

Original Articles

# National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1 – executive summary



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**Abstract:** Various organizations and agencies have issued recommendations for the management of dyslipidemia. Although many commonalities exist among them, material differences are present as well. The leadership of the National Lipid Association (NLA) convened an Expert Panel to develop a consensus set of recommendations for patient-centered management of dyslipidemia in clinical medicine. The current Executive Summary highlights the major conclusions in Part 1 of the recommendations report of the NLA Expert Panel and includes: (1) background and conceptual framework for formulation of the NLA Expert Panel recommendations; (2) screening and classification of lipoprotein lipid levels in adults; (3) targets for intervention in dyslipidemia management; (4) atherosclerotic cardiovascular disease risk assessment and treatment goals based on risk category; (5) atherogenic cholesterol—non-high-density lipoprotein cholesterol and low-density lipoprotein cholesterol—as the primary targets of therapy; and (6) lifestyle and drug therapies intended to reduce morbidity and mortality associated with dyslipidemia.

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Various organizations and agencies have issued recommendations for the management of dyslipidemia.<sup>1-7</sup> Although many commonalities exist among them, material differences are present as well. The leadership of the National Lipid Association (NLA) convened an Expert Panel to develop a consensus set of recommendations for patient-centered management of dyslipidemia in clinical medicine.

The current Executive Summary highlights the major conclusions in Part 1 of the recommendations report of the NLA Expert Panel. The Executive Summary does not include a comprehensive reference list, but citations have been included for several key publications. The full report will include additional details on the rationale for the recommendations and citations to published research considered in the panel's deliberations. A presentation containing the main elements of these recommendations was made available to the public and other organizations involved with the prevention of atherosclerotic cardiovascular disease (ASCVD) to solicit input during an open comment period. Comments and suggestions were received from many members of the NLA as well as other individuals and organizations and were collated for consideration and adjudication by the panel in formulating the final set of recommendations contained herein.

Part 1 of the NLA Expert Panel Recommendations for Patient-Centered Management of Dyslipidemia, will cover:

- Background and conceptual framework for formulation of the NLA Expert Panel recommendations;
- Screening and classification of lipoprotein lipid levels in adults;
- Targets for intervention in dyslipidemia management;
- ASCVD risk assessment and treatment goals based on risk category;
- Atherogenic cholesterol—non-high-density lipoprotein cholesterol (non-HDL-C) and low-density lipoprotein cholesterol (LDL-C)—as the primary targets of therapy; and
- Lifestyle and drug therapies intended to reduce morbidity and mortality associated with dyslipidemia.

Part 2 is in development and will cover the following topics:

- Lifestyle therapies;
- Groups with special considerations:
  - Children, adolescents, pregnant women, and older patients;
  - Gender and ethnic differences;
  - Patients with congestive heart failure;
  - Patients with human immunodeficiency virus;
  - Patients with selected chronic inflammatory states and immune disorders;
  - Patients with residual risk despite statin therapy;
- Strategies to assist with patient adherence; and
- Team-based collaborative care.

## Background and conceptual framework for formulation of the NLA Expert Panel recommendations

Clinical decisions often need to be made in the absence of ideal or complete evidence, and well-informed experts will not always evaluate or interpret the evidence base in the same way. Clinical recommendations aim to assist clinicians in making decisions about the best strategies for management of a condition, taking into account potential benefits and risks of the available options. An overarching principle in the NLA Expert Panel recommendations is that they are intended to inform, not replace, clinical judgment. A *patient-centered* approach dictates that clinical judgment take into account the circumstances, objectives, and preferences of each individual patient.<sup>7,8</sup> The patient should be an active participant in the process, having engaged with the clinician in a dialogue about the objectives of therapy, including potential risks and side effects as well as benefits and costs. When patients understand and participate in decisions to select specific treatment strategies, this tends to enhance commitment to long-term adherence.

The NLA recognizes the major contribution that dyslipidemia management has made to the progressive reduction in ASCVD morbidity and mortality that has been observed during the past decade.<sup>9</sup> This reduction in risk occurred under the guidance provided by previous documents, most notably the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) Guidelines.<sup>1,10</sup> The NLA Expert Panel consensus view is that the evidence that has accumulated since the 2004 update of the NCEP ATP III guidelines warrants a modest refinement of previous lipid-related risk management strategies, as outlined in the present report.

The evidence base considered in the development of consensus for these recommendations emphasized results from randomized controlled trials (RCTs) to evaluate interventions on clinical ASCVD events (mainly myocardial infarction, coronary death, and stroke), including subgroup assessments and pooled analyses from multiple trials, where available. Although the panel acknowledges that the primary results from RCTs represent the strongest evidence from which to draw conclusions about benefits and risks of treatment strategies, it also recognizes that the available RCT evidence has limitations, and is often incomplete, or of uncertain relevance to patients with characteristics that may differ in important ways from those who participated in the RCTs. Therefore, evidence from epidemiological and genetic studies as well as metabolic and mechanistic investigations has also been considered.

## Major conclusions of the NLA Expert Panel

The NLA Expert Panel found the evidence to be compelling to support the following conclusions, which guided the development of the recommendations.

1. An elevated level of cholesterol carried by circulating apolipoprotein (apo) B-containing lipoproteins (non-HDL-C and LDL-C, termed *atherogenic cholesterol*) is a root cause of atherosclerosis, the key underlying process contributing to most clinical ASCVD events.
2. Reducing elevated levels of atherogenic cholesterol will lower ASCVD risk in proportion to the extent that atherogenic cholesterol is reduced. This benefit is presumed to result from atherogenic cholesterol lowering through multiple modalities, including lifestyle and drug therapies.
3. The intensity of risk-reduction therapy should generally be adjusted to the patient's absolute risk for an ASCVD event.
4. Atherosclerosis is a process that often begins early in life and progresses for decades before resulting in a clinical ASCVD event. Therefore, both intermediate-term and long-term/lifetime risk should be considered when assessing the potential benefits and hazards of risk-reduction therapies.
5. For patients in whom lipid-lowering drug therapy is indicated, statin treatment is the primary modality for reducing ASCVD risk.
6. Non-lipid ASCVD risk factors should also be managed appropriately, particularly high blood pressure, cigarette smoking, and diabetes mellitus.

### Importance of lifestyle therapies

An additional tenet of the NLA Expert Panel recommendations is the centrality of lifestyle therapies to ASCVD prevention. The application of pharmacotherapy to dyslipidemia management has been enormously successful. Many large-scale RCTs, involving, in aggregate, hundreds of thousands of participants, have shown that drug therapies (particularly statins) that lower atherogenic cholesterol levels are effective for reducing ASCVD morbidity and mortality. However, results from observational studies also strongly suggest that lifestyle habits have an important impact on atherogenic cholesterol levels as well as other related disturbances such as obesity, hypertension, and insulin resistance. Thus, although drug therapy may be needed in those with sufficient risk, the NLA Expert Panel's consensus view was that lifestyle therapies are an important element of risk-reduction efforts, whether or not drug therapy is also used.

### Usefulness of treatment goals

Most RCTs of lipid-lowering drug therapies have tested drug treatment against a placebo control, or a more intensive with a less-intensive treatment regimen. The strategy of treating patients to a specific level of LDL-C or non-HDL-C has not been tested in any of the large trials assessing ASCVD morbidity and mortality. Nevertheless, taken together, results from RCTs that have employed various methods for lowering atherogenic cholesterol (pharmacotherapy, diet,

ileal bypass surgery) have indicated that lower on-treatment levels have been consistently associated with lower absolute risk for an ASCVD event.<sup>5,11</sup> These findings align with results from observational studies that suggest a log-linear relationship between the levels of atherogenic cholesterol and absolute ASCVD event risk.

The Expert Panel's consensus view is that treatment goals are useful as means to ensure that the aggressiveness of therapy to lower atherogenic cholesterol is matched to absolute risk for an event. Moreover, treatment goals facilitate effective communication between patients and clinicians, providing an easily interpretable means through which the clinician can communicate progress toward meeting treatment objectives, thus supporting efforts to maximize long-term adherence to the treatment plan.

### Screening and classification of initial lipoprotein lipid levels

In all adults ( $\geq 20$  years of age), a fasting or nonfasting lipoprotein profile should be obtained at least every 5 years. At a minimum, this should include total cholesterol and HDL-C, which allows calculation of non-HDL-C (total cholesterol minus HDL-C). If fasting (generally 9 to 12 hours), the LDL-C level may be calculated, provided that the triglyceride concentration is  $< 400$  mg/dL. Classifications for lipoprotein lipid levels are shown in [Table 1](#).

**Table 1** Classifications of cholesterol and triglyceride Levels in mg/dL

<b>Non-HDL-C*</b>	
<130	Desirable
130–159	Above desirable
160–189	Borderline high
190–219	High
$\geq 220$	Very high
<b>LDL-C</b>	
<100	Desirable
100–129	Above desirable
130–159	Borderline high
160–189	High
$\geq 190$	Very high
<b>HDL-C</b>	
<40 (men)	Low
<50 (women)	Low
<b>Triglycerides</b>	
<150	Normal
150–199	Borderline high
200–499	High
$\geq 500$	Very high <sup>†</sup>

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol.

\*Non-HDL-C = total cholesterol minus HDL-C.

<sup>†</sup>Severe hypertriglyceridemia is another term used for very high triglycerides in pharmaceutical product labeling.

Lipoprotein lipid levels should be considered in conjunction with other ASCVD risk determinants to assess treatment goals and strategies, as covered later in this report.

If atherogenic cholesterol levels (non-HDL-C and LDL-C) are in the desirable range, lipoprotein lipid measurement and ASCVD risk assessment should be repeated in 5 years, or sooner based on clinical judgment. Examples of changes that might prompt earlier rescreening include changes in ASCVD risk factors (including weight gain), a premature ASCVD event in a first-degree relative, evidence of ASCVD in the patient, or a new potential secondary cause of dyslipidemia. For those with atherogenic cholesterol in the desirable range, public health recommendations regarding lifestyle should be emphasized.

## Targets of intervention in dyslipidemia management

### Non-HDL-C and LDL-C

When intervention beyond public health recommendations for long-term ASCVD risk reduction is employed, levels of atherogenic cholesterol (non-HDL-C and LDL-C) should be the primary targets for therapies. LDL-C comprises ~75% of the cholesterol in circulation carried by lipoprotein particles other than HDL, although this percentage may be lower in those with hypertriglyceridemia.

Although LDL-C has traditionally been the primary target of therapy, the NLA Expert Panel's consensus view is that non-HDL-C is a better primary target for modification than LDL-C. Non-HDL-C comprises the cholesterol carried by all potentially atherogenic particles, including LDL, intermediate density lipoproteins, very low-density lipoproteins (VLDL) and VLDL remnants, chylomicron remnants, and lipoprotein (a). Epidemiological studies have shown that non-HDL-C is a stronger predictor of ASCVD morbidity and mortality than LDL-C.<sup>12</sup> Pooled analyses of data from intervention studies have shown that non-HDL-C changes and levels during treatment are more strongly associated with risk for coronary heart disease (CHD) than changes in LDL-C or on-treatment levels of LDL-C.<sup>13,14</sup> Moreover, when on-treatment values are discordant (i.e., only 1 of the 2 is elevated), risk is more closely aligned with non-HDL-C than LDL-C.<sup>14</sup>

Possible explanations for the superiority of non-HDL-C over LDL-C for predicting ASCVD event risk include: (1) as with LDL, some triglyceride-rich lipoprotein remnants enter the arterial wall, and thus contribute to the initiation and progression of atherosclerosis, (2) non-HDL-C correlates more closely than LDL-C with apo B, thus more closely correlates with the total burden of atherogenic particles, and (3) elevated levels of triglycerides and VLDL-C reflect hepatic production of particles with greater atherogenic potential, such as those having poor interactivity with hepatic receptors, resulting in longer residence time in the circulation.

Although both non-HDL-C and LDL-C are termed atherogenic cholesterol, non-HDL-C is listed first to emphasize its primary importance. Both non-HDL-C and LDL-C are considered targets for lipid-altering therapy, and goals for therapy have been defined for both (Tables 2 and 3). Using non-HDL-C as a target for intervention also simplifies the management of patients with high triglycerides. Non-HDL-C incorporates the triglyceride level indirectly, because the triglyceride concentration is highly correlated with the VLDL-C concentration. Goal levels of non-HDL-C may be attained by targeting either or both of the main components of non-HDL-C; LDL-C and VLDL-C. However, it should be emphasized that goal thresholds apply to non-HDL-C and LDL-C, because discordance may occur, and effective management of atherogenic cholesterol would ideally result in achieving goal levels for both.

Desirable levels of atherogenic cholesterol for primary prevention (ie, those without clinical evidence of ASCVD or other very high-risk conditions) are <130 mg/dL for non-HDL-C and <100 mg/dL for LDL-C (Tables 2 and 3). Support for these thresholds derives primarily from population studies showing low ASCVD incidence rates in groups with levels in these ranges, including those with genetic variants that result in below-average levels of atherogenic cholesterol throughout life.<sup>15</sup> These levels are further supported by data from RCTs showing that risk for ASCVD events is reduced with a variety of atherogenic cholesterol-lowering interventions, including cholesterol-lowering drugs and dietary modification, in a pattern that is generally consistent with expectations based on observational evidence.<sup>5,16–19</sup>

### Apo B

Apo B is considered an optional, secondary target for treatment. Epidemiological studies have generally shown that both apo B and non-HDL-C are better predictors of ASCVD risk than LDL-C. Because each potentially atherogenic lipoprotein particle contains a single molecule of apo B, the apo B concentration is a direct indicator of the number of circulating particles with atherogenic potential. Apo B and non-HDL-C share the advantage that neither requires fasting for accurate assessment. Non-HDL-C is

**Table 2** Treatment goals for non-HDL-C, LDL-C, and Apo B in mg/dL

Risk Category	Treatment Goal		
	Non-HDL-C	LDL-C	Apo B*
Low	<130	<100	<90
Moderate	<130	<100	<90
High	<130	<100	<90
Very High	<100	<70	<80

Apo, apolipoprotein; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol.

\*Apo B is a secondary, optional target of treatment.

**Table 3** Criteria for ASCVD risk assessment, treatment goals for atherogenic cholesterol, and levels at which to consider drug therapy

Risk category	Criteria	Treatment goal		Consider drug therapy	
		Non-HDL-C mg/dL	LDL-C mg/dL	Non-HDL-C mg/dL	LDL-C mg/dL
Low	<ul style="list-style-type: none"> <li>• 0–1 major ASCVD risk factors</li> <li>• Consider other risk indicators, if known</li> </ul>	<130	<100	≥190	≥160
Moderate	<ul style="list-style-type: none"> <li>• 2 major ASCVD risk factors</li> <li>• Consider quantitative risk scoring</li> <li>• Consider other risk indicators*</li> </ul>	<130	<100	≥160	≥130
High	<ul style="list-style-type: none"> <li>• ≥3 major ASCVD risk factors</li> <li>• Diabetes mellitus (type 1 or 2)<sup>†</sup> <ul style="list-style-type: none"> <li>○ 0–1 other major ASCVD risk factors and</li> <li>○ No evidence of end organ damage</li> </ul> </li> <li>• Chronic kidney disease stage 3B or 4<sup>‡</sup></li> <li>• LDL-C ≥190 mg/dL (severe hypercholesterolemia)<sup>§</sup></li> <li>• Quantitative risk score reaching the high-risk threshold<sup>  </sup></li> </ul>	<130	<100	≥130	≥100
Very high	<ul style="list-style-type: none"> <li>• ASCVD</li> <li>• Diabetes mellitus (type 1 or 2) <ul style="list-style-type: none"> <li>○ ≥2 other major ASCVD risk factors or</li> <li>○ Evidence of end-organ damage<sup>¶</sup></li> </ul> </li> </ul>	<100	<70	≥100	≥70

For patients with ASCVD or diabetes mellitus, consideration should be given to use of moderate or high-intensity statin therapy, irrespective of baseline atherogenic cholesterol levels.

ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

\*For those at moderate risk, additional testing may be considered for some patients to assist with decisions about risk stratification. See Tables 4 and 11 and text for additional details.

†For patients with diabetes plus 1 major ASCVD risk factor, treating to a non-HDL-C goal of <100 mg/dL (LDL-C <70 mg/dL) is considered a therapeutic option.

‡For patients with chronic kidney disease (CKD) Stage 3B (glomerular filtration rate [GFR] 30–44 mL/min/1.73 m<sup>2</sup>) or Stage 4 (GFR 15–29 mL/min/1.73 m<sup>2</sup>) risk calculators should not be used because they may underestimate risk. Stage 5 CKD (or on hemodialysis) is a very high-risk condition, but results from randomized, controlled trials of lipid-altering therapies have not provided convincing evidence of reduced ASCVD events in such patients. Therefore, no treatment goals for lipid therapy have been defined for stage 5 CKD.

§If LDL-C is ≥190 mg/dL, consider severe hypercholesterolemia phenotype, which includes familial hypercholesterolemia. Lifestyle intervention and pharmacotherapy are recommended for adults with the severe hypercholesterolemia phenotype. If it is not possible to attain desirable levels of atherogenic cholesterol, a reduction of at least 50% is recommended. For familial hypercholesterolemia patients with multiple or poorly controlled other major ASCVD risk factors, clinicians may consider attaining even lower levels of atherogenic cholesterol. Risk calculators should not be used in such patients.

||High-risk threshold is defined as ≥10% using Adult Treatment Panel III Framingham Risk Score for hard coronary heart disease (CHD; myocardial infarction or CHD death), ≥15% using the 2013 Pooled Cohort Equations for hard ASCVD (myocardial infarction, stroke, or death from CHD or stroke), or ≥45% using the Framingham long-term (to age 80) cardiovascular disease (CVD; myocardial infarction, CHD death or stroke) risk calculation. Clinicians may prefer to use other risk calculators, but should be aware that quantitative risk calculators vary in the clinical outcomes predicted (eg, CHD events, ASCVD events, cardiovascular mortality); the risk factors included in their calculation; and the timeframe for their prediction (eg, 5 years, 10 years, or long-term or lifetime). Such calculators may omit certain risk indicators that can be very important in individual patients, provide only an approximate risk estimate and require clinical judgment for interpretation.

¶End-organ damage indicated by increased albumin/creatinine ratio (≥30 mg/g), CKD, or retinopathy.

favored over apo B by the NLA Expert Panel because it is universally available, requiring no additional expense, and because apo B has not been consistently superior to non-HDL-C in predicting ASCVD event risk.

Cholesterol-lowering drug therapies, especially statins, alter the relationship between atherogenic cholesterol and apo B, often lowering the cholesterol concentration more than the apo B level. Apo B is a potential contributor to residual ASCVD risk because it may remain elevated in some individuals who have attained their treatment goals for non-HDL-C and LDL-C (discussed in the following

section). If apo B is used as an optional target for treatment, goals are <90 mg/dL for primary prevention and <80 mg/dL for those with very high risk, although measurement of apo B is generally not necessary until the patient has been treated to his or her goal levels for atherogenic cholesterol (Table 2).

Clinicians may consider measuring LDL particle concentration as an alternative to apo B.<sup>20</sup> The NLA Expert Panel acknowledges that measurement of LDL particle concentration can be useful clinically, particularly once non-HDL-C and LDL-C goals have been attained.

**Table 4** Criteria for clinical identification of the metabolic syndrome (any 3 or more of the listed components)<sup>21</sup>

Measure	Categorical cut points
1. Elevated waist circumference*	≥40 inches (≥102 cm) in men ≥35 inches (≥88 cm) in women
2. Elevated triglycerides (drug treatment with a triglyceride-lowering agent is an alternate indicator <sup>†</sup> )	≥150 mg/dL
3. Reduced HDL-C	<40 mg/dL in men <50 mg/dL in women
4. Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥130 and/or diastolic ≥85 mm Hg
5. Elevated fasting glucose (drug treatment of elevated glucose is an alternate indicator <sup>‡</sup> )	≥100 mg/dL

HDL-C, high-density lipoprotein cholesterol.

\*American Heart Association/National Heart, Lung and Blood Institute guidelines for metabolic syndrome suggest waist circumference thresholds of ≥37 inches (≥94 cm) in men and ≥32 inches (≥80 cm) in women as optional cut points for individuals or populations with increased insulin resistance, including those of Asian descent (alternate values have also been published for other groups).<sup>5</sup>

<sup>†</sup>The most commonly used drugs for elevated triglycerides are fibric acids, nicotinic acid, and high-dose long-chain omega-3 fatty acids. A patient taking any of these drugs may be presumed to have elevated triglycerides.

<sup>‡</sup>Most patients with type 2 diabetes mellitus will have the metabolic syndrome by these criteria.

## Triglycerides

An elevated triglyceride level is not a target of therapy per se, except when very high (≥500 mg/dL). When triglycerides are between 200 and 499 mg/dL, the targets of therapy are non-HDL-C and LDL-C. When the triglyceride concentration is very high (≥500 mg/dL, and especially if ≥1000 mg/dL), reducing the concentration to <500 mg/dL to prevent pancreatitis becomes the primary goal of therapy.

## HDL-C

The level of HDL-C is an important risk indicator and used in risk factor counting and quantitative risk assessment. Low HDL-C is also a component of the metabolic syndrome. HDL-C is not recommended as a target of therapy

per se, but the level is often raised as a consequence of efforts to reduce atherogenic cholesterol through lifestyle and drug therapies.

## Metabolic syndrome

Metabolic syndrome is recognized as a multiplex risk factor for both ASCVD and type 2 diabetes mellitus (Table 4).<sup>21</sup> Increased adiposity and insulin resistance appear to be central pathophysiologic features of this cluster of inter-related metabolic and hemodynamic disturbances including elevations in blood pressure, triglycerides and glucose as well as depressed HDL-C. The presence of the metabolic syndrome indicates high potential to benefit from lifestyle therapies, particularly weight loss if overweight/obese, and increased physical activity. Successful lifestyle intervention will reduce adiposity and insulin resistance, improving

**Table 5** Drugs that may elevate LDL-C or triglyceride concentrations

Drugs that elevate LDL-C	Drugs that elevate triglycerides
<ul style="list-style-type: none"> <li>• Some progestins</li> <li>• Anabolic steroids</li> <li>• Danazol</li> <li>• Isotretinoin</li> <li>• Immunosuppressive drugs (cyclosporine)</li> <li>• Amiodarone</li> <li>• Thiazide diuretics</li> <li>• Glucocorticoids</li> <li>• Thiazolidinediones</li> <li>• Fibric acids (in severe hypertriglyceridemia)</li> <li>• Long chain omega-3 fatty acids (in severe hypertriglyceridemia, if containing docosahexaenoic acid)</li> </ul>	<ul style="list-style-type: none"> <li>• Oral estrogens</li> <li>• Tamoxifen</li> <li>• Raloxifene</li> <li>• Retinoids</li> <li>• Immunosuppressive drugs (cyclosporine, sirolimus)</li> <li>• Interferon</li> <li>• Beta-blockers (especially non-beta 1-selective)</li> <li>• Atypical antipsychotic drugs (fluperlapine, clozapine, olanzapine)</li> <li>• Protease inhibitors</li> <li>• Thiazide diuretics</li> <li>• Glucocorticoids</li> <li>• Rosiglitazone</li> <li>• Bile acid sequestrants</li> <li>• L-asparaginase</li> <li>• Cyclophosphamide</li> </ul>

LDL-C, low-density lipoprotein cholesterol.

**Table 6** Diet characteristics and diseases/disorders/altered metabolic states that may elevate LDL-C and/or triglyceride concentrations

Cause	Elevate LDL-C	Elevate triglycerides
<b>Diet</b>		
Positive energy balance	✓	✓
High saturated fat	✓	
High trans fats	✓	
High glycemic load		✓
Excess alcohol		✓
Weight gain	✓	✓
Anorexia nervosa	✓	
<b>Diseases/disorders/altered metabolic states</b>		
Chronic kidney disease	✓	✓
Nephrotic syndrome	✓	✓
Obstructive liver disease	✓	
Diabetes mellitus		✓
Metabolic syndrome		✓
HIV infection	✓	✓
Autoimmune disorders	✓	✓
Hypothyroidism	✓	✓
Pregnancy	✓	✓
Polycystic ovary syndrome	✓	✓
Menopause transition with declining estrogen levels	✓	✓

HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol.

multiple physiological disturbances that may contribute to risk, including the metabolic syndrome components as well as indicators of inflammation and thrombogenicity.

### Secondary causes of dyslipidemia

Some conditions or medications can produce adverse changes in lipid levels and should be considered when evaluating patients with dyslipidemia. Medications that may elevate levels of LDL-C and/or triglycerides are shown in Table 5. Conditions that may produce adverse changes in lipid levels are summarized in Table 6.

### ASCVD risk assessment and treatment goals based on risk category

In addition to lipoprotein lipid levels, ASCVD risk assessment includes evaluation of other major ASCVD risk factors (Table 7), clinical evidence of ASCVD (Table 8), and other conditions known to be associated with high or very high risk for an ASCVD event, including LDL-C  $\geq 190$  mg/dL (severe hypercholesterolemia phenotype), type 1 or 2 diabetes mellitus, and chronic kidney disease (CKD) Stage 3B or higher (glomerular filtration rate  $< 45$  mL/kg/1.73 m<sup>2</sup>) (Table 9). For these high- and very high-risk groups, quantitative risk scoring will often

**Table 7** Major risk factors for ASCVD\*

- Age
  - Male  $\geq 45$  years
  - Female  $\geq 55$  years
- Family history of early CHD<sup>†</sup>
  - $< 55$  years of age in a male first-degree relative or
  - $< 65$  years of age in a female first-degree relative
- Current cigarette smoking
- High blood pressure ( $\geq 140/\geq 90$  mm Hg or on blood pressure medication)
- Low HDL-C
  - Male  $< 40$  mg/dL
  - Female  $< 50$  mg/dL

ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol.

\*Levels of non-high-density lipoprotein cholesterol and low-density lipoprotein cholesterol are not listed because these risk factors are used to assess risk category and treatment goals for atherogenic lipoprotein cholesterol levels. Diabetes mellitus is not listed because it is considered a high- or very high-risk condition for ASCVD risk assessment purposes.

<sup>†</sup>CHD is defined as myocardial infarction, coronary death, or a coronary revascularization procedure.

underestimate ASCVD event risk, so is generally not recommended unless a validated equation for that population subset is used.

ASCVD risk is classified into four categories, as shown in Table 3. Risk category is used both for the purpose of defining treatment goals for atherogenic cholesterol (as well as apo B) and for defining the level of atherogenic cholesterol elevation at which pharmacotherapy to lower atherogenic cholesterol might be considered. Lifestyle therapies should be emphasized and monitored in all patients with elevated levels of atherogenic cholesterol, whether or not pharmacotherapy for dyslipidemia management is used. Risk assessment will often proceed according to the steps as outlined in Table 10.

### Very high risk

Those with clinical evidence of ASCVD, as defined in Table 8, and patients with diabetes plus  $\geq 2$  major ASCVD

**Table 8** Criteria for classification of ASCVD

- Myocardial infarction or other acute coronary syndrome
- Coronary or other revascularization procedure
- Transient ischemic attack
- Ischemic stroke
- Atherosclerotic peripheral arterial disease
  - Includes ankle/brachial index  $< 0.90$
- Other documented atherosclerotic diseases such as:
  - Coronary atherosclerosis
  - Renal atherosclerosis
  - Aortic aneurysm secondary to atherosclerosis
  - Carotid plaque,  $\geq 50\%$  stenosis

ASCVD, atherosclerotic cardiovascular disease.

**Table 9** High- or very high-risk patient groups

Quantitative risk scoring is not necessary for initial risk assessment in patients with the following conditions:<sup>\*</sup>

- Diabetes mellitus, type 1 or 2
- Chronic kidney disease, stage  $\geq 3B$
- LDL-C  $\geq 190$  mg/dL: severe hypercholesterolemia phenotype, which includes FH
- ASCVD

ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

<sup>\*</sup>Patients in these categories are all at *high* or *very high* risk for an ASCVD event and should be treated accordingly.

risk factors (Table 7), or evidence of end-organ damage, are considered to be at very high risk. These patients have the most aggressive goals for atherogenic cholesterol (non-HDL-C  $< 100$  mg/dL, LDL-C  $< 70$  mg/dL). For those at very high risk, pharmacotherapy is recommended for patients who have atherogenic cholesterol levels above goal. In addition, pharmacotherapy with a statin is considered a therapeutic option for those in whom atherogenic cholesterol and apo B levels are below the goal thresholds.

End-stage (stage 5) CKD is associated with very high risk for ASCVD events. However, data from RCTs of lipid-altering therapies have not consistently shown benefits in this group. Moreover, use of intensive lipid-lowering drug therapies in this group to achieve low levels of atherogenic cholesterol may not be practical. Therefore, goals for atherogenic cholesterol levels in stage 5 CKD have not been defined and are instead considered a matter of clinical judgment.

### High risk

Those at high risk include patients with  $\geq 3$  major ASCVD risk factors or a high-risk condition, including diabetes mellitus with 0 to 1 additional major ASCVD risk factors, CKD stage 3B or 4, or LDL-C  $\geq 190$  mg/dL.

As an option for those with 2 major ASCVD risk factors, the clinician may wish to perform quantitative risk scoring to estimate 10-year or long-term/lifetime risk for an ASCVD or CHD event. This will facilitate identification of patients who may be classified as high risk in the absence of any of the high risk conditions listed previously. The panel considers the threshold of high risk to be as follows for three of the most commonly used risk calculators:

**Table 10** Sequential steps in ASCVD risk assessment

1. Identify patients with either **very high-risk** or **high-risk** conditions.
  - Very High Risk**
  - a. ASCVD
  - b. Diabetes mellitus with  $\geq 2$  other major ASCVD risk factors or end-organ damage<sup>\*</sup>
  - High Risk**
  - a. Diabetes mellitus with 0–1 other major ASCVD risk factors
  - b. Chronic kidney disease stage 3B or 4<sup>†</sup>
  - c. LDL-C  $\geq 190$  mg/dL (severe hypercholesterolemia phenotype)
2. Count major ASCVD risk factors.
  - a. If 0–1 and no other major indicators of higher risk, assign to **low-risk** category. Consider assigning to a higher risk category based on other known risk indicators, when present.
  - b. If  $\geq 3$  major ASCVD risk factors are present, assign to **high-risk** category.
3. If 2 major ASCVD risk factors, **risk scoring** should be considered and additional testing may be useful for some patients.
  - a. If quantitative risk scoring reaches the **high-risk** threshold,<sup>‡</sup> assign to **high-risk** category.
  - b. Consider assigning to **high-risk** category if other risk indicators are present based on additional testing (see Table 11).
  - c. If, based on above steps, no indication is present to assign to **high-risk**, assign to **moderate-risk** category.

*Further risk assessment is not required after identifying the highest applicable risk level.*

ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

<sup>\*</sup>End-organ damage indicated by increased albumin/creatinine ratio ( $\geq 30$  mg/g), chronic kidney disease (CKD), or retinopathy.

<sup>†</sup>For patients with CKD stage 3B (glomerular filtration rate [GFR] 30–44 mL/min/1.73 m<sup>2</sup>) or stage 4 (GFR 15–29 mL/min/1.73 m<sup>2</sup>) risk calculators should not be used because they may underestimate risk. Stage 5 CKD (or on hemodialysis) is a very high-risk condition, but results from randomized, controlled trials of lipid-altering therapies have not provided convincing evidence of reduced ASCVD events in such patients. Therefore, no treatment goals for lipid therapy have been defined for stage 5 CKD.

<sup>‡</sup>High-risk threshold is defined as  $\geq 10\%$  using Adult Treatment Panel III Framingham Risk Score for hard coronary heart disease (CHD; myocardial infarction or CHD death),  $\geq 15\%$  using the 2013 Pooled Cohort Equations for hard ASCVD (myocardial infarction, stroke or death from CHD or stroke), or  $\geq 45\%$  using the Framingham long-term (to age 80) CVD (myocardial infarction, CHD death or stroke) risk calculation. Clinicians may prefer to use other risk calculators, but should be aware that quantitative risk calculators vary in the clinical outcomes predicted (eg, CHD events, ASCVD events, cardiovascular mortality); the risk factors included in their calculation; and the timeframe for their prediction (eg, 5 years, 10 years, or long-term or lifetime). Such calculators may omit certain risk indicators that can be very important in individual patients, provide only an approximate risk estimate and require clinical judgment for interpretation.

- ATP III Framingham risk calculator:  $\geq 10\%$  10-year risk for a hard CHD event (myocardial infarction or CHD death);
- Pooled Cohort Equations (American College of Cardiology/American Heart Association):  $\geq 15\%$  10-year risk for a hard ASCVD event (myocardial infarction, stroke, or death from CHD or stroke); and
- Framingham long-term (30-year to age 80) risk calculator:  $\geq 45\%$  risk for CVD (myocardial infarction, CHD death, or stroke).

*It should be noted that these thresholds are not intended to indicate “statin benefit groups,” (ie, those in whom statin therapy has shown benefits regarding ASCVD event risk reduction). Results from primary prevention RCTs have shown that the relative risk for ASCVD events is reduced with statin therapy compared with control groups in whom incidence rates for ASCVD are relatively low (approximately 5.0% to 7.5% 10-year risk projected from rates observed over shorter observation periods).<sup>22–24</sup> In addition, scoring calculators based on population statistics provide only an approximate risk estimate for individual patients and require clinical judgment for interpretation. This is particularly true when applied to groups that may differ in average risk level compared with the population from which the equations were developed. In some patients, the ASCVD risk estimate will be in the moderate or high category based primarily on non-lipid risk factors such as smoking or hypertension. In such cases, attention to these risk determinants may be of primary importance.*

The goals of therapy for those at high risk are non-HDL-C  $< 130$  mg/dL and LDL-C  $< 100$  mg/dL, with consideration given to drug therapy in those whose atherogenic cholesterol levels are higher than these goal levels, generally after a trial of lifestyle therapy. However, drug treatment may be started concurrently with lifestyle therapy in some high risk patients, such as those who are unlikely to be able to attain goal levels of atherogenic cholesterol without drug therapy (eg, patients with LDL-C  $\geq 190$  mg/dL) or with diabetes mellitus and 0 to 1 other major ASCVD risk factors.

### Moderate risk

Individuals with 2 major ASCVD risk factors, in the absence of conditions that place them into the high- or very high-risk categories, are considered to be at moderate risk (approximately 5% to  $< 15\%$  10-year risk for an ASCVD event). Quantitative risk scoring may be performed to identify those who should be reclassified as high risk (see the previous section).

Categorical risk factor counting and quantitative risk assessment provide similar results in most cases. Quantitative risk scoring may be helpful to refine decisions about risk stratification by accounting for variability in risk factor level or intensity and interactions between age and ASCVD

risk factors.<sup>1</sup> It also provides an estimate of absolute risk, which may be useful as an educational tool. The NLA Expert Panel recommends that quantitative risk scoring should be the initial step in decision-making when there is uncertainty about the value of initiating pharmacotherapy for such patients. This step should generally be completed before investigation of secondary risk factors because the patient incurs no additional cost. However, most risk equations do not incorporate secondary risk factors, which may be important to consider in specific patients.

The greatest potential utility exists for assessment of secondary ASCVD risk factors among patients with 2 major ASCVD risk factors to identify those for whom the threshold for consideration of pharmacotherapy could be lowered. Factors that might be considered are shown in Table 11. As additional data become available regarding prediction, discrimination, and accuracy, it should be possible to more clearly define optimal strategies for application of these tests in clinical practice.

In some patients, 10-year risk for an ASCVD event may be lower than the high risk threshold, but lifetime risk may be substantially elevated. This is especially true in women

**Table 11** Risk indicators (other than major ASCVD risk factors) that might be considered for risk refinement\*

1. A severe disturbance in a major ASCVD risk factor, such as multipack per day smoking or strong family history of premature CHD
2. Indicators of subclinical disease, including coronary artery calcium
  - $\geq 300$  Agatston units<sup>†</sup> is considered *high risk*
3. LDL-C  $\geq 160$  mg/dL and/or non-HDL-C  $\geq 190$  mg/dL
4. High-sensitivity C-reactive protein  $\geq 2.0$  mg/L<sup>‡</sup>
5. Lipoprotein (a)  $\geq 50$  mg/dL (protein) using an isoform insensitive assay
6. Urine albumin/creatinine ratio  $\geq 30$  mg/g

ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol.

\*The presence of 1 or more of the risk indicators listed may be considered, in conjunction with major ASCVD risk factors, to reclassify an individual into a higher risk category. Except in the case of evidence of subclinical disease defining the presence of ASCVD, reclassification to a higher risk category is a matter of clinical judgment. Doing so will alter the threshold for consideration of pharmacotherapy and/or the treatment goals for atherogenic cholesterol. Many other ASCVD risk markers are available, but the National Lipid Association Expert Panel consensus view is that those listed have the greatest clinical utility.

<sup>†</sup>Or coronary artery calcium  $\geq 75$ th percentile for age, sex, and ethnicity. For additional information, see the Coronary Artery Calcium Score Reference Values web tool.<sup>27</sup>

<sup>‡</sup>Because of high intraindividual variability, multiple high-sensitivity C-reactive protein (hs-CRP) values should be obtained before concluding that the level is elevated; hs-CRP should not be tested in those who are ill, have an infection, or are injured. If hs-CRP level is  $> 10$  mg/L, consider other etiologies such as infection, active arthritis, or concurrent illness.

and young adults (<40 years of age). In such individuals, calculation of long-term/lifetime risk may be particularly useful as an adjunct to the 10-year ASCVD or CHD event risk.<sup>25,26</sup>

The goals of therapy for those at moderate risk are non-HDL-C <130 mg/dL and LDL-C <100 mg/dL with consideration given to drug therapy in those with values at least 30 mg/dL above these levels (Table 3). However, the presence of one or more secondary risk factors may prompt the clinician to consider drug therapy for a patient in whom atherogenic cholesterol level is higher than the goal level.

### Low risk

Individuals with 0 or 1 major ASCVD risk factors are generally at low risk for an ASCVD event (<5% 10-year ASCVD event risk). Quantitative risk scoring is not typically necessary for such patients. Lifestyle therapies are the primary modalities for management of atherogenic cholesterol levels in such patients, although consideration may be given to pharmacotherapy in those with non-HDL-C 190 to 219 mg/dL (LDL-C 160 to 189 mg/dL). Also, in some individuals, a severe disturbance in a single major ASCVD risk factor (eg, strong family history of CHD or multipack per day smoking), a known disturbance in a secondary risk factor (eg, lipoprotein (a)  $\geq$ 50 mg/dL), or evidence of subclinical disease (eg, coronary artery calcium [CAC]  $\geq$ 300 Agatston units<sup>27</sup>) (Table 11) might justify classifying the patient into the moderate or the high-risk category, prompting consideration of pharmacotherapy at lower levels of atherogenic cholesterol. If information about secondary risk factors or subclinical disease is known for such patients, this should be considered when assigning the risk category and in making decisions about the use of pharmacotherapy.

## Application of lifestyle and drug therapies intended to reduce morbidity and mortality associated with dyslipidemia

### Lifestyle therapies

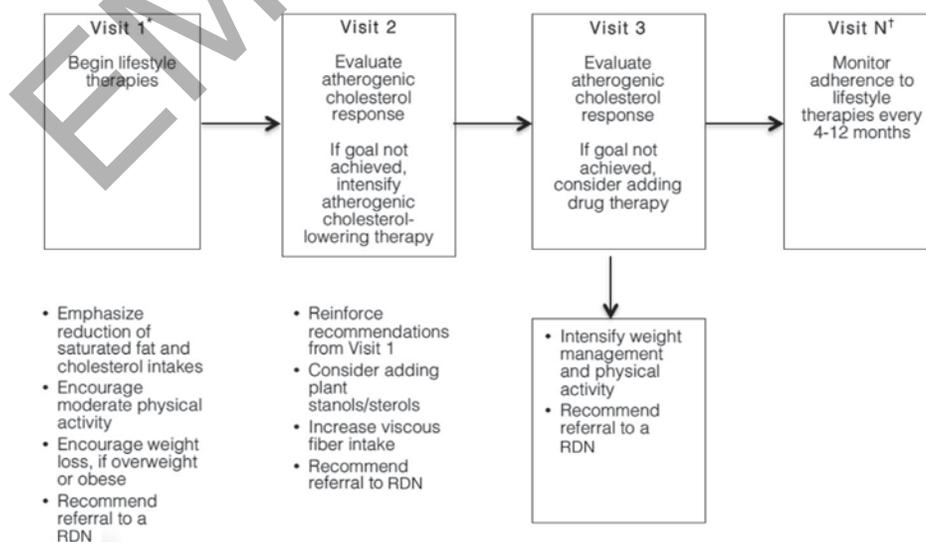
Figure 1 shows a model of the steps in application of lifestyle therapies. For patients at low or moderate risk, lifestyle therapies should be given an adequate trial (at least 3 months) before initiation of drug therapy. In patients at very high risk, drug therapy may be started concurrently with lifestyle therapies. This may also be the case for selected patients in the high-risk category if the clinician feels it is unlikely that lifestyle therapies alone will be sufficient to reach goal, or if the patient has a high risk condition such as diabetes mellitus or CAC  $\geq$ 300 Agatston units.

#### Visit 1

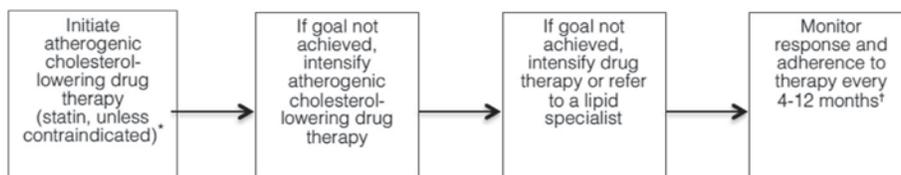
Lifestyle therapies include a diet low in saturated fat (<7% of energy), moderate or higher intensity physical activity ( $\geq$ 150 minutes per week), and weight loss (5% to 10% of body weight) for those who are overweight or obese. Where available, referral to a registered dietitian nutritionist (RDN) is recommended to facilitate dietary modification and to an exercise specialist for guided instruction on a suitable exercise program.

#### Visit 2

If sufficient progress is not made toward achieving atherogenic cholesterol goals, consideration may be given to the use of dietary adjuncts, including plant sterols/stanols (2 to 3 g/d) and viscous fibers (5 to 10 g/d). Dietary and other lifestyle recommendations should be reinforced



**Figure 1** Model of steps in lifestyle therapies. \*For people at high or very risk for ASCVD in whom drug therapy is indicated, it may be started concomitantly with lifestyle therapies. For other patients, a trial of lifestyle therapies should be undertaken before initiation of drug therapy. †In most cases, goal levels should be achieved in approximately 6 months. RDN, registered dietitian nutritionist.



**Figure 2** Progression of atherogenic cholesterol-lowering drug therapy. \*A moderate- or high-intensity statin should be first-line drug therapy for treatment of elevated levels of atherogenic cholesterol, unless contraindicated. In a patient with very high triglycerides ( $\geq 500$  mg/dL), a triglyceride-lowering drug may be considered for first-line use to prevent pancreatitis. Other atherosclerotic cardiovascular disease risk factors should be managed appropriately in parallel. †In most cases, goal levels should be achieved in approximately 6 months.

and referrals to a RDN and exercise specialist are recommended.

### Visit 3

If goal levels of atherogenic cholesterol have been attained, responses to therapy should be monitored at intervals of 6 to 12 months. If goal levels have not been attained and the patient's levels remain above the threshold for consideration of drug therapy, drug treatment might be initiated.

## Cholesterol-lowering drug therapies

Figure 2 shows a model for progression of cholesterol-lowering drug therapy. When used, drug therapy should generally be initiated with moderate to high intensity statin therapy to take advantage of demonstrated ASCVD risk-reduction benefits.<sup>11,28–30</sup>

### Patient-centered approach

Before initiation of lipid-lowering drug therapy for ASCVD risk reduction, the clinician should have a discussion with the patient about treatment objectives as well as the potential for adverse effects, possible interactions with other drugs or dietary supplements, lifestyle and medication adherence, and patient preferences. Drug therapy for elevated levels of atherogenic cholesterol is generally maintained for an extended period. A large percentage of patients (more than 50% in some studies) prescribed a lipid-lowering drug discontinue refilling the prescription within one year. Therefore, a discussion with the patient of the importance of continued adherence to achieve ASCVD event risk reduction is important. The clinician should convey that alternative agents and regimens are available in the event that side effects occur with a given medication or dosage level.

### Thresholds for consideration of drug therapy

Because of the availability of inexpensive, generic statin medications with favorable safety and tolerability profiles, and demonstrated efficacy for reducing ASCVD event risk, even in relatively low-risk patients, the NLA Expert Panel consensus view is that risk thresholds for initiating drug treatment should be lowered as compared with the NCEP ATP III.<sup>1,10</sup> However, although these medications may be relatively inexpensive and well-tolerated, overuse would

result in unnecessary side effects and ancillary costs (eg, physician visits, laboratory testing). Recommendations on such matters always involve a tradeoff between sensitivity (capturing the greatest fraction of the potential risk reduction in the population) and specificity (minimizing the number treated who would not have experienced an ASCVD event). The thresholds selected represent the consensus views of the NLA Expert Panel. Some clinicians may prefer to prescribe drug therapy (mainly statin treatment) to patients with lower levels of risk or atherogenic cholesterol. Such an approach may be considered based on clinical judgment and patient preferences in light of data from primary prevention RCT data showing ASCVD event risk reduction with statin therapy compared with control groups with projected 10-year ASCVD event rates as low as approximately 5% to 7.5%.<sup>22–24</sup>

### Initiation of drug therapy

Unless contraindicated, first-line drug therapy for treatment of elevated atherogenic cholesterol levels is a moderate- or high-intensity statin (see Table 12 for statin intensity categories). A moderate-intensity statin will generally lower LDL-C by 30% to  $<50\%$  and a high-intensity statin by  $\geq 50\%$ , although individual patient responses should be expected to vary considerably. Some clinicians prefer to start with a high-intensity statin and reduce the dosage if the patient experiences intolerance. Others prefer to start with a moderate-intensity statin and titrate upward if additional lowering of atherogenic cholesterol is desired.

**Table 12** Intensity of statin therapy\*

High-intensity daily dosage ↓ LDL-C $\geq 50\%$	Moderate-intensity daily dosage ↓ LDL-C 30% to $<50\%$
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Fluvastatin 40 mg bid
	Fluvastatin XL 80 mg
	Lovastatin 40 mg
	Pitavastatin 2–4 mg
	Pravastatin 40–80 mg
	Rosuvastatin 5–10 mg
	Simvastatin 20–40 mg

bid, twice per day; LDL-C, low-density lipoprotein cholesterol.

\*Individual responses to statin therapy should be expected to vary in clinical practice. Moderate- or high-intensity statin therapy is preferred unless not tolerated.

Because patients commonly discontinue therapy when they experience side effects, it is important for the clinician to apply the strategy that he or she feels will produce the greatest likelihood of long-term adherence in a given patient.

Some patients have contraindications for, or intolerance to, statin therapy. For such patients, non-statin drug therapy may be considered. Non-statin drug classes for lipid management include cholesterol absorption inhibitors, bile acid sequestrants, fibric acids, long-chain omega-3 fatty acid concentrates, and nicotinic acid. Bile acid sequestrants, fibric acids, and nicotinic acid have been shown to reduce CHD or ASCVD event rates in placebo-controlled RCTs.<sup>1,31–35</sup> A summary of the lipid effects of the main classes of drugs available in the United States for treatment

of dyslipidemia is shown in Table 13. Two additional classes of medications are also available with more limited indications for the treatment of patients with homozygous familial hypercholesterolemia (FH): an antisense oligonucleotide that targets the messenger RNA for apo B, and a microsomal triglyceride transfer protein inhibitor.

### Follow-up visits

If the goal levels of atherogenic cholesterol have not been achieved, the statin dosage may be increased, or the patient might be switched to a more efficacious agent. If, after an adequate trial of the highest intensity statin therapy tolerated, goal levels of atherogenic cholesterol have not been achieved, the clinician may consider referral to a lipid specialist, or addition of a second cholesterol-lowering agent. Once goal levels of atherogenic cholesterol have been achieved, response to therapy should be monitored periodically, within 4 to 12 months, to confirm continued success in maintenance of goal levels and patient adherence.

In some patients taking high-intensity statin therapy, atherogenic cholesterol levels may drop to low levels (eg, LDL-C <40 mg/dL). At present, no evidence suggests harm with such low circulating cholesterol levels, and therapy may be continued in such patients, particularly those at very high ASCVD event risk, in the absence of signs or symptoms of intolerance.

Monitoring of atherogenic cholesterol levels is also important from the perspective of the evaluation of health care systems. Information on attainment and maintenance of goal levels of atherogenic cholesterol allows mechanisms to be implemented for providing feedback to providers regarding quality of health care delivery.

### Management of patients with hypertriglyceridemia

For patients with very high triglycerides ( $\geq 500$  mg/dL), the primary objective of therapy is to lower the triglyceride level to <500 mg/dL to reduce the risk of pancreatitis. For patients with hypertriglyceridemia who have high triglycerides (200 to 499 mg/dL), the primary objective of therapy is to lower levels of atherogenic cholesterol (non-HDL-C and LDL-C) to reduce risk for an ASCVD event.

Lifestyle interventions are a key to efforts to reduce triglycerides, including weight loss if overweight or obese (initially targeting loss of 5% to 10% of body weight), physical activity ( $\geq 150$  minutes per week of moderate or higher intensity activity), and restriction of alcohol and sugar/refined carbohydrate intakes.

For those with very high triglycerides ( $\geq 500$  mg/dL), chylomicronemia will generally be present. For such patients, a low-fat diet (<15% of energy) may be helpful to reduce entry of new chylomicron particles into the circulation. For patients with triglycerides <500 mg/dL, partial replacement of dietary carbohydrate (especially sugars and other refined carbohydrates) with a combination of unsaturated fats and proteins may help to reduce the triglyceride and non-HDL-C concentrations.<sup>36,37</sup>

**Table 13** Drugs affecting lipoprotein metabolism

Drug class, agents, and daily doses	Lipid/lipoprotein effects	
Statins*	LDL-C	↓18–55%
	Non-HDL-C	↓15–51%
	HDL-C	↑5–15%
	TG†	↓7–30%
Bile acid sequestrants‡	LDL-C	↓15–30%
	Non-HDL-C	↓4–16%
	HDL-C	↑3–5%
	TG	↑0–10%
Nicotinic acid§	LDL-C	↓5–25%
	Non-HDL-C	↓8–23%
	HDL-C	↑15–35%
	TG	↓20–50%
Fibric acids	LDL-C¶	↓5–↑20%
	Non-HDL-C	↓5–19%
	HDL-C	↑10–20%
	TG	↓20–50%
Cholesterol absorption inhibitor	LDL-C	↓13–20%
	Non-HDL-C	↓14–19%
	HDL-C	↑3–5%
	TG	↓5–11%
Long-chain omega-3 fatty acid drugs	LDL-C¶	↓6%–↑25%
	Non-HDL-C	↓5–14%
	HDL-C	↓5%–↑7%
	TG	↓19–44%

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; TG, triglycerides.

\*See Table 12 for a description of statins and doses.

†TG reduction with statins, particularly high-potency statins, is higher in patients with hypertriglyceridemia, producing reductions in the range of 20% to 50%.

‡Cholestyramine (4–16 g), colestipol (5–20 g), and colesevelam (2.6–3.8 g).

§Immediate-release (crystalline) nicotinic acid (1.5–3 g), extended-release nicotinic acid (1–2 g), and sustained-release nicotinic acid (1–2 g).

||Gemfibrozil, fenofibrate, and fenofibric acid.

¶For fibric acids and long-chain omega-3 fatty acid drugs, LDL-C may increase in patients with very high TG, except for omega-3 products that contain eicosapentaenoic acid only, and no docosahexaenoic acid.

When drug therapy is indicated in a patient with hypertriglyceridemia, an agent that primarily lowers triglycerides and VLDL-C (fibric acids, high-dose [2 to 4 g/d] long-chain omega-3 fatty acids, or nicotinic acid) should be the first-line agent if the fasting triglyceride concentration is  $\geq 1000$  mg/dL, because these will generally produce the largest reductions in triglycerides. For patients with triglycerides 500 to 999 mg/dL, a triglyceride-lowering agent or a statin (if no history of pancreatitis) may be reasonable first-line drug options.

For patients with high triglycerides (200 to 499 mg/dL), a statin will generally be first-line drug therapy. Statins are the most effective agents for reducing levels of atherogenic cholesterol and apo B, and evidence from hypertriglyceridemic subgroups in RCTs shows that statins lower ASCVD event risk in patients with elevated triglycerides in this range.<sup>38</sup> If maximum tolerated statin therapy does not lower non-HDL-C below goal levels in patients with triglycerides 200 to 499 mg/dL, adding an agent that primarily lowers triglycerides and VLDL-C may help to achieve atherogenic cholesterol goals. Subgroup analyses from cardiovascular outcomes studies provide suggestive evidence of reduced ASCVD event risk with the addition of a triglyceride-lowering agent to statin therapy, particularly in patients with the combination of elevated triglycerides and low HDL-C.<sup>39-41</sup>

### Statin intolerance and side effects

Symptoms reported with statin use include mainly muscle-related complaints (myalgias), although there have been some anecdotal reports of short-term memory impairment.<sup>42-44</sup> Observational studies have failed to find significant evidence for memory loss in those on longer-term statin therapy. It is important to remember that musculoskeletal complaints are common in elderly patients without statin therapy, so an evaluation of such complaints to assess other possible causes should be undertaken before attributing such symptoms to statin therapy. It is also common for patients to have concomitant therapies with the potential to interact with statins, increasing the risk of muscle symptoms.<sup>45</sup> For patients with statin intolerance, symptoms may improve when the patient is switched to a different statin. Other strategies that may be employed include limiting the daily dosage and modified regimens such as every other day or once weekly dosing with statins, which have a long half-life. In some patients, it may be possible to switch to an alternative concomitant therapy to enhance statin tolerance. For patients who cannot tolerate a statin with the previously discussed strategies, a non-statin drug alone or in combination with another cholesterol-lowering agent may be considered.

A modest increase in risk for type 2 diabetes mellitus has been observed with statin therapy in RCTs, and higher intensity statin therapy appears to increase risk to a greater extent than less intensive regimens.<sup>46</sup> The increase in diabetes incidence appears to occur mainly in those with diabetes risk factors, such as the metabolic syndrome components. However, these analyses also suggest that several

ASCVD events are prevented for each excess case of diabetes produced by statin therapy, or higher intensity statin therapy. Therefore, the panel recommends that glucose or glycated hemoglobin be checked before initiation of statin therapy and within 1 year afterward in those with diabetes risk factors. In addition, lifestyle therapies should be emphasized, both to aid in lowering levels of atherogenic cholesterol and for reducing diabetes risk.

### Combination drug therapy

Therapy with a statin plus a second (or third) agent may be considered for patients who have not reached their treatment goals for atherogenic cholesterol levels, particularly in patients with very high or high risk. The maximum *tolerated* statin dosage should generally be used before add-on therapy is considered. Much of the available data for the effects of add-on therapy on ASCVD events are from RCTs in which add-on therapy was administered to patients with relatively low levels of atherogenic cholesterol during statin treatment. Thus, limited RCT evidence is available to guide therapy in the patient taking the highest tolerated dosage of a statin, whose levels of atherogenic cholesterol remain above treatment goals.

Observational data as well as results from RCTs comparing lower and higher intensity statin therapy, suggest that ASCVD event risk is associated with levels of atherogenic cholesterol, and that larger reductions in atherogenic cholesterol levels are associated with greater ASCVD event benefits.<sup>1,5,18,47</sup> The association between on-treatment levels of LDL-C (and non-HDL-C) appears to follow a log-linear relationship, which is consistent with the view that the primary mechanism of action of statins is through reductions in levels of atherogenic lipoproteins, reflected by reductions in circulating concentrations of atherogenic cholesterol.<sup>5,10,47</sup> Moreover, results from studies of different approaches to cholesterol lowering suggest that the degree of risk reduction with statin therapy for a given reduction in atherogenic cholesterol is similar to that observed with other cholesterol-lowering interventions, including other medications, diet, and ileal bypass surgery.<sup>5,17,18</sup>

Therefore, until data are available from RCTs to better define the potential benefits and risks of add-on therapies in patients whose levels of atherogenic cholesterol remain elevated while taking the highest tolerated dosage of a statin, the NLA Expert Panel recommends that consideration be given to use of combination therapy with agents that further lower non-HDL-C and LDL-C to achieve goal levels of atherogenic cholesterol. The recommendation also extends to use of non-statin drug therapies, alone or in combination, to achieve atherogenic cholesterol goals in patients who have contraindications or are intolerant to statin therapy.

### Treatment of patients with severe hypercholesterolemia

Patients with the severe hypercholesterolemia phenotype (LDL-C  $\geq 190$  mg/dL), if untreated, have markedly

**Table 14** LDL apheresis\*

NLA criteria from expert panel on FH	FDA-approved indication
<p>LDL apheresis may be considered for the following patients who, after 6 months, do not have adequate response to maximum tolerated drug therapy:</p> <ul style="list-style-type: none"> <li>• Functional homozygous FH with LDL-C <math>\geq</math>300 mg/dL (or non-HDL-C <math>\geq</math>330 mg/dL)</li> <li>• Functional heterozygous FH with LDL-C <math>\geq</math>300 mg/dL (or non-HDL-C <math>\geq</math>330 mg/dL) and 0 to 1 risk factors</li> <li>• Functional heterozygous FH with LDL-C <math>\geq</math>200 mg/dL (or non-HDL-C <math>\geq</math>230 mg/dL) and high risk characteristics, such as 2 risk factors or high lipoprotein (a) <math>\geq</math>50 mg/dL using an isoform insensitive assay</li> <li>• Functional heterozygous FH with LDL-C <math>\geq</math>160 mg/dL (or non-HDL-C <math>\geq</math>190 mg/dL) and very high risk characteristics (established CHD, other cardiovascular disease, or diabetes)</li> </ul>	<p>LDL apheresis is considered medically necessary when patients have failed diet and maximum drug therapy from at least 2 separate classes of hypolipidemic drugs for at least 6 months in addition to any 1 of the following criteria:</p> <ul style="list-style-type: none"> <li>• Homozygous FH with LDL-C <math>\geq</math>500 mg/dL</li> <li>• Heterozygous FH with LDL-C <math>\geq</math>300 mg/dL</li> <li>• Functional heterozygous FH with LDL-C <math>\geq</math>200 mg/dL in patients with coronary artery disease</li> </ul>

CHD, coronary heart disease; FDA, Food and Drug Administration; FH, familial hypercholesterolemia; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; NLA, National Lipid Association; non-HDL-C, non-high-density lipoprotein cholesterol.

\*The NLA criteria<sup>48,50</sup> are more inclusive than the FDA-approved indication criteria. Clinicians should be aware of this with regard to reimbursement.

elevated lifetime risk for ASCVD, particularly premature ASCVD.<sup>48</sup> Many such patients have FH, an autosomal dominant (monogenic) form of hypercholesterolemia resulting from reduced expression of LDL receptors.<sup>49</sup> Other forms of severe hypercholesterolemia result from production of defective apo B that does not have normal interactivity with hepatic LDL receptors, and from gain of function mutations in the proprotein convertase subtilisin/kexin type 9 (PCSK9) gene.<sup>49</sup>

In some patients with severe hypercholesterolemia, it may not be possible to achieve goal levels of atherogenic cholesterol, even with combination drug therapy. When this is the case, an alternative goal is to lower atherogenic cholesterol levels by at least 50%. New classes of medications (eg, PCSK9 inhibitors) are under investigation that, if shown to be safe and efficacious, may make attainment of goal levels of atherogenic cholesterol practical for a greater fraction of patients with severe hypercholesterolemia.

Mipomersen, an injectable antisense inhibitor of apo B synthesis, when given in combination with maximum tolerated doses of lipid-lowering therapy, can reduce LDL-C by an additional 25% in homozygous FH patients, but even the addition of mipomersen does not achieve the recommended LDL-C target in the vast majority of homozygous FH patients. In addition, injection site reactions, hepatic fat, and liver enzyme elevations are common. Lomitapide, an oral inhibitor of microsomal triglyceride transfer protein, can also reduce LDL-C levels by up to by 50% in homozygous FH patients on maximum tolerated lipid-lowering therapy and LDL apheresis. However, given its mechanism of action, gastrointestinal side effects and elevation in liver enzymes and hepatic fat are common. Because of the risk of hepatotoxicity, mipomersen and lomitapide are available only through Risk Evaluation and Mitigation Strategy programs.

For selected patients with severe hypercholesterolemia, LDL apheresis may be considered. Table 14 shows the NLA Expert Panel on FH criteria for consideration of LDL apheresis.<sup>48,50</sup> These criteria are more inclusive than the Food and Drug Administration-approved indications, which clinicians should be aware of with regard to reimbursement.

### Treatment of patients with progressive atherosclerosis, or recurrent events, despite evidence-based therapy

Little evidence is available from RCTs to guide treatment of patients with progressive atherosclerosis, or recurrent events, despite receiving high-intensity statin therapy. The NLA Expert Panel consensus view is that very aggressive therapy to lower atherogenic cholesterol levels to values well below goal thresholds may be considered for such patients, although it is acknowledged that this approach is not clearly supported by clinical trial evidence. Investigation of other potential causes, such as an elevated level of lipoprotein (a) or other secondary risk factors may be warranted. Non-lipid risk factors should be well-controlled in such patients.

### Updates to this document

Because the evidence in clinical medicine related to lipid management is always evolving, these recommendations will undergo annual review with revision as necessary to reflect important changes to the evidence base.

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