Hyperlipidemia: Management – Adult – Inpatient/Ambulatory Clinical Practice Guideline

Note: Active Table of Contents – Click each header below to jump to the section of interest

Table of Contents

INTRODUCTION **3**

SCOPE **3**

DEFINITIONS **3**

RECOMMENDATIONS **3**

Risk factors for ASCVD *3*
Screening *4*
Lifestyle Modifications 5
Diet *5*
Physical Activity *5*
Pharmacotherapy for prevention of ASCVD 5
Who should receive statin therapy *5*
Initiating Statin Therapy for Clinical ASCVD and Primary Prevention *7*
Statin therapy monitoring *9*
Management of patients unable to tolerate intensity of statin therapy *10*
Non-statin lipid-lowering drug therapies 12
Ezetimibe *12*
Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors *12*
Bile Acid Binding Resins *13*
Niacin (Nicotinic Acid) *13*
Fibric Acid Derivatives *13*
Omega-3 Fatty Acids *13*
Table 8. General Sequence of Lipid Therapy Based on Lipid Pattern with Lifestyle Changes *15*
Referral to Preventive Cardiology 15

METHODOLOGY **16**

COLLATERAL TOOLS & RESOURCES **20**

REFERENCES **22**

Content Expert(s):
Name: James Stein, MD – Cardiovascular Medicine
Phone Number: (608) 262-2075
Email Address: jhs@medicine.wisc.edu

Name: Amita Singh, MD – Cardiovascular Medicine
Phone Number: (608) 263-2166
Email Address: asingh2@medicine.wisc.edu

Contact for Changes:
Name: Katherine Le, PharmD – Center for Clinical Knowledge Management
Phone Number: (608) 890-5898
Email Address: kle@uwhealth.org

Workgroup Members:
Mark Micek, MD – Internal Medicine
Jeff Huebner, MD – Family Medicine
Amy Bauman, MD – Family Medicine
Katherine Hartkopf, PharmD – Pharmacy
Jessica Norman, PharmD – Pharmacy
Sharon Mladucky, RN – Cardiology

Reviewer(s):
Donald Wiebe, PhD – Laboratory
Carin Bouchard, PharmD – Drug Policy

Committee Approval(s):
Clinical Knowledge Management (CKM) Council (02/22/18)

Introduction

Hyperlipidemia is a major risk factor for first and recurrent Atherosclerotic Cardiovascular Disease (ASCVD) events such as heart attack, sudden cardiac death, ischemic stroke, peripheral artery disease, and arterial revascularization. Hyperlipidemia has the highest population-attributable risk for coronary heart disease (CHD) of all modifiable risk factors for CHD. Lifestyle modifications and medications offer powerful, safe and effective means to improve lipids and reduce ASCVD risk. The primary sources for this guideline are the 2013 ACC/AHA recommendations for management of dyslipidemia and the 2017 update for use of non-statin therapies.

Scope

Intended User(s): Physicians, Advanced Practice Providers, Registered Nurses, Pharmacists

Objective(s): To provide evidence based recommendations on the testing for and management of dyslipidemia in adult patients being treated in the ambulatory care setting.

Target Population: Adult patients being screened/treated for hyperlipidemia at UW Health

Clinical Questions Considered:

- When should statin drug therapy be initiated in patients with dyslipidemia?
- When should statin therapy be titrated and/or non-statin interventions added?
- What dietary modifications are recommended for patients with dyslipidemia?
- What are optimal approaches to managing patients with statin-associated muscle discomfort?

Definitions

Hyperlipidemia – is a condition of elevated cholesterol and/or triglycerides (TG) and may also be referred to as “dyslipidemia”

Recommendations

***Note:** Unless noted otherwise, evidence grade is from the American College of Cardiology/American Heart Association rating scheme.

Risk factors for ASCVD

In addition to hyperlipidemia, the following are independent risk factors for ASCVD:[1]

- Increasing age (especially males ≥45 years old, females ≥55 years old)
- Diabetes mellitus (especially Type 2)
- Cigarette smoking
- Hypertension
- Family history of premature CHD (male first degree relative ≤45 years old; female first degree relative ≤55 years old)

The following factors also increase risk for ASCVD and can be used in shared decision making to guide initiation of pharmacotherapy and intensification of risk. These factors are associated with increased risk of ASCVD but are not considered independent risk factors.

- Metabolic Syndrome[1]
- Elevated high sensitivity C-Reactive Protein (hsCRP >2.0 mg/L)[2]
- Elevated lipoprotein (a)[3], also known as Lp(a)

- Advanced subclinical atherosclerosis (i.e., coronary artery calcification [CAC] score with CAC >300 or > 75th percentile for age/gender/ethnicity-matched subjects using MESA risk calculator[4], ankle-brachial index <0.9, or presence of carotid atherosclerosis)[5]
- Chronic kidney disease (CKD) (i.e., eGFR < 60 mL/min/1.73 m^2)[1]
- Autoimmune diseases (including rheumatoid arthritis, systemic lupus erythematous and Human Immunodeficiency Virus [HIV] infection)[6]

Screening

Patients age 17-21 years

Universal lipid screening is recommended for all patients age 17-21 years *(NHLBI Grade B, strongly recommended)* using non-fasting total cholesterol and high-density lipoprotein cholesterol (HDL-C) measurements.[7,8]

Patients age 22-39 years

Screening with a complete fasting lipid panel is preferred in patients age 22-39 years with or without ASCVD risk factors and to be repeated every 5 years. If a fasting lipid panel cannot be done, consider obtaining non-fasting total cholesterol and HDL-C measurements.[9] If non-fasting total cholesterol, HDL-C or non-HDL-C measurements are abnormal, consider obtaining fasting lipid panel.[9,10] *(NHLBI Grade B, moderate)*

If low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) levels are within acceptable limits (**Table 1**) and the patient does not have any risk factors, consider delaying periodic 5-year screening. *(UW Health Low quality evidence, weak/conditional recommendation)* Patients with ASCVD risk may need to be screened more frequently. *(UW Health Low quality evidence, weak/conditional recommendation)*

Patients age 40-75 years

Screening with a complete fasting lipid panel is preferred in patients age 40-75 years with or without ASCVD risk factors and to be repeated every 5 years. If a fasting lipid panel cannot be done, consider obtaining non-fasting total cholesterol and HDL-C measurements.[9] If non-fasting total cholesterol, HDL-C or non-HDL-C measurements are abnormal, consider obtaining fasting lipid panel.[9,10] *(NHLBI Grade B, moderate)*[9]

If a woman's estimated 10-year ASCVD risk is < 2.5% and LDL-C and TG levels are within acceptable limits (**Table 1**) subsequent screening may be delayed until age 45 years, unless risk factors develop. *(UW Health Very low quality evidence, weak/conditional recommendation.)* Patients with ASCVD risk should be screened more frequently. *(UW Health Low quality evidence, weak/conditional recommendation.)*

Use an ASCVD Risk Estimator calculation tool such as the ACC-AHA Pooled Cohort equation (http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/) *(Class IIa, Level C)* or the HealthDecision tool found in UW HealthLink to evaluate a patient's estimated 10-year ASCVD risk. *(UW Health Very low quality evidence, weak/conditional recommendation)*

Table 1. Acceptable Lipid Results[8,9,11]

Age	Total Cholesterol (mg/dL)	HDL Cholesterol (mg/dL)	Triglycerides (mg/dL)	LDL Cholesterol (mg/dL)	Non-HDL Cholesterol (mg/dL)
0-19 yrs.	< 170	> 45	0-9 yrs.: < 75 10-19 yrs.: < 90	< 110	< 120
Age ≥ 20 yrs.	< 200	Men: > 40 Women: > 50	< 150	< 100	Men: < 160 Women: <150

Lifestyle Modifications

Diet

Providers should counsel all patients that would benefit from a reduction in LDL-C to make the following dietary modifications.[12,13] *(Class I, Level A).* These changes can reduce ASCVD risk, and can reduce LDL-C by 20-24% (are as effective as a low dose statin.)[12,14-16]

- Consume a diet that emphasizes vegetables, fruits and whole grains and that includes low fat dairy products, poultry, fish, and legumes (e.g., DASH diet, AHA Diet, USDA Food pattern). *The Mediterranean Diet can be healthy but has a lower evidence grade due to lower quality trial data.[12,17] It is associated with moderate fat intake and can easily lead to weight gain as well, so it is not the preferred approach for dietary modification with goal of LDL-C reduction.*
- Limit intake of sweets, sugar-sweetened beverages, and red meats/processed meats.
- Reduce percent of calories from saturated fat and trans fat to <5-6% of total calories. (This can lead to an LDL-C reduction of 8-10% depending on current dietary pattern).[16,18]
- Reduce dietary cholesterol to < 200 mg/day (may reduce LDL-C by 3-5% depending on current dietary pattern)[12,16,18]
- Increase intake of soluble fiber (e.g., oats, beans). Adding psyllium (i.e., Metamucil®, 6-12 g/day) can reduce LDL-C by 5-10%.[16,18]
- Replacing dietary butter or vegetable-oil based margarines with plant sterols or stanol margarines can reduce LDL-C by 7-15%.[16,18]

Physical Activity

Patients should be advised to engage in aerobic physical activity at least 3-4 times a week, lasting on average 40 minutes/session and of moderate to vigorous intensity to reduce LDL-C and non-HDL cholesterol levels.[12,18] *(Class IIa, Level A).* Physical exercise improves cardio-respiratory fitness and reduces ASCVD risk, though its effects on cholesterol levels are modest unless they are accompanied by weight loss. TG levels are more responsive to exercise and weight loss than cholesterol levels. Exercise has inconsistent effects on HDL-C though.

Pharmacotherapy for prevention of ASCVD

Statin medications are the primary drug class to treat dyslipidemia and reduce risk of ASCVD because of their long-term track records of safety and efficacy for lipid improvements and reducing ASCVD risk.[19,20] Interventional and epidemiological trials with statins and non-stain agents demonstrate that that ASCVD risk decreases by ~20-25% per year for every 39 mg/dL reduction in LDL-C.[21]

NOTE: In patients who have TGs > 500 mg/dL the primary risk is pancreatitis and hyperviscosity so lowering TGs with lifestyle and medication interventions is the primary initial goal, not ASCVD risk reduction. Once TG levels are controlled, consider additional lipid-lowering for ASCVD prevention. **(see Table 8 - General Sequence of Lipid Therapy Based on Lipid Pattern with Lifestyle Changes)

Who should receive statin therapy

ASCVD event reduction with statin therapy benefits four groups of patients:[22]

- Patients with clinical ASCVD (i.e., acute coronary syndromes [ACS], myocardial infarction [MI], stable/unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease [PAD] of atherosclerotic origin)
- Patients with LDL-C levels $\geq$ 190 mg/dL

- Patients age 40-75 years old with diabetes mellitus and LDL-C 70-189 mg/dL (note: stronger evidence for type 2 than type 1 diabetes mellitus and if LDL-C is > 100 mg/dL)
- Patients without clinical ASCVD, LDL-C <190 mg/dL, no diabetes mellitus, age 40-75 years with estimated 10-year ASCVD risk $\geq$ 7.5%

Clinician-Patient Discussion Prior to Statin Therapy Initiation for Primary Prevention
Prior to initiating or if considering statin therapy for primary prevention of ASCVD , a patient-health care provider discussion should focus on the patient's estimated 10-year ASCVD risk, management of other ASCVD risk factors, expected ASCVD event reduction, potential drug interactions, adverse drug effects and costs.[22] *(Class IIa, Level C)* The HealthDecision Tool on 10-year ASCVD risk in HealthLink may be a useful tool for this discussion. This discussion may also serve as an opportunity to discuss lifestyle modifications to prevent ASCVD.[20] The discussion should include/consider family history of premature heart disease, presence of LDL-C >160 mg/dL, presence of subclinical atherosclerosis, and hsCRP level.

UW Health does not recommend routinely screening for presence of subclinical atherosclerosis however it may be detected on ultrasound, CT, or MRI scans performed for other clinical purposes or when patients obtain these tests at their own discretion. (UW Health Low quality of evidence, weak/conditional recommendation)

<u>Prior to Starting Statin Therapy</u>

- Check ALT (CK levels may be checked too especially if patient is at increased risk for myalgia or myositis and having a baseline value may be useful) *(Class I, Level B)*
- Rule out and treat common secondary causes of hyperlipidemia based upon history and physical exam, using laboratory tests if needed. These include: *(Class IIa, Level B)*
    - Overweight/obesity
    - Hypothyroidism
    - Chronic kidney disease
    - Chronic liver disease
    - Certain medications (e.g., beta blockers, diuretics, cyclosporine, certain antipsychotics, estrogen, progesterone, testosterone, isotretinoin)
    - Alcohol use
    - Adverse dietary habits
- Identify and document presence of any muscle or joint symptoms *(Class IIa, Level B)*
- Identify and document any prior adverse response(s) to lipid-lowering medications, including symptoms, timing of onset/offset, drug name, and dose
- Educate patient about statin myopathy. Key counseling points include:
    - The true prevalence of statin myalgia is not known and likely ~5%; serious muscle side effects like myositis and rhabdomyolysis occur in < 1/1000-2000 people[23]
    - Of people who did not tolerate 2-3 statins, 70-80% can tolerate a different statin
    - Statin muscle aches are mainly due to a strong nocebo effect. The vast majority of muscle aches on statins are not due to statin.[24,25]
    - Statin muscle aches tend to be diffuse and symmetric with weakness. They affect the larger muscle groups first and are distinct from joint pain or nocturnal leg cramps. They tend to present within the first 2-3 months of therapy.

Very High LDL-C Levels

LDL-C levels > 190 mg/dL often indicate the presence of a genetic dyslipidemia, especially when it is present since early in life and accompanied by family members with premature ASCVD. These patients are at a very high risk of premature ASCVD and the ASCVD risk calculator should not be used to estimate risk in these patients. *(UW Health High quality evidence, strong recommendation)*

A high LDL-C level by itself does not constitute the presence of familial hypercholesterolemia (FH), a disease typically characterized by total cholesterol values between over 300 mg/dL and premature ASCVD. There are several classification methods for diagnosing heterozygous FH but most rely on the presence of a gene mutation or uncommon physical findings. Gene mutations are found in < 2% of unselected individuals with LDL-C levels over 190 mg/dL. Often, severely elevated cholesterol levels are present due to polygenic abnormalities, commonly in conjunction with acquired abnormalities from adverse diet and other lifestyle habits. Routine genetic screening is not recommended. *(UW Health Low quality evidence, weak/conditional recommendation)* Regardless of cause, treatment of high LDL-C is recommended because it will reduce the ASCVD risk in these patients.[19,26,27] *(UW Health Moderate quality evidence, strong recommendation)*

Initiating Statin Therapy for Clinical ASCVD and Primary Prevention

Table 2. Summary of solubility, metabolism and formulation availability of select statins

Drug	Solubility[28]	Cytochrome P450 Metabolism[29,30]	Generic?[29]	Dosages availabile[29]
Atorvastatin	Lipophilic	CYP3A4	Yes	10 mg, 20 mg, 40 mg, 80 mg tablets
Fluvastatin	Lipophilic	CYP2C9 (CYP2C8 and CYP3A4 minor)	Yes (immediate release and extended-release)	Immediate release:: 20 mg, 40 mg capsules Extended-release: 80 mg capsules
Lovastatin	Lipophilic	CYP3A4	Yes (immediate release)	IR: 10 mg, 20mg, 40 mg tablets Extended-release: 20mg, 40mg, 50 mg tablets
Pitavastatin	Lipophilic	CYP2C9, (minimally by CYP2C8)	No	1 mg, 2mg, 4 mg tablets
Pravastatin*	Hydrophilic	Non-CYP metabolism	Yes	10 mg, 20 mg, 40 mg, 80 mg tablets
Rosuvastatin*	Hydrophilic	CYP2C9	Yes	5 mg, 10 mg, 20 mg, 40 mg tablets
Simvastatin	Lipophilic	CYP3A4	Yes	5 mg, 10 mg, 20 mg, 40 mg, 80 mg tablets Oral suspension (brand): 20mg/5 mL, 40mg/4 mL

**Pravastatin and rosuvastatin may be preferred in patients with a history of statin intolerance due to hydrophilicity and in patients with complex medical regiments who are at risk for drug interactions because of how they are metabolized. Note that pravastatin has a lower potency compared to other statin drugs.*

Table 3. Statin therapy intensity and suggested statin dosing

	High intensity	Moderate intensity	Low intensity
Goal LDL-C reduction	> 50%	30-<50%	< 30%
Suggested statin dosing	• Atorvastatin 40-80 mg • Rosuvastatin 20-40 mg	• Atorvastatin 10-20 mg • Rosuvastatin 5-10 mg • Simvastatin 20-40 mg • Pravastatin 40-80 mg • Lovastatin 40 mg • Fluvastatin 80 mg • Pitavastatin 2-4 mg	• Simvastatin 10 mg • Pravastatin 10-20 mg • Lovastatin 20 mg • Fluvastatin 20-40 mg • Pitavastatin 1 mg

- *Note: LDL-C responses to statins vary between individuals.*
- *Note: Atorvastatin and rosuvastatin are generally preferred given generic-formulation availability, efficacy, and side-effect profiles.*
- *Note: All statins have a higher risk of side effects at their highest dose*

Table 4. Clinical ASCVD[20]

Patient group	Statin Therapy	Evidence rating
Age ≤ 75 years, and no safety concerns*	High intensity statin	*Class I, level A*
Age > 75 years or pt w/ safety concerns	Moderate intensity statin	*Class I, level A*

**Characteristics predisposing individuals to adverse effects from statins include but are not limited to: multiple or serious comorbidities including impaired renal or hepatic function, history of previous statin intolerance or muscle disorders, unexplained ALT elevations >3 times upper level of normal, patient characteristics or concomitant use of drugs affecting statin metabolism, age >75 years*

Table 5. Primary Prevention of ASCVD of patients without diabetes mellitus [12]

Patient group	Management Recommendation	Evidence rating
Age ≥ 21 years, LDL-C ≥ 190 mg/dL	Use high-intensity statin unless contraindicated	*Class I, Level B*
	Achieve ≥ 50% reduction of LDL-C	*Class IIa, Level B*
	May consider LDL non-statin therapy to further reduce LDL-C levels	*Class IIB, Level C*
Age 40-75 years, LDL-C 70-189 mg/dL, estimated 10-year ASCVD risk ≥ 7.5 %	Moderate or high intensity statin	*Class I, level A*
Age 40-75 years, LDL-C 70-189 mg/dL, estimated 10-year ASCVD risk 5-7.4 %	Consider moderate intensity statin	*Class IIa, level B*
LDL-C <190 and • **Age < 40 years or > 75 years, or** • **10-year ASCVD risk < 5%**	Statin therapy may be considered in select individuals	*Class IIb, level C*

Table 6. Primary Prevention of ASCVD of patients with diabetes mellitus [12]

Patient group	Management Recommendation	Evidence rating
Age 40-75 years, with diabetes, estimated 10-year ASCVD risk < 7.5 %	Moderate intensity statin	*Class I, level A*
Age 40-75 years, with diabetes, estimated 10-year ASCVD risk ≥ 7.5 %	Consider high intensity statin	*Class IIa, level B*
• **Age < 40 years with diabetes** • **Age > 75 years, or** • **LDL-C < 70mg/dL**	Evaluate potential for ASCVD benefits and for adverse effects and drug-drug interactions and consider patient preferences prior to initiating/continuing/intensifying statin therapy	*Class IIa, level C*

Patients with diabetes should be encouraged to adhere to heart-healthy lifestyle to prevent ASCVD. (Class I, Level B)

Primary Prevention of ASCVD of patients with chronic kidney disease who are not on dialysis (CKD)

For CKD patients who are not on dialysis, it is recommended to follow lipid-lowering recommendations outlined above in **Table 5. Primary Prevention of ASCVD of patients without diabetes mellitus.**

- Lipid-lowering therapy should not be *routinely* initiated in patients on chronic hemodialysis, however initiation of statins or statin/ezetimibe combination should be *personalized*, based on the patient's ASCVD risk, lipid levels, life expectancy, and expected time to transplant, if the patient is a candidate.[20,31] *(UW Health High level quality of evidence, strong recommendation)*
- In patients already receiving statin or statin/ezetimibe combination at the time of dialysis initiation, these agents may be continued.[31] *(KDIGO 2C)*

Statin therapy monitoring

It is very important to monitor lipid profiles after starting statin therapy to assure response to therapy (% reduction in LDL-C and optional targets) and to assure compliance.[22] *It is a common and incorrect perception that repeated lipid profiles are unnecessary with statin therapy.* Verification of on-treatment effect is an essential part of monitoring statin therapy success. The magnitude of anticipated effect depends on the potency of therapy; a 30-50% reduction of LDCL-C is optimal for moderate intensity therapy whereas a ≥ 50% reduction is the goal for high-intensity therapy.

- To ensure response to therapy and assess compliance, re-check the lipid profile 4-12 weeks after statin initiation or with any change in therapy.[22] *(Class I, Level A)*
- Once a stable dose and response have been established, monitoring frequency may be reduced to yearly.[20] *(UW Health Low quality of evidence, weak/conditional recommendation)*
- Routinely monitoring hepatic function with ALT levels or muscle injury with CK levels is not recommended unless patient is symptomatic.[22] *(Class IIa, Level C)*

Management of patients unable to tolerate intensity of statin therapy

For inpatients who complain of statin myalgia, rule out rhabdomyolysis (severe muscle weakness, dark urine, signs or symptoms of renal dysfunction with high CK level). *(UW Health Moderate quality of evidence, weak/conditional recommendation)* Routine measurement of CK levels is not necessary unless clinically the suspicion of rhabdomyolysis is high.[22,24,25] *(Class IIa, Level C)*

Most myalgias on statins are due to other causes: excessive exercise, alcohol use, hypothyroidism, certain medications, injuries, anxiety, possible vitamin D deficiency, metabolic or primary muscle disorders, etc. or a nocebo effect.[22,25]

For patients unable to tolerate the recommended intensity of statin therapy due to muscle or other symptoms, establish their relationship to statin therapy by the following:[22] *(Class IIa, Level B)*

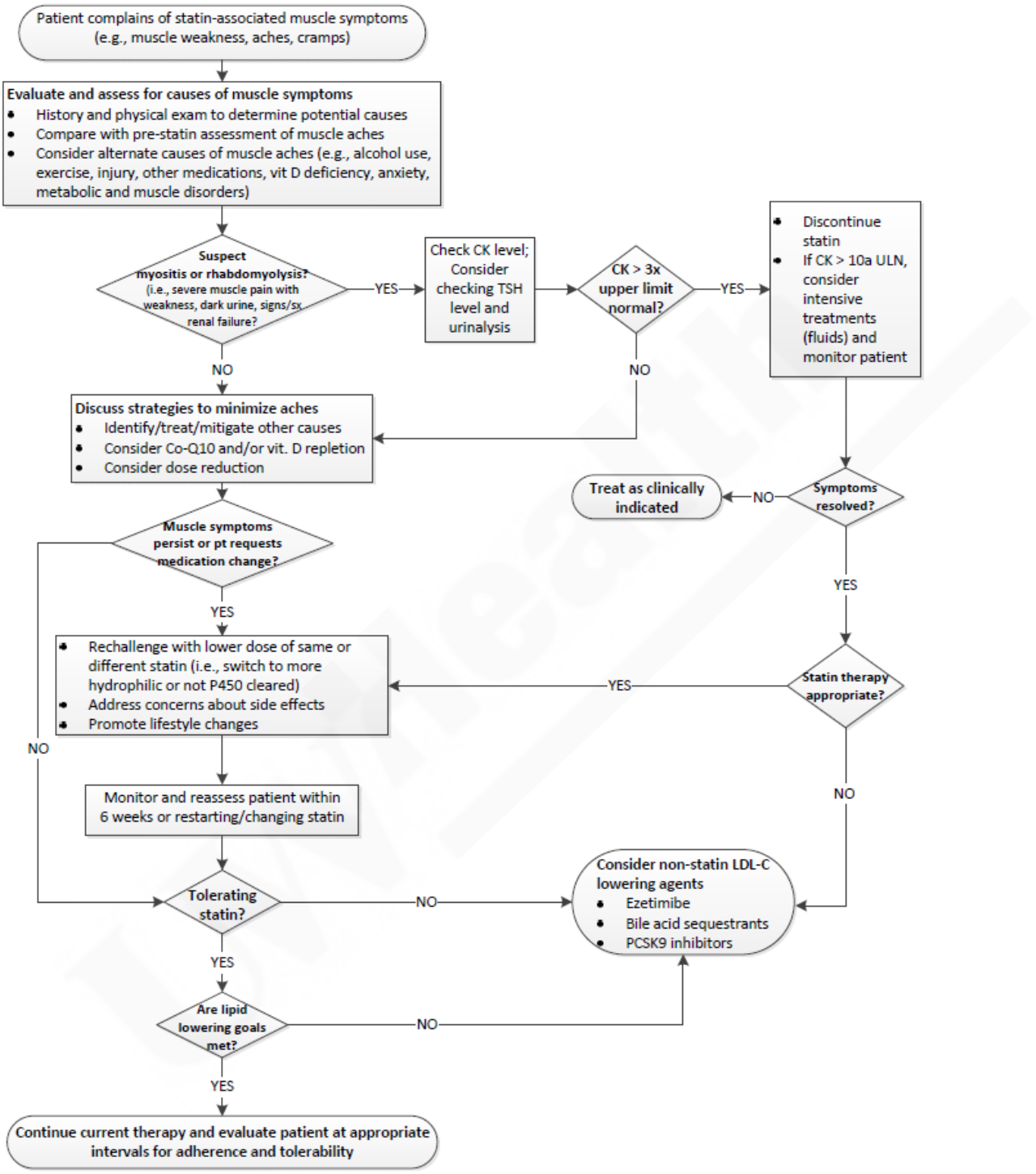
- Discontinue or reduce the dose of the statin if muscle or other symptoms develop during statin therapy
- Once mild to moderate muscle or other symptoms resolve, rechallenge with same dose of statin or lower; if muscle symptoms recur, discontinue statin and rechallenge with progressively lower doses of same drug or with different statin
- If muscle symptoms persist > 2 months after statin discontinuation, consider other conditions that may increase risk for muscle symptoms.

Strategies for managing statin related muscle symptoms include:[20,23-25]

- Dose reductions
- Alternative dosing schedules (e.g., low-dose atorvastatin or rosuvastatin twice-weekly may be tolerated and effective)
- Switching to a hydrophilic statin (i.e., rosuvastatin, pravastatin)
- Switching to a statin which is less likely to be affected by CYP3A4 drug interactions (i.e., rosuvastatin, pravastatin, fluvastatin, pitavastatin)[25] from a statin affected by CYP3A4 clearance (i.e., lovastatin, simvastatin, atorvastatin).

For an overview on how to manage statin-related muscle symptoms, see Figure 1. *(UW Moderate quality of evidence, weak/conditional recommendation)*

Figure 1. Management of statin related muscle symptoms[20,23-25]



Some patients find that coenzyme Q10 supplementation (100-200 mg twice a day) alleviates muscle aches, though this has not been proven in clinical trials.[24] Some recommend screening for low vitamin D status and repleting vitamin D before attributing muscle aches to statins.[23,24]

Non-statin lipid-lowering drug therapies

These medications should be considered for patients who have not achieved their target LDL-C reduction (30-49% for moderate intensity; ≥50% for high-intensity statin), or have not met optimal LDL-C targets (<100 mg/dL for primary ASCVD prevention, < 70 mg/dL for secondary ASCVD prevention) and non-HDL-C targets (<130 mg/dL for primary ASCVD prevention, < 100 mg/dL for secondary ASCVD prevention) after medication compliance has been assured, lifestyle efforts to improve lipids have been intensified, and typically, maximally tolerated statin dose has been achieved.[19]

Prior to initiating or considering non-statin therapy, a patient-provider discussion should focus on management of other ASCVD risk factors, expected ASCVD event reduction, potential drug interactions, adverse drug effects and costs. *(Class IIa, Level C)*

Ezetimibe

Ezetimibe (10 mg daily) is a selective inhibitor of intestinal cholesterol absorption and is very well tolerated. In the IMPROVE-IT, SHARP, and SEAS studies, ezetimibe in conjunction with a statin reduced ASCVD events more than statin therapy alone.[32-34] It typically leads to LDL-C reductions of 15-20%.[35] Considerations which may favor ezetimibe as the initial choice for add-on therapy to a statin include:[19]

- patients who require <25% additional lowering of LDL-C
- patients with recent ACS <3 months
- cost considerations with availability of generic ezetimibe and future cost savings
- ease of use as oral agent with low pill burden
- patient preferences, and
- $\geq$ 2 of the following: heart failure, hypertension, age >75 years, diabetes mellitus, stroke, CABG, PAD, eGFR <60 ml/min/1.73 m^2, and smoking.

Other factors that may indicate a need for more aggressive lipid-lowering include Metabolic Syndrome, elevated coronary artery calcification burden, high Lp(a), and high hsCRP.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

The FDA has approved 2 fully human monoclonal antibodies that bind to PCSK9 near its catalytic site and inhibit binding of PCSK9 to the LDL receptor thus increasing LDL receptor density. These drugs are: alirocumab (dosing 75-150 mg subcutaneously [SQ] every 2 weeks or 300 mg SQ monthly) and evolocumab (dosing 140 mg SQ every 2 weeks or 420 mg SQ monthly). [19]

Both agents were approved as an adjunct to diet and maximally tolerated statin therapy for treatment of adults with heterozygous FH or patients with clinical ASCVD who require additional lowering of LDL-C.[19] These agents dramatically reduce LDL-C levels by 50-60% above statin therapy, with favorable short term safety and ASCVD outcomes reductions over 1 to 2 years. A meta-analysis and the FOURIER trial demonstrated the benefit of evolocumab in patients with clinical ASCVD and at least 1 major risk factor (age ≥65 years, prior MI or non-hemorrhagic stroke, current daily cigarette smoking, symptomatic PAD with prior MI or stroke) or 2 minor risk factors (history of non-MI-related coronary revascularization, residual coronary artery disease with ≥40% stenosis in ≥2 large vessels, HDL-C <40 mg/dL for men and <50 mg/dL for women, hsCRP >2 mg/L, or metabolic syndrome).[22,36,37]

Bile Acid Binding Resins

Bile acid binding resins/bile acid sequestrants are second line agents for treating elevated LDL-C levels in people who are not willing or unable to take ezetimibe. Although they reduce ASCVD events, they have significant side effects including constipation, deficiencies of fat soluble vitamins, alterations in the binding of other medications, and tend to be very expensive.[29] They are associated with increases in triglycerides and should not be used in individuals with TGs over 200-300 mg/dL. Colesevelam is a pill form that is better tolerated and less likely to bind other medications (i.e., does not bind to digoxin, warfarin, or statins.)[30] It additionally lowers glycosylated hemoglobin by 0.3-0.5%, but 6 pills a day present a compliance barrier and it often is not covered by insurance.[38]

Niacin (Nicotinic Acid)

Niacin is a third line agent for treatment of high cholesterol or high triglycerides but is no longer used regularly because of its side effect profile, which includes severe flushing and itching in most patients requiring co-administration of aspirin or nonsteroidal anti-inflammatory drugs.[30] It also causes hyperglycemia, liver function abnormalities, gastric ulcers, hyperuricemia and increases the risk of myalgias. Importantly, in the era of statin use, it has not been demonstrated to reduce cardiovascular risk when used in combination with statins, although an older study showed that it can reduce cardiovascular disease risk as monotherapy.[19] It previously was used to raise HDL-C levels; however HDL-C cholesterol level is not a primary target of lipid-lowering therapy. In general, this medication is avoided.[29] Typically doses $\geq$ 2000 mg a day need to be used to lower LDL-C effectively, although lower doses may affect triglycerides and HDL-C.[29]

Fibric Acid Derivatives

These medications primarily are used in individuals with very high triglycerides to prevent pancreatitis although they can be useful in individuals with combined dyslipidemia who have high triglycerides and low HDL-C to reduce ASCVD risk. Gemfibrozil (600 mg twice daily) and fenofibrate (multiple doses, typically used at the 160-201mg daily dose but lower doses can be effective too) will reduce triglycerides by 30-50%, but in most patients LDL-C will increase.[35] These medications can cause abdominal discomfort and gallstones as well as increases in serum creatinine that are due to reduced tubular secretion rather than impaired filtration.[30] In conjunction with statins they increase the risk of myalgia and rhabdomyolysis although this risk is less with fenofibrate than gemfibrozil.[30]

Omega-3 Fatty Acids

Available as a dietary supplement or by prescription, 3-4 grams daily of docosahexaenoic acid (DHA) with eicosapentaenoic acid (EPA) can be used to lower TGs in individuals with very high triglycerides levels who are at risk for pancreatitis.[29] Other omega-3 fatty acids such as alpha linolenic acid have much less of an effect on the lipid profile. Use of these medications is limited by lack of evidence for ASCVD risk reduction, high pill burden, bruising, belching, abdominal discomfort, and the potential to raise blood sugar.[29,30] Clinical trials looking at the efficacy of omega-3 fatty acids for reducing ASCVD risk are ongoing.

Table 7. Non-Statin Lipid Lowering Drug Therapies[19,29,30,35,39]

Drug/ Drug class	Mechanism of Action[30]	Place in therapy	Maintenance Dosing	Comments
Ezetimibe	selective inhibitor of intestinal cholesterol absorption	Adjunct to statin therapy	10 mg daily	• Generally well tolerated • Generic and brand formulations available • Not metabolized by P450 enzymes
PCSK9 inhibitors	Humanized antibody to PCSK9; inhibits binding of PCSK9 to LDL receptor and increases LDL receptor density	Adjunct to diet and max tolerated statin therapy for adults with heterozygous FH or with clinical ASCVD who require additional lowering of LDL-C	Evolocumab: 140 mg every 2 weeks or 420 mg once monthly Alirocumab: 75-150 mg every 2 weeks or 300 mg monthly	• Require refrigeration for storage but may be stored at room temperature if used within 30 days
Bile acid resins	Binds bile acid in terminal ileum and prevents reabsorption	Used to treat elevated LDL-C levels in people unable or not willing to take ezetimibe	Colestipol: 5-30 grams/day in 1-2 divided doses Colesevelam: 3.75 g daily in 1-2 divided doses Cholestyramine: 4-24 grams daily in divided doses	• Constipation and bloating common side effects which may be relieved by increasing dietary fiber • May impair absorption of certain drugs (e.g., warfarin, aspiring, ezetimibe, pravastatin, fluvastatin)
Niacin	Inhibits very low density lipoprotein (VLDL) secretion, and HDL degradation	Used to increase HDL-C however not used often since HDL-C is not a target of therapy	1-3.5 grams daily	• Causes vasodilation and flushing, requiring co-administration of aspirin or NSAID to mitigate effect • Also worsens insulin resistance, may cause gout, gastric ulcers, and transaminase elevations
Fibric acid derivatives	Decreases VLD production and increases clearance	Adults with very high triglycerides to prevent pancreatitis; may be used in adults with combined dyslipidemia with high triglycerides and low HDL-C to reduce ASCVD risk.	Gemfibrozil: 600 mg twice daily Fenofibrate: 43-200 mg daily	• Increased risk of myopathy when used with statins (fenofibrate preferred with statin use) • Increased risk of cholesterol gallstones • Can potentiate effect of anticoagulants
Omega-3 fatty acids	Reduces hepatic production of triglycerides and VLDL	Used in adults with very high triglycerides to prevent pancreatitis	2-4 grams of EPA+DHA daily	• Does not increase risk of myopathy when used with statin however may increase liver enzymes • Common side effect is belching • Can be stored in freezer to reduce belching

Table 8. General Sequence of Lipid Therapy Based on Lipid Pattern with Lifestyle Changes

Medication Sequence	Lipid Pattern		
	TG < 200 mg/dL	TG 200-499 mg/dL	TG ≥500 mg/dL
First	**Statin**	**Statin**	**Fibrate**
Second	Add ezetimibe (consider bile acid resin)	Add ezetimibe	Add Omega-3 fatty acids/fish oil
Third	Add PCSK9 inhibitor	Add PCSK9 inhibitor	Add niacin or statin
Fourth	*Consider:* Bile acid resin, niacin, lomitapide*, mipomersen*, LDL apheresis	*Consider:* niacin, lomitapide*, LDL apheresis	*Consider:* niacin, lomitapide*, plasmapheresis

*__Note__: Lomitapide and mipomersen are FDA-indicated for homozygous FH and only available through certified pharmacies enrolled in each drug's respective Risk Evaluation and Mitigation Strategy (REMS) program.

Referral to Preventive Cardiology

Referral to the UW Preventive Cardiology Clinic is appropriate for patients with severe hypercholesterolemia that is not responsive to statin therapy or with hypertriglyceridemia not responsive to therapy with fibrates. *(UW Health Very low quality of evidence, strong recommendation)*

Referral is not necessary for isolated elevations of LDL-C (>190 mg/dL) unless the elevation has been *confirmed and treatment with a statin attempted*. Patients with a strong family history of premature heart disease and multiple risk factors, especially dyslipidemia in conjunction with hypertension and/or a family history of premature heart disease are especially appropriate for referral, as are patients with dyslipidemia refractory to standard medical therapy. This clinic is *not appropriate for patients whose main issue is obesity and looking for a weight loss resource*.

The Preventive Cardiology Ancillary Services are available without a MD consultation and include nutrition, exercise prescription, risk reduction counseling, and cardiac rehabilitation. Those services can be ordered via UW HealthLink by consulting preventive cardiology-ancillary services, inside UW, then selecting the service needed.

Disclaimer

Clinical practice guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This guideline outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

Methodology

Development Process

Each guideline is reviewed and updated a minimum of every 3 years. All guidelines are developed using the guiding principles, standard processes, and styling outlined in the UW Health Clinical Practice Guideline Resource Guide. This includes expectations for workgroup composition and recruitment strategies, disclosure and management of conflict of interest for participating workgroup members, literature review techniques, evidence grading resources, required approval bodies, and suggestions for communication and implementation.

Methods Used to Collect the Evidence:

The following criteria were used by the guideline author(s) and workgroup members to conduct electronic database searches in the collection of evidence for review.

Literature Sources:

- Electronic database search (e.g., PubMed)
- Databases of systematic reviews (e.g., Cochrane Library)
- Hand-searching journals, external guidelines, and conference publications

Time Period: December 2017 to February 2018

The following is a list of various search terms that were used individually or in combination with each other for literature searches on PubMed: ASCVD, familial hypercholesterolemia, coronary calcium score, lipid, statin, non-statin, ACC/AHA guideline.

Methods to Select the Evidence:

Literary sources were selected with the following criteria in thought: English language, subject age (i.e., age ≥17 years), publication in a MEDLINE core clinical journal and strength of expert opinion (e.g., professional society guideline).

Methods Used to Formulate the Recommendations:

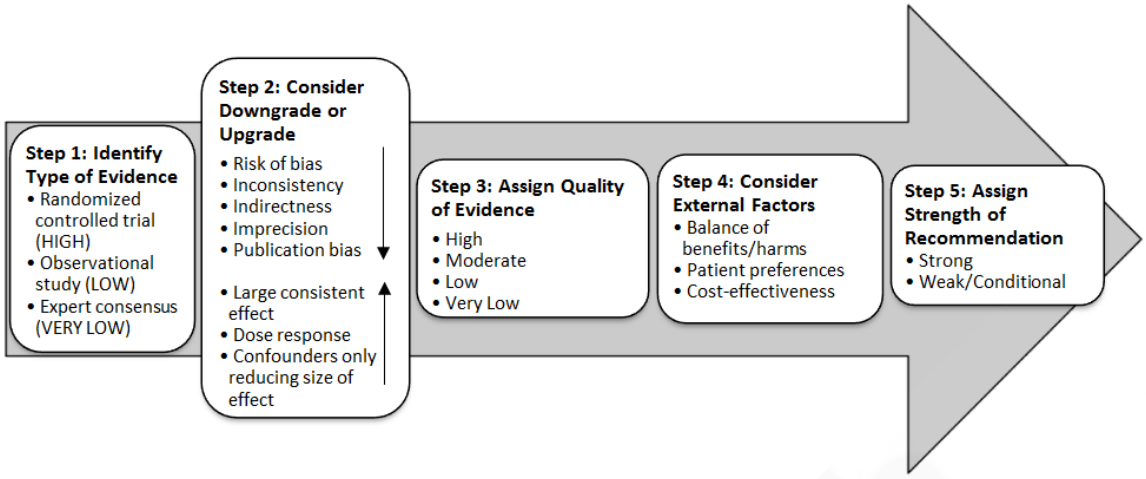
The workgroup members agreed to adopt recommendations developed by external organizations and/or created recommendations internally via a consensus process using discussion of the literature and expert experience/opinion. If issues or controversies arose where consensus could not be reached, the topic was escalated appropriately per the guiding principles outlined in the UW Health Clinical Practice Guideline Resource Guide.

Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations:

Recommendations developed by external organizations maintained the evidence grade assigned within the original source document and were adopted for use at UW Health.

Internally developed recommendations, or those adopted from external sources without an assigned evidence grade, were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see **Figure 1**).

Figure 1. GRADE Methodology adapted by UW Health



Rating Scheme for the Strength of the Evidence/Recommendations:

GRADE Ranking of Evidence

High	We are confident that the effect in the study reflects the actual effect.
Moderate	We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.
Low	The true effect may differ significantly from the estimate.
Very Low	The true effect is likely to be substantially different from the estimated effect.

GRADE Ratings for Recommendations For or Against Practice

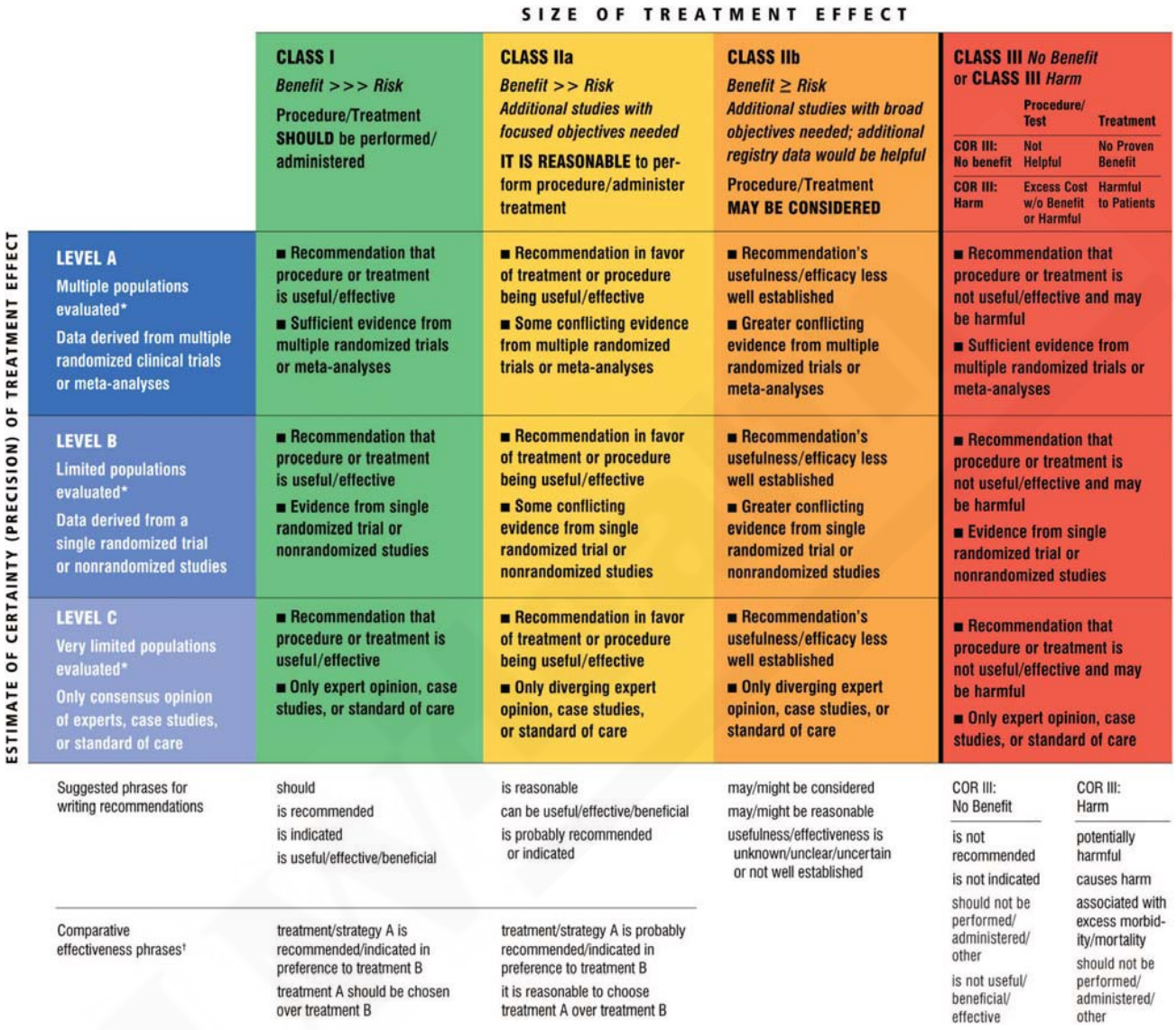
Strong	The net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.
Weak/conditional	Recommendation may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.

National Heart, Lung, and Blood Institute (NHLBI) Grading Scheme

Grade	Strength of Recommendation
A	**Strong recommendation:** There is high certainty based on evidence that the net benefit† is substantial.
B	**Moderate recommendation:** There is moderate certainty based on evidence that the net benefit is moderate to substantial, or there is high certainty that the net benefit is moderate.
C	**Weak recommendation:** There is at least moderate certainty based on evidence that there is a small net benefit.
D	**Recommendation against:** There is at least moderate certainty based on evidence that it has no net benefit or that risks/harms outweigh benefits.
E	**Expert opinion ("There is insufficient evidence or evidence is unclear or conflicting, but this is what the Work Group recommends.")** Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, but the Work Group thought it was important to provide clinical guidance and make a recommendation. Further research is recommended in this area.
N	**No recommendation for or against ("There is insufficient evidence or evidence is unclear or conflicting.")** Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, and the Work Group thought no recommendation should be made. Further research is recommended in this area

*In most cases, the strength of the recommendation should be closely aligned with the quality of the evidence; however, under some circumstances, there may be valid reasons for making recommendations that are not closely aligned with the quality of the evidence (e.g., strong recommendation when the evidence quality is moderate, like smoking cessation to reduce CVD risk or ordering an ECG as part of the initial diagnostic work-up for a patient presenting with possible MI). Those situations should be limited and the rationale explained clearly by the Work Group.
†Net benefit is defined as benefits minus risks/harms of the service/intervention

ACC/AHA Rating



SIZE OF TREATMENT EFFECT

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT

	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/Test / Treatment COR III: No benefit — Not Helpful / No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful / Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

GRADE Methodology adapted by Kidney Disease Improving Global Outcomes (KDIGO)

Implications			
Grade	**Patients**	**Clinicians**	**Policy**
Level 1 **"We recommend"**	Most people in your situation would want the recommended course of action and only a small proportion would not	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 **"We suggest"**	The majority of people in your situation would want the recommended course of action, but many would not.	Difference choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

Grade	Quality of Evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often will be far from the truth.

Recognition of Potential Health Care Disparities: None identified.

Collateral Tools & Resources

The following collateral tools and resources support staff execution and performance of the evidence-based guideline recommendations in everyday clinical practice.

Metrics

The following performance metrics are obtained for either accreditation purposes or due to participation in a quality program (i.e., Wisconsin Collaborative for Healthcare Quality.)

Domain	Metric Description
At Risk Population - Coronary Artery Disease	Coronary Artery Disease (CAD) Composite: All or Nothing Scoring: Drug Therapy for Lowering LDL-Cholesterol
At Risk Population - Ischemic Vascular Disease	Ischemic Vascular Disease (IVD): Complete Lipid Panel and LDL Control (<100 mg/dL)
At Risk Population - Ischemic Vascular Disease	Statin use for patients ages 18 through 75 years with IVD unless contraindicated
At Risk Population – Diabetes Mellitus	Statin use for patients ages 18 to 75 years with Diabetes Mellitus unless contraindicated
Stroke National Hospital Inpatient Quality Measures	Ischemic stroke patients with LDL greater than or equal to 100 mg/dL, or LDL not measured, or who were on a lipid-lowering medication prior to hospital arrival are prescribed statin medication at hospital discharge.

Related Guidelines

Prevention and Management of Obesity – Adult – Ambulatory
Chronic Kidney Disease: Diagnosis and Management – Adult – Ambulatory
Preventive Health Care – Adult/Pediatric – Ambulatory
Standards of Medical Care in Diabetes – Adult/Pediatric – Inpatient/Ambulatory

Patient Resources

1. HFFY #519: Food Guidelines to Reduce LDL Cholesterol and Triglycerides
2. HFFY #5419: Heart Healthy Living for Women
3. HFFY #5668: A Health Guide for Women 50 or Older
4. HFFY #5669: A Health Guide for Men 50 or Older
5. HFFY #6196: Improving Your Lipid (Cholesterol) Level
6. HFFY #6419: A Health Guide for Men 50 or Older
7. HFFY #7466: Familial Hypercholesterolemia (FH) in Children
8. HFFY #7617: My Child's Lipoprotein (a) Level
9. HFFY #7739: Your Risk of Heart and Vascular Disease
10. HFFY #7979 Getting Ready for your Fasting Blood Draw
11. Healthwise: Cholesterol and Triglycerides Tests
12. Healthwise: Cholesterol and Triglycerides Tests: Pediatric
13. Healthwise: Cholesterol and Triglycerides Tests: Teen
14. Healthwise: Well Visit: 18 to 50 Years
15. Healthwise: Well Visit: 50 to 65 Year Men
16. Healthwise: Well Visit: 50 to 65 Year Women
17. Healthwise: Well Visit: Over 65 Years
18. Health Information: Cholesterol in Children and Teens
19. Health Information: Lipid Panel

Smartset
Hyperlipidemia [87]

Protocols
Laboratory Screening and Chronic Disease Monitoring Laboratory Test Ordering in Primary Care – Adult/Pediatric – Ambulatory [93]
Primary Care Lipid Management for Prevention of Atherosclerotic Cardiovascular Disease – Adult – Ambulatory [163]
Diabetes Lab Ordering – Adult – Ambulatory [21]

References

1. Amsterdam E, Blumenthal R, Wong N. *ASPC Manual of Preventive Cardiology.* New York, UNITED STATES: Demos Medical Publishing; 2014.
2. Yousuf O, Mohanty BD, Martin SS, et al. High-sensitivity C-reactive protein and cardiovascular disease: a resolute belief or an elusive link? *J Am Coll Cardiol.* 2013;62(5):397-408.
3. Erqou S, Kaptoge S, Perry PL, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *Jama.* 2009;302(4):412-423.
4. McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation.* 2006;113(1):30-37.
5. Mehta PK, Wei J, Wenger NK. Ischemic Heart Disease in Women: A Focus on Risk Factors. *Trends in cardiovascular medicine.* 2015;25(2):140-151.
6. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J.* 2016;37(29):2315-2381.
7. Bamba V. Update on Screening, Etiology, and Treatment of Dyslipidemia in Children. *J Clin Endocrinol Metab.* 2014:jc20133860.
8. Adolescents EPoIGfCHaRRiCa, National Heart Ln, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics.* 2011;128 Suppl 5:S213-256.
9. National Cholesterol Education Program (NCEP) Expert Panel on Detection Ea, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation.* 2002;106(25):3143-3421.
10. Helfand M, Carson S. Screening for Lipid Disorders in Adults: Selective Update of 2001 US Preventive Services Task Force Review. In. *Evidence Syntheses, No. 49*. Rockville, MD: Agency for Healthcare Research and Quality; 2008.
11. Elshazly MB, Martin SS, Blaha MJ, et al. Non-high-density lipoprotein cholesterol, guideline targets, and population percentiles for secondary prevention in 1.3 million adults: the VLDL-2 study (very large database of lipids). *J Am Coll Cardiol.* 2013;62(21):1960-1965.
12. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;63(25 Pt B):2960-2984.
13. Jenkins DJ, Kendall CW, Marchie A, et al. Effects of a dietary portfolio of cholesterol-lowering foods vs lovastatin on serum lipids and C-reactive protein. *Jama.* 2003;290(4):502-510.
14. Rosenthal RL. Effectiveness of altering serum cholesterol levels without drugs. *Proceedings (Baylor University Medical Center).* 2000;13(4):351-355.
15. Van Horn L, Carson JA, Appel LJ, et al. Recommended Dietary Pattern to Achieve Adherence to the American Heart Association/American College of Cardiology (AHA/ACC) Guidelines: A Scientific Statement From the American Heart Association. *Circulation.* 2016;134(22):e505-e529.
16. National Heart L, and Blood Institute. Your Guide to Lowering Your Cholesterol with TLC. In: Services USDoHaH, ed. Bethesda, MD: National Heart, Lung and Blood Institute; 2005.
17. Fung TT, Hu FB, Wu K, Chiuve SE, Fuchs CS, Giovannucci E. The Mediterranean and Dietary Approaches to Stop Hypertension (DASH) diets and colorectal cancer. *The American Journal of Clinical Nutrition.* 2010;92(6):1429-1435.
18. Sacks FM, Lichtenstein AH, Wu JHY, et al. Dietary Fats and Cardiovascular Disease: A Presidential Advisory From the American Heart Association. *Circulation.* 2017;136(3):e1-e23.
19. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American

College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol.* 2017;70(14):1785-1822.
20. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;63(25 Pt B):2889-2934.
21. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet.* 2016;388(10059):2532-2561.
22. Stone NJ, Robinson JG, Lichtenstein AH, et al. Treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: synopsis of the 2013 American College of Cardiology/American Heart Association cholesterol guideline. *Ann Intern Med.* 2014;160(5):339-343.
23. Saxon DR, Eckel RH. Statin Intolerance: A Literature Review and Management Strategies. *Prog Cardiovasc Dis.* 2016;59(2):153-164.
24. Rosenson RS, Baker S, Banach M, et al. Optimizing Cholesterol Treatment in Patients With Muscle Complaints. *J Am Coll Cardiol.* 2017;70(10):1290-1301.
25. Vandenberg BF, Robinson J. Management of the Patient with Statin Intolerance. *Current Atherosclerosis Reports.* 2010;12(1):48-57.
26. Safarova MS, Kullo IJ. My Approach to the Patient With Familial Hypercholesterolemia. *Mayo Clin Proc.* 2016;91(6):770-786.
27. Robinson JG. Management of Familial Hypercholesterolemia: A Review of the Recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *Journal of Managed Care Pharmacy.* 2013;19(2):139-149.
28. Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. *Fundam Clin Pharmacol.* 2005;19(1):117-125.
29. McEvoy G, Snow EK, American Society of Health-System P. *AHFS Drug Information 2017.* Bethesda, MD: American Society of Health System Pharmacists; 2017.
30. Katzung BG. *Basic & clinical pharmacology.* 2018.
31. Group. KDIGOKCW. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl.* 2013;3(1):1-150.
32. Giugliano RP, Cannon CP, Blazing MA, et al. Benefit of Adding Ezetimibe to Statin Therapy on Cardiovascular Outcomes and Safety in Patients With vs. Without Diabetes: Results from IMPROVE-IT. *Circulation.* 2017.
33. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet.* 2011;377(9784):2181-2192.
34. Rossebo AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med.* 2008;359(13):1343-1356.
35. Sando KR, Knight M. Nonstatin therapies for management of dyslipidemia: a review. *Clin Ther.* 2015;37(10):2153-2179.
36. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med.* 2017;376(18):1713-1722.
37. Karatasakis A, Danek BA, Karacsonyi J, et al. Effect of PCSK9 Inhibitors on Clinical Outcomes in Patients With Hypercholesterolemia: A Meta-Analysis of 35 Randomized Controlled Trials. *J Am Heart Assoc.* 2017;6(12).
38. Handelsman Y. Role of bile acid sequestrants in the treatment of type 2 diabetes. *Diabetes Care.* 2011;34 Suppl 2:S244-250.
39. Koski RR. Omega-3-acid Ethyl Esters (Lovaza) For Severe Hypertriglyceridemia. *Pharmacy and Therapeutics.* 2008;33(5):271-303.