

2018 Guideline on the Management of Blood Cholesterol

GUIDELINES MADE SIMPLE

A Selection of Tables and Figures

Updated June 2019



Top 10 Take-Home Messages to Reduce Risk of Atherosclerotic Cardiovascular Disease (ASCVD) through Cholesterol Management (1 of 3)

1 *In all individuals, emphasize heart-healthy lifestyle across the life-course.*

A healthy lifestyle reduces atherosclerotic cardiovascular disease (ASCVD) risk at all ages. In younger individuals, healthy lifestyle can reduce development of risk factors and is the foundation of ASCVD risk reduction. In young adults 20 to 39 years of age, an assessment of lifetime risk facilitates the clinician–patient risk discussion (see #6) and emphasizes intensive lifestyle efforts. In all age groups, lifestyle therapy is the primary intervention for metabolic syndrome.

2 *In patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy*

The more LDL-C is reduced on statin therapy, the greater will be subsequent risk reduction. Use a maximally tolerated statin to lower LDL-C levels by $\geq 50\%$.

3 *In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of nonstatins to statin therapy.*

Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions. In very high-risk ASCVD patients, it is reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥ 70 mg/dL (≥ 1.8 mmol/L). In patients at very high risk whose LDL-C level remains ≥ 70 mg/dL (≥ 1.8 mmol/L) on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable, although the long-term safety (>3 years) is uncertain and cost effectiveness is low at mid-2018 list prices.

4 *In patients with severe primary hypercholesterolemia (LDL-C level ≥ 190 mg/dL [≥ 4.9 mmol/L]), without calculating 10-year ASCVD risk, begin high-intensity statin therapy.*

If the LDL-C level remains ≥ 100 mg/dL (≥ 2.6 mmol/L), adding ezetimibe is reasonable. If the LDL-C level on statin plus ezetimibe remains ≥ 100 mg/dL (≥ 2.6 mmol/L) and the patient has multiple factors that increase subsequent risk of ASCVD events, a PCSK9 inhibitor may be considered, although the long-term safety (>3 years) is uncertain and economic value is uncertain at mid-2018 list prices.

Top 10 Take-Home Messages to Reduce Risk of Atherosclerotic Cardiovascular Disease (ASCVD) through Cholesterol Management (2 of 3)

5 *In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥ 70 mg/dL (≥ 1.8 mmol/L), start moderate-intensity statin therapy without calculating 10-year ASCVD risk.*

In patients with diabetes mellitus at higher risk, especially those with multiple risk factors or those 50 to 75 years of age, it is reasonable to use a high-intensity statin to reduce the LDL-C level by $\geq 50\%$.

6 *In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy.*

Risk discussion should include a review of major risk factors (e.g., cigarette smoking, elevated blood pressure, LDL-C, hemoglobin A1C [if indicated], and calculated 10-year risk of ASCVD); the presence of risk-enhancing factors (see #8); the potential benefits of lifestyle and statin therapies; the potential for adverse effects and drug–drug interactions; consideration of costs of statin therapy; and patient preferences and values in shared decision-making.

7 *In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥ 70 mg/dL (≥ 1.8 mmol/L), at a 10-year ASCVD risk of $\geq 7.5\%$, start a moderate-intensity statin if a discussion of treatment options favors statin therapy.*

. Risk-enhancing factors favor statin therapy (see #8). If risk status is uncertain, consider using coronary artery calcium (CAC) to improve specificity (see #9). If statins are indicated, reduce LDL-C levels by $\geq 30\%$, and if 10-year risk is $\geq 20\%$, reduce LDL-C levels by $\geq 50\%$.

“Top Ten Messages” is continued in the next page.

Top 10 Take-Home Messages to Reduce Risk of Atherosclerotic Cardiovascular Disease (ASCVD) through Cholesterol Management (3 of 3)

8 *In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy (see #7).*

Risk-enhancing factors include family history of premature ASCVD; persistently elevated LDL-C levels ≥ 160 mg/dL (≥ 4.1 mmol/L); metabolic syndrome; chronic kidney disease; history of preeclampsia or premature menopause (age < 40 years); chronic inflammatory disorders (e.g., rheumatoid arthritis, psoriasis, or chronic HIV); high-risk ethnic groups (e.g., South Asian); persistent elevations of triglycerides ≥ 175 mg/dL (≥ 1.97 mmol/L); and, if measured in selected individuals, apolipoprotein B ≥ 130 mg/dL, high-sensitivity C-reactive protein ≥ 2.0 mg/L, ankle-brachial index < 0.9 and lipoprotein (a) ≥ 50 mg/dL or 125 nmol/L, especially at higher values of lipoprotein (a). Risk-enhancing factors may favor statin therapy in patients at 10-year risk of 5-7.5% (borderline risk).

9 *In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥ 70 mg/dL- 189 mg/dL (≥ 1.8 -4.9 mmol/L), at a 10-year ASCVD risk of $\geq 7.5\%$ to 19.9%, if a decision about statin therapy is uncertain, consider measuring CAC.*

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

10 *Assess adherence and percentage response to LDL-C-lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed.*

Define responses to lifestyle and statin therapy by percentage reductions in LDL-C levels compared with baseline. In ASCVD patients at very high-risk, triggers for adding nonstatin drug therapy are defined by threshold LDL-C levels ≥ 70 mg/dL (≥ 1.8 mmol/L) on maximal statin therapy (see #3).

Secondary ASCVD Prevention

First Statin Benefit Group

Very High-Risk for Future ASCVD Events*

Table 4

Major ASCVD Events
Recent acute coronary syndrome (within the past 12 months)
History of myocardial infarction (other than recent acute coronary syndrome event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ankle brachial index <0.85, or previous revascularization or amputation)
High-Risk Conditions
Age ≥ 65 years
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or PCI outside of the major ASCVD event(s)
Diabetes Mellitus
Hypertension
Chronic kidney disease (eGFR 15-59 mL/min/1.73 m ²)
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 heart failure

*Very High Risk includes a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions.

Severe Hypercholesterolemia

Second Statin Benefit Group

Recommendations for Primary Severe Hypercholesterolemia [LDL-C \geq 190 mg/dL (\geq 4.9 mmol/L)]

COR	LOE	Recommendations
I	B-R	1. In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL or higher, (\geq 4.9 mmol/L) maximally tolerated statin therapy is recommended.
IIa	B-R	2. In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL or higher (\geq 4.9 mmol/L) who achieve less than 50% reduction in LDL-C while receiving maximally tolerated statin therapy and/or have an LDL-C level of 100 mg/dL (\geq 2.6 mmol/L) or higher, ezetimibe therapy is reasonable.
IIb	B-R	3. In patients 20 to 75 years of age with a baseline LDL-C 190 mg/dL or higher (\geq 4.9 mmol/L), who achieve less than a 50% reduction in LDL-C levels and have fasting triglycerides 300 mg/dL or lower (\leq 3.4 mmol/L) while taking maximally tolerated statin and ezetimibe therapy, the addition of a bile acid sequestrant may be considered.
IIb	B-R	4. In patients 30 to 75 years of age with heterozygous FH and with an LDL-C level of 100 mg/dL or higher (\geq 2.6 mmol/L) while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered.
IIb	C-LD	5. In patients 40 to 75 years of age with a baseline LDL-C level of 220 mg/dL or higher (\geq 5.7 mmol/L) who achieve an on-treatment LDL-C level of 130 mg/dL or higher (\geq 3.4 mmol/L) while receiving maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered.
Value Statement: Uncertain Value (B-NR)		6. Among patients with FH without evidence of clinical ASCVD taking maximally tolerated statin and ezetimibe therapy, PCSK9 inhibitors provide uncertain value at mid-2018 US list prices.

Diabetes Mellitus in Adults

Third Statin Benefit Group

Diabetes-specific Risk Enhancers That Are Independent of Other Risk Factors in Diabetes

Table 5

- Long duration (≥ 10 years for type 2 diabetes or ≥ 20 years for type 1 diabetes)
- Albuminuria ≥ 30 mcg albumin/mg creatinine
- eGFR < 60 ml/min/1.73 m²
- Retinopathy
- Neuropathy
- ABI < 0.9

Primary Prevention Over the Life span

Fourth Statin Benefit Groups

Selected Examples of Candidates for Coronary Artery Calcium Measurement Who Might Benefit from Knowing CAC Score is Zero

Table 8

1. Patients reluctant to initiate statin who wish to understand their risk and potential for benefit more precisely
2. Patients concerned about need to re-institute statin therapy after discontinuation for statin associated symptoms
3. Older patients (men 55 to 80; women 60-80 years old) with low burden of risk factors who question whether they would benefit from statin therapy
4. Middle-aged adults (40-55 years old) with PCE calculated 10-year risk for ASCVD 5 to <7.5% with factors that increase their ASCVD risk, even though they are in a borderline risk group

ASCVD indicates atherosclerotic cardiovascular disease; CAC, coronary artery calcium; LDL-C, low-density lipoprotein cholesterol; and PCE, pooled cohort equations.

Caveats: If patient is intermediate risk and if a risk decision is uncertain and a CAC score is performed, it is reasonable to withhold statin therapy unless higher risk conditions such as cigarette smoking, family history of premature ASCVD, or diabetes are present, and to reassess CAC score in 5-10 years. Moreover, if CAC is recommended, it should be performed in facilities that have current technology that delivers the lowest radiation possible.

Treatment Considerations

High-, Moderate-, and Low-Intensity Statin Therapy*

Table 3

	High-Intensity	Moderate-Intensity	Low-Intensity
LDL-C Lowering [†]	≥50%	30% to 49%	<30%
Statins	Atorvastatin (40 mg [‡]) 80 mg Rosuvastatin 20 (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

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.

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 (13). 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.

Boldface type indicates specific statins and doses that were evaluated in RCTs, and the Cholesterol Treatment Trialists’2010 meta-analysis. All these RCTs demonstrated a reduction in major cardiovascular events.

Italic type indicates statins and doses that have been approved by the FDA but were not tested in the RCTs reviewed.

*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.

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

[‡]Evidence from 1 RCT only: downtitration if unable to tolerate atorvastatin 80 mg in the IDEAL (Incremental Decrease through Aggressive Lipid Lowering) study.

[§]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.

Treatment Considerations

Statin Associated Side Effects (SASE) (1 of 2)

Table 11

Statin Associated Side Effects	Frequency	Predisposing Factors	Quality of Evidence
Statin Associated Muscle Symptoms (SAMS) <ul style="list-style-type: none"> Myalgias (CK normal) 	Infrequent (1%–5%) in RCTs/frequent (5%–10%) in observational studies and clinical setting	Age, female, low BMI, high- risk medications (CYP3A4 inhibitors, OATP1B1 inhibitors), comorbidities (HIV, renal, liver, thyroid, pre-existing myopathy), Asian descent, excess alcohol, high levels of physical activity and trauma.	RCTs cohorts/observational
<ul style="list-style-type: none"> Myositis/Myopathy (CK >ULN) with concerning symptoms/objective weakness 	Rare		RCTs cohorts/observational
<ul style="list-style-type: none"> Rhabdomyolysis (CK >10xULN + renal injury) 	Rare		RCTs Cohorts/observational
<ul style="list-style-type: none"> Statin-associated autoimmune myopathy (SAAM) (HMGCR Ab's, incomplete resolution) 	Rare		Case reports
New onset Diabetes Mellitus	Depends on population; more frequent if diabetes mellitus risk factors such as BMI ≥30, fasting blood glucose ≥100 mg/dL; metabolic syndrome or A1c ≥6% are present	Diabetes risk factors/ metabolic syndrome High-intensity statin therapy	RCTs/Meta-analyses

Table 11 is continued in the next page. For references please see page 18.

Treatment Considerations

Statin Associated Side Effects (SASE) (2 of 2)

Table 11 (continued from previous page)

Statin Associated Side Effects	Frequency	Predisposing Factors	Quality of Evidence
Liver <ul style="list-style-type: none"> • Transaminase elevation 3xULN 	Infrequent		RCTs/cohorts/observational Case reports
<ul style="list-style-type: none"> • Hepatic Failure 	Rare		
CNS <ul style="list-style-type: none"> • Memory/Cognition 	Rare		Case reports; no increase in memory/cognition problems in three large scale RCTs
Cancer	No definite association		RCTs/meta-analyses
Other <ul style="list-style-type: none"> • Renal Function • Cataracts • Tendon Rupture • Hemorrhagic Stroke • Interstitial Lung Disease • Low Testosterone 	Unfounded Unfounded Unfounded Unfounded Unfounded 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. “