)	Moderate-intensity statin to reduce LDL-C 30–49%
If risk decision is uncertain	Consider measuring coronary artery calcium (CAC) score [b]
If no risk enhancers	Emphasize heart-healthy lifestyle
5–7.4% (borderline risk)	
If risk enhancers (see Table 3)	Discuss moderate-intensity statin therapy
If no risk enhancers	Emphasize heart-healthy lifestyle
< 5% (low risk)	Emphasize heart-healthy lifestyle
If age 20–39	
If family history of premature ASCVD and LDL-C ≥ 160 mg/dL	Consider statin
Others	Emphasize heart-healthy lifestyle

Adapted from: 2018 Guideline on the Management of Blood Cholesterol: Guidelines Made Simple (updated June 2019). Washington, DC: American College of Cardiology, 2019.

[a] Very high-risk for future ASCVD events: Either multiple ASCVD events or 1 major and multiple high-risk conditions.

- Major ASCVD events: acute coronary syndrome within past 12 months, history of myocardial infarction (other than recent syndrome), history of ischemic stroke, symptomatic peripheral arterial disease.
- High-risk conditions: age ≥ 65, heterozygous familial hypercholesterolemia, history of prior coronary artery bypass surgery or PCI outside of the major ASCVD events, diabetes mellitus, hypertension, chronic kidney disease (eGFR < 60 mL/min/1.73m^2), current smoking, persistently elevated LDL-C (LDL-C ≥ 100 mg/dL) despite maximally tolerated statin therapy and ezetimibe, history of congestive heart failure.

[b] Coronary artery calcium (CAC) score: if CAC = 0, lower risk, no statin (unless diabetes, family history of premature ASCVD, or cigarette smoker); if CAC is 1–99, statin is favored (especially age ≥ 55); if CAC ≥ 100 or ≥ 75th percentile for age, sex, and ethnicity, initiate a statin.

Table 6. Statin Dose Intensity and Equivalency Chart*

Statin Intensity	%LDL-C Reduction	Statin (HMG-CoA Reductase Inhibitor) Options						
		Rosuvastatin	Atorvastatin	Pitavastatin	Simvastatin	Lovastatin	Pravastatin	Fluvastatin
High-Intensity (lowers LDL-C ≥ 50%)	63	40 mg ($11 gen, $242 br)						
	62							
	61							
	60		80mg ($8 gen, $508 br)					
	59							
	58							
	56	20 mg ($8 gen, $242 br)						
	54							
	52	10 mg ($7 gen, $242 br)						
	50		40mg ($7 gen, $508 br)					
Moderate-Intensity (lowers LDL-C 30–49%)	48							
	46							
	44	5 mg ($10 gen, $242 br)						
	42		20mg ($7 gen, $508 br)	4 mg (N/A gen, $293 br)	40 mg ($4 gen, $261 br)			
	40							
	38					80mg ($8 gen, $263 br)	80 mg ($13 gen, $367 br)	
	36							
	34				20 mg ($4 gen, $261 br)			80mg ($137 gen, $350 br)
	32			2 mg (N/A gen, $293 br)			40 mg ($8 gen, $183 br)	
	30		10mg ($6 gen, $356 br)	1 mg (N/A gen, $293 br)	10 mg ($4 gen, $150 br)	40mg ($6 gen, $132 br)	20mg ($9 gen, $125 br)	
Low-Intensity (lowers LDL-C < 30%)	28							
	26				5 mg ($5 gen, $75 br)	20 mg (54 gen, $79 br)		40mg ($122 gen, $175 br)
	24							
	22							
	20					10 mg ($5 gen, $44 br)	10mg ($7 gen, $63 br)	20mg ($122 gen, $88 br)
	18							

Note: Consider the similar cost for generics after considering the potential for drug interactions (Tables 8 and 9). The high potency statins are preferred with dose adjustment, as needed. Avoid simvastatin and lovastatin because of increased drug interactions and myopathy. 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 (30-49% reduction in LDL-C, lighter shading).

Table 7. Drug Therapy Summary

Drug & Strength	Dose Range	$/Mo generic [a]	$/Mo brand[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	$6-8	$202-290	39−60% ↓	5−9% ↑	19−37% ↓	Statins are contraindicated in pregnancy/lactation. Pre-menopausal women should be advised regarding the risks of statins on the fetus, the need for birth control methods, and stopping statins upon missing a menstrual cycle. 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 the upper limit of normal, but < 3 times the upper limit of normal): 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 9). Routine creatine kinase (CK) screening not proven beneficial. Avoid in combination with gemfibrozil. Dose adjustments are recommended for patients with eGFR < 60 mL/min/1.73m^2. No dose adjustment necessary for atorvastatin. See <u>UMHS Management of Chronic Kidney Disease</u> 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 should be avoided considering other options. ***Strong CYP3A4 inhibitors can increase atorvastatin, lovastatin, and simvastatin exposure increasing risk for muscle injury. See Table 10 for dose limitations with interaction drugs.
Rosuvastatin (Crestor)* 5, 10, 20, 40 mg	5−40 mg/d	$10-11	$92 all	45−63 % ↓	8−14 % ↑	10−35% ↓	
<u>Moderate Potency</u> Pitavastatin (Livalo) 1, 2, 4 mg	1−4 mg/d	N/A	$335	32−43% ↓	5−8 ↑	15−18%↓	
Simvastatin (Zocor)** 5, 10, 20, 40 mg	5−40 mg/d	$5	$76-133	26−47% ↓	8−16% ↑	12−33% ↓	
<u>Low Potency</u> Fluvastatin (Lescol XL) 20, 40 mg capsule 80 mg ER tablet	20−80 mg/d [b]	$70-135	N/A 80mg XL: $348 80mg ER: $250	19−32% ↓	3−8% ↑	0−11% ↓	
Lovastatin (Altoprev 24-hour)*** 10, 20, 40 mg	10−80 mg/d [b]	$5-8	$1064	24−40% ↓	5−19% ↑	3−22% ↓	
Pravastatin (Pravachol) 0, 20, 40, 80 mg	10−40 mg/d	$7-8	$125-129	18−35% ↓	4−16% ↑	1−25% ↓	

There is no established safety data for statins with ALT > 3x the upper limit of normal (ULN); generally, avoid statins when ALT > 3x ULN, unless found to be related to known liver disease and risk/benefit is appropriate; severe liver disease is rare with statins. If ALT is > 2x ULN at baseline, evaluate for liver disease; if present, monitor; a further moderate increase in ALT is expected.

Kim H, Kim TM, Yang SJ, Baik SY, Lee SH, Cho JH, Lee H, Yim HW, Choi IY, Yoon KH, Kim HS. Change in ALT levels after administration of HMG-CoA reductase inhibitors to subjects with pretreatment levels three times the upper normal limit in clinical practice. <u>Cardiovasc Ther.</u> 2018 Jun;36(3):e12324. doi: 10.1111/1755-5922.12324. Epub 2018 Mar 6.

Table 7. Drug Therapy Summary, continued

Drug & Strength	Dose Range	$/Mo gen [a]	$/Mo br [a]	LDL-C	HDL-C	TG	General Cautions about Drug Class
Absorption Inhibitors							
Bile Acid Resins:							Effective and safe with statins.
Cholestyramine (Questran, Questran Light) 4 g resin/variable g powder	4−12 g BID	$18–48	$48-144	15−30% ↓	3−5% ↑	0–20% ↑	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	$163	$700	15−18% ↓	3% ↑	9−10% ↑	Can increase triglyceride levels, avoid if TG level > 300 mg/dL.
Colestipol (Colestid) 5 g powder/1g tab	5–15 g BID	$26-72	$137-409	15−30% ↓	3−5% ↑	0–20% ↑	
Ezetimibe (Zetia)	10 mg/d	$9	$373	15−20% ↓	1−4% ↑	5−8% ↓	Ezetimibe is effective and safe with statins.
Fibric Acid Derivatives							
Fibrates							Obtain baseline ALT, monitor at physician discretion, unless at increased risk (see text).
Gemfibrozil (Lopid) 600 mg tablet	600 mg BID	$11	$435	± 10%	10% ↑	43% ↓	Contraindicated in hepatic disease or severe renal disease with GFR < 10 mL/min. Risk of myopathy with statins. Dosage should be reduced in chronic kidney disease. Do not use gemfibrozil in conjunction with statins.
Fenofibrates							
Antara (micronized) 43, 130 mg capsules	43−130 mg/d	N/A	$186-549	17−35% ↓	2−34% ↑	32−53% ↓	Use lowest initial starting dose of fenofibrate dosage form in elderly.
Fenoglide 40, 120 mg tablets	40−120 mg/d	N/A	$400-1200				Increases effect of warfarin. Dosage should be reduced in chronic kidney disease. Renal function should be checked periodically, particularly when it may impact renal function in the cardiorenal syndrome
Lipofen 50, 150 mg capsules	50−150 mg/d	N/A	$117-258				
Tricor 48, 145 mg tablets	48−145 mg/d	$11-12	$18-34				The FDA has concluded that the totality of the scientific evidence no longer supports the conclusion that a drug-induced reduction in triglyceride levels and/or increase in HDL-C levels in statin-treated patients results in a reduction in the risk of cardiovascular events. Fibrates should not be used in conjunction with statins for reduction in cardiovascular risk.
Triglide 50, 160 mg tablets	50−160 mg/d	N/A	$369				
Fenofibric Acid							
Fibricor 35, 105 mg tablet	35–105 mg/d	$69	$533-1064				
TriLipix 45, 135 mg delayed release capsule	45–135 mg/d	$18-33	$98-292				

Table 7. Drug Therapy Summary, continued

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) (Niacor) 50, 100, 250, 500 mg	500−1500 mg TID	$116-230	$349-698	5−25% ↓	15−35% ↑	20−50% ↓	Take with meals to avoid flushing or gastrointestinal upset. Can pre-medicate with aspirin 325 mg, 30 minutes prior to dose to reduce flushing. Take Niaspan ER at bedtime with a low-fat snack. With Niaspan ER follow titration schedule: weeks 1–4: 500 mg at bedtime; weeks 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. Check LFTs at baseline and 6 weeks after start or dosage change; monitor every 6–12 months thereafter. Causes glucose intolerance; caution in established or borderline diabetes. May cause gastrointestinal 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. The FDA has concluded that the totality of the scientific evidence no longer supports the conclusion that a drug-induced reduction in triglyceride levels and/or increase in HDL-C levels in statin-treated patients results in a reduction in the risk of cardiovascular events. Niacin should not be used in conjunction with statins for reduction in cardiovascular risk.
Niacin Extended Release (ER) (Niaspan) 500, 750, 1000 mg	1000−2000 mg/d	$24-44	$296-592	7−16% ↓	14−22% ↑	16−38% ↓	
PCSK9 Inhibitors (continued on next page)							
Alirocumab (Praluent) 75 mg/mL, 150 mg/mL	75–150 mg subcutaneously every 2 weeks; 300 mg subcutaneously every 4 weeks	N/A	$500-1200	43–64% ↓	4.6–8.9% ↑	6.5–17.35% ↓	For LDL-C > 190 mg/dL with family history of premature ASCVD or very high LDL-C, consider referring to a lipid specialist for management. Used as add on therapy to statins in very high-risk patients. Available in solution prefilled syringe or solution autoinjector for subcutaneous injection. Maximum dose of 150 mg every 2 weeks. No dosing adjustment required for renal or hepatic impairment. Can cause diarrhea, hypersensitivity reaction, myalgia, flu-like symptoms, and cough. No known significant drug interactions.

Table 7. Drug Therapy Summary, continued

Drug & Strength	Dose Range	$/Mo gen [a]	$/Mo br [a]	LDL-C	HDL-C	TG	General Cautions about Drug Class
PCSK9 Inhibitors, continued							
Evolocumab (Repatha) 140 mg/mL, 420 mg/3.5 mL	140 mg subcutaneously every 2 weeks; 420 mg subcutaneously every month	N/A	$150-490				For LDL-C > 190 mg/dL with family history of premature ASCVD or very high LDL-C, consider referring to a lipid specialist for management. Used for add on therapy to statins in very high-risk patients. Available in solution for subcutaneous injection. 420 mg/3.5 mL dose should be given over 9 minutes or in 3 separate 140 mg/mL injections consecutively within 30 minutes. No dosing adjustment required for renal or hepatic impairment. Can cause hypertension, dizziness, gastroenteritis, flu-like symptoms, injection site reaction, URI, cough, and myalgia. No known significant drug interactions.
Combination Products							
Ezetimibe and simvastatin (Vytorin) 10/10, 10/20, 10/40, 10/80 mg	10/10–10/80 (ezetimibe/ simvastatin) mg/d	$56-74	$302 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 result in a reduction in the risk of cardiovascular events compared to statin monotherapy.

[a] Cost = Average Wholesale Price minus 10%. AWP from Lexicomp Online 02/2020. For generic drugs, Maximum Allowable Cost plus $3 from BCBS of Michigan MAC List, 02/2020.

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

[c] Generic niacin immediate release (IR) is inexpensive but not federally regulated and not well tolerated. 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 8. Common Drug Interactions

	Interactive Agent(s)	Clinical Manifestations
Statins [a,b]	Fluconazole, itraconazole, ketoconazole, posaconazole	Increased risk of myopathy
	Cyclosporine, tacrolimus	Increased risk of myopathy [c]
	Clarithromycin, erythromycin	Increased risk of myopathy [c]
	Verapamil, diltiazem, amlodipine	Increased risk of myopathy [c]
	HIV protease inhibitors (eg, 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 a lower risk of drug interactions with other medications metabolized through the CYP3A4 system than other statins. Simvastatin has a higher risk of myopathy compared to other statins.

[b] Grapefruit juice increases the 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 statins not metabolized by the CYP3A4 enzymes, such as pravastatin, fluvastatin, rosuvastatin, and pitavastatin.

Table 9. Simvastatin and Lovastatin Contraindications and Dose Limitations

Simvastatin	Lovastatin
Contraindicated with simvastatin: Calcineurin inhibitors (cyclosporine/tacrolimus/sirolimus) Clarithromycin Danazol Erythromycin Gemfibrozil HIV protease inhibitors Itraconazole Ketoconazole Posaconazole Nefazodone Do not exceed 10 mg simvastatin daily with: Diltiazem* Verapamil* Do not exceed 20 mg simvastatin daily with: Amiodarone Amlodipine Ranolazine	Contraindicated with lovastatin: Clarithromycin Erythromycin HIV protease inhibitors Itraconazole Ketoconazole Nefazodone Posaconazole Telaprevir Avoid with lovastatin: Cyclosporine/tacrolimus Gemfibrozil Do not exceed 20 mg lovastatin daily with: Danazol Diltiazem Ranolazine Verapamil 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 10. Management of Statin-Intolerant Patients

1. **Discontinue statin.** For patients with mild to moderate muscle symptoms that develop during statin therapy, stop the statin until the symptoms can be evaluated. If more than moderate pains or sudden onset of pain or weakness occurs, 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 or myopathy (eg, hypothyroidism, influenza, exercise, reduced renal or hepatic function, rheumatologic disorders, steroid myopathy, vitamin D deficiency, or primary muscle diseases). Consider drug interactions, such as 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 muscle symptoms or elevated CK do not resolve completely after 2 months without statin treatment, 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 after 2 months without statin treatment, and no contraindication 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, stop the original statin. After muscle symptoms resolve, start an alternative low dose statin (preferably rosuvastatin or pravastatin, and avoid trials of lovastatin or simvastatin), and titrate up slowly to maximum tolerable dose.
6. **Intermittent statin dosing.** If the patient has failed a trial of a second statin, consider a trial of low dose twice weekly or alternate day dosing of a long-acting statin, such as atorvastatin or rosuvastatin.
7. **Consider referral to lipid specialist.** If the patient has failed 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, which 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 declines in smoking.

Issues. Many studies have shown that CHD patients are not adequately treated. Less than half of adults with high LDL-C receive treatment. The situation is likely worse for secondary prevention of ASCVD in those without CHD. Why do we fail to screen and adequately treat cholesterol? Cost may be an issue for some patients. Lack of adherence to treatment recommendations, despite insurance coverage, is another. Patient education about the benefits and general need for lifelong treatment may help improve adherence. 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 patients with diabetes mellitus, chronic kidney disease (CKD stages 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/TIA, great vessel arterial disease, and clinical peripheral arterial disease (PAD).

This guideline focuses on the groups that would benefit the most from treatment with a statin (HMG-CoA reductase inhibitor) in terms of ASCVD risk reduction and treatment strategies, in the context of cardiovascular risk. It also discusses the importance of triglycerides and the major classes of medications and their place in therapy. **Statins remain the primary treatment of choice.**

In patients with chronic kidney disease, the approach to lipid management depends on CKD 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 the management of severe or familial dyslipidemias, which typically involves lipid specialists.

Etiology, Treatment Benefit, and Strategy

Etiology. Many studies support the causal link between 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 have 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 is 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 age < 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 medications, with many patients also using complementary and alternative therapies. Of these, trial evidence has shown most benefit with medications.

Statins have shown the greatest reduction in total cholesterol and LDL-C, and the most dramatic reduction in CHD events. In primary prevention studies, every 40 mg/dL decrease in LDL-C is associated with a 20% reduction in cardiovascular event rates, regardless of baseline LDL-C. In secondary prevention trials, statins have also reduced CHD and total mortality.

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 reductions in ASCVD events, CHD mortality, and total mortality. Statins have shown reductions in different secondary prevention groups, including patients with CHD, acute coronary syndrome, and peripheral and cerebrovascular disease. All subgroups, including the elderly and females, have benefited. Older trials used statins that lowered LDL-C 30–40% with approximately 30% event reduction. Newer trials have convincingly shown that high-intensity statin treatment (eg, rosuvastatin 40 mg daily or atorvastatin 80 mg daily), is more effective in reducing events than lower intensity statin treatment. 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 additional 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 large randomized controlled trial (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 (first-ever myocardial infarction, stroke, hospitalization for unstable angina, arterial revascularization, or cardiovascular death) was reduced 44% (P<0.00001). All subgroups benefited.

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-risk (10-year risk < 6%), intermediate-risk (10-year risk 6–20%), and high-risk (10-year risk ≥ 20%), found that 4.3 years of statin therapy would reduce CHD events by 0.75%, 1.63%, and 2.51%, respectively, with NNTs of 133, 61, and 40. Statins are not considered cost effective in the low-risk group, but are cost-effective in the intermediate-risk group, and as in the high risk group may be cost saving in those with high LDL-C and risk enhancers.

For patients with diabetes and no other ASCVD risk factors, statin therapy may reasonably be delayed until age 40 since statin use in diabetics under age 40 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 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 a risk-based treatment strategy for most patients.

Risk-based treatment. The 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults provided a new perspective on LDL-C treatment benefit and strategy to achieve it. Rather than focusing on targets for LDL-C levels, the recommendations reflect using the appropriate intensity of statin therapy to reduce ASCVD risk in those patient populations most likely to benefit. The 2018 ACC/AHA/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol identified some additional risk subgroups and LDL-C levels relevant to treatment decisions.

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 four main patient risk groups (one for secondary prevention and three for primary prevention) are:

Secondary prevention
- Clinical ASCVD (coronary heart disease, stroke and peripheral arterial disease)

Primary prevention
- LDL-C ≥ 190 mg/dL (age ≥ 20)
- Diabetes mellitus Type 1 or 2 and age 40–75 years
- Other patients (see Table 5)

Table 5 provides more detail regarding each of these groups, their subgroups, and the associated levels of risk. It also shows recommendations, based on potential risk, benefit, and harm of treatment, for moderate-intensity or high-intensity statin treatment and non-statin pharmacological treatment. Healthy lifestyle is recommended for all.

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, as well as those with great vessel and peripheral arterial disease, all of presumed atherosclerotic origin.

For primary prevention (in patients with 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. Much of the argument against early screening was prior to the very low cost of statins.

Most guidelines agree that there is good evidence for screening men age ≥ 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 (age 65–73 years). PROSPER looked at older adults (age 70–82 years), 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 20–35 and women age 20–45) who are at increased risk for CHD.

The 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 (total cholesterol, triglycerides, HDL-C, and LDL-C). 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 adherence is an issue, a non-fasting lipid profile is adequate to assess cardiovascular risk and to monitor statin adherence. 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 adherence. If lipids are obtained non-fasting and are abnormal (ie, total cholesterol > 200 mg/dL, HDL-C < 40 mg/dL, or triglycerides > 350 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. At the Michigan Medicine, 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 lipid panels should be obtained before initiating therapy.

Patients with acute coronary syndrome who have not had 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 and high triglycerides. The American Heart Association/American College of Cardiology (AHA/ACC) guidelines for prevention of CAD recommend considering additional medication directed at these abnormal lipids, including niacin and fibrates. However, the role of combination therapy is controversial. No studies show combination therapy reduces 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.

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

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

Assess ASCVD Risk Factors

Assess level of ASCVD risk using the four categories of risk groups likely to benefit. 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, and age ≥ 20 years. See Table 1 for common secondary causes of lipid disorders and treat as appropriate.
- Diabetes mellitus type 1 or 2, age 40–75 years, and LDL-C 70–189 mg/dL.
- Calculate 10-year ASCVD risk for those age 40–79 years. See Table 2 for calculation.
- Chronic kidney disease. Refer to the UMHS Management of Chronic Kidney Disease clinical care guideline 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.
- In younger adults age 20–39 years, assessing lifetime risk facilitates the clinician-patient risk discussion and emphasizes intensive lifestyle efforts.
- Risk-enhancing factors may favor statin therapy in patients with borderline risk (10-year risk of 5–7.4%).

Controversy currently exists concerning use of the ACC/AHA Pooled Cohort Equation to calculate 10-year risk for ASCVD (see Table 2). It may over-estimate risk, and there is concern regarding the 10-year ASCVD risk score cutoff of ≥ 7.5% resulting in over-treating the primary prevention patient population. The 7.5% cutoff score is reasonable to use as 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 more diverse patient population included in the Pooled Cohort Equation, we recommend using the Pooled Cohort Equation rather than calculating the Framingham score. The Framingham score is based upon a population that is largely composed of middle-aged, non-Hispanic Whites, and calculates CHD risk rather than ASCVD risk (which includes CVA).

Checking a high-sensitivity C-reactive protein (hs-CRP) is currently *not* recommended as a cardiovascular disease screening test for average-risk adults without symptoms, but is included as a risk enhancer for those who are at borderline risk.

Coronary Artery Calcium (CAC) score is most helpful in intermediate-risk patients to further stratify their risk level. Additional considerations in younger persons with first degree relatives with major ASCVD event prior to age 40, elevated Lipoprotein (a), HDL-C < 35mg/dL, smokers, diabetes with another risk factor, and CKD.

If a decision about statin therapy is uncertain (including statin intolerant or patients reluctant to take statins) in adults age 40–75 years, without diabetes mellitus, with LDL-C levels from 70–189 mg/dL, who have a 10-year ASCVD risk of 7.5–19.9%, consider measuring the CAC score.

- If the CAC score is zero, treatment with statin therapy may be withheld or delayed, except in cigarette smokers, those with diabetes mellitus, and those with a strong family history of premature ASCVD.
- If the CAC score is 1–99, statin therapy is favored, especially in those age ≥ 55 years.
- If CAC is ≥ 100 or ≥ 75th percentile, statin therapy is indicated unless otherwise deferred by the outcome of clinician-patient risk discussion.

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. For all patients in all age groups, encourage healthy lifestyle activities. These include smoking cessation, dietary changes, weight loss if overweight or obese, and exercise. These interventions have been shown to reduce cardiovascular disease risk independent of their influence on lipids. They are discussed in more detail below.

Follow-up. Patients with normal screening lipids are generally rechecked at 4- to 6-year intervals because lipids may gradually worsen over time, and patients 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. Recommend a healthy lifestyle for all patients, whether they are taking cholesterol lowering drugs or not. The reductions in total cholesterol and LDL-C induced by a combination of dietary therapy and pharmacologic therapy are generally greater than for either approach alone. Recommend smoking cessation, dietary changes, weight loss if overweight or obese, and exercise. Consider referral to a dietitian for persons age 20-39 years, particularly for those with more than one risk factor and a 39% or greater lifetime risk by the ACC/AHA risk estimator.

Smoking cessation. In persons with CHD, smoking cessation reduces the 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 meta-analysis found no increase in risk for major adverse events with nicotine therapy, although 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. The 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk recommends a diet 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. Emphasize what should be eaten rather than what should not be eaten. Recommend increasing consumption of fruits and vegetables rich in fiber, fish, and linolenic acid (canola oil, soy, flax seed). Whole grains 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 trial published in 2013 demonstrated that adults at high risk for CVD events who ate a Mediterranean diet supplemented with olive oil or mixed nuts had significantly fewer major cardiovascular events, including myocardial infarction, stroke, and CVD death, than those in the control group.

The plant stanols (sitostanol and sitostanol esters) can lower LDL-C by approximately 10% by reducing absorption of cholesterol. These occur naturally in bran cereals, whole wheat, legumes, and nuts, are available in soft margarine and can be used as a spread on bread products and vegetables. Caplets are available be taken as 2-3 g daily. While outcome data (ie, evidence for reduction of CVD events) has not been demonstrated with plant stanols, dietary studies low in fat and high in fiber and vegetables do. Margarines derived by hydrogenation to trans-fatty acids should be avoided because they 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. The 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 acids via dietary change or supplements have been shown to improve CHD and CHD mortality in some, but not all studies. A meta-analysis suggests that supplementation with omega-3 fatty acids does not reduce the 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. The REDUCE-IT trial evaluated icosapent ethyl (Vascepa™), a prodrug that is converted to EPA, taken as 2 g twice daily. The trial showed that in men and women with clinical atherosclerosis or diabetes and other risk factors on statins, with triglycerides 135-499 mg/dL, icosapent ethyl resulted in a 25% reduction in CV events when compared to placebo. The benefit was not related to the level or reduction in triglycerides. Two placebo controlled studies of EPA and DPA showed no benefit.

Taking 2–4 grams of EPA and DHA per day can lower triglycerides 20–40%. Lovaza and Vascepa are FDA-approved fish oil supplements available by prescription. Vascepa contains only an EPA prodrug, while Lovaza 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. OTC omega-3 fatty acid sources are available at a much lower price, but they are not regulated, and require more capsules to achieve the same dose.

Fish oil supplements are a reasonable adjunct to secondary prevention in 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 potential adverse effects. Clinical significant bleeding has been reported at higher doses. 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 total cholesterol. 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 total cholesterol 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, showed improvements in hemoglobin A1c, but no reductions in LDL-C. 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-C with exercise training is inversely related to the pre-training HDL-C level. Exercise training less consistently lowers total cholesterol, triglycerides, and LDL-C. However, exercise training increases the effect that reducing dietary fat intake has on lowering total cholesterol, LDL-C, and triglycerides. The non-lipid effects of exercise are more important and those on lipids.

Decreased dietary fat intake alone causes reduced LDL-C and HDL-C. However, the addition of exercise training and polyunsaturated fatty acids and monunsaturated fatty acids 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 (eg, 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 possible coronary protective effect of moderate alcohol (1–3 ounces/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 patients with diabetes or other causes of hypertriglyceridemia. The coronary protective effects of alcohol may be offset by increased mortality from other causes. If alcohol intake is more than moderate (1 standard drink daily for women, and 1–2 standard drinks daily for men), reduction is recommended.

Pharmacologic Treatment: Statins

Statins are the first-line agents for lipid management. They 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 adverse effects. Fibrates are well tolerated, but have minimal impact on LDL-C and have not shown results in terms of event reduction. Niacin is effective at improving metabolic syndrome profiles, ie, low HDL-C/high triglycerides, but considering the newer options has no role in ASCVD risk reduction. In contrast, ezetimibe (Zetia), a drug that blocks cholesterol ester absorption, lowers the LDL-C by 15-20% and was effective as an adjunct to simvastatin in patients with a previous MI and LDL-C ≥ 70 mg/dL.

Individual statins. Statins are the best-studied lipid-lowering drugs and show the most benefit in terms of absolute LDL-C reduction and patient outcome. Large clinical event trials have included atorvastatin, lovastatin, pravastatin, simvastatin, and rosuvastatin. Statins are considered to have a class effect.

High intensity statins reduce clinical events more than low intensity statins. Rosuvastatin is the most potent agent. Pravastatin is not metabolized by CYP450 (liver), and has fewer drug interactions. Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin are available as generics.

Table 6 presents dosing equivalents across statins for high-intensity dosing (≥ 50% LDL-C reduction) and moderate-intensity dosing (30–49% LCL-C reduction). Table 7 presents a summary of information regarding commonly used lipid lowering drugs.

Adverse effects. The most common adverse effect from statins is myalgias (ie, muscle pain or soreness), weakness, or cramping without CK elevation, which resulted in dropouts of 5% among trial patients. No evidence confirms that myalgias are more common with one statin than another. Rhabdomyolysis (CK > 10,000 IU/L or CK > 10 times the upper limit of normal, plus elevation in serum creatinine) is a potentially life-threatening complication of statin therapy, with a 10% mortality rate. For statin monotherapy, the average incidence of rhabdomyolysis is 0.44 per 10,000 person-years.

Observed rates of new-onset diabetes vary 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 (eg, 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 9. High dose simvastatin and lovastatin (ie, 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.

Some patients are more likely to have adverse effects from statins, particularly those individuals who have multiple and serious co-morbidities. These include impaired renal or hepatic function, a history of previous statin intolerance or muscle disorders, unexplained ALT elevations > 3 times the upper limit of normal, concomitant use of drugs affecting statin metabolism, excess alcohol, and age > 75 years. If any of these predisposing characteristics are present, moderate-intensity statin therapy may be preferred in individuals for 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 8), primarily increasing the risk of myopathy. For example, adding a fibrate to a statin increases the risk of rhabdomyolysis to 5.98 per 10,000 person-years. Other drugs that increase risks are inhibitors of cytochrome P450 enzymes. Atorvastatin, lovastatin, and simvastatin are metabolized by CYP3A4, while fluvastatin, rosuvstatin and to some extent pitavastatin are metabolized by CYP2C9. Pravastatin is not metabolized by the CYP enzymes. Inhibitors of CYP enzymes that can affect statin metabolism include cyclosporine, azole 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 9). A large amount of grapefruit juice (> 1 quart/day) also increases the blood level of the statins that are metabolized by the CYP450 3A4 system.

In immunocompromised patients and those with systemic illnesses such as diabetes, it may be best to switch from atorvastatin, simvastatin and lovastatin to drugs not metabolized by CYP3A4. Whenever possible, avoid using the interacting drug rather than modifying the patient's statin therapy. If an interacting drug cannot be avoided, either adjust the dose of these statins or consider an alternative with less potential for drug-drug interactions. If a patient experiences myopathy on any statin, the statin should be stopped immediately.

Intolerance. Statin intolerance is a common problem in primary and specialty care, generally due to myalgias. 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 10.

Pregnancy. Statins are contraindicated in pregnancy due to risk of teratogenicity and possible risk of delayed fetal development. Women of child bearing potential should generally avoid statins. Do not use statins in women who are pregnant or lactating.

Initiating statin therapy. Once a patient's risk category has been assessed, discuss statin therapy with the patient. Determine the recommended intensity of statin dosing, and initiate statin therapy. Follow up on the response to statin therapy in terms of patient tolerance and lipid profile response. Monitor ALT in those with known liver disease, risk factors for liver disease, or 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 (those 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. The 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, which is 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.

Studies show that both statin-treated and placebo-treated patients seem to experience the same rate of muscle symptoms. The actual rate of statin-related muscle symptoms in the clinical population is unclear.

Statins interact with several other drugs (see Table 8). If potential interactions are a concern, the usual approach is to try 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.

Patient preferences regarding medications, likely need for lifetime therapy, and ability to manage costs should also be addressed.

Check baseline ALT. A baseline measurement of ALT should be obtained before initiating statin therapy. See Table 4 for monitoring recommendations when ALT is abnormal.

Statin dosing based on risk group. The ACC/AHA guidelines for dosing (see Table 6 for Statin Dose Intensity and 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 ≥ 20 years = high-intensity.
- Diabetes Mellitus Type 1 or 2, and age 40–75 years, with LDL-C 70–189 mg/dL
  - If no other ASCVD risk, moderate-intensity.
  - If at higher risk (eg, multiple ASCVD risk factors or age 50–75 years), consider a high-intensity statin to reduce the LDL-C level by ≥ 50%.
- ≥ 7.5% estimated 10-year ASCVD risk, and age 40–75 years, with LDL-C 70–189 mg/dL, without diabetes mellitus, 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, potential for adverse effects, and patient preferences regarding 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 those who are on other potentially hepatotoxic medications. Liver function tests (LFTs) should be measured if symptoms suggesting hepatotoxicity arise (eg, 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 there are no concerns over liver function, and LFTs are normal, no further monitoring is required.

Routine CK monitoring is not recommended in individuals receiving statin therapy. Moderate CK elevations (< 800 IU) do not necessarily indicate toxicity or increased risk of myopathy. Baseline CK measurement is reasonable for those 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. In ASCVD patients at very high risk, if patient is on maximal statin therapy and LDL-C level is ≥ 70 mg/dL, consider adding non-statin drug therapy. (See below.)

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 the lifestyle modifications that are the cornerstones 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 stopped statin treatment by one year if their copayment was > $20/month and by 3.9 years if their copayment was < $10/month. Insurance records of statin dispensing are becoming less reliable indicators of statin adherence because statin medications are increasingly being filled without an insurance claim, eg, 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. Adding non-statin therapy may be considered in high-risk patients who:

- Are completely statin intolerant.
- Have an inadequate response to statins (high-intensity therapy should show ≥ 50% reduction in LDL-C, moderate-intensity therapy should show 30–49% reduction in LDL-C).
- Are not able to tolerate the recommended statin intensity.
- Have severe hypertriglyceridemia (> 500 mg/dL) necessitating the use of fibrates or fish oil to prevent pancreatitis.

Adherence to statin therapy and lifestyle should be reassessed and re-emphasized before addition of a non-statin drug. Combination therapy of statins with fibrates significantly increases the risk of myopathy and rhabdomyolysis.

In patients at very high-risk for ASCVD and on maximally tolerated statin, if LDL-C is ≥ 70 mg/dL, consider addition of non-statins to statin therapy. Very high-risk includes a

history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.

- Consider adding ezetimibe.
- If on ezetimibe therapy and LDL-C level remains ≥ 70 mg/dL, consider adding a PCSK9 inhibitor. (Note: for PCSK9 inhibitors, long-term safety [> 3 years] is uncertain and cost effectiveness is low at mid-2018 list prices.)

In patients with severe primary hypercholesterolemia (LDL-C level ≥ 190 mg/dL), without calculating 10-year ASCVD risk, begin high-intensity statin therapy. If the LDL-C level remains ≥ 100 mg/dL:

- Consider adding ezetimibe.
- If on statin plus ezetimibe and the LDL-C level remains ≥ 100 mg/dL and the patient has multiple factors that increase subsequent risk of ASCVD events, consider adding a PCSK9 inhibitor. (Note: for PCSK9 inhibitors, long-term safety [> 3 years] is uncertain and cost effectiveness is uncertain at mid-2018 list prices.)

Bile acid resins. Cholestyramine, colestipol, and colesevelam are generally considered second line because of poor patient tolerability to their adverse 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 triglycerides ≥ 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 adverse effects are bloating, nausea, constipation, and abdominal pain. Non-gastrointestinal 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. Adverse effects can be reduced somewhat by titrating up slowly. Colesevelam has been shown to have a lower incidence of gastrointestinal 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 by blocking cholesterol transport at the intestinal brush border. It can lower LDL-C by 15–20% alone. Ezetimibe should be considered for patients who are statin intolerant or who are not meeting statin LDL-C percent reduction goals with maximal tolerated statin therapy alone. See the UMHS Management of Chronic Kidney Disease 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 > 3 times the upper limit of normal occur.

PCSK9 inhibitors. PCSK9 inhibitors include alirocumab (Praluent) and evolocumab (Repatha). PCSK9 inhibitors are human monoclonal antibodies that bind to the PCSK9 inhibitor and decrease the degradation of the LDL receptor. Both alirocumab and evolocumab are given as subcutaneous injections either every 2 weeks or every 4 weeks. Potential LDL-C reduction with these medications is 43–64% when added to highest tolerated dose of statins. Consider PCSK9 inhibitors in secondary ASCVD prevention or in patients with severe hypercholesterolemia (LDL-C ≥ 190 mg/dL) if they do not achieve the desired LDL-C lowering on maximum tolerated statin therapy along with ezetimibe. PCSK9 inhibitors decrease LDL-C levels further when added to statin therapy. PCSK9 inhibitors also improve cardiovascular outcomes when added to statin therapy. These medicines are generally well tolerated. The most common adverse effects include injection site reactions, stomach upset, cough, dizziness, and myalgias. No clinically significant drug interactions have been reported with either evolocumab or alirocumab. PCSK9 inhibitors are expensive and can be cost-prohibitive for patients.

Fibrates. Fibrates available in the US include gemfibrozil and fenofibrate. 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 on the fenofibrate studies. The FDA has concluded that the totality of the scientific evidence no longer supports the conclusion that a drug-induced reduction in triglyceride levels and/or increase in HDL-C levels in statin-treated patients results in a reduction in the risk of cardiovascular events. Therefore fibrates should ***not*** be used in conjunction with statins for reduction in cardiovascular events.

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 patients with hypercholesterolemia, and 12% in patients with combined hyperlipidemia, metabolic syndrome, and type 2 diabetes. 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 who have severe triglyceride elevation (> 500 mg/dL) despite lifestyle changes, to help prevent pancreatitis.

Adverse effects of fibrates are generally gastrointestinal, including nausea, dyspepsia, and changes in bowel habits. The risk of cholestasis and need for cholecystectomy is increased. Fibrates carry a small risk of myopathy as monotherapy. Fibrates may cause a small reversible increase in creatinine, and dose adjustment in chronic kidney disease patients is recommended. Contraindications include severe

renal or liver disease, preexisting gallbladder disease, and pregnancy.

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 adverse effects of niacin. The greatest benefit for niacin alone would be in patients with a low HDL-C and moderate elevation of triglycerides, or for those intolerant to statins. The FDA has concluded that the totality of the scientific evidence no longer supports the conclusion that a drug-induced reduction in triglyceride levels and/or increase in HDL-C levels in statin-treated patients results in a reduction in the risk of cardiovascular events. Therefore niacin should ***not*** be used in conjunction with statins for reduction in cardiovascular events. Rare cases of rhabdomyolysis have been associated with concomitant use of statins and niacin in doses > 1 g.

Patients on niacin should have baseline testing of ALT, 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. Prescription niacin products include Niacor (IR), and Niaspan, an extended-release formulation taken at bedtime, which is associated with better side-effect tolerance and adherence. "Flush-free" and "no flush" preparations are also marketed OTC, but contain very little to no active niacin and should not be used. Dietary supplements are not subject to the same FDA regulations as prescription products; OTC niacin products may not be therapeutically equivalent to the prescription-only products.

Adverse effects of niacin include flushing, pruritus, gastrointestinal disturbances, fatigue, glucose intolerance, and gout. The vasoactive symptoms are reduced by pre-medicating with aspirin 325 mg by mouth 30 minutes prior, slow titration of the niacin dose, 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 > 2–3 times the upper limit of normal. Niacin should be discontinued in patients experiencing persistent severe cutaneous symptoms, persistent hyperglycemia, acute gout, unexplained abdominal pain or gastrointestinal symptoms, or if new-onset atrial fibrillation or weight loss occurs. Niacin ER has fewer adverse 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 use no more than 2 g/day.

Triglycerides

High triglycerides have been associated with an increase in coronary events in population studies, and an increase in event rate and mortality in CHD secondary prevention studies, independent of statin treatment. However, 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. 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. The FDA has concluded that the totality of the scientific evidence no longer supports the conclusion that a drug-induced reduction in triglyceride levels and/or increase in HDL-C levels in statin-treated patients results in a reduction in the risk of cardiovascular events.

Complementary and Alternative Treatment

Complementary and alternative therapies may affect lipid levels, although evidence 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 instead be based on direct indications (eg, relief of hot flashes), and 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 adverse 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 nephrotoxins. Advise patients not to use red yeast rice products due to lack of effectiveness and the lack of manufacturing standards leading to concerns for safety.

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

Garlic. Many patients use garlic for hyperlipidemia, but evidence suggests that it is less effective than initially thought. The Natural Medicines Comprehensive Database downgraded garlic to a rating of "possibly ineffective." Garlic can cause drug interactions and increase the 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 include policosanol, chitosan, and gugulipid (extract from the resin of Indian thorny tree). They should be avoided.

Special Populations for Preventive Therapy

Women. Studies have shown a significant treatment benefit in women. A meta-analysis on the effect of statins on risk of CHD found a similar benefit in women as in men. 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 compared to their male counterparts. For this reason, USPSTF recommends starting screening in women age 45 and older who are at increased risk for CHD and in all men age 35 and older. The American College of Physicians (ACP) has a somewhat similar age difference, recommending screening of 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 that takes into consideration possible risk reduction, adverse effects, and contraindications. For lipid management in patients with ESRD, see UMHS CKD guideline.

Individuals Age > 75 Years. Randomized controlled trials support the continuation of statins beyond age 75 years in those who are already taking and tolerating these drugs, as well as the use of moderate-intensity statin therapy for secondary prevention in individuals age > 75 years who have clinical ASCVD. However limited data are available regarding primary prevention among individuals age > 75 years. Initiation of statins for primary prevention in individuals age > 75 years 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 interactions, and patient preferences should precede the initiation of statin therapy for primary prevention in older individuals. In patients with increasing co-morbidities, or patients with a limited life expectancy, it is reasonable to consider stopping statin treatment.

Related National Guidelines

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

American College of Cardiology/American Heart Association Task Force report: 2018 ACC/AHA /AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC /NLA/PCNA Guideline on the Management of Blood Cholesterol (2019)

American Diabetes Association: Standards of medical care in diabetes (2020)

US Preventive Services Task Force: Screening for lipid disorders in adults (2016)

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 (eg, population inclusions and exclusions).

Preventive care and screening: fasting LDL-C test. The percentage of patients age 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 age 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 age 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 age 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 age 18–75 years with diabetes who received at least one lipid profile within 12 months (MU, GPRO, PGIP age 40–75 years).

Diabetes and LDL-C control. The percentage of patients age 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 age 18–75 years with congestive heart failure who had an LDL-C test in the measurement year (PGIP).

Ischemic vascular disease (IVD) and lipid profile and LDL-C control. The percentage of patients age 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 2000 version 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.

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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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Listed on the first page are members of the team that reviewed the previous version of this guideline and produced this update. The following individuals developed earlier versions of this guideline, parts of which continue to be used in this updated guideline:

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