

Cholesterol and Cardiovascular Risk

Clinician Guide

August 2018

Introduction This Clinician Guide was developed to assist primary care physicians and other clinicians in the outpatient management of cholesterol for primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD). KP National Cholesterol and Cardiovascular Risk Guideline adopted the 2013 recommendations developed by the American College of Cardiology Foundation (ACC)/American Heart Association (AHA), with minor modifications. It is not intended or designed as a substitute for the reasonable exercise of independent clinical judgment by practitioners.

Definitions

- ▶ Clinical atherosclerotic cardiovascular disease (ASCVD) includes acute coronary syndromes, history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, carotid stenosis $\geq 50\%$, or symptomatic peripheral arterial disease presumed to be of atherosclerotic origin.
- ▶ Subclinical ASCVD includes asymptomatic coronary artery disease (e.g. abnormal coronary calcium score, non-obstructive CAD on coronary angiography), or peripheral artery disease (e.g. aortic atherosclerosis or abnormal ankle brachial index (ABI) detected on screening).
- ▶ 10-year ASCVD Risk is risk of fatal or nonfatal myocardial infarctions or strokes in adults. A region may choose which tool (and corresponding cut-point) to use for calculating 10-year ASCVD risk based on regional needs. Kaiser Permanente ASCVD Risk Estimator (KPARE) of 10% correlates approximately with ACC/AHA ASCVD Risk of 15% and Framingham Risk Score of 15% (used in SPRINT) at the population level.

Key Points

- ▶ For all adults, encourage a heart-healthy lifestyle to reduce the risk of ASCVD. This includes regular physical activity, weight reduction and maintenance, smoking cessation, and controlling blood pressure and diabetes.
- ▶ Focus on treatment of blood cholesterol to reduce ASCVD risk in adults.
- ▶ Identify adults most likely to benefit from cholesterol-lowering therapy, i.e., those in the 4 statin benefit groups.
- ▶ Identify and address safety issues related to cholesterol treatment options.

Cholesterol Treatment

Four Statin Benefit Groups

- ▶ Recommend statin therapy for adults in risk groups for which a demonstrated ASCVD risk reduction benefit has been shown to outweigh the risks. See Table 1 for the 4 groups in which statins have been shown to reduce ASCVD.
- ▶ There is no recommendation for or against specific LDL-C or non-HDL-C targets for the primary or secondary prevention of ASCVD.

- ▶ There is no recommendation for or against the initiation or discontinuation of statins in patients with NYHA class II-IV ischemic systolic heart failure or in patients on maintenance hemodialysis.
- ▶ There is no recommendation for or against the initiation or discontinuation of statins in patients with abdominal aortic aneurysm (AAA) in the absence of other significant cardiovascular risk factors or without elevated estimated 10-year ASCVD risk.

TABLE 1. FOUR STATIN BENEFIT GROUPS

Secondary Prevention	Adults with clinical ASCVD
Primary Prevention	Adults aged 21 and older with primary elevations of LCL-C \geq 190 mg/dl Adults with diabetes aged 40-75 years who have LDL-C 70 to 189 mg/dL Adults without diabetes aged 40-75 years with 10-year ASCVD risk \geq 7.5% and LDL-C 70 to 189 g/dL

Cholesterol Treatment Recommendations by Statin Benefit Group

SECONDARY PREVENTION

Adults with Clinical ASCVD

- ▶ **Aged \leq 75 years:** Initiate or continue a high-intensity statin as first-line therapy unless contraindicated.
 - If contraindicated or characteristics predisposing to statin-associated adverse effects are present, use a moderate-intensity statin as the second option if tolerated.
 - If unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity.
- ▶ **Aged $>$ 75 years:** Consider evaluating the potential ASCVD risk-reduction benefits, adverse effects, and drug-drug interactions and consider patient preferences when initiating a moderate- or high-intensity statin. Consider continuing statin therapy in those who are tolerating it.

PRIMARY PREVENTION

Aged \geq 21 Years with LDL-C \geq 190 mg/dL

- ▶ Evaluate for secondary causes of hyperlipidemia
- ▶ Initiate or continue high-intensity statin therapy unless contraindicated.
 - 10-year ASCVD risk estimation is not required.
 - If unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity.
- ▶ Consider intensifying statin therapy to achieve at least a 50% LDL-C reduction.
- ▶ After the maximum intensity of statin therapy has been achieved, consider addition of a nonstatin drug to further lower LDL-C. Evaluate the potential for ASCVD risk-reduction benefits, adverse effects, and drug-drug interactions, and consider patient preferences.

- Diabetes, Aged 40-75 Years, and LDL-C 70-189 mg/dL**
- ▶ Initiate or continue moderate-intensity statin therapy. Consider high-intensity statin therapy for adults with diabetes and 10-year ASCVD risk $\geq 7.5\%$.
 - ▶ If aged < 40 or > 75 years, consider evaluating the potential for ASCVD risk-reduction benefits, adverse effects, and drug-drug interactions, and consider patient preferences when deciding to initiate, continue, or intensify statin therapy.

- No Diabetes, Aged 40-75 Years, and LDL-C 70-189 mg/dL**
- ▶ For adults with 10-year ASCVD risk:
 - **$\geq 10\%$ (very elevated risk):**
Treat with a moderate- to high-intensity statin.
 - **7.5-9.9% (elevated risk):**
Consider treatment with a moderate- to high-intensity statin after a discussion of potential benefits, risks, and patient preferences for treatment.
 - **5.0-7.4% (slightly elevated risk):**
Consider offering treatment with a moderate-intensity statin after a discussion of potential benefits, risks, and patient preferences for treatment.

Cholesterol Treatment Recommendations by Statin Benefit Group

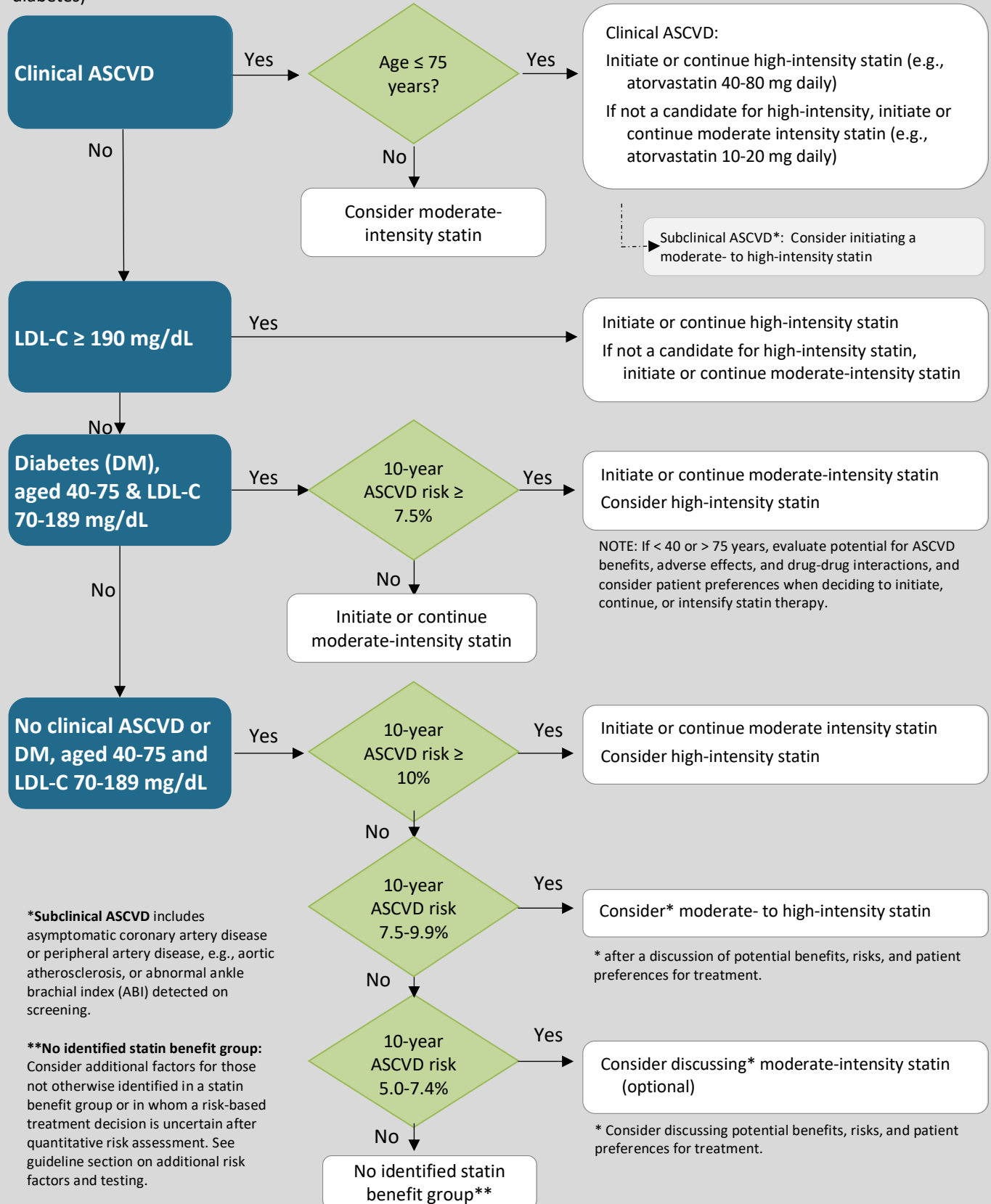
PRIMARY PREVENTION

- Subclinical ASCVD or No Identified Statin Benefit Group**
- ▶ In patients with asymptomatic (subclinical) noncoronary atherosclerosis (including asymptomatic peripheral arterial disease (PAD), carotid stenosis and aortic atherosclerosis), assess ASCVD risk and consider a moderate- to high-intensity statin to reduce the risk of developing symptomatic cardiovascular disease or cardiovascular disease progression.
 - ▶ Consider additional factors for those not otherwise identified in a statin benefit group or in whom a risk-based treatment decision is uncertain after quantitative risk assessment.
 - Additional risk factors include baseline LDL-C ≥ 160 mg/dL or other evidence of genetic hyperlipidemias, lifetime risk of ASCVD, family history of premature ASCVD with onset < 55 years in a first-degree male relative or < 65 years in a first-degree female relative, testing for high-sensitivity C-reactive protein (hsCRP), ankle-brachial index (ABI), or coronary artery calcium (CAC).
 - Order testing for additional risk factors only if the result will prompt a therapeutic decision and the clinician and patient agree to initiate statin therapy if the result is abnormal and to forgo statin therapy if the result is normal. Use shared decision making to discuss significant differences in convenience, cost, invasiveness, and radiation exposure.

FIGURE 1: ASCVD Statin Benefit Groups

Encourage a heart-healthy lifestyle to reduce the risk of ASCVD

(e.g., regular physical activity, weight reduction and maintenance, smoking cessation, and controlling blood pressure and diabetes)



Optimizing Statin Therapy

- ▶ Use the maximum tolerated intensity of statin in individuals for whom a high- or moderate-intensity statin is recommended but not tolerated.

Insufficient Response to Statin Therapy

- ▶ Focus on treatment of blood cholesterol to reduce ASCVD risk in adults.
- ▶ In individuals who have a less-than-anticipated therapeutic response or are intolerant of the recommended intensity of statin therapy:
 - Reinforce medication adherence;
 - Reinforce adherence to intensive lifestyle changes; and
 - Exclude secondary causes of hyperlipidemia.
- ▶ Consider using the following indicators of anticipated therapeutic response to the recommended intensity of statin therapy. Focus is on the intensity of the statin therapy. As an aid to monitoring:
 - High-intensity statin therapy generally results in an average LDL-C reduction of $\geq 50\%$ from the untreated baseline.
 - Moderate-intensity statin therapy generally results in an average LDL-C reduction of 30-50% from the untreated baseline.
 - LDL-C levels and percent reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards.
- ▶ In individuals at higher ASCVD risk receiving the maximum tolerated intensity of statin therapy who continue to have a less than-anticipated therapeutic response, consider adding a nonstatin cholesterol-lowering drug(s) if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. Higher-risk individuals include:
 - Those with clinical ASCVD ≤ 75 years of age.
 - Those with baseline LDL-C ≥ 190 mg/dL.
 - Those aged 40-75 years with diabetes mellitus.
- ▶ In individuals who are candidates for statin treatment but are completely statin intolerant, consider using nonstatin cholesterol lowering drugs that have been shown to reduce ASCVD events in RCTs (i.e., ezetimibe) if the ASCVD risk-reduction benefits outweigh the potential for adverse effects.
- ▶ Give preference to non-statin cholesterol-lowering drugs shown to reduce ASCVD events in RCTs (i.e., ezetimibe).
- ▶ In individuals with clinical ASCVD on maximum tolerated oral lipid-lowering therapy (statin, ezetimibe, +/- bile acid sequestrant) and with persistently elevated lipids (e.g., LDL ≥ 130 mg/dL), consider discussing adding PCSK9 inhibitor with a lipid specialist (i.e., designated lipid specialist, cardiologist, or endocrinologist).

Lipid Panel Screening and Risk Assessment

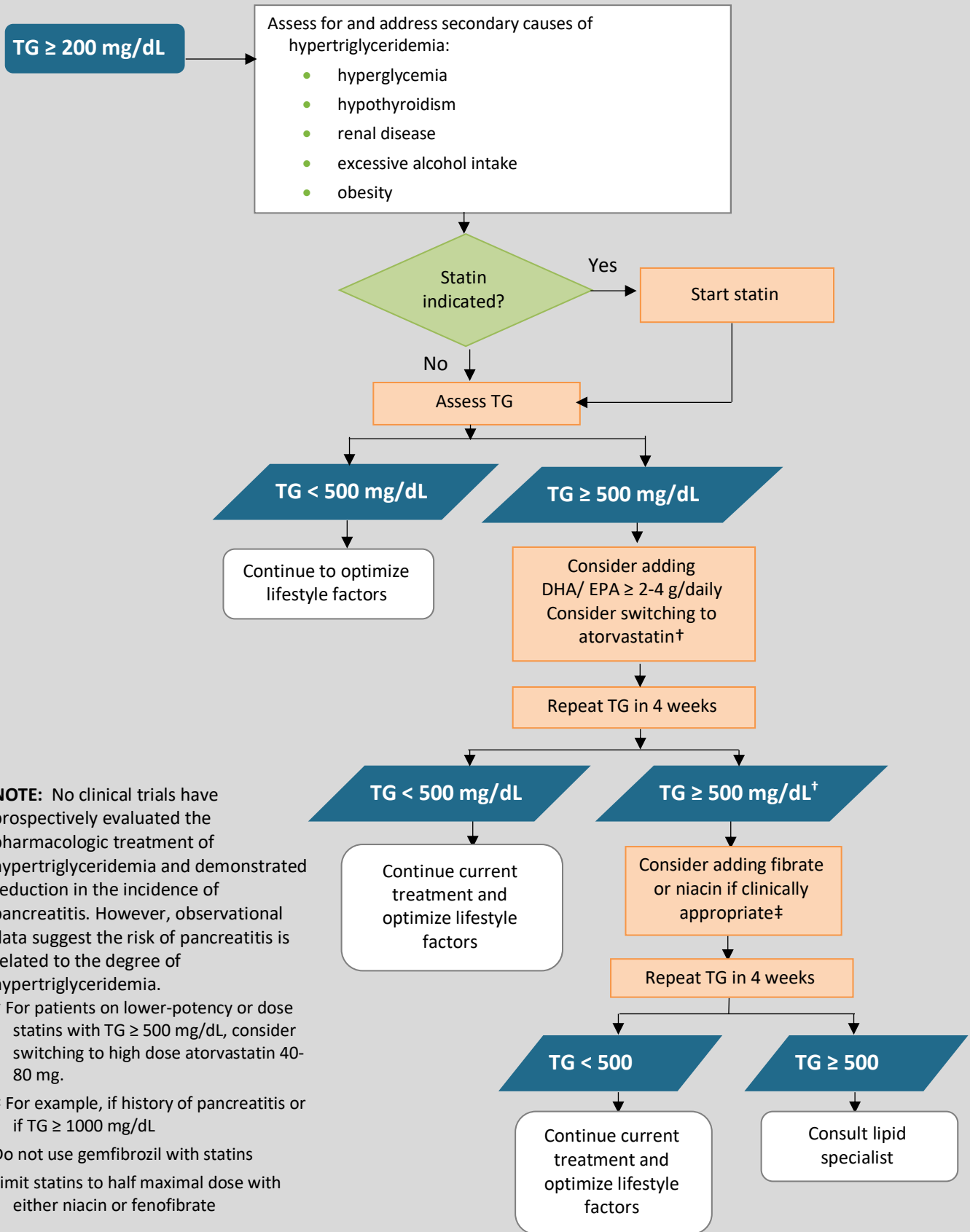
- ▶ In adults aged 20-39 years, consider a baseline lipid panel if not done previously or if previous result is not known. This facilitates discovery and treatment of LDL ≥ 190 mg/dL.
- ▶ In adults aged 40-75 years, consider a lipid panel at least every 5 years. This minimum applies to those with or without ASCVD, on or off treatment.
- ▶ Consider assessing 30-year or lifetime ASCVD risk based on traditional risk factors in adults aged 20-59 years without ASCVD and who are not at high short-term risk.

A risk calculator for this assessment is available at:

<http://tools.cardiosource.org/ASCVD-Risk-Estimator/>

- ▶ The contribution to risk assessment for a first ASCVD event of ApoB, CKD, albuminuria, or cardiorespiratory fitness is uncertain at present.
- ▶ Consider not ordering the Carotid Intima-Media Test (CIMT) for routine measurement in clinical practice for risk assessment for a first ASCVD event.

FIGURE 2: TRIGLYCERIDE (TG) TREATMENT ALGORITHM



- Triglyceride Treatment**
- ▶ There is evidence that elevated TG levels are independently associated with increased risk of atherosclerosis. However, not all people with high TG levels are at increased risk, and neither the threshold for initiation of therapy nor the goal of therapy is known. Although there is direct evidence that lowering LDL-C reduces the risk of CAD events, there are no clinical trials to demonstrate that reducing TG levels will reduce CAD events. There is expert opinion that a desirable TG level is <150 mg/dL, but there are no studies to support the benefit of obtaining this level.
 - ▶ When making treatment decisions, consider an individual's other lipid levels and nonlipid CAD risk factors. Although there is no direct evidence, there is consensus that TG ≥ 500 mg/dL warrants treatment to prevent pancreatitis. Specific recommendations for treating high TG levels are presented in the triglyceride algorithm (Figure 2).

Statin Safety Recommendations

- ▶ Women of childbearing potential
 - Statins are classified as pregnancy Category X and are contraindicated during pregnancy and lactation.
 - Discuss the potential risks to the fetus should pregnancy occur.
 - Discuss practicing effective contraceptive measures consistently while taking statins.
 - Advise women using statins to stop them and contact their OB/GYN provider immediately if they become pregnant.
 - In women planning a pregnancy, discontinue statins prior to conception.
- ▶ To maximize the safety of statins, select the appropriate statin and dose in men and non-pregnant/non-nursing women based on patient characteristics, level of ASCVD risk, and potential for adverse effects. ASCVD risk is based on the presence of clinical ASCVD, diabetes mellitus, LDL-C ≥ 190 mg/dL, or level of estimated 10-year ASCVD risk.
- ▶ Use moderate-intensity statin therapy in individuals in whom high-intensity statin therapy would otherwise be recommended when characteristics predisposing them to statin-associated adverse effects are present.
- ▶ Characteristics predisposing individuals to statin adverse effects 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 alanine aminotransferase (ALT) elevations > 3 times upper limit of normal (ULN)
 - Patient characteristics or concomitant use of drugs affecting statin metabolism
 - Age > 75 years
 - Additional characteristics that may modify the decision to use higher statin intensities may include but are not limited to:
 - History of hemorrhagic stroke
 - Asian ancestry
- ▶ Evaluate adults receiving statin therapy for new-onset diabetes mellitus according to current diabetes screening guidelines. Encourage those who develop diabetes mellitus during statin therapy to adhere to a heart-healthy dietary pattern, engage

in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events.

- ▶ For adults taking any dose of statins, consider using caution in those aged >75 years and in those taking concomitant medications that alter drug metabolism, multiple drugs, or drugs for conditions that require complex medication regimens (e.g., those who have undergone solid organ transplantation or are receiving treatment for HIV). A review of the manufacturer’s prescribing information may be useful before initiating any cholesterol-lowering drug.
- ▶ As on-treatment LDL-C falls to very low levels, there is no recommendation to decrease statin dose.
- ▶ Initiating simvastatin at 80 mg daily or increasing the simvastatin dose to 80 mg daily may be harmful.

CK Measurement

- ▶ Do not routinely measure creatine kinase (CK) in individuals receiving statin therapy.
- ▶ Consider baseline measurement of CK for individuals believed to be at increased risk for adverse muscle events based on a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the risk of myopathy.
- ▶ During statin therapy, consider measuring CK in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or generalized fatigue.

Hepatic Function

- ▶ Perform baseline measurement of ALT before initiating statin therapy.
- ▶ During statin therapy, consider measuring hepatic function if symptoms suggesting hepatotoxicity arise (e.g., unusual fatigue or weakness, loss of appetite, abdominal pain, dark-colored urine or yellowing of the skin or sclera).

TABLE 2. STATIN THERAPY OPTIONS BY INTENSITY		
HIGH INTENSITY* Daily dose lowers LDL-C by approx. ≥ 50%	MODERATE INTENSITY Daily dose lowers LDL-C by approx. 30-50%	LOW INTENSITY Daily dose lowers LDL-C by < 30%
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Simvastatin 20-40 mg Atorvastatin 10-20 mg Lovastatin 40-80 mg Pravastatin 40-80 mg Rosuvastatin 5-10 mg Fluvastatin XL 80 mg Fluvastatin 40 mg bid Pitavastatin 2-4 mg	Simvastatin 10 mg Lovastatin 20 mg Pravastatin 10-20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg
*Initiating simvastatin 80 mg is no longer recommend. For those people who are already taking and tolerating simvastatin 80 gm daily, it can be considered a high-intensity statin.		

TABLE 3: STATIN DRUG INTERACTIONS

NONHIV, NONHEPATITIS C MEDICATIONS:		
Current therapy:	Guidance:	Avoid:
Amiodarone	Use atorvastatin up to 20 mg, and 40 mg with caution	Avoid simvastatin > 20 mg Avoid lovastatin > 40 mg
Amlodipine	Use atorvastatin up to 80 mg	Avoid simvastatin > 20 mg Avoid lovastatin > 20 mg
Ranolazine	Use atorvastatin up to 40 mg, and 80 mg with caution	Avoid simvastatin and lovastatin
Clarithromycin, erythromycin, or telithromycin.	For short-term course, statin should be interrupted Consider azithromycin as alternative when long-term therapy is indicated If long-term therapy with clarithromycin is necessary, use atorvastatin up to 20 mg	Avoid simvastatin and lovastatin
Cyclosporine	Use pravastatin up to 20 mg or rosuvastatin up to 5 mg	Avoid simvastatin, atorvastatin, and lovastatin
Danazol	Use atorvastatin up to 20 mg or rosuvastatin any dose	Avoid simvastatin Avoid lovastatin >20mg
Diltiazem, dronedarone, or verapamil	Use atorvastatin up to 40 mg and 80 mg with caution	Avoid simvastatin > 10 mg Avoid lovastatin > 20 mg
Dronedarone	Use atorvastatin up to 40 mg	Avoid simvastatin > 10 mg Avoid lovastatin > 20 mg
Gemfibrozil	Stop gemfibrozil in those on statins or needing statins. For TG ≥ 500 mg/dL, add EPA/DHA 2-4 g/day and retest. If TG remain elevated, see TG algorithm (Fig 2)	
Itraconazole, ketoconazole, or posaconazole,	Use atorvastatin up to 20 mg or rosuvastatin any dose	Avoid simvastatin and lovastatin. For short-term course, statin should be interrupted
Nefazodone	Use atorvastatin up to 10 mg, or rosuvastatin any dose	Avoid simvastatin and lovastatin
HIV MEDICATIONS:		
Current therapy:	Guidance:	Avoid:
Atazanavir, atazanavir-cobicistat, lopinavir (<i>ritonavir boosted</i>)	Use atorvastatin up to 10 mg or rosuvastatin up to 10 mg	Avoid simvastatin and lovastatin
Darunavir, darunavir-cobicistat, elvitegravir-cobicistat, fosamprenavir, or saquinavir (<i>ritonavir boosted</i>)	Use atorvastatin up to 20 mg, or rosuvastatin up to 20 mg	Avoid simvastatin and lovastatin
Nonritonavir boosted or other protease inhibitors	Use atorvastatin up to 20 mg, and 40 mg with caution	Avoid max dose of any statin Avoid simvastatin and lovastatin
Tipranavir	Use rosuvastatin up to 20 mg	Avoid atorvastatin, simvastatin, and lovastatin
HEPATITIS C MEDICATIONS:		
Current therapy:	Guidance:	Avoid:
Ledipasvir/sofosbuvir	Use atorvastatin up to 40 mg	Avoid rosuvastatin
Simeprevir	Use atorvastatin up to 40 mg or rosuvastatin up to 10 mg	
References: Statin package inserts. Lexicomp HIV medications: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf		

Assessing/Managing Muscle Symptoms during Statin Treatment

- ▶ Consider evaluating and treating symptoms, including pain, tenderness, stiffness, cramping, weakness, or fatigue, in statin-treated patients:
 - To avoid unnecessary discontinuation, obtain a history of prior or current muscle symptoms to establish a baseline before initiating statin therapy.
 - If unexplained severe muscle symptoms or fatigue develop during statin therapy, promptly discontinue the statin and address the possibility of rhabdomyolysis by evaluating CK, creatinine, and a urinalysis for myoglobinuria.
 - If mild-to-moderate muscle symptoms develop during statin therapy:
 - Discontinue the statin until the symptoms can be evaluated.
 - Evaluate for other conditions that might increase risk for muscle symptoms (e.g., hypothyroidism, reduced renal or hepatic function, rheumatologic disorders [polymyalgia rheumatic], steroid myopathy, vitamin D deficiency, or primary muscle diseases).
 - If muscle symptoms resolve and no contraindication exists, give patient the original or a lower dose of the same statin to establish a causal relationship between the muscle symptoms and statin therapy.
 - If a causal relationship exists, discontinue the original statin. Once muscle symptoms resolve, use a low dose of a different statin.
 - Once a low dose of a statin is tolerated, gradually increase the dose as tolerated.
 - If muscle symptoms or elevated CK levels 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 or if the predisposing condition has been treated, resume statin therapy at the original dose.
- ▶ For patients presenting with a confusional state or memory impairment while on statins, consider evaluation for nonstatin causes (e.g., exposure to other drugs, systemic and neuropsychiatric causes, etc.), as well as adverse effects associated with statin therapy.

Non-statin Safety Recommendations

Cholesterol-Absorption Inhibitors

- ▶ Consider obtaining baseline ALT levels before initiating ezetimibe. When ezetimibe is coadministered with a statin, monitor transaminase levels as clinically indicated, and discontinue ezetimibe for persistent ALT elevations > 3 times ULN.

Bile Acid Sequestrants (BAS)

- ▶ In individuals with baseline triglyceride levels ≥ 300 mg/dL or type III hyperlipoproteinemia, consider not using BAS because severe triglyceride elevations might occur. (A lipid panel should be obtained before BAS is initiated, 3 months after initiation, and at least a minimum of every 5 years thereafter).

- ▶ Consider using BAS with caution if baseline triglyceride levels are 250-299 mg/dL, and evaluate a lipid panel in 4 to 6 weeks after initiation. Discontinue the BAS if triglycerides exceed 400 mg/dL.

Fibrates

- ▶ Consider not using gemfibrozil in patients on statin therapy due to an increased risk for muscle symptoms and rhabdomyolysis.
- ▶ Consider fenofibrate concomitantly with a low- or moderate-intensity statin only if the benefits from ASCVD risk reduction or triglyceride lowering when triglycerides are ≥ 500 mg/dL are judged to outweigh the potential risk of adverse effects.
- ▶ Evaluate renal status before fenofibrate initiation, within 3 months after initiation, and periodically thereafter.
- ▶ Assess renal safety with both a serum creatinine level and an eGFR based on creatinine.
 - If eGFR is 30-59 mL/min per 1.73 m², do not exceed 54 mg/day of fenofibrate.
 - Do not use fenofibrate if moderate or severe renal impairment, defined as eGFR <30 mL/min per 1.73 m², is present.
 - If eGFR decreases persistently to ≤ 30 mL/min per 1.73 m² during follow-up, discontinue fenofibrate.

Omega-3 Fatty Acids

- ▶ If using EPA and/or DHA for severe hypertriglyceridemia (i.e., TG ≥ 500 mg/dL), consider evaluating for GI disturbance, skin change, and bleeding.

Niacin

- ▶ Order baseline ALT levels, fasting blood glucose or hemoglobin A1C, and uric acid before initiating niacin and again during up-titration to a maintenance dose and periodically thereafter.
- ▶ Consider not using niacin if:
 - Baseline ALT levels are > 2 -3 times upper limit of normal.
 - Persistent severe cutaneous symptoms, persistent hyperglycemia, acute gout or unexplained abdominal pain or gastrointestinal symptoms occur.
 - New-onset atrial fibrillation or weight loss occurs.
- ▶ If adverse effects from niacin occur, reconsider potential for ASCVD benefits and adverse effects before reinitiating niacin therapy.
- ▶ To reduce the frequency and severity of adverse cutaneous symptoms:
 - Consider starting niacin at a low dose and titrate to a higher dose over a period of weeks as tolerated.
 - Consider taking niacin with food or premedicating with aspirin 325 mg 30 minutes before niacin dosing to alleviate flushing symptoms.
 - If an extended-release preparation is used, consider increasing the dose of extended-release niacin from 500 mg/day to a maximum of 2,000 mg/day over 4 to 8 weeks, with the dose of extended release niacin increasing not more than weekly.

- If immediate-release niacin is chosen, consider starting at a dose of 100 mg 3 times daily and up-titrate to 3 g/day, divided into 2-3 doses.

TERMINOLOGY		
Recommendation Language	Strength*	Action
Start, initiate, prescribe, treat, etc.	Strong affirmative	Provide the intervention. Most individuals should receive the intervention; only a small proportion will not want the intervention.
Consider starting, etc.	Conditional affirmative	Assist each patient in making a management decision consistent with personal values and preferences. The majority of individuals in this situation will want the intervention, but many will not. Different choices will be appropriate for different patients.
No recommendation for or against	None	Given that the balance between desirable and undesirable effects, the evidence quality, the values and preferences, and the resource allocation implications of an intervention do not drive a recommendation in one particular direction, recommendations will be made at the discretion of the individual clinician.
Consider stopping, etc.	Conditional negative	Assist each patient in making a management decision consistent with personal values and preferences. The majority of individuals in this situation will not want the intervention, but many will. Different choices will be appropriate for different patients.
Stop, do not start, etc.	Strong negative	Do not provide the intervention. Most individuals should not receive the intervention; only a small proportion will want the intervention.

*Refers to the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects.

DISCLAIMER

This guideline is informational only. It is not intended or designed as a substitute for the reasonable exercise of independent clinical judgment by practitioners, considering each patient's needs on an individual basis. Guideline recommendations apply to populations of patients. Clinical judgment is necessary to design treatment plans for individual patients.