CME MOC

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ACC/AHA lipid guidelines: Personalized care to prevent cardiovascular disease

ABSTRACT

The 2018 and 2019 guidelines from the American College of Cardiology and American Heart Association reflect the complexity of individualized cholesterol management. The documents address more detailed risk assessment, newer nonstatin cholesterol-lowering drugs, special attention to patient subgroups, and consideration of the value of therapy, all with the aim of creating personalized treatment plans for each patient. Overall, the guidelines recommend shared decision-making to meet the individual needs of each patient.

KEY POINTS

Emphasize a heart-healthy lifestyle for all patients across their life span.

A discussion with the patient is the cornerstone of shared decision-making and should include the patient's 10-year risk of atherosclerotic cardiovascular disease according to the Pooled Cohort Equations, as well as risk-enhancing factors.

Statins are the foundation of pharmacologic therapy, to which ezetimibe and, if necessary, a proprotein convertase subtilisin/kexin type 9 inhibitor can be added to achieve lipid goals.

Special treatment algorithms are outlined for certain patient subgroups, such as certain ethnic groups, adults with chronic kidney disease, those with human immunodeficiency virus infection, and women.

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The American College of Cardiology (ACC) and American Heart Association (AHA) Task Force on Clinical Practice Guidelines published its most recent guidelines for cholesterol management in 2018,[1] and followed it with guidelines for primary prevention of cardiovascular disease in 2019.[2]

The new guidelines have updated patient risk assessment and treatment options in primary and secondary prevention. In primary prevention, the guidelines provide clarity regarding decision-making in patients at intermediate risk of atherosclerotic cardiovascular disease ("intermediate" meaning a 7.5%–20% 10-year risk).

In secondary prevention, the guidelines group patients according to their risk (high risk vs very high risk) and incorporate new nonstatin therapies as add-on, evidence-based treatment options when low-density lipoprotein (LDL-C) remains above the 70 mg/dL threshold. The guidelines also discuss the cost and value of each treatment option for each treatment group.

Here, we review the recent guidelines and discuss the most important changes for clinical practice.[1–3]

CLASSES OF RECOMMENDATION, LEVELS OF EVIDENCE

The guidelines award classes of recommendations, signifying the certainty of benefit compared with the estimated risk and the strength of the recommendation.

- Class I (strong)—benefit greatly exceeds risk; treatment is recommended
- Class IIa (moderate)—benefit exceeds risk; treatment is reasonable
- Class IIb (weak)—benefit equals or exceeds risk; treatment might be reasonable
- Class III: No benefit (moderate)—benefit equals risk; treatment is not recommended
- Class III: Harm (strong)—risk exceeds benefit.

The guidelines also award levels of evidence to their recommendations:

- Level A—high-quality evidence
- Level B-R—moderate-quality evidence from randomized controlled trials
- Level B-NR—moderate quality evidence from nonrandomized trials
- Level C-LD—limited data
- Level C-EO—expert opinion.

STATINS AND OTHER OPTIONS

In addition to a heart-healthy lifestyle, statins are the foundation of lipid management

In addition to a heart-healthy lifestyle (which should be encouraged for all patients across their life course), statins are the foundation of lipid management. Statin therapy is divided into 3 categories of intensity:

High-intensity, aiming for at least a 50% reduction in LDL-C. Examples:

- Atorvastatin 40–80 mg daily
- Rosuvastatin 20–40 mg daily.

Moderate-intensity, aiming at a 30% to 49% reduction in LDL-C. Examples:

- Atorvastatin 10–20 mg
- Fluvastatin 80 mg daily
- Lovastatin 40–80 mg
- Pitavastatin 1–4 mg daily
- Pravastatin 40–80 mg daily
- Rosuvastatin 5–10 mg
- Simvastatin 20–40 mg daily.

Low-intensity, aiming at a LDL-C reduction of less than 30%. Examples:

- Fluvastatin 20–40 mg daily
- Lovastatin 20 mg daily
- Pravastatin 10–20 mg daily
- Simvastatin 10 mg daily.

Nonstatin drugs

The nonstatin LDL-lowering drugs such as ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors can be added to statin therapy, as recent randomized clinical trials found them to improve cardiovascular outcomes in patients with atherosclerotic cardiovascular disease.[4–7]

Ezetimibe decreases cholesterol absorption and consequently lowers LDL-C levels by about 20%. A large randomized trial in patients who recently had acute coronary syndromes showed that ezetimibe modestly reduced cardiovascular risk over 7 years of follow-up when added to their regimen of moderate-intensity statin therapy.[4,5]

PCSK9 inhibitors lower LDL-C by 50% to 60% by binding to PCSK9, inhibiting labeling of LDL receptors for degradation, thus prolonging LDL receptor activity at the cell membrane. Several trials showed that PCSK9 inhibitors reduce cardiovascular risk in patients with stable atherosclerotic cardiovascular disease or recent acute coronary syndromes who are already on moderate- or high-intensity statin therapy.[4,6,7]

PRIMARY PREVENTION

The new guidelines advocate a multifaceted approach to primary prevention of atherosclerotic cardiovascular disease through cholesterol management. As the risk due to high cholesterol levels is cumulative over the life span, the guidelines encourage lifestyle therapy for primary prevention at all ages and in all patient categories. Additionally, they outline decision algorithms to create a therapy that suits the individual needs of each patient (**Table 1**).

Statin benefit groups

The new guidelines keep the same statin benefit groups defined in the previous (2013) ACC/AHA guidelines.[8] Statin therapy recommendations are specifically given for the following groups:

Adults with severe hypercholesterolemia

If a patient age 20 to 75 has LDL-C levels of 190 mg/dL or higher, you do not need to cal-

TABLE 1

Primary preventive therapy in different patient subgroups

Severe hypercholesterolemia

Initiate high-intensity statin therapy immediately, irrespective of 10-year risk of atherosclerotic cardiovascular disease (ASCVD)

Adding ezetimibe is reasonable if low-density lipoprotein cholesterol (LDL-C) is ≥ 190 mg/dL or there is less than 50% reduction in LDL-C levels with maximal tolerated statins

Consider adding a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor in patients with heterozygous familial hypercholesterolemia or with LDL-C ≥ 220 mg/dL with maximally tolerated statins and ezetimibe

Diabetes mellitus in adults

Irrespective of 10-year ASCVD risk, initiate moderate-intensity statin therapy immediately

Aim for reduction of LDL-C by at least 50%

Adults age 40–75 with LDL-C levels 70–189 mg/dL

Before starting statins, engage in clinician-patient risk discussion, evaluating risk factors, 10-year ASCVD risk, risk enhancers (Table 2), patient's preference, costs, and adverse effects of statins

Use coronary artery calcium score to guide decision if risk is still unclear

Children and young adults

Assess risk factors in children age 0–19 years

Initiate statin therapy if patients have severely abnormal lipid profiles or clinical presentation of familial hypercholesterolemia and cannot be treated by 3 months lifestyle therapy

Ethnicity

Review racial and ethnic features that can influence ASCVD risk and intensity of treatment (Table 3)

Adults with chronic kidney disease

Starting moderate-intensity statin alone or in combination with ezetimibe can be useful

Adults with chronic inflammatory disorders and HIV

In adults age 40–75 with LDL-C 70–189 mg/dL with a 10-year ASCVD risk of over 5%, discuss moderate- or high-intensity statin therapy

Women

History of premature menopause (before age 40) or history of pregnancy-related disorders (hypertension, preeclampsia, gestational diabetes, small-for-gestational-age infants, and preterm deliveries) are risk-enhancing factors and should influence lifestyle and pharmacologic therapy decisions

Based on information in references 1 and 2.

culate the 10-year risk. Rather, high-intensity statin therapy should be started right away to lower LDL-C by at least 50%.

If the LDL-C level remains higher than 100 mg/dL with maximal tolerated statin therapy, ezetimibe can be added (class IIb recommendation, ie, weak recommendation, but benefit exceeds risk).

If the patient has a risk factor for atherosclerotic cardiovascular disease and his or her LDL-C level remains higher than 100 mg/dL even after adding ezetimibe to the statin, a PCSK9 inhibitor may be considered.

Adults with diabetes mellitus

Moderate-intensity statin therapy is indicated in adults with diabetes, regardless of their 10-

If a patient age 20 to 75 has LDL-C ≥ 190 mg/dL, start high-intensity statin therapy right away

TABLE 2

Risk enhancers

Family history of premature atherosclerotic cardiovascular disease (in men age < 55 or in women age < 65)

Primary hypercholesterolemia
- Low-density lipoprotein cholesterol 160–180 mg/dL
- Non-high-density lipoprotein cholesterol 190–219 mg/dL

Metabolic syndrome: 3 or more of the following:
- Increased waist circumference by ethnically appropriate cut points
- Fasting triglyceride level > 150 mg/dL
- High blood pressure
- Elevated glucose
- Low high-density lipoprotein cholesterol (< 40 mg/dL in men, < 50 mg/dL in women)
- Chronic kidney disease (estimated glomerular filtration rate 15–59 mL/min/1.73 m^2)

Chronic inflammatory conditions (eg, psoriasis, rheumatoid arthritis, lupus, human immunodeficiency virus infection, acquired immunodeficiency syndrome)

History of premature menopause (age < 40) and history of pregnancy-associated conditions that increase later risk of atherosclerotic cardiovascular disease such as preeclampsia

High-risk ethnicity or race (eg, South Asian)

Lipids or biomarkers associated with elevated risk
- Persistently elevated hypertriglyceridemia (≥ 175 mg/dL nonfasting)
- Elevated high-sensitivity C-reactive protein (≥ 2.0 mg/L)
- Elevated lipoprotein (a) (≥ 50 mg/dL or ≥ 125 nmol/L)
  (relative indication for measurement: family history of premature atherosclerotic cardiovascular disease)
- Elevated apolipoprotein B (≥ 130 mg/dL)
  (relative indication for measurement: triglycerides ≥ 200 mg/dL)
- Ankle-brachial index < 0.9

year risk. However, it is reasonable to start high-intensity statin treatment if the patient also has multiple risk factors. Similarly, the 2019 guidelines of the American Diabetes Association advocate high-intensity statin therapy in patients who have additional risk factors or a 10-year risk of an atherosclerotic cardiovascular disease event higher than 20%.[9]

Adults age 40–75, without diabetes, with LDL-C levels 70–189 mg/dL

In this group, the guidelines say to use a risk calculator to determine if the patient needs lipid-lowering medication.

Use the Pooled Cohort Equations, which are based on age, sex, race, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, and whether the patient is receiving treatment for high blood pressure, has diabetes, or smokes (class I recommendation). This tool gives an estimate of the patient's risk of a cardiovascular event within the next 10 years, which the guidelines categorize as follows:

- Low risk: < 5%
- Borderline risk: 5%–7.5%
- Intermediate risk: 7.5%–20%
- High risk: > 20%.

The addition of the "borderline" group (only the 2018 guidelines specifically mention and explain primary preventive treatment in the "borderline" risk category) reflects the uncertainty of treatment strategies for patients at intermediate risk, while treatment recommendations for high- and low-risk groups are well established.[10]

The US Preventive Services Task Force[11] recommends statins as primary preventive therapy for adults age 40 to 75 with no history of cardiovascular disease, 1 or more risk factors, and a calculated 10-year risk of 10% or greater (grade A recommendation—there is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial). However, it gives a lower recommendation for low-intensity statin therapy for people with a lower 10-year risk, ie, between 7.5% and 10%. (grade C—they recommend selectively offering or providing it to individual patients based on professional judgment and patient preferences; there is at least moderate certainty that the net benefit is small).

Discuss the risk with the patient. After evaluating 10-year risk, clinicians should discuss it with the patient before initiating statin therapy. Risk discussions are the cornerstone of the shared decision-making process.

Review risk-enhancing factors. During the risk discussion, one should review not only the patient's 10-year risk according to the Pooled Cohort Equations, but also risk factors not included in the Pooled Cohort Equations. The guidelines describe these as "risk-enhancing factors" (**Table 2**).

TABLE 3

Racial and ethnic differences in atherosclerotic cardiovascular disease risk and coronary artery calcium scores

	Asian	Hispanic and Latino	Black, Native American, and Alaskan
ASCVD risk	South Asians[a] have higher ASCVD risk than East Asians[b]	Individuals from Puerto Rico have the highest ASCVD risk[15] CVD mortality is higher in Hispanics than whites	Increased ASCVD risk[14] Greater rates of CHD events compared with non-Hispanic white populations[17]
CAC score	South Asian men have similar CAC burden to non-Hispanic white men, but higher CAC compared with blacks and Latinos[18] South Asian women have similar CAC scores compared with other ethnic and racial groups[18]	Lower CAC burden compared with Asian-Americans and non-Hispanic whites[16]	Lower CAC scores compared with whites and Hispanics[16]

[a]Individuals from Bangladesh, India, Nepal, Pakistan, and Sri Lanka make up most of the South Asian group.
[b]Individuals from Japan, Korea, and China make up most of of the East Asian group.

ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; CHD = coronary heart disease; CVD = cardiovascular disease

For patients at borderline or intermediate risk, risk-enhancing factors are particularly useful to review during the risk discussion, and the guidelines give especially detailed instructions in the decision algorithm for patients in these groups. This acknowledges the criticisms of the previous 2013 guidelines that they led to overprescription of statins due to many patients fitting the intermediate-risk category, and called for additional risk stratification tools.[12]

By evaluating risk-enhancing factors, patients' risk can be revised and preventive treatment prescribed only to those at higher risk, while avoiding overprescription for those at low risk. The guidelines give a class IIA recommendation to starting or intensifying statin therapy if risk-enhancing factors are present in borderline- and intermediate-risk adults.

In unclear cases, consider coronary artery calcium measurement. If, in view of this evidence, the patient and clinician favor statin therapy, statins should be initiated at a moderate intensity to lower LDL-C by 30% to 49%. However, if the risk decision is still unclear even after reviewing the Pooled Cohort Equations and risk enhancers, the coronary artery calcium score can be added to guide decisions.

A great body of research indicates that the coronary artery calcium score is an effective tool to stratify risk and improve risk estimation.[13] If the score is 1 to 99, statin therapy is suggested, especially in patients older than 55. If the score is 100 or higher or patients are in the 75th percentile or higher for coronary artery calcium, statin therapy is clearly indicated. If the score is 0, statin therapy may be safely withheld unless the patient smokes or has premature cardiovascular disease.

Therapy recommendations for patients on either extreme of 10-year risk are more straightforward.

For patients at low risk (< 5%), clinicians should still emphasize lifestyle changes to reduce risk modifiable factors.

For patients at high risk (> 20%), clinicians should clearly recommend statin therapy aimed at lowering LDL-C by at least 50%.

Physicians should use additional risk-stratification tools for patients at borderline and intermediate risk

Primary prevention in children and young adults

The guidelines pay special attention to cholesterol management in subgroups. The most important updates are specific recommenda-

tions for children and young adults.

The guidelines acknowledge that atherosclerosis is a lifelong process and that the effects of high cholesterol levels accumulate across an entire lifetime. This is why, unlike previous guidelines, the 2018/2019 guidelines recommend primary preventive therapy for children and young adults.

Risk factor assessment and identification of family history of hypercholesterolemia or inherited dyslipidemia should already occur for children age 0 to 19 years. Also, if children have severely elevated lipid levels related to obesity, intensive lifestyle therapy should be implemented.

Primary prevention for other populations at risk

The current recommendations also make specific recommendations for cholesterol treatment algorithms for specific patient subgroups, in which treatment decisions were previously unclear.

Primary prevention: Ethnicity

The ACC/AHA guidelines state in a class IIA recommendation that race and ethnicity influence the risk of atherosclerotic cardiovascular disease and the choice of treatment. Risk varies widely among and within ethnic groups, affecting treatment decisions (**Table 3**).[14–18] In particular, the guidelines point out that South Asian individuals have higher risk, as do those who identify as Native American or Alaskan native compared with non-Hispanic white populations.[14]

Black populations have higher rates of coronary heart disease even though they have lower coronary artery calcium scores

Socioeconomic status and acculturation level (extent of assimilation to the dominant culture—in this case American culture) can affect the burden of atherosclerotic cardiovascular disease. For instance, a cross-sectional study showed that acculturation was associated with higher cardiovascular risk in Hispanic participants.[15]

Moreover, ethnicity also affects other aspects of risk classification, such as coronary artery calcium scores. Studies suggest that ethnicity influences the pathobiologic processes of vessel atherogenesis.[19] Hispanic patients have a lower coronary artery calcium burden than Asian-Americans and non-Hispanic whites.[16] However, cardiovascular mortality rates are higher in Hispanics than in whites and Asians. Black populations also have higher rates of coronary heart disease even though they have lower coronary artery calcium scores compared with whites.[14,17] Variabilities in risk of atherosclerotic cardiovascular disease in different populations call for different clinical management of cholesterol levels.

The guidelines remark specifically on the heightened statin sensitivity of East Asian populations,[20] and suggest that Japanese patients might benefit from similar risk reductions with lower statin doses instead of the higher dosages used for other ethnic groups. A secondary prevention trial showed that moderate-intensity pitavastatin therapy was beneficial for Japanese individuals with clinically stable coronary artery disease.[21]

Metabolism of statins also seems to be affected by ethnicity. Higher rosuvastatin plasma levels were observed in Asian Indian, Chinese, Malay, and Japanese people than in white patients.[22] Thus, lower starting doses of rosuvastatin are recommended for these populations, and clinicians should be cautious when up-titrating rosuvastatin.

Primary prevention in adults with chronic kidney disease

Chronic kidney disease is a risk-enhancing factor. Moderate-intensity statin therapy in combination with ezetimibe can be useful in adults age 40 to 75 with chronic kidney disease who have greater than a 7.5% risk of atherosclerotic cardiovascular disease risk and are not treated with dialysis or kidney transplant (class of recommendation IIa). If patients are currently undergoing dialysis and already receiving a statin, it is reasonable to continue statin therapy despite potential decreased efficacy in this population.

Primary prevention in adults with chronic inflammatory disorders and HIV

Human immunodeficiency virus infection and other chronic inflammatory disorders are risk-enhancing factors. In a class IIA recommendation, the guidelines state that in this subgroup of patients, adults age 40 to 75 with LDL-C 70 to 189 mg/dL with a 10-year atherosclerotic cardiovascular disease risk of over 7.5%, moderate or high-intensity statin therapy should be discussed. In addition to evaluating risk factors, a fasting lipid profile

can be used to guide statin therapy. Before and 4 to 12 weeks after starting anti-inflammatory or antiretroviral therapy, fasting lipid profiles and atherosclerotic cardiovascular disease risk factors can be used to monitor lipid-lowering medications.

Primary prevention issues specific to women

The new guidelines identify the following conditions specific to women as risk-enhancing factors:

- Premature menopause (before age 40)
- Pregnancy-associated disorders such as hypertension, preeclampsia, gestational diabetes, and diabetes mellitus
- Infants small for gestational age
- Preterm deliveries.

The guidelines give a class I recommendation to intensively discussing lifestyle intervention and potential benefit of statin therapy in case of these conditions.

Women with these conditions could also benefit from additional risk-stratification tools like coronary artery calcium scoring to guide decisions about statin therapy. A cross-sectional study in 446 women suggest that earlier cardiovascular risk screening including coronary artery calcium scoring might benefit women with preterm deliveries.[23] Other studies showed that women with hypertensive disorders of pregnancy could benefit from earlier risk stratification through the coronary artery calcium score.[24]

Pregnant women should not take statins, however, even if they have severe hypercholesterolemia. This recommendation is based on animal data, in which teratogenic effects of statins in high doses and disruption of the cholesterol synthesis in the fetus were observed. However, recent evidence has not confirmed the teratogenic potential of statins.[25] Nevertheless, while new safety data are reassuring, suspension of statins is still advisable.[26]

The guidelines also give specific recommendations regarding statin therapy when planning or during pregnancy. Sexually active women on statin therapy are advised to use effective forms of contraception (class I recommendation). Women planning to become pregnant should stop statin therapy 1 to 2 months before pregnancy is attempted. If women become pregnant while using a statin, they should stop taking it as soon as pregnancy is discovered.

TABLE 4

Key points on secondary prevention[a]

Patient subgroup	Guideline recommendation
At very high risk[b]	If low-density lipoprotein cholesterol (LDL-C) levels are ≥ 70 mg/dL with the maximal tolerated statin therapy, it is reasonable to add ezetimibe
	If LDL-C level is ≥ 70 mg/dL on maximal tolerated statin and ezetimibe, it is reasonable to add a PCSK9 inhibitor
Not at very high risk	
Age ≤ 75	Goal is LDL-C reduction by 50%
	Use moderate-intensity statins if high-intensity statins are not tolerated
	If LDL-C ≥ 70 mg/dL on high-intensity statins, it is reasonable to add ezetimibe
Age > 75	Starting or continuing either moderate- or high-intensity statins is reasonable

[a]Secondary prevention refers to patients with clinical atherosclerotic cardiovascular disease (ASCVD), ie, those with a history of acute coronary syndrome, myocardial infarction, stable or unstable angina, arterial revascularization, stroke, transient ischemic attack, or peripheral artery disease.
[b]Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions (age ≥ 65, heterozygous familial hypercholesterolemia, history of coronary artery bypass surgery or percutaneous coronary intervention, diabetes mellitus, hypertension, chronic kidney disease, current smoking, persistently elevated LDL-C, or history of heart failure).

Based on information in reference 1.

SECONDARY PREVENTION: ATHEROSCLEROTIC DISEASE

High-intensity statin therapy is recommended for all patients with atherosclerotic cardiovascular disease, including acute coronary syndromes, myocardial infarction, stable or unstable angina, or with a history of coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral artery disease including aortic aneurysm, all of atherosclerotic origin.

The new guidelines recognize 2 phenotypes in secondary prevention: high risk and very high risk (**Table 4**). Very high risk in-

cludes a history of multiple major atherosclerotic cardiovascular disease events or 1 major event and multiple high-risk conditions.

The reduction in risk is proportional to the decrease of LDL-C levels. The authors also provide instructions on the use of nonstatin medications as part of secondary prevention. In patients with a very high risk and LDL-C levels higher than 70 mg/dL on maximal tolerated statin therapy, it is reasonable to add ezetimibe. Further, in patients at very high risk whose LDL-C level remains higher than 70 mg/dL on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable.

MONITORING RESPONSE TO LDL-C-LOWERING THERAPY

As in the last guidelines, the current ones suggest assessing adherence and percentage response after initiating or changing the dose of LDL-C-lowering medications and lifestyle changes, with repeat lipid measurements 4 to 12 weeks after therapy is started. This can be repeated every 3 to 12 months as needed.

Sexually active women on statin therapy should use effective forms of contraception

COST AND VALUE CONSIDERATIONS

The 2018 guidelines comment on the importance of considering the value of treatment in therapy decisions.[1]

The authors reviewed the cost-effectiveness of PCSK9 inhibitors using simulation models. These revealed that, to be cost-effective, the prices of PCSK9 inhibitors will have to be reduced by at least 70% in the United States from 2018 levels. However, since PCSK9 inhibitors have an incremental cost-effective ratio of $141,800 to $450,000 per quality-adjusted life-year added, the cost-effectiveness of these drugs improves only if used for very high-risk patients. This is reflected in the current guidelines, which suggest adding PCSK9 inhibitors only after maximal tolerated doses of statins and ezetimibe have not improved LDL-C levels significantly in very high-risk atherosclerotic cardiovascular disease patients or those with a family history of premature atherosclerotic cardiovascular disease. However, in mid-2018, when the 2018 guidelines were written, the US list prices of PCSK9 inhibitors were roughly $14,000 a year; now (in 2019) costs have been reduced to a little more than $6,000 a year.

STATIN ADVERSE EFFECTS

The new guidelines additionally address patients' and clinicians' fears of adverse effects of statins. They specifically recommend that the clinician-patient risk discussion also review possible adverse events and how these can be managed.

The guidelines advocate reviewing the net clinical benefit of statins and comparing the potential for reduction in risk of atherosclerotic cardiovascular disease with the risk of statin-associated side effects and drug interactions (class I recommendation, level of evidence A). Observed adverse effects include myalgias, elevation of creatine kinase, and transaminitis.[8]

When adverse effects occur, clinicians should lower the dose or dosing frequency, prescribe an alternate statin, or combine statin with nonstatin therapy. If symptoms persist despite these measures, nonstatin therapies with proven efficacy in randomized controlled trials are recommended. In recent clinical trials, evolocumab[27] as well as alirocumab[28] performed well in lowering LDL-C in statin-intolerant patients.

Muscle symptoms are the most common statin-related adverse effects. Subjective myalgia occurred in 1% to 15% of participants in randomized controlled trials but in 5% to 20% of patients in observational studies. In a class I recommendation, the authors write that patients with statin-associated muscle symptoms should undergo a detailed assessment of symptoms, and nonstatin causes and predisposing factors should be taken into consideration.

Further, statins slightly increase the risk of diabetes mellitus in patients with prediabetes. However, the guidelines clearly state that therapy should not be discontinued because of this, as the advantages of statins are much greater than the risk of diabetes mellitus.[29,30]

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