

Lipid Management in 2026: New Guidelines, New Therapies, Practical Updates

Colton PharmD Candidate 2026, and Megan Herink, Pharm.D., Oregon State University Drug Use Research and Management

Dyslipidemia refers to abnormal low density lipoprotein cholesterol (LDL-C), hypertriglyceridemia, and elevated lipoprotein(a) (Lp(a)). Patients may have one or all of these conditions. In patients with atherosclerotic cardiovascular disease (ASCVD) and at high risk for ASCVD, lowering lipid levels is critical to lower the risk for future cardiovascular (CV) events. This newsletter will discuss updated guidelines and proven therapies for CV risk reduction.

Guideline Updates

The 2026 American College of Cardiology / American Heart Association (ACC/AHA) Guideline for the Management of Dyslipidemia is a significant update from their previous guideline published in 2018 (Table 1).¹ Class of Recommendation (COR) and Level of Evidence definitions are included in Appendix 1. Lifestyle management is foundational for ASCVD risk reduction and should accompany pharmacological therapy. While statins remain the foundation of lipid-lowering therapy, the updated guidelines emphasize reducing cumulative lifetime exposure to atherogenic lipoproteins through earlier interventions, individualized risk assessment, and intensification of therapy when indicated. The updated guideline also expands the role of biomarkers and non-statin therapies, broadening lipid management beyond LDL-C alone.

Table 1: Comparison of ACC/AHA Dyslipidemia Guidelines¹

Topic	2018 Guideline	2026 Guideline
LDL goals	Less emphasis on fixed targets	≤ 55 mg/dl in high-risk ASCVD
Lp(a)	Limited role	One time testing recommended
ApoB	Limited role	Recommended in high-risk patients once LDL-C goals met
Risk Estimation	Pooled Cohort Equations	PREVENT equations
Non-statins	Selective use	Earlier use to achieve LDL-C goals

Abbreviations: ApoB: apolipoprotein B, ASCVD: atherosclerotic cardiovascular disease, CV: cardiovascular, Lp(a): lipoprotein(a), LDL-C: low density lipoprotein cholesterol, PREVENT: Predicting Risk of cardiovascular disease EVENTS

Risk Assessment

One major update to the guideline is the adoption of the Predicting Risk of cardiovascular disease events-ASCVD (PREVENT-ASCVD) equation for both 10-year and 30-year risk estimations in patients aged 30 to 79 years for primary prevention.¹ This replaces the previously recommended

Pooled Cohort Equations. PREVENT incorporates additional clinical variables and provides a broader assessment of CV and kidney risk. The Pooled Cohort Equation defined high risk as 10-year estimated risk > 20%, whereas PREVENT uses a lower cutoff of 10-year estimated risk ≥ 10%. The guidelines identify a net-benefit threshold as low as an estimated 10-year risk of 3% for consideration of lipid lowering therapy¹ However, this is a 2a Recommendation and risk estimates should be personalized based on risk enhancers.

Beyond LDL: Tackling Residual Risk

LDL-C remains the traditional lipid marker for ASCVD risk assessment and treatment targets, but it reflects the cholesterol mass within LDL particles rather than the number of atherogenic lipoproteins. Since 2018, additional evidence has emerged regarding the utility of measuring apolipoprotein B (ApoB), which better reflects the number of atherogenic particles, and Lp(a).¹ In the 2026 guideline, the committee gives a Class 2a recommendation (moderate strength) for using ApoB to inform treatment options in patients on lipid-lowering therapy who have already met cholesterol goals.¹ A large cohort study found that, among non-HDL-C, triglycerides (TG), and ApoB, only ApoB remained significantly associated with myocardial infarction (MI) incidence after adjustment in both primary and secondary prevention settings.²

The guideline recommends a baseline Lp(a) measurement to assess ASCVD risk (Class 1, strong recommendation).¹ Elevated Lp(a) is largely genetically determined and increases ASCVD risk. Lp(a) is minimally modified by lifestyle factors and no FDA-approved medications effectively reduce Lp(a), although several therapies are in development (Table 2).³ Their clinical role will depend on results from CV outcome trials. The Phase III trial of pelacarsen was recently reported to have not reduced CV events compared with placebo, despite lowering Lp(a) levels.⁴

Table 2: Lp(a) Lowering Medications in Phase 3 Trials³

Drug	Mechanism	Plasma reduction in Lp(a)
Pelacarsen	Antisense oligonucleotide	Up to 80%
Olpasiran	siRNA	Up to 98%
Lepodisiran	siRNA	Up to 94%

Abbreviations: Lp(a) – lipoprotein(a), siRNA – small interfering RNA

Lipoprotein Goals for ASCVD Risk Reduction

The primary goal of treatment in the 2018 ACC/AHA guideline was to achieve a percentage reduction in LDL-C from baseline based on medication intensity. The updated guideline recommends more aggressive LDL-C lowering with absolute LDL-C and non-HDL goals (**Table 3**), prompting earlier consideration of treatment intensification, including in primary prevention.¹ At a high level, the guideline categorizes patients into risk groups: borderline/intermediate risk, high-risk, ASCVD not at very high risk, and very-high risk ASCVD. Risk enhancers (e.g. family history, inflammatory conditions) to consider in patients at borderline and intermediate risk are included in **Appendix 1**.

Table 3: Guideline Recommended Cholesterol Goals¹

ASCVD risk / clinical setting	LDL-C goal	Non-HDL-C goal
Borderline/intermediate primary prevention	<100 mg/dL	<130 mg/dL
High-risk primary prevention and ASCVD not at very high risk	<70 mg/dL	<100 mg/dL
ASCVD at very high risk	<55 mg/dL	<85 mg/dL
• <100 mg/dL: PREVENT-ASCVD risk < 10%; selected patients with diabetes, severe hypercholesterolemia, or subclinical atherosclerosis • <70 mg/dL: High-risk primary prevention (≥10% risk), including patients with diabetes or severe hypercholesterolemia plus additional ASCVD risk factors, ASCVD not at very high risk • <55 mg/dL: ASCVD at very high risk; also selected patients with severe hypercholesterolemia/FH or extensive subclinical atherosclerosis		
Abbreviations: ASCVD – atherosclerotic cardiovascular disease; FH – familial hypercholesterolemia; HDL-C – high density lipoprotein cholesterol; LDL-C – low density lipoprotein cholesterol		

Primary Prevention:

For all patients being assessed for ASCVD risk, a Strong recommendation with high-quality evidence supports health behavior recommendations. Moderate intensity statin initiation is recommended (Class 1 recommendation) for adults ages 30-79 for the primary prevention of ASCVD with intermediate risk (10-year risk 5% to < 10%) and borderline risk (Class 2 a recommendation) (3% to < 5%) when risk enhancers are present. High intensity statin therapy is recommended (Class 1 recommendation) for high-risk primary prevention (10-year risk ≥ 10%).¹ If LDL-C and non-HDL-C goals are not met in high-risk primary prevention, the guideline gives a Class 2a recommendation for adding ezetimibe and a Class 2b recommendation for adding a (proprotein convertase subtilisin/kexin type 9) PCSK9 monoclonal antibody or bempedoic acid.¹ Like the previous guidelines, moderate- to-high-intensity statins are recommended in adults with diabetes, depending on ASCVD risk factors.

Special Populations

The 2026 ACC/AHA dyslipidemia guideline also highlights special populations with increased risk of ASCVD events, independent of traditional risk factors. These include people living with HIV and adults with chronic kidney disease (CKD) stage 3 or higher.¹ A Class 1 recommendation supports starting statin therapy in people living with HIV who are on stable antiretroviral therapy. This recommendation is supported by the REPRIEVE trial, which demonstrated a reduction in the risk of major adverse cardiovascular events (MACE) with pitavastatin 4 mg once daily compared to placebo in patients with HIV and low to moderate ASCVD risk.⁵ Moderate intensity statin therapy is recommended in adults with CKD stage 3 or higher without ASCVD (Class 1 Recommendation). The guideline also recommends considering reproductive risk factors when personalizing decisions about lipid-lowering therapy initiation ¹

Clinical ASCVD:

Like the 2018 guidelines, the 2026 update categorizes those with clinical ASCVD as high risk and very high risk.¹ Very high risk includes patients with 2 or more major ASCVD events or 1 major ASCVD event plus 2 or more high-risk conditions. The guideline gives a Class 1 recommendation to initiate high intensity statin to achieve an LDL-C goal of ≤ 70 in high-risk ASCVD and ≤ 55 in very high-risk ASCVD.¹ A class 2a recommendation supports adding ezetimibe, bempedoic acid, or a PCSK9 inhibitor to achieve these goals, with no preference for one agent over another.

A clinical trial published after release of the 2026 guidelines found that evolocumab, a PCSK9 inhibitor, added to standard lipid lowering therapy reduces ASCVD events in patients without a history of MI or stroke who were at a high risk for a first major CV event.⁶ Half of the patients had high-risk diabetes. In this study, evolocumab reduced the risk of MACE (6.2% versus 8.0%; hazard ratio [HR] 0.75; 95% confidence interval [CI] 0.65 to 0.86).⁶ This is the first trial to demonstrate a CV benefit with a PCSK9 inhibitor in patients without prior MI or stroke, suggesting that intensive lipid lowering with PCSK9 inhibition may benefit selected patients with high ASCVD risk before a first major event.

Pharmacologic Therapy

Statins continue to be the recommended pharmacologic treatment for primary and secondary prevention of ASCVD. Non statin medications are recommended when LDL-C or non-HDL-C goals are not met based on risk category. Medications with proven CV risk reduction are prioritized (**Table 4**) for secondary ASCVD prevention, with no preference among ezetimibe, bempedoic acid, and PCSK9 inhibitors for patients with ASCVD.¹ The updated guideline recommends selecting a non-statin medication based on the degree of additional LDL-C lowering needed and patient preference.¹ Icosapent ethyl is the only triglyceride-lowering medication that has demonstrated a reduction in ASCVD events when added to statin therapy in

individuals at high ASCVD risk with moderate TG elevations (≥ 150 mg/dL).¹¹

Inclisiran is a small interfering ribonucleic acid (siRNA) that inhibits hepatic production of PCSK9, resulting in decreased circulating LDL-C levels.⁷ Inclisiran is administered subcutaneously every 6 months and demonstrated up to a 50% reduction in LDL-C when added to statin therapy.¹ However, CV outcome trials are still ongoing. The ACC/AHA guideline gives a Class 2a recommendation to consider inclisiran in adults with very-high-risk clinical ASCVD who cannot tolerate evolocumab or alirocumab or who have a strong preference for less frequent dosing.¹

Table 4: Cardiovascular Outcome Trials for Non-Statins¹

Drug	Patient	Duration	CV Outcome (ARR/NNT)	LDL-Lowering
Evolocumab	ACS	2 yr	1.5% / 67	60%
Alirocumab	ACS	3 yr	1.6% / 63	60%
Ezetimibe	ACS	6 yr	2% / 50	20%
Bempedoic acid	CVD or CV risk with SI	2 yr	1.6% / 63	25%
Icosapent Ethyl	CVD or CV risk and TG ≥ 150	5 yr	4.8% / 21	-

Abbreviations: ACS – acute coronary syndrome; ARR – absolute risk reduction; CV – cardiovascular; CVD – cardiovascular disease; NNT – number needed to treat; SI – statin intolerance; TG – triglycerides; yr – years

Newer Therapies

Apolipoprotein CIII (APOC3) inhibitors are a newer class of medications that reduce APOC3 protein through mRNA interference, leading to increased clearance of plasma triglycerides (TGs).⁸ Two FDA approved agents, olezarsen and plzasiran, are approved for TG lowering in patients with familial chylomicronemia syndrome (FCS). More recently, olezarsen was FDA approved for severe hypertriglyceridemia (TG ≥ 500 mg/dl) based on two phase 3 trials demonstrating significantly greater reductions in TG level at 6 months and a lower incidence of acute pancreatitis compared to placebo.

There are two newly approved PCSK9 inhibitors, lerodalcibep and enlicitide.^{9,10} Lerodalcibep is a smaller molecule that can be administered subcutaneously in a smaller volume once monthly and offers extended room-temperature stability for up to 3 months. It is FDA approved to reduce LDL-C in adults with hypercholesterolemia.⁹ Enlicitide is the first oral PCSK9 inhibitor indicated to reduce LDL-C in adults with hypercholesterolemia.¹⁰ The magnitude of LDL-C reduction is generally consistent with that observed with other monoclonal antibody PCSK9 inhibitors. Cardiovascular outcome trials are ongoing; until outcome data are available, PCSK9 inhibitors with

proven CV risk reduction, such as alirocumab and evolocumab, are preferred.

Key Takeaways from 2026 ACC/AHA Dyslipidemia Guideline

- Healthy dietary patterns, regular physical activity, maintenance of a healthy weight, healthy sleep, stress management, and avoidance of tobacco products should be emphasized to reduce ASCVD risk
- Consider Lp(a) measurement at least once in adulthood.
- ApoB can uncover residual risk despite acceptable LDL-C
- Lower LDL-C targets are becoming increasingly important for high-risk patients.
- Early intervention may produce greater lifetime cardiovascular benefits.
- Use PREVENT equations when assessing primary prevention risk
- Consider statin therapy earlier in patients with CKD, HIV, chronic inflammatory conditions, or other risk enhancing conditions
- If LDL-C goals are not achieved while on a maximally tolerated statin, consider adding ezetimibe, bempedoic acid, or PCSK9 inhibitors based on patient factors and LDL-C lowering

Conclusion

The 2026 ACC/AHA guideline shifts dyslipidemia management toward earlier, more intensive, and more individualized treatment, with greater emphasis on absolute LDL-C and non-HDL-C goals, PREVENT risk estimation, and Lp(a) and ApoB assessment. Newer therapies, including oral PCSK9 inhibitors and APOC3 inhibitors targeting severe hypertriglyceridemia, expand the available treatment options for patients with dyslipidemia. In primary care, clinicians should use the updated risk assessment and treatment goals to identify patients who may benefit from earlier statin therapy or addition of non-statin treatment while incorporating risk enhancers and patient preferences into shared decision-making

Peer Reviewed by: Tracy Klein, PhD, APRN, FAANP, FRE, FAAN, Professor, College of Nursing, WSU Faculty Regent, Washington State University Vancouver

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Appendix 1:

Table A1: ACC/AHA Guideline Class of Recommendations

Class I (strong)	Benefit >>> Risk
Class 2a (moderate)	Benefit >> Risk
Class 2b (weak)	Benefit ≥ Risk
Class 3 (No benefit)	Benefit = Risk
Class 3 (Harm)	Risk > Benefit

Table A2: ACC/AHA Guideline Level of Evidence

Level A	- High-Quality evidence from > 1 RCT - Meta-analysis of RCTs
Level B-R (randomized)	- Moderate quality evidence from 1 or more RCTs - Meta-analysis of moderate quality RCTs
Level B-R (nonrandomized)	- Moderate quality evidence from 1 or more nonrandomized studies - Meta-analysis of such studies
Level C-D (limited data)	- Studies with limitations in design or execution - Physiological or mechanistic studies
Level C-EO (Expert Opinion)	Consensus of expert opinion based on clinical experience

Table A3: Risk Enhancers

Risk Enhancers
- History of premature ASCVD in a parent or sibling - Higher risk ancestry (South Asian, Filipino) - High polygenic risk - Chronic inflammatory diseases - Lp(a) ≥ 125 nmol/L or ≥ 50 mg/dl - hsCRP ≥ 2 mg/dl on > 1 occasion - TG persistently ≥ 175 mg/dl (nonfasting) and ≥ 150 mg/dl (fasting) - Cardiovascular-kidney-metabolic syndrome - LDL-C ≥ 160-189 mg/dl, non-HDL-C ≥ 190-219 mg/dl or apoB ≥ 120 mg/dl - Reproductive risk markers (premature menopause, preeclampsia, gestational diabetes, gestational hypertension, preterm delivery)
Abbreviations: ASCVD – atherosclerotic cardiovascular disease; apoB – apolipoprotein B; HDL-C – high density lipoprotein-cholesterol; hsCRP – high sensitivity C-reactive protein; LDL-C: low density lipoprotein-cholesterol; Lp(a): lipoprotein (a); TG-triglycerides