Cholesterol Management of ASCVD Risk Reduction

Based on the 2018 AHA/ACC/multisociety Guideline on the Management of Blood Cholesterol and the 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-C Lowering in the Management of ASCVD Risk

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Last Updated April 2024. Note: In March 2024, Bempedoic acid was approved to reduce the risk of myocardial infarction and coronary revascularization in adults who are unable to take recommended statin therapy (including those not taking a statin) with established cardiovascular disease, or at high risk for a CVD event but without established CVD. This updated indication was made after the publication of current clinical guidelines referenced below.

Secondary ASCVD Prevention in Adults with Clinical ASCVD

Clinical ASCVD includes the following: history of ACS or MI, stable/unstable angina, ischemic stroke/transient ischemic attack, coronary/arterial revascularization or peripheral artery disease (presumed to be of atherosclerotic origin)

Use maximally tolerated statin and consider adding nonstatin therapies to achieve specific **LDL targets** based upon subgroup

Criteria for Defining Very High Risk

***Very high risk ASCVD** is defined as a history of multiple major ASCVD events **or** one major ASCVD event and multiple high-risk conditions

Major ASCVD Events
- Any recent ACS (in last 12 months)
- History of MI (other than recent ACS)
- History of ischemic stroke
- Symptomatic PAD

High-Risk Conditions
- Age ≥65 years
- Heterozygous familial hypercholesterolemia
- History of prior CABG surgery or PCI outside of the major ASCVD event(s)
- Diabetes
- Hypertension
- Chronic kidney disease
- History of congestive heart failure
- Current smoker
- Persistently elevated LDLC (≥100 mg/dL) despite max-tolerated statin and ezetimibe

ASCVD Not at Very High Risk*

Target **≥50%** LDL reduction and LDL **<70 mg/dL**

↓ If not reached on max-tolerated statin ↓

Consider adding **ezetimibe**

↓ If LDL targets not reached ↓

Consider adding **PCSK9 mAb** [§] (in addition to or in place of ezetimibe)

↓ If LDL targets not reached ↓

Consider adding **bempedoic acid**

↓ If LDL targets not reached ↓

Refer to lipid specialist and RD/RDN

Very High Risk ASCVD*

Target **≥50%** LDL reduction and LDL **<55 mg/dL**

↓ If not reached on max-tolerated statin ↓

Consider adding **ezetimibe** and/or **PCSK9 mAb** [¶ §]

↓ If LDL targets not reached ↓

Consider adding **second** nonstatin (e.g., ezetimibe + PCSK9 mAb)

↓ If LDL targets not reached ↓

Consider adding **bempedoic acid**

↓ If LDL targets not reached ↓

Refer to lipid specialist and RD/RDN

Baseline LDL ≥190 mg/dL without clinical/genetic FH diagnosis

Target **≥50%** LDL reduction and LDL **<70 mg/dL**

↓ If not reached on max-tolerated statin ↓

Consider lipid specialist and RD/RDN referral

Consider adding **ezetimibe** and/or **PCSK9 mAb** [¶ §]

↓ If LDL targets not reached ↓

Consider adding **bempedoic acid**

↓ If LDL targets not reached ↓

Refer to lipid specialist and RD/RDN

Under care of lipid specialist, if LDL persistently >200 mg/dL consider LDL apheresis

Baseline LDL ≥190 mg/dL with clinical/genetic FH diagnosis

Target **≥50%** LDL reduction and LDL **<55 mg/dL**

↓ If not reached on max-tolerated statin ↓

Consider lipid specialist and RD/RDN referral

Consider adding **ezetimibe** and/or **PCSK9 mAb** [¶ §]

↓ If LDL targets not reached ↓

Consider adding **bempedoic acid**

↓ If LDL targets not reached ↓

Refer to lipid specialist and RD/RDN

Under care of lipid specialist, if inadequate response to max-tolerated statin with or without ezetimibe/PCSK9 inhibitors:
- Consider LDL apheresis in patients with HeFH or HoFH
- Consider evinacumab or lomitapide in patients with HoFH

[¶] **Ezetimibe** may be preferred as the initial nonstatin agent in those requiring **<25%** additional LDL reduction, while a **PCSK9 mAb** may be preferred in those requiring **>25%** additional LDL reduction. The simultaneous addition of two agents may be considered in patients requiring greater LDL reduction than likely achievable with one agent alone.

[§] Consider replacing PCSK9 mAb with **inclisiran** in those with PCSK9 mAb adherence or tolerability issues. PCSK9 mAbs (alirocumab, evolocumab) are currently the preferred PCSK9 inhibitors over inclisiran due to available safety and CV outcomes data. If inclisiran is used, it should replace the PCSK9 mAb as there is no evidence or mechanistic plausibility for use together. Consider referral to lipid specialist for use.

Primary ASCVD Prevention

Assess and discuss ASCVD risk in each subgroup, promote healthy lifestyle to reduce ASCVD risk

LDL ≥190 mg/dL

Use max-tolerated statin

Target **≥50%** LDL reduction and LDL **<100 mg/dL**

↓ If LDL targets not reached ↓

Consider lipid specialist & RD/RDN referral

Consider adding **ezetimibe** and/or **PCSK9 mAb** [¶ §]

↓ If LDL targets not reached ↓

Consider adding **second** nonstatin (e.g., ezetimibe + PCSK9 mAb)

↓ If LDL targets not reached ↓

Consider adding **bempedoic acid**

↓ If LDL targets not reached ↓

Refer to lipid specialist and RD/RDN

Under care of lipid specialist, if **HoFH** and inadequate response to max-tolerated statin with or without ezetimibe/PCSK9 inhibitors:
- Consider LDL apheresis
- Consider evinacumab or lomitapide

Adults with diabetes (LDL <190 mg/dL)

Age 20-39 years: Diabetes-specific risk enhancers*? Consider statin

Age 40-75 years

Age >75 years: Discuss the risk-benefit of statin prior to initiation

10-year ASCVD risk ≥7.5%, diabetes-specific risk enhancers*, or subclinical atherosclerosis?

No → **Use moderate-intensity statin**

Target **30-49%** LDL reduction and LDL **<100 mg/dL** (or non-HDL <130 mg/dL)

↓ If LDL targets not reached ↓

Increase to **high-intensity statin**

If LDL targets not reached

Yes → **Use high-intensity statin**

Target **≥50%** LDL reduction and LDL **<100 mg/dL** (or non-HDL <130 mg/dL)

If 10-yr ASCVD Risk ≥20%: Target **≥50%** LDL reduction and LDL **<70 mg/dL** (or non-HDL <100 mg/dL)

↓ If LDL targets not reached ↓

Consider adding **ezetimibe**

May consider bile acid sequestrant if fasting TG <300 mg/dL or if ezetimibe has inadequate response or is not tolerated

PCSK9 mAbs, inclisiran, and bempedoic acid currently do not have an established place in therapy for primary prevention in patients with diabetes without either ASCVD or baseline LDL ≥190 mg/dL

Adults without diabetes (LDL 70-189 mg/dL)

Age 20-39 years

Generally focus on implementing **healthy lifestyle changes** to reduce lifetime ASCVD risk

Age 40-75 years

Assess 10-year ASCVD risk

<5% Low-Risk → Promote healthy lifestyle to reduce ASCVD risk

5% to <7.5% Borderline-Risk → Consider risk-enhancing factors^ and **discuss** use of **moderate-intensity statin**

Target **30-49%** LDL reduction and LDL **<100 mg/dL**

≥7.5% to <20% Intermediate-Risk → Consider **moderate-intensity statin**

Target **30-49%** LDL reduction and LDL **<100 mg/dL**

≥20% High-Risk → **Use high-intensity statin**

Target **≥50%** LDL reduction and LDL **<70 mg/dL**

↓ If LDL targets not reached ↓

Increase to **high-intensity statin**

↓ If LDL targets not reached ↓

Consider adding **ezetimibe**

The use of PCSK9 mAbs is not routinely recommended for primary prevention due to limited data

Age > 75 years:

If LDL 70-189 mg/dL, consider initiation of a **moderate-intensity statin** upon **clinician-patient discussion**

If there is **clinical uncertainty** regarding the need for statin therapy in patients with **borderline-** or **intermediate-risk**, their **CAC score** may be used to help reach a decision

CAC = 0 AU	→	Consider **deferring statin** & reassess in 3-5 years (if no high-risk conditions present)	
CAC 1-99 AU and < 75th percentile†	→	Consider **moderate-intensity statin** — Target 30-49% LDL reduction and LDL <100 mg/dL	→ If LDL targets not reached, consider **high-intensity statin**
CAC ≥ 100 AU or ≥ 75th percentile†	→	Consider **moderate- or high-intensity statin** — Target LDL % reduction based on statin intensity and achieve LDL <70 mg/dL	→ If LDL targets not reached **consider ezetimibe**
CAC ≥ 1000 AU	→	Consider **high-intensity statin** — Target ≥50% LDL reduction and LDL <70 mg/dL	→ If LDL targets not reached consider **ezetimibe**, then consider **PCSK9 mAb**

† percentile for corresponding age/sex/race

*Diabetes-Specific Risk Enhancers

- Long duration of diabetes (≥10 years for type 2, ≥20 years for type 1)
- UACR ≥30
- eGFR <60 mL/min
- Retinopathy
- Neuropathy
- ABI <0.9

*ASCVD Risk Score ↗

^Risk-Enhancing Factors

Medical History/Demographics
- Family history of premature ASCVD (males <55 years; females <65 years)
- Primary hypercholesterolemia (LDL 160-189 mg/dL)
- Chronic kidney disease (with or without albuminuria)
- Metabolic syndrome
- History of premature menopause (before age 40) or preeclampsia
- Chronic inflammatory disorders (e.g., psoriasis, RA, HIV/AIDS)
- High-risk race/ethnicities (e.g., South Asian ancestry)

Biomarkers
- Persistently elevated, primary hypertriglyceridemia (≥ 175 mg/dL)
- CRP ≥2.0 mg/dL
- Lp(a) level ≥50 mg/dL (or >125 nmol/L)
- apoB ≥130 mg/dL
- Ankle-brachial index (ABI) <0.9

ACS: acute coronary syndrome
apoB: apolipoprotein B
ASCVD: atherosclerotic cardiovascular disease
AU: Agatston unit
BAS: bile acid sequestrant
CAC: coronary artery calcium
CRP: C-reactive protein
FH: familial hypercholesterolemia
HDL: high-density lipoprotein cholesterol
HeFH: heterozygous familial hypercholesterolemia
HoFH: homozygous familial hypercholesterolemia
LDL: low-density lipoprotein cholesterol
Lp(a): lipoprotein (a)
MI: myocardial infarction
PAD: peripheral artery disease
PCSK9 mAb: proprotein convertase subtilisin/kexin type 9 monoclonal antibody
RD/RDN: registered dietitian/dietitian nutritionist
UACR: urine albumin creatinine ratio

References: Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. [2] Writing Committee, Lloyd-Jones DM, Morris PB, et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2022;80(14):1366-1418. doi:10.1016/j.jacc.2022.07.006