2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

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2. High Blood Cholesterol and ASCVD

2.1. Measurements of LDL-C and Non–HDL-C

Recommendations for Measurements of LDL-C and Non–HDL-C Referenced studies that support recommendations are summarized in Online Data Supplement 1.		
COR	**LOE**	**Recommendations**
I	B-NR	**1. In adults who are 20 years of age or older and not on lipid-lowering therapy, measurement of either a fasting or a nonfasting plasma lipid profile is effective in estimating ASCVD risk and documenting baseline LDL-C (S2.1-1–S2.1-6).**
I	B-NR	**2. In adults who are 20 years of age or older and in whom an initial nonfasting lipid profile reveals a triglycerides level of 400 mg/dL (≥4.5 mmol/L) or higher, a repeat lipid profile in the fasting state should be performed for assessment of fasting triglyceride levels and baseline LDL-C (S2.1-1–S2.1-4).**
IIa	C-LD	**3. For patients with an LDL-C level less than 70 mg/dL (<1.8 mmol/L), measurement of direct LDL-C or modified LDL-C estimate is reasonable to improve accuracy over the Friedewald formula (S2.1-7–S2.1-9).**
IIa	C-LD	**4. In adults who are 20 years of age or older and without a personal history of ASCVD but with a family history of premature ASCVD or genetic hyperlipidemia, measurement of a fasting plasma lipid profile is reasonable as part of an initial evaluation to aid in the understanding and identification of familial lipid disorders.**

3. Therapeutic Modalities

3.1. Lipid-Lowering Drugs

Among lipid-lowering drugs, statins are the cornerstone of therapy, in addition to healthy lifestyle interventions. Other LDL-lowering drugs include ezetimibe, bile acid sequestrants, and PCSK9 inhibitors. Triglyceride-lowering drugs are fibrates and niacin; they have a mild LDL-lowering action, but RCTs do not support their use as add-on drugs to statin therapy (S3.1-1). Characteristics of LDL-lowering drugs are summarized in Table S3 in the Web Supplement.

3.1.1. Statin Therapy

The intensity of statin therapy is divided into 3 categories: high-intensity, moderate-intensity, and low-intensity (S3.1.1-1). High-intensity statin therapy typically lowers LDL-C levels by ≥50%, moderate-intensity statin therapy by 30% to 49%, and low-intensity statin therapy by <30% (Table 3). Of course, the magnitude of LDL-C lowering will vary in clinical practice (S3.1.1-2). Certain Asian populations may have a greater response to certain statins (S3.1.1-3). Pharmacokinetic profiles among statins are heterogeneous (Table S4 in the Web Supplement). Statin safety has been extensively evaluated (S3.1.1-4). Statin-associated side effects are discussed in Section 5. Common medications that may potentially interact with statins are listed in Table S5 in the Web Supplement. More information on statin drug–drug interactions can be obtained from the ACC LDL-C Manager (http://tools.acc.org/ldl) (S3.1.1-5).

Table 3. High-, Moderate-, and Low-Intensity Statin Therapy*

	High Intensity	Moderate Intensity	Low Intensity
LDL-C lowering†	≥50%	30%–49%	<30%
Statins	**Atorvastatin (40 mg‡) 80 mg** **Rosuvastatin 20 mg (*40 mg***	**Atorvastatin 10 mg** (20 mg) **Rosuvastatin** (5 mg) **10 mg** **Simvastatin 20–40 mg§**	Simvastatin 10 mg
	…	**Pravastatin 40 mg** (80 mg) **Lovastatin 40 mg** (80 mg) Fluvastatin XL 80 mg **Fluvastatin 40 mg BID** Pitavastatin 1–4 mg	**Pravastatin 10–20 mg** **Lovastatin 20 mg** Fluvastatin 20–40 mg

*Percent reductions are estimates from data across large populations. Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice (S3.1.1-2).

†LDL-C lowering that should occur with the dosage listed below each intensity.

‡Evidence from 1 RCT only: down titration if unable to tolerate atorvastatin 80 mg in the IDEAL (Incremental Decrease through Aggressive Lipid Lowering) study (S3.1.1-18).

§Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA because of the increased risk of myopathy, including rhabdomyolysis.

Percent LDL-C reductions with the primary statin medications used in clinical practice (atorvastatin, rosuvastatin, simvastatin) were estimated using the median reduction in LDL-C from the VOYAGER database (S3.1.1-2). Reductions in LDL-C for other statin medications (fluvastatin, lovastatin, pitavastatin, pravastatin) were identified according to FDA-approved product labeling in adults with hyperlipidemia, primary hypercholesterolemia, and mixed dyslipidemia (S3.1.1-6).

Boldface type indicates specific statins and doses that were evaluated in RCTs (S3.1.1-7–S3.1.1-19), and the Cholesterol Treatment Trialists' 2010 meta-analysis (S3.1.1-20). All these RCTs demonstrated a reduction in major cardiovascular events.

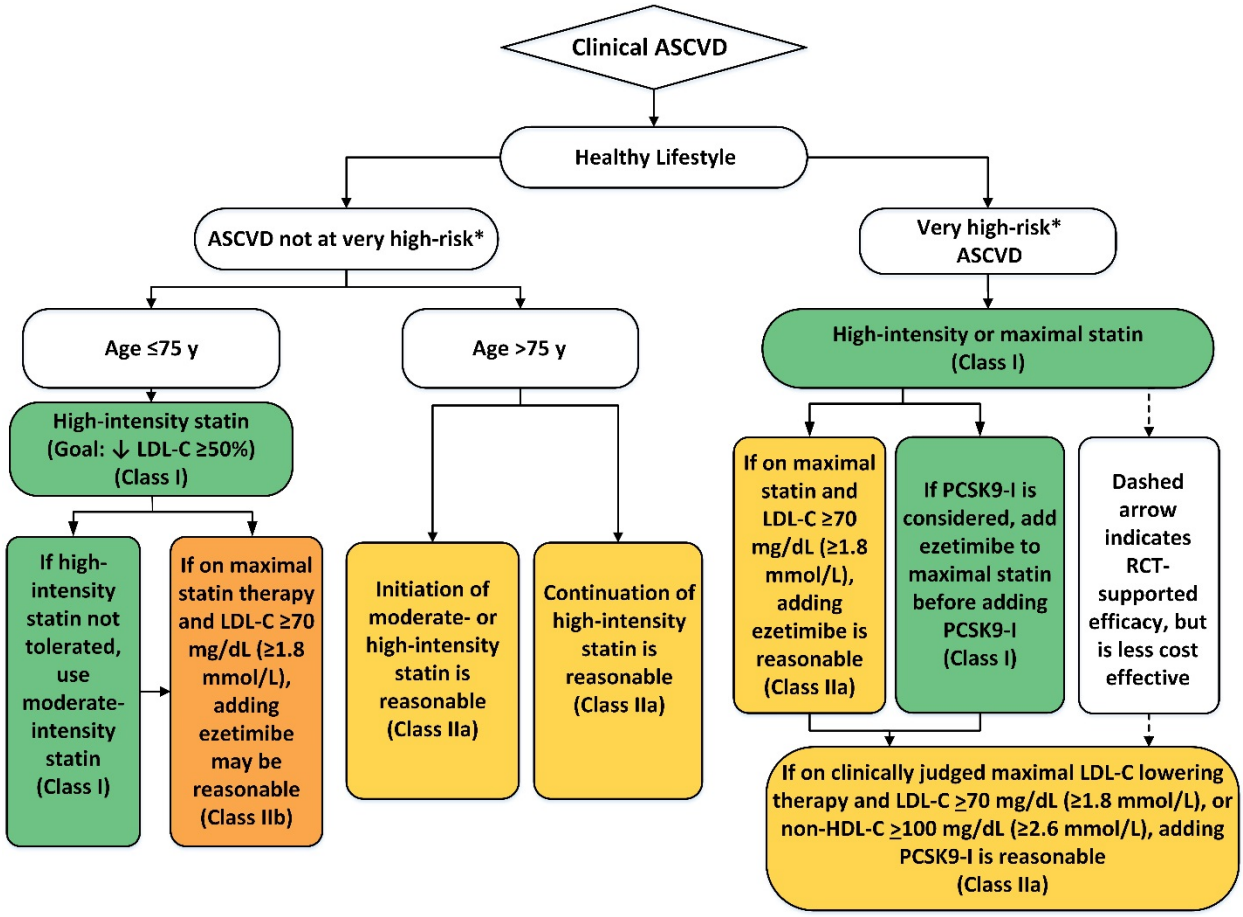
BID indicates twice daily; FDA, U.S. Food and Drug Administration; LDL-C, low-density lipoprotein cholesterol; RCT, randomized controlled trial; VOYAGER, an indiVidual patient data meta-analysis Of statin therapY in At risk Groups: Effects of Rosuvastatin, atorvastatin and simvastatin; and XL, extended release.

4. Patient Management Groups

4.1. Secondary ASCVD Prevention

Recommendations for Statin Therapy Use in Patients With ASCVD Referenced studies that support recommendations are summarized in Online Data Supplements 6, 7, 8 and in the Systematic Review Report (Figure 1).		
COR	**LOE**	**Recommendations**
I	**A**	**1. In patients who are 75 years of age or younger with clinical ASCVD,* high-intensity statin therapy should be initiated or continued with the aim of achieving a 50% or greater reduction in LDL-C levels (S4.1-1–S4.1-5).**
I	**A**	**2. In patients with clinical ASCVD in whom high-intensity statin therapy is contraindicated or who experience statin-associated side effects, moderate-intensity statin therapy should be initiated or continued with the aim of achieving a 30% to 49% reduction in LDL-C levels (S4.1-3, S4.1-6–S4.1-13).**

Figure 1. Secondary Prevention in Patients With Clinical ASCVD



Colors correspond to Class of Recommendation in Table 2.

Clinical ASCVD consists of acute coronary syndrome (ACS), those with history of myocardial infarction (MI), stable or unstable angina or coronary other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm, all of atherosclerotic origin.

Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions (Table 4).

ACS indicates acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction; and PCSK9i, PCSK9 inhibitor.

Table 4. Very High-Risk* of Future ASCVD Events

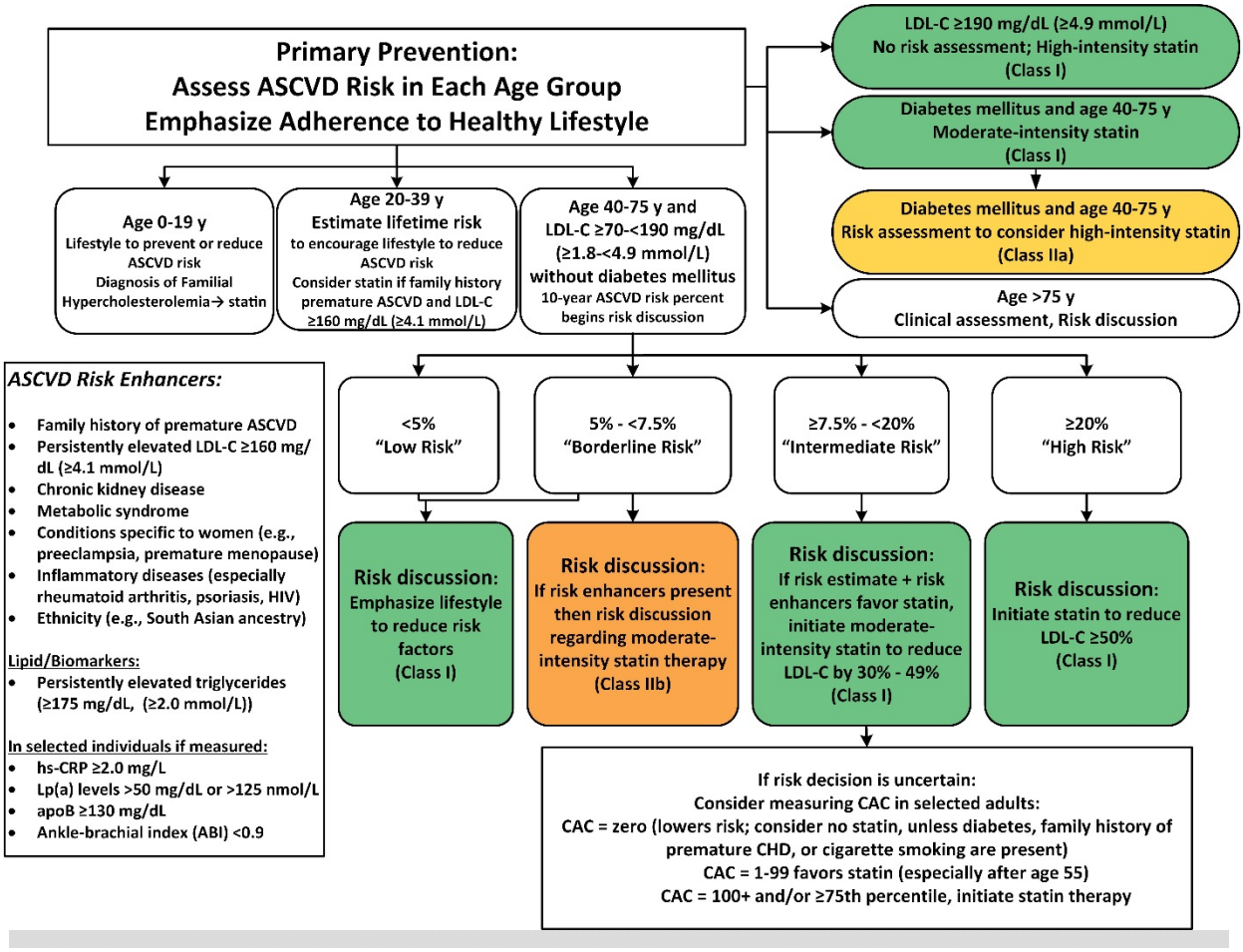
Major ASCVD Events
Recent ACS (within the past 12 mo)
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation (S4.1-39))
High-Risk Conditions
Age ≥65 y
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes mellitus
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m^2) (S4.1-15, S4.1-17)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

*Very high-risk includes a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions.
ABI indicates ankle-brachial index; ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; LDL, low-density lipoprotein cholesterol; and MI, myocardial infarction.

4.2. Severe Hypercholesterolemia (LDL-C ≥190 mg/dL [≥4.9 mmol/L])

Recommendations for Primary Severe Hypercholesterolemia (LDL-C ≥190 mg/dL [≥4.9 mmol/L]) Referenced studies that support recommendations are summarized in Online Data Supplements 9 and 10.		
COR	**LOE**	**Recommendations**
I	**B-R**	**1. In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher, maximally tolerated statin therapy is recommended (S4.2-1–S4.2-7).**
IIa	**B-R**	**2. In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL (≥4.9 mmol/L) or higher who achieve less than a 50% reduction in LDL-C while receiving maximally tolerated statin therapy and/or have an LDL-C level of 100 mg/dL (≥2.6 mmol/L) or higher, ezetimibe therapy is reasonable (S4.2-8–S4.2-10).**

Figure 2. Primary Prevention



Colors correspond to Class of Recommendation in Table 2.
apoB indicates apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; human immunodeficiency virus; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; and Lp(a), lipoprotein (a).

4.4.1. Evaluation and Risk Assessment

4.4.1.1. Risk-Enhancing Factors

Moderate intensity generic statins allow for efficacious and cost-effective primary prevention in patients with a 10-year risk of ASCVD ≥7.5% (S4.4.1.1-1). Since 2013 ACC/AHA guidelines (S4.4.1.1-2), the HOPE-3 RCT (S4.4.1.1-3) provided additional support for this finding. The pooled cohort equation (PCE) is the single most robust tool for estimating 10-year risk in U.S. adults 40 to 75 years of age. Its strength can be explained by inclusion of major, independent risk factors. One limitation on the PCE when applied to individuals is that age counts as a risk factor and dominates risk scoring with advancing age. Age is a powerful population risk factor but does not necessarily reflect individual risk. Another factor influencing risk are baseline characteristics of populations (baseline risk). These characteristics include both genetic and acquired risk factors other than established major risk factors. Variation in baseline risk accounts for difference in risk in different ethnic groups. Absolute risk predictions depend on the baseline risk of a population (e.g., the U.S. population). These considerations in patients at intermediate risk leave room in

the clinician-patient risk discussion to withhold or delay initiation of statin therapy, depending on age, pattern of risk factors, and patient preferences and values.

In sum, the PCE is a powerful tool to predict population risk, but it has limitations when applied to individuals. One purpose of the clinician patient risk discussion is to individualize risk status based on PCE as well as other factors that may inform risk prediction. Among these other factors are the risk-enhancing factors discussed in this guideline. These risk-enhancing factors are listed in Table 6, and evidence base and strength of association with ASCVD are shown in Table S6 in the Web Supplement. In the general population, they may or may not predict risk independently of PCE. But in the clinician–patient risk discussion they can be useful for identifying specific factors that influence risk. Their presence helps to confirm a higher risk state and thereby supports a decision to initiate or intensify statin therapy. They are useful for clarifying which atherogenic factors are present in a particular patient. And in some patients, certain risk-enhancing factors carry greater lifetime risk than denoted by 10-year risk prediction in the PCE. Finally, several risk-enhancing factors may be specific targets therapy beyond those of the PCE.

A few comments may illustrate the potential usefulness of risk-enhancing factors in the patient discussion. LDL-C ≥160 mg/dL (≥4.1 mmol/L), apoB ≥130 mg/dL (particularly when accompanied by persistently elevated triglycerides), and elevated Lp(a) denote high lifetime risk for ASCVD and favor initiation of statin therapy. The presence of family history of ASCVD, premature menopause, and patients of South Asian race appear to convey a higher baseline risk and are stronger candidates for statin therapy. Conditions associated with systemic inflammation (chronic inflammatory disorders, metabolic syndrome, chronic renal disease, and elevated hsCRP) appear to predispose to atherothrombotic events, which reasonably justifies statin therapy in intermediate-risk patients.

Table 6. Risk-Enhancing Factors for Clinician–Patient Risk Discussion

Risk-Enhancing Factors
• **Family history of premature ASCVD** (males, age <55 y; females, age <65 y) • **Primary hypercholesterolemia** (LDL-C, 160–189 mg/dL [4.1–4.8 mmol/L); non–HDL-C 190–219 mg/dL [4.9–5.6 mmol/L])* • **Metabolic syndrome** (increased waist circumference, elevated triglycerides [>175 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 in women mg/dL] are factors; tally of 3 makes the diagnosis) • **Chronic kidney disease** (eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation) • **Chronic inflammatory conditions** such as psoriasis, RA, or HIV/AIDS • **History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia** • **High-risk race/ethnicities** (e.g., South Asian ancestry) • **Lipid/biomarkers**: Associated with increased ASCVD risk o Persistently* elevated, primary hypertriglyceridemia (≥175 mg/dL); o If measured: ▪ **Elevated high-sensitivity C-reactive protein** (≥2.0 mg/L) ▪ **Elevated Lp(a):** A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor especially at higher levels of Lp(a).

Table 7. Checklist for Clinician–Patient Shared Decision-Making for Initiating Therapy

Checklist Item	Recommendation
ASCVD risk assessment	• Assign to statin treatment group; use ASCVD Risk Estimator Plus.* o In lower-risk primary-prevention adults 40-75 y of age with LDL-C ≥70 mg/dL (≥1.8 mmol/L). o Not needed in secondary prevention, in those with LDL-C ≥190 mg/dL (≥4.9 mmol/L), or in those 40-75 y of age with diabetes mellitus. • Assess other patient characteristics that influence risk. See Risk-Enhancing Factors (Section 4.4.1.3. and Table 6) • Assess CAC (Section 4.4.1.4.) if risk decision is uncertain and additional information is needed to clarify ASCVD risk. o Use decision tools to explain risk (e.g., ASCVD Risk Estimator Plus,* Mayo Clinic Statin Choice Decision Aid).
Lifestyle modifications	• Review lifestyle habits (e.g., diet, physical activity, weight or body mass index, and tobacco use). • Endorse a healthy lifestyle and provide relevant advice, materials, or referrals. (e.g., CardioSmart, AHA Life's Simple 7, NLA Patient Tear Sheets, PCNA Clinicians' Lifestyle Modification Toolbox, cardiac rehabilitation, dietitian, smoking cessation program).
Potential net clinical benefit of pharmacotherapy	• Recommend statins as first-line therapy. • Consider the combination of statin and nonstatin therapy in selected patients. • Discuss potential risk reduction from lipid-lowering therapy. • Discuss the potential for adverse effects or drug–drug interactions.
Cost considerations	• Discuss potential out-of-pocket cost of therapy to the patient (e.g., insurance plan coverage, tier level, copayment).
Shared decision-making	• Encourage the patient to verbalize what was heard (e.g., patient's personal ASCVD risk, available options, and risks/benefits). • Invite the patient to ask questions, express values and preferences, and state ability to adhere to lifestyle changes and medications. • Refer patients to trustworthy materials to aid in their understanding of issues regarding risk decisions. • Collaborate with the patient to determine therapy and follow-up plan.

*ASCVD Risk Predictor Plus is available at: http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/. Accessed September 1, 2018.

AHA indicates American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CKD, chronic kidney disease; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol; PCNA, Preventive Cardiology Nurses Association and NLA, National Lipid Association.

IIb	C-LD	2. In adults with advanced kidney disease that requires dialysis treatment who are currently on LDL-lowering therapy with a statin, it may be reasonable to continue the statin (S4.5.4-2).
III: No Benefit	B-R	3. In adults with advanced kidney disease who require dialysis treatment, initiation of a statin is not recommended (S4.5.4-3, S4.5.4-4).

4.5.5. Adults With Chronic Inflammatory Disorders and HIV

Recommendations for Adults With Chronic Inflammatory Disorders and HIV Referenced studies that support recommendations are summarized in Online Data Supplement 39.		
COR	**LOE**	**Recommendations**
IIa	B-NR	1. In adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL (1.7 to 4.8 mmol/L) who have a 10-year ASCVD risk of 7.5% or higher, chronic inflammatory disorders and HIV are risk-enhancing factors and in risk discussion favor moderate-intensity statin therapy or high-intensity statin therapy (S4.5.5-1–S4.5.5-12).
IIa	B-NR	2. In patients with chronic inflammatory disorders or HIV, a fasting lipid profile and assessment of ASCVD risk factors can be useful as (a) a guide to benefit of statin therapy and (b) for monitoring or adjusting lipid-lowering drug therapy before and 4 weeks to 12 weeks after starting inflammatory disease–modifying therapy or antiretroviral therapy (S4.5.5-12–S4.5.5-20).
IIa	B-NR	3. In adults with RA who undergo ASCVD risk assessment with measurement of a lipid profile, it can be useful to recheck lipid values and other major ASCVD risk factors 2 to 4 months after the patient's inflammatory disease has been controlled (S4.5.5-21–S4.5.5-23).

5. Statin Safety and Statin-Associated Side Effects

Recommendations for Statin Safety and Statin-Associated Side Effects Referenced studies that support recommendations are summarized in Online Data Supplements 40 and 41.		
COR	**LOE**	**Recommendations**
I	A	1. A clinician–patient risk discussion is recommended before initiation of statin therapy to review net clinical benefit, weighing the potential for ASCVD risk reduction against the potential for statin-associated side effects, statin–drug interactions, and safety, while emphasizing that side effects can be addressed successfully (S5-1–S5-7).
I	A	2. In patients with statin-associated muscle symptoms (SAMS), a thorough assessment of symptoms is recommended, in addition to an evaluation for nonstatin causes and predisposing factors (S5-3–S5-7).
I	B-R	3. In patients with indication for statin therapy, identification of potential predisposing factors for statin-associated side effects, including new-onset diabetes mellitus and SAMS, is recommended before initiation of treatment (S5-3–S5-7).
I	B-R	4. In patients with statin-associated side effects that are not severe, it is recommended to reassess and to rechallenge to achieve a maximal LDL-C lowering by modified dosing regimen, an alternate statin or in combination with nonstatin therapy (S5-3–S5-8).
I	B-R	5. In patients with increased diabetes mellitus risk or new-onset diabetes mellitus, it is recommended to continue statin therapy, with added emphasis on adherence, net clinical benefit, and the core principles of regular moderate-intensity physical activity, maintaining a healthy dietary pattern, and sustaining modest weight loss (S5-8–S5-12).
I	C-LD	6. In patients treated with statins, it is recommended to measure creatine kinase levels in individuals with severe statin-associated muscle symptoms, objective muscle weakness, and to measure liver transaminases (aspartate aminotransferase, alanine aminotransferase) as well as total bilirubin and alkaline phosphatase (hepatic panel) if there are symptoms suggesting hepatotoxicity (S5-13–S5-15).
I	B-R	7. In patients at increased ASCVD risk with chronic, stable liver disease (including non-alcoholic fatty liver disease) when appropriately indicated, it is reasonable to use statins after obtaining baseline measurements and determining a schedule of monitoring and safety checks (S5-16–S5-18).
IIa	B-R	8. In patients at increased ASCVD risk with severe statin-associated muscle symptoms or recurrent statin-associated muscle symptoms despite appropriate statin rechallenge, it is reasonable to use RCT proven nonstatin therapy that is likely to provide net clinical benefit (S5-5, S5-6, S5-19).
III: No Benefit	B-R	9. Coenzyme Q10 is not recommended for routine use in patients treated with statins or for the treatment of SAMS (S5-20, S5-21).
III: No Benefit	C-LD	10. In patients treated with statins, routine measurements of creatine kinase and transaminase levels are not useful (S5-13–S5-15).

Synopsis

Statin therapy is usually well tolerated and safe (S5-1, S5-14, S5-22–S5-24). As with other classes of medications, associated side effects are seen. Instead of the label *statin intolerance*, the present guideline prefers *statin-associated side effects* because the large majority of patients are able to tolerate statin rechallenge with an alternative statin or alternative regimen, such as reduced dose or in combination with nonstatins. Although infrequent or rare in clinical trials, statin-associated side effects can be challenging to assess and manage (S5-25, S5-26). The most frequent are SAMS. SAMS usually are subjective myalgia, reported observationally in 5% to 20% of patients (S5-11–S5-14). SAMS often result in nonadherence and can adversely impact ASCVD outcomes (S5-27–S5-29). Statins modestly increase risk of incident diabetes mellitus in susceptible individuals (S5-8–S5-11), but this should not be cause for discontinuation (Table 11).

Table 11. Statin-Associated Side Effects (SASE)

Statin-Associated Side Effects	Frequency	Predisposing Factors	Quality of Evidence
Statin-associated muscle symptoms (SAMS)			
Myalgias (CK normal)	Infrequent (1% to 5%) in RCTs; frequent (5% to 10%) in observational studies and clinical setting	Age, female sex, low body mass index, high-risk medications (CYP3A4 inhibitors, OATP1B1 inhibitors), comorbidities (HIV, renal, liver, thyroid, preexisting myopathy), Asian ancestry, excess alcohol, high levels of physical activity, and trauma	RCTs cohorts/observational
Myositis/myopathy (CK > ULN) with concerning symptoms or objective weakness	Rare		RCTs cohorts/observational
Rhabdomyolysis (CK >10× ULN + renal injury)	Rare		RCTs cohorts/observational
Statin-associated autoimmune myopathy (HMGCR antibodies, incomplete resolution)	Rare		Case reports
New-onset diabetes mellitus	Depends on population; more frequent if diabetes mellitus risk	Diabetes mellitus risk factors/metabolic syndrome	RCTs/meta-analyses

	factors are present, such as body mass index ≥30, fasting blood sugar ≥100 mg/dL; metabolic syndrome, or A1c ≥6% (S5-8).	High-intensity statin therapy	
Liver			
Transaminase elevation 3× ULN	Infrequent		RCTs/ cohorts/observational Case reports
Hepatic failure	Rare		
Central nervous system			
Memory/cognition	Rare/unclear		Case reports; no increase in memory/cognition problems in 3 large-scale RCTs
Cancer	No definite association		RCTs/meta-analyses
Other			
Renal function	Unclear/unfounded		
Cataracts	Unclear		
Tendon rupture	Unclear/unfounded		
Hemorrhagic stroke	Unclear		
Interstitial lung disease	Unclear/unfounded		
Low testosterone	Unclear/unfounded		

CK indicates creatine kinase; HIV, human immunodeficiency virus; HMGCR, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; SAMS, statin-associated muscle symptoms; SAAM, statin-associated autoimmune myopathy; SASE, statin associated side effects; and ULN, upper limit of normal.