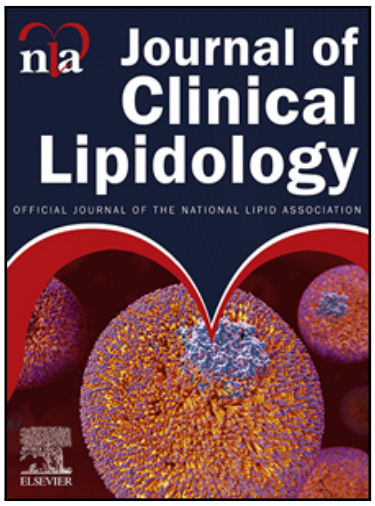

LDL Cholesterol Management Simplified in (Adults) - Lower for Longer is Better: Guidance from the National Lipid Association

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Highlights

- LDL-C is a well-established causal factor for the development of atherosclerotic cardiovascular disease (ASCVD) that should be monitored in a timely manner and may be modified through both lifestyle and pharmaceutical interventions.
- The primary goals for LDL-C management are to achieve an acceptable level for the patient's risk category and to maintain that over time.
- **L*ower LDL-C for longer is better*** to reduce ASCVD risk.
- Despite the existence of cholesterol guidelines, universal screening ages, risk assessment tools, and recommendations for LDL-C management based on risk, data show that LDL-C measurement and management in patients with ASCVD are not meeting guideline-directed objectives.

LDL Cholesterol Management Simplified in (Adults) - Lower for Longer is Better: Guidance from the National Lipid Association

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Abstract
ASCVD remains the #1 cause of death in the United States and has been on the rise for more than a decade after more than 40 years of steady decline. Low-density lipoprotein cholesterol (LDL-C) is a well-established causal factor for the development of ASCVD that should be monitored in a timely manner and may be modified through both lifestyle and pharmacological interventions. The primary goals for LDL-C management are to achieve an acceptable level for the patient's risk category and to maintain that over time because lower for longer is better to reduce ASCVD risk.

Despite the existence of cholesterol guidelines, universal screening ages, risk assessment tools, and recommendations for LDL-C management based on risk, data show that LDL-C measurement and management in patients with ASCVD are not meeting guideline-directed

objectives. Further, there is no single clinical guideline that presents LDL-C measurement frequency, risk assessment, management, and desirable LDL-C levels for adults based on risk.

This document aims to summarize the numerous guidelines and recommendations from leading professional organizations to help clinicians and patients improve evidence-based measurement and management of LDL-C.

LDL Cholesterol Management Simplified (Adults) - Lower for Longer is Better: Guidance from the National Lipid Association

This document is designed to offer straightforward guidance to primary care providers in family practice, internal medicine, pediatrics, obstetrics/gynecology, and other clinicians who manage lipids.

Key Points:

1. Morbidity and mortality associated with atherosclerotic cardiovascular disease (ASCVD) are on the rise after decades of steady decline, with an increasing incidence observed in younger and middle-aged populations; ASCVD remains the #1 cause of death in the US.[1]
2. Low-density lipoprotein (LDL) is the building block of arterial wall plaque.[2]
3. Low-density lipoprotein cholesterol (LDL-C) is a validated marker for the amount of plasma LDL. It is a surrogate marker for the burden of circulating atherogenic lipoproteins which are the primary drivers of intimal plaque formation.[3]
4. Reducing LDL-C improves ASCVD outcomes.[4]
5. With treatment, ASCVD events are reduced proportionately to the degree of LDL-C lowering.[5]
6. The level of ASCVD risk should inform intensity of treatment to lower LDL-C.
7. Lipid panel testing should be done regularly in adults to evaluate ASCVD risk and to monitor effectiveness and adherence to LDL-C lowering treatment.[5]
8. Evidence shows that achieving LDL-C levels as low as 10-40 mg/dL is safe for patients.[6, 7]
9. Referrals to lipid specialists should be considered for care of the complex patient.
10. **The primary goals for LDL-C management are to achieve an acceptable level for the patient's risk category and to maintain that over time because *lower for longer is better* to reduce ASCVD risk.**

Introduction

The wealth of accumulative data from clinical trials, genetic studies, registries, and real-world experiences, combined with the growing array of effective therapies and evolving treatment targets, has resulted in extensive and complex guidelines. These guidelines often vary among expert groups and can be challenging to interpret and tailor to individual patients. This article is intended to provide a clear and concise reference which simplifies LDL-C management for non-lipid specialists.

LDL-C as a biomarker of ASCVD risk

ASCVD is the leading cause of death in the United States (US) and globally, accounting for approximately 25% of all deaths in the US. Fixed and modifiable risk factors for the development of ASCVD include:

- Sex
- Age
- Family history and genetic predisposition
- Overweight and obesity

- Smoking and other forms of nicotine use
- Hypertension
- Insulin resistance, pre-diabetes, diabetes mellitus
- Atherogenic lipoproteins including LDL-C, lipoprotein(a), and triglyceride-rich remnants
- Pro-inflammatory and pro-thrombotic conditions such as chronic systemic inflammatory diseases
- Poor sleep quality and/or quantity, as well as social determinants of health are emerging risk enhancing factors

ASCVD mortality rates have been on the rise since 2010, reversing a >4 decade trend of decline in age adjusted mortality rates due to ASCVD, with data indicating that estimated ASCVD prevalence in the US has increased from 18.3 million in 2014 to 24 million in 2019 with 31.2% considered to be very high-risk for recurrent events:[8] There is also a disproportionate increase in rates of ASCVD in younger and middle-aged populations.

Primary and secondary prevention of ASCVD requires an accurate estimation of risk of both future and recurrent cardiovascular events. Risk assessments must reflect a combination of clinical and demographic information, including information from lipid panel results.

The LDL-C level is the focus of this article and is a highly relevant biomarker (indicator) of ASCVD risk, with high LDL-C generally indicative of high ASCVD risk and very low LDL-C levels generally indicative of low ASCVD risk (in the absence of other major risk factors).[3] While LDL-C remains the primary target for lipid-lowering therapy and is a strong marker of ASCVD risk, it does not fully capture the burden of atherogenic lipoproteins in all patients. In individuals with hypertriglyceridemia, diabetes, obesity, or metabolic syndrome, non–HDL-C and apolipoprotein B (apo B) offer superior risk assessment by accounting for all atherogenic particles. The National Lipid Association (NLA) and other major guidelines recommend consideration of apo B or non–HDL-C as secondary targets, particularly in high-risk patients or when triglyceride levels are elevated. Inclusion of these markers supports a more comprehensive approach to risk stratification and treatment optimization beyond LDL-C alone.[9]

Major adverse cardiovascular events (MACE) are reduced proportionately to the **degree of LDL-C lowering**, the **level of LDL-C lowering achieved, and the length of time over which a lower level is maintained.** There is a dose dependent, log-linear, independent association between the magnitude of exposure to LDL-C and the risk of ASCVD events.[4] Further, numerous randomized controlled trials (RCTs) with LDL-C lowering medicines, including statin and non-statin therapies, demonstrate a linear relationship between LDL-C reduction and relative ASCVD risk reduction. Together, these results have informed clinical guidelines, clinical practice, and the guidance supporting the view that lower for longer is better.[9]

Lipid Panel/LDL-C Screening Frequency

National and international guidelines provide that all adults should have lipids evaluated at least every 5 years.[4] Adults who are at increased risk due to diabetes, family history of elevated lipids, premature heart disease or stroke should be checked more frequently (annually). Finally, individuals on lipid-lowering therapy should have lipids assessed 4-12 weeks after initiating therapy, or dose adjustment, and every 3-12 months thereafter to monitor therapeutic response and adherence, as appropriate.

For completeness, all children should have their lipid panel screened between the ages of 9-11 and again between the ages of 17-21.[11] If there is a family history of familial hypercholesterolemia (FH) or significant premature coronary disease in first degree relatives, testing as early as age 2 should be performed.

Universal Lipid Screening: Guideline-Directed Intervals		
Children 9-11 Years Old	Young Adults 17-21 Years Old	Adults 21+ Years Old
		

Additional Lipid Screening Intervals	
4-12 Weeks	4-12 weeks after initiating lipid-lowering therapy or dose change to assess response & adherence.
3-12 Months	Every 3-12 months thereafter to monitor response & adherence to lipid-lowering therapy.
Annually	Individuals (1) at increased risk for heart disease, stroke, and other CVD risk or (2) on lipid-lowering therapy.
Young Children	Children with a family history of (1) hypercholesterolemia or (2) early CVD should have lipids tested as early as 2 years of age.

Desirable LDL-C Targets for Adults

LDL-C management should be individualized based on each patient's specific situation. Evidence supports an LDL-C target of <100 mg/dL for healthy adults in the general population. Individuals at risk for ASCVD, including those with very high baseline LDL-C levels suggestive of a genetic cause such as familial hypercholesterolemia (FH), individuals with multiple risk factors for ASCVD, or those already diagnosed with ASCVD, may require lower LDL-C levels. Higher plaque burden and higher plaque progression rate are situations where more intensive LDL-C lowering therapy should be considered.

Adult Populations	Desirable LDL-C
Optimal LDL-C for Healthy Adults[4]	< 100 mg/dL
Patients with: • No clinical ASCVD and baseline LDL-C ≥190 mg/dL • Calculated 10-year ASCVD risk of 7.5-19.9% by American Heart Association/American College of Cardiology pooled cohort equation	< 100 mg/dL
High-Risk CVD patients,[12] including those with: • Familial Hypercholesterolemia, without a prior event • Type 2 diabetes mellitus • Clinical ASCVD without other high-risk features • Primary prevention with an estimated 10-year risk of an event ≥ 20% in pooled cohort risk calculation • Coronary artery calcium score >100 AU or ≥75th percentile of the score distribution for age and sex	< 70 mg/dL
Very High-Risk CVD Patients,[12] including those with multiple major events or with multiple high-risk conditions: • Major ASCVD Events: ◦ Recent acute coronary syndrome (within 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 ABI <0.85 or previous revascularization) • High-Risk Conditions: ◦ Age ≥65 years ◦ Heterozygous familial hypercholesterolemia ◦ History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s) ◦ Diabetes mellitus ◦ Hypertension ◦ Chronic kidney disease (estimated glomerular filtration rate 15-59 mL/min/1.73m^2) ◦ Current smoking ◦ Persistently elevated LDL-C (LDL-C ≥100 mg/dL despite maximally tolerated statin therapy and ezetimibe) ◦ History of congestive heart failure	< 55 mg/dL

Special considerations[12]

- LDL-C >190 in adults indicates severe hypercholesterolemia and may identify familial hypercholesterolemia. The initial goal of therapy is at least a 50% reduction in LDL-C with adjustment based on comorbidities.
- Following a major cardiovascular event occurring while on optimal therapy for lipid lowering, further adjunctive therapy is warranted.

How Low Can You Go? Safety of Low LDL-C

With the pharmacological resources currently available, we can achieve unprecedented LDL-C reduction, which raises the question whether it is possible to achieve an LDL-C level that is "too low." RCTs, population, and genetic studies of low LDL-C provide insight.

Healthy infants are born with LDL-C levels between 30-70 mg/dL which remains low during the life stage with the greatest growth and development.[6] Additionally, individuals who inherit genetic variants that cause lifetime exposure to low LDL-C appear to have normal life expectancy, no sign of end-organ compromise, or other related pathological conditions. The exception are those individuals who develop medical complications due to the presence of a rare genetic variant, whereby they are unable to form certain lipoprotein particles.[13] Many studies point to the safety of low LDL-C levels and progressively lower risk of ASCVD events down to levels below 30 mg/dL. No evidence of harm has been identified including in other metabolic pathways which utilize cholesterol in their synthesis, such as neural sheath formation.[14]

There are some studies showing possible links to increased incidence or accelerated diagnosis of diabetes in patients on statins, incidence of hemorrhagic stroke, and cataract formation, but each of these require long term follow-up studies to determine causality. Currently the analysis of benefit compared to harm strongly favors statin use in those with sufficient ASCVD risk to warrant pharmacologic intervention.[15]

Lifestyle Modification to lower LDL-C

Guidelines for treating conditions such as high LDL-C emphasize the importance of healthy lifestyle habits. These topics should be discussed with every patient at every visit:[16]

- Healthy eating patterns
- Regular exercise
- Adequate restorative sleep
- Avoiding risky behaviors (e.g. tobacco use, excessive alcohol)
- Stress management
- Fostering healthy relationships

Nutrition and healthy dietary patterns play a crucial role in lowering and maintaining LDL-C levels. To improve dietary habits, patients should replace foods high in saturated fats and heavily processed items with options that are rich in fiber, such as fruits, vegetables, whole grains, and lean protein sources, all of which have been shown to help lower LDL-C and are consistent with a plant-forward approach. If cooking oil is used, oils rich in unsaturated fatty acids are preferred over saturated fatty acids. The following diagram, modified from Nutrition interventions for adults with dyslipidemia: **A Clinical Perspective from the National Lipid Association**, depicts dietary patterns that are either favorable or detrimental to lipids and overall health.[17]

Foods & Components to Emphasize	Foods & Components to Limit	Examples of Healthy Dietary Patterns

• Fruit, with emphasis on whole fruit
• Vegetables, especially colorful vegetables
• Whole grains
• Healthy protein sources
  ◦ Nut, seeds, legumes/pulses
  ◦ Fish & other seafood
  ◦ Low-fat or fat-free dairy products
  ◦ Lean cuts of meat or poultry
• Non-tropical, plant oils
	• Foods high in saturated & trans fatty acids
	  ◦ Animal fats
	  ◦ Tropical oils
	• Processed meats
	• Refined grains & added sugars
	• Highly processed foods
	• Foods with high sodium content
	• Alcohol
		• Mediterranean
		• DASH (Dietary Approaches to Stop Hypertension)
		• Healthy vegetarian/vegan
		• Healthy U.S. style

LDL-C Pharmacological Treatment

Patients at risk for ASCVD may benefit from pharmacotherapy, including those with very high baseline LDL-C levels suggestive of a genetic cause such as familial hypercholesterolemia (FH), individuals with multiple risk factors for ASCVD, or those already diagnosed with ASCVD.

Statin therapy, which is the cornerstone of pharmacotherapy for LDL-C reduction, reduces ASCVD risk in most individuals, and may be sufficient to reach desirable LDL-C levels. Based on the Cholesterol Treatment Trialists Collaboration meta-analysis of 27 statin RCT's (statin vs. placebo and high intensity vs. moderate intensity statin), for every 1 mmol/L (~39 mg/dL) reduction in LDL-C there is a corresponding 22% reduction in ASCVD event risk.[18] It should be noted that statin therapy does not seem to reduce ASCVD in adults receiving hemodialysis or those who have significant heart failure. However, stopping statin therapy in these individuals is not advised if it is well tolerated. Additionally, other proven LDL-C lowering therapies have also been shown to safely lower LDL-C and reduce ASCVD risk and should be used if statin therapy alone does not achieve therapeutic objectives or is not tolerated.[10]

Statin Medicines	
Medicine	**Anticipated* % LDL-C Reduction**
Low-Intensity Statins ☐ Simvastatin 10 mg ☐ Lovastatin 20 mg ☐ Pravastatin 10-20 mg ☐ Fluvastatin 20-40 mg	**<30%**
Moderate-Intensity Statins ☐ Atorvastatin 10-20 mg ☐ Pravastatin 40-80 mg ☐ Rosuvastatin 5-10 mg ☐ Pitavastatin 1-4 mg ☐ Simvastatin 20-40 mg ☐ Fluvastatin XL 80 ☐ Lovastatin 40-80 mg ☐ Fluvastatin 40 mg (twice daily)	**30-49%**
High-Intensity Statins ☐ Atorvastatin 40-80 mg ☐ Rosuvastatin 20-40 mg	**≥50%**

A subset of patients may be partially or completely intolerant to statins, have very high LDL-C levels that are not adequately reduced by tolerated statin doses, exhibit a refractory response to therapy due to genetic factors, or require other disease state medications that preclude statin use.[19] In such cases, non-statin therapies may be required to achieve optimal LDL-C reduction. Given the variability in individual response to statins, even at full therapeutic doses, **routine monitoring for both efficacy and tolerability is essential to guide ongoing management.**[5]

Use of statin monotherapy supported by lifestyle changes may be sufficient to reach desirable LDL-C levels, however, other proven pharmacotherapies are also available to optimize LDL-C. Based upon contemporary clinical trial evidence, LDL-C lowering therapy should start with statins, then if response is incomplete, or a statin regimen that is tolerated cannot be found, non-statin LDL-C lowering pharmacotherapy should be considered. The specific medicine should be selected based upon a variety of factors including:

- Safety
- Tolerability
- LDL-C lowering efficacy
- RCT evidence supporting use
- Desirable LDL-C and expectations of treatment
- Patient preference
- Convenience and cost of therapy
- Availability

Non-statin LDL-C lowering pharmacotherapy also reduces ASCVD risk. Contemporary RCTs demonstrate ASCVD risk reduction in adults when ezetimibe is added to moderate intensity statin. Similarly, those in whom PCSK9 monoclonal antibody inhibition (PCSK9i) is added to high-intensity statin therapy, and even in individuals with stable ASCVD for whom PCSK9i are added to high-intensity statins, attain increased risk reduction.[12]

Bempedoic acid, another non-statin, has demonstrated ASCVD risk reduction in high-risk adults, especially those with diabetes mellitus, who are on low dose or no statin because of statin intolerance. High dose icosapent ethyl has minimal impact on LDL-C, but demonstrated ASCVD risk reduction in adults with established ASCVD or high-risk patients with diabetes with hypertriglyceridemia.[12]

Non-Statin Medicines
to Add to Statin Therapy for Further LDL-C Lowering

Medicine	Anticipated* % LDL-C Reduction	MACE Benefit
☐ Ezetimibe	**15-25%**	**Yes**
Bempedoic Acid		
☐ Bempedoic acid	**14-21%**	**Yes**
☐ Bemepdoic acid + ezetimibe	**30-47%**	**Yes**
PCSK9 Inhibitor		
☐ Alirocumab 75 mg Q2W^	**47%**	**Yes**
☐ Alirocumab 150 mg Q2W^	**58%**	**Yes**
☐ Evolocumab 140 mg Q2W^	**60%**	**Yes**
☐ Inclisiran	**50%**	**Pending**

^Every 2 weeks
PCSK9: proprotein convertase subtilisin/kexin type 9
MACE: Major adverse cardiovascular event

While niacin is no longer recommended as a routine therapy for LDL-C lowering or ASCVD risk reduction due to lack of incremental benefit when added to statins in contemporary trials, it may still have a limited role in select clinical scenarios. Historical data prior to the availability of statins, demonstrate that niacin monotherapy reduced ASCVD events and mortality in men with established cardiovascular disease. Although current guidelines favor other non-statin therapies due to superior efficacy and tolerability, niacin may be considered in rare cases of multidrug intolerance or if cost or access constraints limit other options.[20]

Bile acid sequestrants can be used in contemporary care, but they have a high degree of limiting side effects of bloating and constipation. Older trials suggested benefit from bile acid

sequestrants, but this drug class has been mostly abandoned because of difficult side effects and modest potency.[21]

Two other pharmacotherapies are FDA-approved for LDL-C lowering specifically in individuals with the rare condition homozygous FH: lomitapide and evinacumab, but further details will not be reviewed here.[12] Similarly, apheresis remains an option by which to achieve optimal LDL-C and Lp(a) lowering, but these treatments are reserved for special situations that generally require a clinical lipid specialist.

Therefore, non-statin medications are most often used as an adjunct to statin therapy, but in individuals who are unable to tolerate any dose of any statin, there is no contraindication to utilizing them as monotherapy.

The risk of atherosclerotic cardiovascular disease (ASCVD) events is directly proportional to the achieved LDL-C concentration, with benefit observed down to levels below 20 mg/dL.[6] Reflecting this relationship, some international guidelines endorse aggressive LDL-C lowering in very high-risk populations. The European Atherosclerosis Society recommends an LDL-C goal of <40 mg/dL for patients with recurrent events, while the Lipid Association of India advocates for a target <30 mg/dL in individuals classified as extreme risk.[22,23]

The crucial message for patients is to emphasize the goal of lipid lowering therapy as an important mechanism to reduce ASCVD risk. Specifically:

- LDL-C is the building block for atheroma formation (arterial plaque) and
- **Reducing plasma LDL-C** allows healing and regression of atherosclerotic plaque burden, and thus improves outcomes related to CVD morbidity and mortality.

Find a Lipid Specialist

Mitigating ASCVD risk involves a multifaceted approach that stresses the importance of a medical team. A certified Lipid Specialist brings specialized training in complex lipid management, enabling comprehensive evaluation, treatment, and ongoing monitoring. They collaborate with the primary care team and engage essential teammates to ensure coordinated and effective care. Key aspects of care include:

- Diagnosis and management of the underlying causes of hyperlipidemia
- Assessment of ASCVD risk
- Identification and management of comorbidities and risk-enhancing factors
- Optimal treatment:
    - Thoughtful recommendation of appropriate drug therapies
    - Assessment of medical protocols potentially adversely affecting lipid profile results
    - Escalation of treatment as needed through dose adjustments of statins, transitions to higher-potency statins, or introduction of non-statin adjunctive or monotherapy options

The National Lipid Association defines a Lipid Specialist as a healthcare professional certified by the American Board of Clinical Lipidology (ABCL) specializing in the identification and

management of dyslipidemias and related metabolic disorders which lead to atherosclerotic cardiovascular disease (ASCVD) and other morbidities.

The ABCL offers the only certification of its kind for licensed physicians, Advanced Practice Professionals, and other healthcare professionals in the United States and Canada. Physicians designated as Diplomates of the American Board of Clinical Lipidology and other healthcare professionals designated as Clinical Lipid Specialists (CLS) demonstrate their commitment to improving the care for patients with dyslipidemia and related comorbidities.[24] To find a lipid specialist, visit https://www.learnyourlipids.com/find-a-clinician/.

Conclusion

In conclusion, LDL-C is a well-established causal factor for the development of ASCVD that should be monitored in a timely manner and may be modified through both lifestyle and pharmaceutical interventions.

Remember, for LDL-C: ***lower for longer is better***.

Note, measurement and management of LDL-C does not lessen the importance of attention to other elements of the lipid profile, including lipoprotein (a), triglycerides, and very low-density lipoproteins, as well as management of other modifiable ASCVD risk factors.

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