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National Lipid Association Annual Summary of Clinical Lipidology 2016

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Abstract: The National Lipid Association (NLA) Annual Summary of Clinical Lipidology is a yearly updated summary of principles important to the patient-centered evaluation, management, and care of patients with dyslipidemia. This summary is intended to be a "living document," with future annual updates based on emerging science, clinical considerations, and new NLA Position, Consensus, and Scientific Statements, thus providing an ongoing resource that applies the latest in medical science towards the clinical management of patients with dyslipidemia. Topics include the NLA Recommendations for Patient-Centered Management of Dyslipidemia, genetics, Familial Hypercholesterolemia, secondary causes of dyslipidemia, biomarkers and advanced lipid testing, nutrition, physical activity, obesity, adiposopathy, metabolic syndrome, diabetes mellitus, lipid pharmacotherapy, lipid-altering drug interactions, lipoprotein apheresis, dyslipidemia management and treatment based upon age (children, adolescents, and older individuals), dyslipidemia considerations based upon race, ethnicity and gender, dyslipidemia and human immune virus infection, dyslipidemia and immune disorders, adherence strategies and collaborative care, and lipid-altering drugs in development. Hyperlinks direct the reader to sentinel online tables, charts, and figures relevant to lipidology, access to online atherosclerotic cardiovascular disease risk calculators, worldwide lipid guidelines, recommendations, and position/scientific statements, as well as links to online audio files, websites, slide shows, applications, continuing medical education opportunities, and patient information.

Bays HE, Jones PH, Orringer CE, Brown VW, Jacobson TA. On behalf of the NLA Annual Summary of Clinical Lipidology Working Group: Aberg JA, Aspry KE, Ballantyne CM, Bays HE, Bramlett DA, Braun LT, Brinton EA, Brown AS, Brown WV, Daniels S, Deedwania P, Duell PB, Eckel R, Fazio S, Ferdinand KC, Goldberg AC, Guyton JR, Hemphill LC, Jacobson TA, Jones PH, Kellick K, Kris-Etherton P, La Forge R, Liao KP, Maki KC, Moriarty PM, Morris PB, Orringer CE, Rosenson RS, Ross JL, Saseen JJ, Sikand G, Underberg JA, Vijay K, Westman EC, Wild RA, Willard K-E, Wilson DP.

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I. INTRODUCTION

Updates

For this 2016 version, edits to last year's 2015 National Lipid Association (NLA) Annual Summary included updates based upon the National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 2,[48] and expanded discussions of proprotein convertase subtilisin/kexin type 9 inhibitors, which were approved for clinical use in 2015. New sections included lipid considerations of patients with human immunodeficiency virus infection and rheumatoid arthritis. Substantial updates to the 2015 NLA Annual Summary based upon Part 2 of the NLA Recommendations included sections regarding lifestyle therapies, groups with special considerations (e.g., children and adolescents, women, older patients, ethnic and racial groups), patients with residual risk, and strategies to improve patient outcomes by increasing adherence and team-based collaborative care.

Principles

The 2016 NLA Annual Summary of Clinical Lipidology was founded on evidence-based medicine and is generally consistent with established national and international lipid guidelines. Where definitive evidence was lacking, the best available evidence was applied. This summary should not be interpreted as rules or directives with regard to the most appropriate care of any single patient with dyslipidemia, because no set of recommendations or guidelines can have 100% applicability to an individual patient. Thus, evaluation and treatment decisions should be based on patient-centered, individual circumstances. As such, this document should be used in conjunction with, and not a replacement for the preferences of patients with dyslipidemia and the judgment of their treating clinicians.

Appendix A and B Table and Figure Hyperlink Format

Highlighted hyperlinks within the document lead to Appendix A and B. When viewed online, hyperlinks in Appendix A and B, as well as hyperlinks in the E link section lead to applicable publications, tables, figures, and charts. In an age of wide-scale availability of Internet access, computers, smartphones, and tablets, the intent is to provide a central directory of information applicable for both medical science, as well as for the day-to-day management of patients with dyslipidemia. Providing electronic links to tables, figures, charts, and publications allows for better maintaining a summary document format, easier access to more in-depth information, and greater comprehensiveness of material important in the evaluation and management of patients with dyslipidemia.

Lipid Recommendations, Lipid Guidelines, and ASCVD Risk Calculators

Multiple scientific organizations have issued opinions on how dyslipidemia is best evaluated and managed. A listing and brief comparison of some of these lipid recommendations and guidelines are electronically linked in Appendix B. Appendix B also provides hyperlinks to online calculators which may assist clinicians assess ASCVD risk.

Review Board Charge 2016

The Review Board was charged with updates to the previous year's version of of the NLA Annual Summary of

Clinical Lipidology. The Review Board was comprised of NLA members, NLA national officers, the Editor of the *Journal of Clinical Lipidology*, Guest Editor of this document, and other invited reviewers. The NLA Review Board was constituted to allow for a broad perspective and diversity regarding the science and clinical considerations in the evaluation and treatment of patients with dyslipidemia. The NLA Annual Summary of Clinical Lipidology Review Board was instructed to incorporate evidence-based medicine as well as expert opinion.

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II. NLA RECOMMENDATIONS FOR PATIENT-CENTERED MANAGEMENT OF DYSLIPIDEMIA

Lipid evaluation and management principles[1,2]

- Basic principles in the evaluation and management of dyslipidemia for the purpose of reducing atherosclerotic cardiovascular disease (ASCVD) risk include:
  - An elevated level of atherogenic cholesterol is reflective of an increase in circulating apolipoprotein B (apo B) containing lipoproteins, and is most often clinically assessed by measuring non high density

lipoprotein cholesterol (non-HDL-C) and low density lipoprotein cholesterol (LDL-C).

- An increase in atherogenic cholesterol-containing lipoprotein particles is the key underlying process contributing to most clinical ASCVD events.
  - The term *atherogenic cholesterol* is intended to denote the cholesterol carried by atherogenic lipoproteins, even as it is recognized that circulating apo B-containing and cholesterol-containing lipoproteins themselves more precisely promote atherosclerosis.
- Reducing elevated levels of atherogenic cholesterol will lower ASCVD risk in proportion to the reduction in the totality of cholesterol carried by atherogenic lipoproteins, as might be practically assessed by measuring the surrogate of non-HDL-C.
- The reduction in ASCVD risk is presumed to result from the lowering of atherogenic cholesterol and atherogenic lipoproteins via multiple modalities, including lifestyle, pharmacotherapy, lipoprotein apheresis, and perhaps certain gastrointestinal surgeries.
- Lipid-altering therapies that reduce atherogenic cholesterol and atherogenic lipoproteins may not always have ASCVD outcomes data upon regulatory approval. Such lipid-altering agents are most likely to ultimately be shown to reduce ASCVD risk when:
  - The hypothesis of the potential benefit of the therapeutic agent is based upon an accepted mechanism of action, applicable genetic models, and epidemiological studies known to reduce ASCVD risk.
  - Supported by experimental animal studies.
  - Supported by aggregated phase II or later phase human clinical trial data with post hoc or interim analyses demonstrating reductions in ASCVD events, without substantive and clinically meaningful adverse effects.
- The intensity of ASCVD risk-reduction therapy should generally be adjusted to the patient's absolute risk for an ASCVD event.
- 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 ASCVD risk-reduction therapies.
- Lifestyle therapies, such as appropriate nutrition and physical activity, are important elements of ASCVD risk reduction, with or without lipid-altering drug therapy.
- For patients in whom lipid-altering drug therapy is indicated, statin treatment is the primary pharmacologic modality for reducing ASCVD risk.
  - Lipid-altering drug therapy, such as the use of statins, is often indicated in patients at high ASCVD risk.
  - For patients who do not have an adequate lipid response to moderate- and high-intensity statins, or who are statin intolerant, or who have contraindications to statin use, additional and/or alternative lipid-altering pharmacotherapies should be considered. The choice of potential additional or alternative lipid-altering drug therapy should be based upon supporting clinical trial evidence of efficacy and safety, or based upon the best available evidence.
- Monitoring non-HDL-C and LDL-C levels, and setting lipid treatment goals are among the most important

tools in implementing a successful lipid management strategy, as it allows the clinician to assess patient response to therapy and identify potential barriers to patient adherence to lipid treatments (eg, adverse experiences, financial concerns, and sociocultural barriers).
- Non-lipid ASCVD risk factors should also be managed appropriately, particularly high blood pressure, cigarette smoking, and diabetes mellitus.

Lipid treatment targets

• Lipid treatment targets are the lipid parameters to be evaluated and managed for the purpose of reducing ASCVD risk, and include:

Non–high-density lipoprotein cholesterol (non–HDL-C)

- While non-HDL-C and LDL-C are co-primary treatment targets, non-HDL-C is the superior treatment target for modification.
- Non–HDL-C is a calculation of total cholesterol minus high-density lipoprotein cholesterol (HDL-C).
- Non–HDL-C comprises the cholesterol carried by all atherogenic particles, including LDL, intermediate-density lipoproteins, very low-density lipoproteins (VLDL) and VLDL remnants, chylomicron remnants, and lipoprotein (a).
- Epidemiological studies support non–HDL-C as a stronger predictor of ASCVD morbidity and mortality than LDL-C.
- Non–HDL-C levels and change during treatment of dyslipidemia are more strongly associated with reduced risk for atherosclerotic coronary heart disease (CHD) than changes in LDL-C, or on-treatment levels of LDL-C.
- When on-treatment values are discordant, CHD risk is more closely aligned with non–HDL-C than LDL-C.
- Explanations for the superiority of non–HDL-C over LDL-C for predicting ASCVD event risk include:
  - Similar to LDL, some triglyceride-rich lipoprotein remnants enter the arterial wall and thus contribute to the initiation and progression of atherosclerosis.
  - Elevated triglyceride-rich lipoproteins, particularly in the post-prandial state, may increase the transformation of subendothelial monocytes to macrophages, and thus promote an atherogenic inflammatory response.
  - Non–HDL-C correlates more closely with apo B than LDL-C, and thus more closely correlates with the total burden of atherogenic particles.
  - 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.

Low-density lipoprotein cholesterol (LDL-C)

- LDL-C is a co-primary lipid treatment target (along with non–HDL-C)
- LDL-C comprises ~75% of the circulating cholesterol carried by lipoprotein particles other than HDL, although this percentage may be lower in patients with hypertriglyceridemia.

Apolipoprotein B (apo B)

- Apo B is an optional, secondary lipid target for treatment.
- Each atherogenic lipoprotein particle contains one molecule of apo B. The apo B concentration is therefore a direct indicator of the number of circulating particles with atherogenic potential.
- Compared with LDL-C levels, epidemiological studies generally support the superiority of apo B and non–HDL-C levels as better predictors of ASCVD risk, with some studies suggesting apo B and non-HDL-C as equivalent in predicting ASCVD risk.[3]
- Apo B and non–HDL-C share the advantage that neither requires fasting for accurate assessment.
- While some studies suggest apo B may be superior to LDL-C and non-HDL-C in predicting future ASCVD risk,[4,5] the NLA Recommendations favor measuring non-HDL-C because it is universally available, requires no additional expense, can be measured either fasting or non-fasting, and clinical trial evidence has not always supported apo B as superior to non-HDL-C in predicting ASCVD risk.[2,3]
- Apo B is a potential marker of residual ASCVD risk because apo B may remain elevated in some individuals who have attained their treatment goals for non–HDL-C and LDL-C, as may occur in patients with elevated triglyceride and lower HDL-C levels.
- 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.
- Measurement of apo B is generally not recommended until the patient has been treated to his or her goal levels for atherogenic cholesterol.

Triglycerides

- An elevated triglyceride level is not a specific target for therapy, except when triglycerides are very high (≥500 mg/dL).
- When the triglyceride concentration is very high (≥500 mg/dL, and especially if ≥1000 mg/dL), the

primary goal of therapy is to reduce the triglyceride level to < 500 mg/dL for the intent of reducing the risk of pancreatitis.
- When triglycerides are between 200 and 499 mg/dL, the primary targets of lipid therapy are non–HDL-C and LDL-C.

High-density lipoprotein cholesterol (HDL-C)

- A reduced HDL-C level is an ASCVD risk factor used in ASCVD risk factor counting and quantitative risk assessment.
- Low HDL-C is a component of the metabolic syndrome.
- HDL-C is not a specific target of therapy; however, HDL-C levels may be increased as a consequence of favorable lifestyle intervention and certain lipid-altering drug therapies.

Lipid treatment goals

- Lipid targets are the lipid parameters to be evaluated and managed for the purpose of reducing ASCVD risk, whereas lipid treatment goals represent the recommended levels of those lipid parameters.
- The lipid and lipoprotein goals recommended by the NLA are based on the central tenet that excessive concentrations of circulating atherogenic lipoproteins and the cholesterol they carry is a root cause of ASCVD. Key concepts regarding these goals include the following:
  - Epidemiologic and observational study evidence supports a log-linear relationship between the levels of atherogenic cholesterol and absolute ASCVD event risk.
  - Various therapeutic modalities that lower atherogenic cholesterol (eg, nutritional intervention, pharmacotherapy, lipoprotein apheresis, ileal bypass surgery, bariatric surgery) reduce ASCVD event risk.
  - Lipid treatment goals are useful to help match the intensity of lipid therapy to the patient's absolute risk for an ASCVD event, an approach that is generally useful in informing treatment decisions.
  - Lipid treatment goals facilitate provider-patient communication and patient adherence.
- Lipid treatment goals are dependent upon the assessment of ASCVD risk.
  - Lipid treatment goals for patients at moderate ASCVD risk include non-HDL-C levels of <130 mg/dL and LDL-C levels of <100 mg/dL, with lipid altering drug therapy considered for moderate ASCVD risk patients with non-HDL-C levels of ≥ 160 mg/dL and LDL-C levels of ≥ 130 mg/dL.
  - Lipid treatment goals for patients at high ASCVD risk include non-HDL-C levels of <130 mg/dL and LDL-C levels of <100 mg/dL, with lipid altering drug therapy considered for high ASCVD risk patients with non-HDL-C levels of ≥ 130 mg/dL and LDL-C levels of ≥ 100 mg/dL.
  - Lipid treatment goals for patients at very high ASCVD risk include non-HDL-C levels of <100 mg/dL and LDL-C levels of <70 mg/dL, with lipid altering drug therapy considered for very high ASCVD risk patients with non-HDL-C levels of ≥ 100 mg/dL and LDL-C levels of ≥ 70 mg/dL.

Lipid screening

- The NLA has recommended basic principles in the screening of lipid levels, which include:
  - All adults (≥20 years of age) should have a fasting or nonfasting lipoprotein profile obtained at least every 5 years.
  - At a minimum, lipid testing should include a total cholesterol (total-C) and HDL-C, which allows calculation of non–HDL-C (total-C − HDL-C).
  - 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.
- When the patient is fasting (generally 9 to 12 hours), LDL-C level may be calculated, provided that the triglyceride concentration is <400 mg/dL.
- Those with atherogenic cholesterol in the desirable range should engage in favorable lifestyle habits and be monitored for the onset of other ASCVD risk factors.

Atherosclerotic cardiovascular disease (ASCVD) risk categories

Atherosclerotic cardiovascular disease (ASCVD) risk assessment

- Clinically, ASCVD risk assessment is a sequential process involving both clinical and laboratory assessment, including evaluation for:
  - Clinical evidence of ASCVD.
  - Other conditions known to be associated with high or very high risk for ASCVD (e.g. ≥ 3 major ASCVD risk factors, diabetes mellitus, chronic kidney disease stage 3B or 4, LDL-C levels ≥ 190 mg/dL).
  - Number of major ASCVD risk factors (i.e., counting ASCVD risk factors).
  - Major risk factors for ASCVD include:
    - Age ≥ 45 years in men and ≥ 55 years in women
    - Family history of atherosclerotic coronary heart disease in a first-degree man relative < 55 years of age, or a first-degree woman relative < 65 years of age
    - Current cigarette smoking

    - High blood pressure (e.g., ≥ 140 mmg Hg systolic or ≥ 90 mm Hg diastolic, or treated with high blood pressure medications
    - Low high density lipoprotein cholesterol levels (e.g., < 40 mg/dL for men, < 50 mg/dL for women)
  - Other risk indicators that might be considered for ASCVD risk refinement include quantitative ASCVD risk scoring or other secondary ASCVD risk indicators (e.g., coronary calcium scoring, high sensitivity C reactive protein, lipoprotein (a), or urine albumin/creatinine ratio).

Very high ASCVD risk

- Patients at very high ASCVD risk include those with clinical evidence of ASCVD and/or diabetes mellitus plus ≥2 major ASCVD risk factors or evidence of end-organ damage (e.g., retinopathy, microalbuminuria (albumin-to-creatinine ratio > 30 mg/g), or chronic kidney disease (estimated glomerulofiltration rate of < 60 mL/min/1.73 m^2).
- Patients at very high ASCVD risk have the most aggressive goals for atherogenic cholesterol (non–HDL-C <100 mg/dL, LDL-C <70 mg/dL).
- End-stage (stage 5) chronic kidney disease (CKD) is associated with very high risk for ASCVD events. Goals for atherogenic cholesterol levels in Stage 5 CKD are not defined since lowering LDL-C levels (e.g., with statins) has yet to demonstrate convincing benefits from the primary outcomes of randomized, controlled trials in dialysis patients.

High ASCVD risk

- Those at high ASCVD risk include patients with:
  - ≥3 major ASCVD risk factors.
  - Diabetes mellitus with 0 to 1 additional major ASCVD risk factors and no evidence of end-organ damage.
  - CKD stage 3B or 4.
  - LDL-C ≥190 mg/dL.
- Quantitative ASCVD risk scoring is an option for patients at moderate ASCVD risk to estimate 10-year or long-term/lifetime risk for an ASCVD or atherosclerotic coronary heart (CHD) event, which may especially apply to the patient without ASCVD disease, but with ASCVD risk factors. High CHD risk is defined as ≥10% using the Adult Treatment Panel III Framingham Risk Score for hard coronary heart disease (non-fatal myocardial infarction or CHD death). The 2013 American College of Cardiology/American Heart Association (ACC/AHA) Pooled Cohort Equations for hard ASCVD (myocardial infarction, stroke, or cardiovascular disease [CVD] death) identifies a ≥ 7.5% ten year ASCVD risk cut-off point to identify patients who may benefit from moderate to high intensity statin. However, this 7.5% cut-off point is not necessarily intended to identify patients at high ASCVD risk (many individual patients age 65 or older have a 10 year risk of 7.5% or more, based largely upon age alone). A CHD risk of 10% or greater using the Framingham Risk Calculator roughly correlates to a 15% or greater ASCVD risk, when using the ACC/AHA Pooled Cohort Equation. Finally, a cut-off point of 45% or greater using the Framingham long-term CVD (myocardial infarction, CHD death or stroke) risk calculation may also identify patients at high CHD risk. These tools help facilitate identification of patients who may be classified as high risk in the absence of the high risk conditions previously listed.
- The NLA Expert Panel views determination of an increase in lifetime ASCVD risk as important in informing the decision of implementation of both intensive lifestyle intervention, as well as possible lipid-altering drug therapy.

Moderate ASCVD risk

- Patients are at moderate ASCVD risk if they have 2 major ASCVD risk factors in the absence of conditions that place them into the high- or very high-risk categories.
- Moderate ASCVD risk individuals have a 5% to <15% 10-year risk for an ASCVD event, when assessed by the ACC/AHA Pooled Risk Cohort calculator.
- Although categorical risk factor counting and quantitative risk assessment provide similar results in most cases, quantitative risk scoring may be performed in patients at moderate ASCVD risk to identify those who should be reclassified as high ASCVD risk and should be performed before other ASCVD risk assessments, such as measurement of biomarkers.
- In patients with two major ASCVD risk factors, consideration should also be given to further refine ASCVD risk assessment, such as calcium score >300 Agatston units; hs-CRP >2.0 mg/L; lipoprotein (a) >50 mg/dL; urine albumin/creatinine ratio ≥30 mg/g; LDL-C ≥160 mg/dL and/or non-HDL-C ≥190 mg/dL; or a severe disturbance in a major ASCVD risk factor (i.e. family history of premature CHD or multipack per day smoking). If any of these findings are present, patients might reasonably be reclassified and managed as having high ASCVD risk.
- In some patients, 10-year risk for an ASCVD event may be below the high-risk threshold, but lifetime risk may be substantially elevated. This is especially true in women 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.

Low ASCVD risk

- Patients are at low ASCVD risk if they have no evidence of current or past ASCVD, and if they have 0 or 1 major ASCVD risk factor.

- Low ASCVD individuals have a <5% 10-year risk for an ASCVD event, and lipid-altering pharmacotherapy is generally only considered when non-HDL-C levels are ≥190 mg/dL or LDL-C levels are ≥160 mg/dL.
- Quantitative risk scoring is not necessary for all individuals at low risk for ASCVD.
- As with other risk categories, clinic judgment in assessing ASCVD risk applies
  - Otherwise low ASCVD risk patients with marked elevation of a single risk factor may best be reclassified as moderate to high ASCVD risk, as might occur with a patient having a multipack per day history of cigarette smoking
  - Patients otherwise at low ASCVD risk with strong family history of ASCVD (especially if "premature" ASCVD) who have markedly elevated lipoprotein (a) may also prompt the clinical decision to reclassify the patient as being at higher ASCVD risk.

III. GENETICS AND CLASSIFICATION OF DYSLIPIDEMIA[6]

Hyperlipidemias

- Dyslipidemia has primary and/or secondary causes, with secondary causes often exacerbating primary dyslipidemia.
- Primary causes of dyslipidemia include single genetic abnormalities that directly affect lipoproteins and their function, as well as polygenetic abnormalities wherein multiple genetic variants contribute to lipid transport abnormalities, resulting in increases or decreases in lipid parameters.
- Diagnosis of lipid genetic abnormalities is usually by clinical presentation.
  - History (including age of onset of ASCVD in the patient and family members).
  - Physical findings such as eruptive xanthomas and tendon xanthomas.
  - Laboratory evaluation such as lipid levels and apolipoprotein assays.
- Diagnosis of more rare dyslipidemias can sometimes be assisted by genetic or functional testing (eg, gene sequencing, LDL receptor activity, and lipoprotein lipase activity).
- The appearance of the serum can provide clues to diagnosis of genetic dyslipidemia.[7]

Hypolipidemias[8,9]

- Just as genetic abnormalities can contribute to elevated lipoprotein and lipid levels, genetic abnormalities can also contribute to low lipoprotein and low lipid levels.
- Examples include hypobetalipoproteinemia, abetalipoproteinemia, proprotein convertase subtilisin/kexin type 9 loss of function, and intestinal Niemann-Pick C1-Like transport protein loss of function.

Clinical role of genetic testing for dyslipidemia

- In evaluating the patient with dyslipidemia who may have a genetic abnormality, laboratories may conduct sequencing of the entire human genome, or may do custom sequencing of one or more genes. Genome-wide association studies (GWAS) may reveal nucleotide polymorphisms, which are two or more alleles at one locus, with gene sequences that code for biological mechanisms contributing to abnormal lipid levels.
- In some countries, patients with marked elevations in LDL-C levels may often undergo systematic genetic sequencing of the LDL receptor, apo B, and proprotein convertase subtilisin/kexin type 9 (PCSK9), as part of a publicly supported program. Defects in the LDL receptor gene are the most common cause of familial hypercholesterolemia (FH); however, genetic abnormalities resulting in a mutated/defective apo B, or gain-of-function PCSK9 may present with the same phenotype.[10]
- The lack of an identifiable genotype does not negate the potential phenotypic expression, and adverse clinical consequences of Familial Hypercholesterolemia.[11]
- In contrast to centers in parts of Europe, few US research sites and testing centers perform genotyping for patients with hypercholesterolemia.
- Cost may be a potential challenge, although the price of genotyping for patients with severe hypercholesterolemia has substantially decreased over time.
- A potential benefit of genotyping is a better opportunity for family cascade screening, and a more definitive knowledge of the genetic cause of hypercholesterolemia that may provide benefits in patient and family counseling.

Illustrative examples of genetic dyslipidemias

- Example #1: Genetic abnormalities leading to LDL receptor dysfunction are among the most common major gene defects in humans, and clinically result in FH.
- Example #2: Genetic gain of function of cholesteryl ester transfer protein (CETP) results in decreased HDL-C levels, whereas a genetic loss of function of CETP increases HDL-C levels; the effect upon ASCVD risk is not clear.[12]
- Example #3: A dominant form of genetic hypercholesterolemia is gain-of-function genetic variant of PCSK9 that can cause phenotypical familial hypercholesterolemia.[13] PCSK9 is a protein that facilitates the degradation of the LDL receptor, resulting in less LDL receptor sites for uptake of circulating LDL particles. With increased

PCSK9 activity via gain-of-function genetic variant, circulating LDL-C levels are increased.

- Example #4: Betasitosterolemia is a rare inherited plant sterol storage disease that can phenotypically mimic FH.
  - Clinical findings of tendon xanthomas and increased ASCVD risk may be out of proportion to the patient's lipid profile, which may demonstrate modest to no increase in LDL-C levels.
  - Betasitosterolemia is an autosomal recessive condition that occurs as a result of mutations in adenosine triphosphate binding cassette transporters (ABC) G5 or ABCG8, which are sterol transporters that facilitate plant sterols and cholesterol efflux from intestinal and hepatic cells into the intestinal and biliary lumen.
  - A lack of gastrointestinal plant sterol secretion back into the gastrointestinal lumen increases circulating phytosterol levels.
  - The diagnosis of betasitosterolemia is typically made by measuring plant sterol levels, not by genotyping of ABCG5/G8.
  - Betasitosterolemia is an example of a genetic condition that requires an accurate diagnosis because ezetimibe is the only lipid-altering drug with a specific Food and Drug Administration (FDA)-indicated use for treating patients with betasitosterolemia.
  - Ezetimibe impairs intestinal plant sterol (and cholesterol) absorption and therefore reduces circulating plant sterol levels.
- Examples of other genetic abnormalities related to dyslipidemia include disorders of lipoprotein (a), apolipoprotein E, apo CIII, Apo-AV, and ABC transporters (ie, Tangier disease). Future genotyping may help identify mutations in these lipid-related parameters, and may also help help identify patients most likely to have adverse experiences with certain medications, such as myopathy to statins.
- Some genetic contributors to dyslipidemia involve a combination of gene variants. For example, many genetic causes of moderate hypertriglyceridemia are likely polygenic in nature, requiring a secondary factor for expression.[7,199]

EVALUATION AND MANAGEMENT OF FAMILIAL HYPERCHOLESTEROLEMIA[14–17]

Genetics

- The FHs represent a group of genetic defects that result in an extreme elevation of LDL-C levels starting in utero, and increased risk of premature atherosclerotic CHD, as much as 20-fold in untreated FH patients.
- Although homozygous FH occurs in approximately 1 out of every 250,000 to 1 million individuals, heterozygous FH is among the most common congenital metabolic disorders, occurring in approximately 1:200 to 1:500 individuals,[18] with an increased rate (1:100) among those of Lebanese, French Canadian, Ashkenazi Jewish, and several South African backgrounds resulting from founder effects.
- FH is most commonly (~90%) an autosomal dominant lack of LDL receptor activity, usually from LDL receptor mutation (with more than 1200 described mutations).
- Less commonly, FH may be due to an apo B-100 gene mutation (eg, Arg3500Gln), which accounts for about 5% of genetically identified FH cases, or PCSK9 gain-of-function mutations (overexpression), leading to increased degradation of the LDL receptor and accounting for about 1% of cases of FH.[19]
- Other potential mechanisms may contribute to the phenotypic presentation of FH.

Lipids

- Patients with homozygous FH (the same genetic defect inherited from each parent) or compound heterozygous FH (different genetic defects inherited from both parents) typically have LDL-C levels >500 mg/dL.
- Patients with heterozygous FH (single genetic defect inherited from either parent) typically have LDL-C levels >160 mg/dL in pediatric patients and >190 mg/dL in adult FH patients.
- Patients with FH may occasionally have elevated triglyceride levels; thus, high triglyceride levels do not exclude the diagnosis of FH.

Diagnosis[18,20–22]

- Several groups have offered diagnostic criteria for FH, including Simon Broome, Dutch Lipid Clinic Network, and MedPed: Dutch Lipid Clinic criteria apply to adults; Simon Broome and MEDPED can also apply to children.
- Diagnostic criteria for FH depend upon measured findings of very high LDL-C levels as well as family history of markedly elevated LDL-C levels and early-onset ASCVD. Given this clinical presentation, tendon xanthomas are pathognomonic for FH, with genetic testing often, but not always, confirmatory.

Screening and genetic testing for familial hypercholesterolemia[15,16]

- Cascade (family) screening for FH is recommended in individuals and families with very high LDL-C levels.
- Genetic testing is generally not required for diagnosis or clinical management of FH; however, a characteristic clinical presentation, coupled with DNA testing by a reliable testing laboratory that confirms an applicable mutation can provide an unequivocal diagnosis.
- The possibility of FH is not excluded by negative DNA testing because genetic testing fails to reveal a specified mutation in approximately 30% of clinically defined FH patients.

Treatment priorities

- Maximize reduction in other ASCVD risk factors
- Maximize nutrition and physical activity interventions
- Lower LDL-C levels by at least 50% or more, to <100 mg/dL, if feasible
- Cascade testing of first-degree relatives should be offered to all individuals with FH.
- The 10-year CHD risk in the FH patient is not adequately predicted by any conventional risk assessment tools; assessment of 10-year risk is not recommended.

Lipid-altering pharmacotherapies for FH: general principles

- High-intensity statins are the pharmacotherapy of first choice for patients with FH, but should be avoided in women who are breastfeeding, who may potentially become pregnant, or who are pregnant because statins have not been adequately studied in pregnant women. Other lipid-altering agents that may be useful in combination with statins, or in combination with each other (for patients who cannot take statins) include ezetimibe, bile acid sequestrants, PCSK9 inhibitors, and niacin.
- In addition to high-intensity statins, 3 other lipid-altering pharmacotherapies have an approved indication to treat patients with homozygous FH.
- Mipomersen is an antisense oligonucleotide that targets the messenger RNA for apo B.
  - Mipomersen is an antisense inhibitor of apo B synthesis that when administered in combination with maximum tolerated doses of lipid-lowering therapy can reduce LDL-C levels by an additional 25% in homozygous FH patients.
  - Mipomersen is an injectable product that may cause injection site reactions.
  - Mipomersen may increase hepatic fat.
  - Mipomersen may increase liver transaminase levels; however, clinical trial data have not reported permanent liver failure.
- Lomitapide is a microsomal triglyceride transfer protein inhibitor, which impairs VLDL secretion and reduces circulating apo B–containing lipoproteins.
  - Lomitapide may reduce LDL-C levels by up to 50% in patients with homozygous FH on maximum tolerated lipid-lowering therapy and LDL apheresis.
  - Common adverse experiences with lomitapide include fat malabsorption, diarrhea, increased liver fat, and elevated liver transaminases.
- Substantially due to the alterations in liver transaminases and increase in hepatic fat, mipomersen and lomitapide are available through Risk Evaluation and Mitigation Strategy programs.
- Evolocumab is a human monoclonal PCSK9 inhibitor that among its indications is treatment for homozygous familial hypercholesterolemia. Compared with placebo in patients with homozygous hypercholesterolemia, evolocumab significantly reduced LDL cholesterol at 12 weeks by 31%, suggesting residual LDL receptor activity in a subset of patients with homozygous FH.[23]
- Other treatment options for lowering cholesterol in patients with FH include LDL apheresis, and in the most severe and resistant cases, portacaval anastomosis and liver transplantation.

IV. SECONDARY CAUSES OF DYSLIPIDEMIA[1,24]

- Beyond genetic considerations, dyslipidemia can also be due to secondary causes.
- A "two hit phenomenon"[24] is commonly encountered in the clinical evaluation and management of patients with primary hyperlipidemia (eg, the relatively common familial combined hyperlipidemia or familial hypertriglyceridemia; the more rare lipoprotein lipase deficiency, apo C-II deficiency, familial dysbetalipoproteinemia).
  - "First hit" = Genetic predisposition.
  - "Second hit" = Exacerbation by secondary factors that worsen lipid levels, often resulting in profound hyperlipidemia.
  - This "second hit" can be of the result of underlying disordered metabolism or disease (e.g., untreated hypothyroidism, inadequately controlled diabetes mellitus) or from drugs that unfavorably alter lipid metabolism.
  - Secondary causes of hyperlipidemia are listed in the Appendix, and many elevate triglycerides either alone, or elevate both triglycerides and LDL cholesterol.
  - Secondary causes of hypertriglyceridemia are often associated with decreases in HDL-C levels. However, alcohol consumption, oral estrogens, and bile acid sequestrants are examples of agents that can increase both triglyceride and HDL-C levels.

V. ADDITIONAL LIPID PARAMETERS[25–31]

High-density lipoprotein cholesterol

- Epidemiologically, HDL-C has an inverse relationship with ASCVD risk, irrespective of sex, race, or ethnicity.
  - Increased HDL-C levels are often associated with decreased risk of ASCVD.
  - Decreased HDL-C levels are often associated with increased ASCVD risk.
- HDL-C may not be causally related to atherosclerosis and cardiovascular events; however, it is a biomarker of ASCVD risk.
- HDL particles include many proteins and lipids that influence the function of HDL and may provide atheroprotection via favorable effects upon atherosclerotic

mechanisms including modulation of inflammation, oxidation, endothelial function, and insulin secretory capacity, as well as removal of free cholesterol from peripheral cells.
- In human studies:
  - Low HDL-C levels are not consistently associated with premature ASCVD.
  - High HDL-C levels are not consistently associated with atheroprotection.
  - Several randomized studies using interventions that raise HDL-C levels (eg, CETP inhibition) have failed to reduce the risk of ASCVD.
- The inverse relationship between HDL-C levels and ASCVD risk may represent an epiphenomenon.
- HDL-C levels are often inversely related to an increase in body fat, waist circumference, insulin resistance, systemic inflammation, and cigarette smoking, all of which can increase ASCVD risk, and thus confound the true relationship between HDL-C levels and the risk of ASCVD.
- HDL-C levels are also inversely associated with elevated triglyceride-rich lipoprotein levels, small (more dense) LDL-P, and increased atherogenic particle number, all which may increase ASCVD risk.
- HDL-C may be a biomarker of ASCVD risk. If HDL-C levels are low (<40 mg/dL in men, <50 mg/dL in women), then it is a ASCVD risk factor; however, it is not currently a target of lipid-altering therapy.
- Therapeutically:
  - HDL-C refers only to the cholesterol content of HDL particles. Pharmacologic increases in the cholesterol content of HDL particles are not proven to reduce ASCVD risk.
  - The clinical relevance of HDL may be more dependent on its ability to induce cholesterol efflux from arterial macrophages.
  - Animal studies support regression of ASCVD with infusible apo A-I/HDL and viral hepatic transfection with apo A-I, suggesting that an increase in the number of HDL particles may have antiatherogenic potential.
  - In humans with ASCVD who have optimal levels of non–HDL-C and LDL-C levels, agents administered for the purpose of increasing HDL-C levels have not demonstrated further reduction in ASCVD risk.
  - Patients unable to achieve non–HDL-C and LDL-C treatment goals with a statin should be considered for combination lipid-altering pharmacotherapy, with the intent of achieving non–HDL-C and LDL-C goals, as opposed to adding pharmacotherapies to specifically increase HDL-C levels.

Low-density lipoprotein particle number

- LDL-C is the cholesterol carried by LDL particles; LDL-P is the LDL particle concentration.
  - Assessing the number of LDL-Ps can be an alternative to measuring apo B.
  - Atherogenic lipoproteins, such as LDL particles, transverse the arterial wall into the subendothelium via a gradient-driven process, independent of LDL receptor activity. The greater the concentration of LDL particles, the greater the rate of passive diffusion into the arterial wall.
  - Once inside the arterial intima, LDL particles that bind to arterial wall proteoglycans are retained, oxidized or otherwise chemically modified, thereby allowing for more rapid uptake by tissue macrophages.
  - Lower circulating LDL particles reduce the potential number of LDL particles that may enter the arterial wall, resulting in less propensity for initiation and promotion of atherosclerosis.
- Patients with elevated triglycerides, low HDL-C levels, and/or diabetes mellitus may have greater elevations of LDL-P for a given LDL-C level. Clinically, an increase in fasting triglyceride levels (not due to hyperchylomicronemia) may suggest the presence of denser low density lipoprotein particles, the presence of an increase in LDL particles per LDL-C level, and thus the presence of a more atherogenic lipid profile.
- The cholesterol content of LDL particles is variable; thus, the cholesterol carried by LDL particles and the number of LDL particles may be discordant.
  - When discordant, LDP-P may better assess ASCVD risk than LDL-C.
  - On-treatment LDP-P may be more predictive of residual ASCVD risk than LDL-C levels.
  - Given that statin therapy reduces non–HDL-C and LDL-C to a greater extent than reducing LDL-P, LDL-P may provide a better assessment of on-treatment residual risk than non–HDL-C or LDL-C measurement. Thus, residual increases in LDL-P may prompt more aggressive lipid-altering therapy.[32]
- Among patients at low ASCVD risk, lipid treatment decisions are unlikely to be altered by use of LDL-P.
- For patients at higher ASCVD risk, especially those who with anticipated discordance between LDL-C and LDL-P, it is unclear if additional LDL-P information should alter initial therapeutic decisions. However, some clinicians may consider measuring LDL-P for selected patients, which may include patients with:
  - Family history of premature ASCVD
  - Elevated triglycerides
  - Low HDL-C levels
  - Metabolic syndrome
  - Diabetes mellitus
  - Recurrent ASCVD events despite therapeutic lifestyle intervention and lipid-altering pharmacotherapy.

Lipoprotein (a)[33]

- Lipoprotein (a) ["lipoprotein little a" or Lp(a)] is an LDL-like particle with an apolipoprotein(a) covalently bound to apoB.

- Lp(a) may impair fibrinolysis, mediate pro-inflammatory effects, activate endothelial cells, recruit monocytes, accelerate macrohage foam cell formation, and transport pro-inflammatory oxidized phospholipids, which may help explain why elevated Lp(a) levels are associated with increased ASCVD risk.[200]
- No favorable function of Lp(a) has yet been identified.
- Lp(a) consists of an LDL, which is attached to a second protein, apo (a).
  - Overall, Lp(a) has a signal peptide region, many repeating kringle domains (amino acid sequences that fold into large loops stabilized by 3 disulfide linkages), a protease domain, apo B, and apo(a).
  - Apo (a) has a structure similar to plasminogen, but no protease activity, and is linked by a disulfide bond to apo B-100.
- Lp(a) concentration, size, and structure (compositional alleles) are highly variable among individuals, which in turn may affect the potential for atherogenicity in an individual patient.
- Lifestyle intervention does not lower Lp(a).
- The following lower Lp(a); however, the clinical implications are unclear[34,35,192]:
  - PCSK9 inhibitors
  - Niacin
  - Mipomersen (apo B antisense)
  - Lomitapide
  - Lipoprotein apheresis
  - Estrogen
- Examples of other agents reported to lower Lp(a) to a minor degree:
  - Androgens
  - Angiotensin-converting enzyme inhibitors
  - Ascorbic acid combined with L-lysine
  - Aspirin
  - Calcium channel antagonists
  - L-carnitine
  - Tamoxifen
  - Thyroxine replacement in hypothyroid patients
- Investigational agents that may lower Lp(a) levels
  - CETP inhibitors
  - Thyroid receptor beta subunit agonists
- Among those at low ASCVD risk, lipid treatment decisions are unlikely to be altered by Lp(a) measurements; thus, Lp(a) measurements are not recommended for routine ASCVD risk assessment in patients at low ASCVD risk.
- In patients at higher ASCVD risk, Lp(a) measurement may be considered for selected patients, especially those with:
  - Family history of premature ASCVD.
  - Recurrent ASCVD events despite therapeutic lifestyle intervention and lipid-altering pharmacotherapy.
  - Familial hypercholesterolemia.

VI. BIOMARKERS AND "ADVANCED LIPID TESTING"[25]

Biomarkers as initial assessment of ASCVD risk[25]

- Biomarkers are lipid and non-lipid parameters beyond those included in a routine lipid profile, which may be of potential use in managing patients with dyslipidemia.
  - These tests are sometimes included in what is often called "Advanced Lipid Testing."
  - Depending upon the initial clinical presentation, some biomarkers may be potentially useful to assess initial ASCVD risk, before starting lipid-altering therapy.

Biomarkers for on-treatment assessment of ASCVD therapy[25]

- Some biomarkers may not only be useful to assess ASCVD risk, but also to monitor the progress of therapy.
- Even if a baseline abnormality in a biomarker can help predict ASCVD risk, interventions that change the same biomarker may not always reduce ASCVD risk.
  - Initial elevations in homocysteine levels are associated with increased ASCVD risk; however, lowering homocysteine levels with B vitamins and folate may not reduce ASCVD risk.[36,37]
- It is important to determine which biomarkers are a measure of increased ASCVD risk at baseline, and thus be potentially useful upon initial clinical assessment, and which biomarkers may play a role in the pathogenesis of ASCVD, and thus may also be useful for on-treatment management decisions.
- Apo B and lipoprotein particle concentration may be useful in some cases to monitor the course of lipid-altering therapy.
- Pathophysiologically, elevated atherogenic particle levels increase ASCVD risk.
  - Atherosclerosis is largely due to incorporation of atherogenic lipoproteins and their cholesterol within the vascular sub-endothelium.
  - Lower atherogenic particle levels are associated with reduced ASCVD risk.
  - One molecule of apo B resides on each atherogenic lipoprotein particle, and thus apo B is a surrogate measure of atherogenic lipoprotein particle number.
  - A reduction in apo B and reduction in lipoprotein particle number are associated with a reduction in ASCVD risk.[38,39]
  - The use of apo B and/or lipoprotein particle number may be of clinical use in monitoring the progress of high ASCVD risk patients, especially where discordance and/or heterogeneity between these biomarkers and LDL-C might be anticipated (eg, adiposopathy,

metabolic syndrome, insulin resistance, type 2 diabetes mellitus).[40–42]

- Few data exist to support monitoring of lipoprotein-associated phospholipase A2 or HDL/LDL subfractions (ie, lipoprotein particle size), because thus far, prospective data are lacking wherein changing either of these parameters with therapeutic interventions reduces ASCVD risk.
  - Determining the effectiveness of a lipid-altering intervention based upon lipoprotein particle size alone may be misleading.[43]
- Lp(a) is a heterogenous lipoprotein similar to LDL, but metabolically distinct.
  - Elevated Lp(a) levels are associated with increased ASCVD risk.
  - Although clinical ASCVD outcomes trials have yet to demonstrate that lowering Lp(a) reduces ASCVD risk, because of its potential casual role in atherogenesis, in applicable and selected patients, some clinicians may choose to monitor lipoprotein (a) during lipid-altering intervention.[44]
- C-reactive protein is an inflammatory marker associated with increased ASCVD risk.
  - When C-reactive protein is reduced with lipid-altering intervention, ASCVD risk may be reduced.
  - In patients with improvement in both lipid levels and C-reactive protein with lipid-altering intervention, the degree by which ASCVD risk is decreased due to a reduction in C-reactive protein is unknown.[45]
  - Given that atherosclerosis is an inflammatory process, some clinicians may find C-reactive protein useful as a measure of effectiveness of lipid-altering intervention in selected, higher ASCVD risk patients.[46]

VII. NUTRITION AND PHYSICAL ACTIVITY

Medical nutrition therapy[1,24,47,48]

Triglyceride-induced pancreatitis[49,50]

- In patients with very high triglyceride levels and acute triglyceride-induced pancreatitis with hyperchylomicronemia, initial management may include hospitalization and fasting.
- Especially if glucose levels are elevated, then insulin therapy may also help reduce triglyceride levels (such as intravenous insulin in patients with poorly controlled diabetes mellitus). However, especially among patients with type 2 diabetes mellitus, the acute effect on chylomicron production may be absent, with the main potential benefit being a reduction in free fatty acid flux, and reduced very low density lipoprotein hepatic secretion.[51]
- When and where available, therapeutic plasma exchange and double-filtration may provide clinical benefit.[193]
- Parenteral nutrition is reserved for severe cases where fasting is prolonged, and enteral nutrition is not feasible or inadequate because of persistent gastrointestinal dysfunction.[52]
- Once active symptoms of pancreatitis have subsided (ie, no nausea and vomiting, resolution of abdominal pain, no requirements for pain medication, and evidence of bowel motility such as bowel movements or active bowel sounds), then a clear liquid diet may be initiated, advancing to a whole food, low fat diet (<6-15% of energy consumption).[53]
- Another nutritional approach is a diet rich in omega-3 fatty acids and medium chain triglycerides.[194]
- When patients with very high triglycerides are managed as an outpatient, then after managing potential secondary causes of hypertriglyceridemia (and other potential causes of pancreatitis), and after implementation of very low fat, limited refined carbohydrate diet, and (when possible), an increase in physical activity, then fasting triglycerides can be monitored every 3-4 days, with an expectation that chylomicron triglycerides may decrease by 20-25% daily.
- Once pancreatitis is resolved and triglycerides are reduced to less than 1000 mg/dL, then non-saturated fats and non trans fats can be gradually increased to 25%, and then 35% of caloric intake.

Medical nutrition therapy for dyslipidemia[24,48,54]

- Beyond treatment of triglyceride-induced acute pancreatitis, appropriate nutritional intervention is also an important strategy for treating dyslipidemia and reducing ASCVD risk.
- Among patients in whom weight reduction is not necessarily the primary therapeutic intent, nutrition therapy for dyslipidemia includes:
  - <7% saturated fat
  - <200 mg/day dietary cholesterol
  - avoidance of trans fat
  - limited proportion of refined carbohydrates and simple sugars
  - Relatively high proportion of vegetables, fruits, legumes, lentils, nuts, fish, low fat dairy, lean meats, and unsaturated oils.
  - Viscous fiber 5-10 gm/day
  - Plant sterols/stanols 2-3 gm/day
- In patients treated with refined carbohydrate restricted nutritional intervention, the increased proportion of dietary fats should preferentially be polyunsaturated and monounsaturated fats, as opposed to saturated fats or trans fats.
- Triglyceride levels are among the lipid parameters most responsive to nutrition intervention.
  - Patients with higher baseline triglyceride levels have the greatest potential for triglyceride reduction with nutrition intervention, such as hypocaloric diets resulting in weight loss in patients with overweight or obesity.

- Within the first 6 to 12 months after the start of a nutrition intervention, carbohydrate restriction ("low-carb diet") typically lowers triglycerides more than a diet higher in carbohydrate intake, especially if associated with weight loss, and especially when compared to a diet composed of energy dense foods low in fiber, and high in refined carbohydrates and added sugars.

- The effect of dietary intervention on LDL-C levels is variable.
  - Among patients who are overweight or obese, in the first few months after weight loss via reduced caloric intake, LDL-C levels may mildly to moderately decrease.
  - On a more long-term basis, following weight loss, LDL-C levels may then:
    - Remain lower than baseline.
    - Return to baseline levels.
    - Increase compared with baseline levels.
- Varied responses of LDL-C levels to nutrition intervention may be related to the nutrient content of the diet, the genetic contribution to baseline LDL-C levels, the baseline lipid profile, the degree of weight loss (in patients with overweight or obesity), the profile of the diet consumed after weight loss, and/or weight loss maintenance or weight regain after weight loss.
- Even if LDL-C levels do not decrease with weight loss in patients with overweight and obesity, fat weight loss may decrease apoB levels.
- HDL-C levels may be affected by factors such as the timing after lifestyle interventions, age, gender, genetics, alcohol intake, physical activity, as well as the energy and nutrient profile of the diet.[55]
  - During active weight loss, especially if achieved through a fat-restricted dietary intake, HDL-C levels may often transiently decrease.
  - After stabilization of body weight, HDL-C levels may return or trend to baseline, and may often increase above baseline, especially with 8% or more weight loss.[56]
  - Fat restricted, higher carbohydrate diets may modestly to moderately decrease HDL-C levels, although no evidence exists that this adversely increases the risk for ASCVD.
  - Carbohydrate-restricted, higher fat diets may modestly to moderately increase HDL-C levels—or at least mitigate HDL-C lowering.
- Weight loss is often a concomitant goal in patients with dyslipidemia because many patients with dyslipidemia are overweight or obese. A cardioprotective eating pattern may include a moderate quantity of carbohydrate, reduced refined carbohydrate (lower glycemic load) and an increased proportion of protein, which is often associated with modest weight loss and improved weight maintenance outcomes.
  - Among patients with overweight or obesity, systematic reviews of randomized clinical trials suggest clinically meaningful changes in ASCVD risk factors with at least a 3% reduction in body weight, with even further improvement with greater weight reduction.
  - Weight loss may have widely variable effects on dyslipidemia, and depends upon the underlying cause of the dyslipidemia, baseline lipid profile and levels, as well as the extent of weight loss and how the weight loss was achieved.
  - Mild body weight loss (e.g., 3 kg) may decrease mean triglyceride by 15 mg/dL.
  - A sustained weight loss of 5 to 8 kg may reduce mean LDL-C approximately 5 mg/dL and increase mean HDL-C levels up to 3 mg/dL.[56]

Adherence to nutrition therapy

- Regarding nutrition intervention for the purposes of both weight loss and treating dyslipidemia, the recommended diet should be based upon sound scientific and clinical support and upon the dietary pattern a patient is most likely to follow long-term.
- Although substantive metabolic differences in lipids (and glucose) are observed within the first 6 months, after 12 months, the variances in weight and metabolic effects of common evidenced-based nutritional therapies tend to wane, with different meal plans having more similar (than dissimilar) weight and metabolic effects.
- Clinical trial data support several nutrition interventions as effective, with the greatest weight and metabolic benefits being observed among patients who are most adherent. Consequently, it is essential that prescribed nutrition interventions for the treatment of dyslipidemia be individualized and include appropriate education and follow-up by a health professional trained in nutrition, such as a dietitian or dietitian nutritionist.[57]

Physical activity[24,48,58]

Effects of physical activity on lipid levels

- Physical activity refers to any bodily movement produced by skeletal muscles that requires energy expenditure.
- The effects of physical activity and exercise training on lipid levels are widely variable among patients.
- At exercise training volumes of 1200 to 2200 kcal/week (eg, 15–20 miles per week of brisk walking or jogging), triglyceride levels may be reduced by 4% to 37%, HDL-C levels increased by 2% to 8%, and LDL-C levels ranging from no change to a 7% reduction.[59–62]
- Among major lipid parameters, physical activity most consistently reduces triglyceride levels, which in addition to potential long-term reductions with routine increases in physical activity, also includes a significant short-term (12–24 hours) reduction in triglyceride levels after a bout of dynamic (aerobic) exercise training.[63]

- Favorable lipid effects may persist for as long as 48 hours after dynamic (aerobic) exercise training, depending on the dose-dependent quantity (intensity and duration) of the exercise.
- More consistent reductions in LDL-C levels are achieved with greater weight reduction.
- Exercise training may also decrease non-HDL cholesterol, total cholesterol, apolipoprotein B, and LDL-P, which reflects a less atherogenic profile.[62,64,65]
- Improvements in lipid parameters are accentuated when increased physical activity is accompanied by negative caloric balance and substantial fat weight loss in patients with overweight or obesity.
- Although resistance training may provide benefits regarding musculoskeletal health then unless resistance training results in clinically meaningful improvements in body composition (ie. decreased body fat), the degree of resistance training achieved by most patients has limited efficacy in substantially affecting fat weight loss or improvement in lipid levels.
    - Any effect on lipids and lipoproteins from the intensity of exercise is small, compared with that of the volume of exercise (ie, kcal expended per week).
    - Although some resistance training studies have reported slight-to-moderate reductions in lipid levels, it is likely that the benefits (if any) of resistance training is related to total net energy expenditure of the session, as is true with aerobic endurance exercise.
- Although the greatest lipid benefits of increased physical activity are when accompanied by weight loss in patients with overweight or obesity, exercise training may improve lipid and lipoproteins parameters, even without substantial reductions in body weight.
- If measured by a standard lipid panel, some patients engaged in regular physical activity may be determined to be "unresponsive" to exercise therapy.
    - Moderate physical exercise volumes and intensities (eg, walking 12 miles per week at 40%–55% of aerobic capacity) can significantly reduce nuclear magnetic resonance spectrometry measured LDL-P, even as total cholesterol and Friedewald-predicted LDL-C levels remain essentially unchanged.[62]
- Some increase in physical activity is better than no physical activity.[66]
    - Even modest amounts of exercise training can prevent a deterioration of the lipid profile (eg, HDL-C levels, LDL and HDL particle size, LDL-P), that is often observed with physical inactivity.
    - "Only" 7 to 10 miles of walking per week may prevent physical inactivity–associated deterioration in these lipid parameters.
    - Moderate-intensity (but not necessarily vigorous-intensity aerobic exercise) of sufficient quantity can promote sustained reductions in triglyceride levels (eg, VLDL triglycerides).[67]

Physical activity, lipids, and weight loss

- Many patients with dyslipidemia are overweight or obese; thus, increasing calorie expenditure by increasing physical activity assists in improved weight loss outcomes and especially weight maintenance.
- Weight loss from increased physical activity is often modest. However, increased physical activity may help mitigate weight loss-associated reductions in resting metabolic rate by modifying body composition (i.e., maintaining or increasing lean body mass), and may counter other weight-regain mechanisms.
- More intensive physical activity, such as 1 hour of daily moderate aerobic exercise (e.g., approximately 300 kcal), can produce at least as much fat loss as equivalent caloric restriction, but with greater insulin sensitivity.
- After one year, increased physical exercise may result in a preferential reduction in visceral adipose tissue compared with caloric restriction alone.[68]

VIII. OBESITY, ADIPOSOPATHY, METABOLIC SYNDROME, AND DIABETES MELLITUS[24,36,69,70]

Obesity as a disease

- Obesity can be defined as "*a chronic, relapsing, multifactorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences*."[69]
- Obesity is a disease wherein increased body fat (as assessed by a reliable measure) results in:
    - "Sick fat disease" (adiposopathy) defined as pathogenic adipocyte or adipose tissue endocrine, immune, and/or other functional abnormalities that promote metabolic disease in genetically and environmentally susceptible individuals.
    - "Fat mass disease," defined as pathogenic biomechanical forces from increased fat mass, resulting in damage or dysfunction to other body tissues.
- Potential contributors to the pathogenic increase in body fat include genetic, epigenetic, environmental, immune, endocrine, neurological, microbiome, and behavioral factors, as well as adverse reactions to obesogenic agents and pharmocotherapies.
- Adiposopathy is an important contributor to dyslipidemia as well as other metabolic disease epidemics such as type 2 diabetes mellitus, high blood pressure, and ASCVD.

Adiposopathic mixed dyslipidemia

- Especially when accompanied by an increase in visceral adiposity and fatty liver, patients with an increase in body fat often develop a dyslipidemia characterized by:
  - Increased triglyceride levels.
  - Increased non–HDL-C levels.
  - Reduced HDL-C levels.
  - Increased proportion of small dense LDL particles.
  - Increased remnant lipoprotein levels.
  - The 2013 Obesity, Adiposity, and Dyslipidemia Consensus Statement from the National Lipid Association termed this characteristic lipid pattern as "adiposopathic mixed dyslipidemia."
- The same adiposopathic mixed dyslipidemic pattern characteristic of the abnormal lipid levels found with the pathogenic adipocyte and adipose tissue dysfunction has sometimes been termed "atherogenic dyslipidemia"; however, other dyslipidemias, such as isolated elevations in cholesterol (without increases in triglyceride levels), are also atherogenic. Hence, "atherogenic dyslipidemia" would not seem to be a selective term for any specific dyslipidemia pattern that promotes atherosclerosis.

Adiposopathy and the metabolic syndrome

- Metabolic syndrome is a collection of clinically identifiable/measurable ASCVD risk factors, whose criteria do not include LDL-C levels. These anatomic (ie. increased waist circumference) and metabolic/clinical abnormalities (eg, increased triglyceride levels, decreased HDL cholesterol levels, increased glucose levels, and increased blood pressure) are often caused by an increase in body fat, especially if the fat weight gain results in adipocyte and adipose tissue dysfunction.
- The NLA has adopted a definition of the metabolic syndrome, similar to the updated National Cholesterol Education Program, Adult Treatment Panel III diagnostic criteria, which include an increase in waist circumference as the only anatomic diagnostic criterion.
- Other metabolic syndrome definitions place yet even more emphasis on the importance of an increase in body fat and development of metabolic disease.[71]

Adiposopathy and Non–HDL-C

- During positive caloric balance, individuals with genetic or environmental predisposition may have impaired adipogenesis (ie, impaired proliferation and/or differentiation) in peripheral subcutaneous adipose tissue, which limits energy (fat) storage.
- Other endocrine and immune derangements of adipocyte and adipose tissue function contribute to "energy overflow," resulting in increased circulating free fatty acids, which contributes to an increase in visceral, pericardiac, and perivascular adiposity. Increased circulating free fatty acids may also promote fatty infiltration of the pancreas contributing to insulinopenia, as well as fatty infiltration of muscle and liver, which may promote insulin resistance.
- An increase in free fatty acid delivery to the liver, especially when associated with fatty liver, often increases the hepatic secretion and triglyceride enrichment of VLDL particles, which is clinically manifest by elevated fasting triglyceride levels.
- In the liver, if glycogen stores are replete, then an increased dietary consumption of carbohydrates may increase circulating insulin and glucose, and through SREBP-1-mediated increase in lipogenic gene expression, increase fat storage in the liver. This may contribute to components of the metabolic syndrome, such as hypertriglyceridemia, low HDL-C levels, and hyperglycemia due to insulin resistance.
- An increase in adiposopathic manifestations of obesity may increase triglyceride rich lipoproteins (eg, VLDL, intermediate density lipoproteins, remnant lipoproteins), which are lipoproteins that carry cholesterol, and are atherogenic.
- In overweight or obese patients (especially those with fatty liver, insulin resistance, or diabetes mellitus), a measure of LDL-C levels alone may not be adequate to assess atherogenic risk, because it fails to measure the cholesterol carried by the triglyceride-rich lipoproteins.
- Measurement of the non–HDL-C level is a lipid parameter that incorporates the cholesterol carried by all atherogenic lipoproteins, including triglyceride-rich lipoproteins.

Clinical management of obesity, adiposopathy, metabolic syndrome, and diabetes mellitus

- Perhaps the most effective measure to reduce ASCVD risk, especially lifetime ASCVD risk, is to prevent and/or delay onset of major ASCVD risk factors (eg, diabetes mellitus, high blood pressure, elevated glucose levels, and dyslipidemia), which can be achieved in many individuals through appropriate nutrition and physical activity and avoidance of the adiposopathic consequences of overweight or obesity.
- Assessing waist circumference may provide clinical guidance for the need of aggressive nutritional intervention and increased physical activity, even without metabolic parameters in the range that might characterize diabetes mellitus, hypertension, and dyslipidemia.[72]
- Carbohydrate restriction has a more favorable impact on the components of the metabolic syndrome than a low fat diet.[73]

- Increase in visceral adiposity is a surrogate measure of global adipose tissue dysfunction.
- Central obesity is a clinical marker of adiposopathy.

- In nonmuscular individuals, body mass index (BMI) is often an acceptable surrogate measure of body fat.
- From a lifetime perspective among patients with overweight and/or obesity, a primary objective is fat weight reduction via evidenced-based interventions, that can be practically implemented, and which the patient is most likely to adhere. Within the first year after implementation of nutritional intervention, a carbohydrate restricted diet may improve triglycerides, HDL-C, and glucose levels more than a fat restricted diet, although LDL-C may be relatively increased.[69,73]
- Management of body weight is among the more common clinical challenges in management of patients with dyslipidemia. Given that many patients with dyslipidemia often have multiple other concurrent illnesses and subject to polypharmacy, it is important for the clinician to have an understanding of the potential effects of pharmacotherapies on body weight.[74–79]

Weight management pharmacotherapy[24,47,69]

- The lipid effects of weight management pharmacotherapy can be highly variable among individuals and is dependent upon the baseline lipid levels, degree of weight lost, and the duration of treatment.
- In overweight patients with adiposopathy, an approximate 5–10% of weight loss can improve adipocyte and adipose tissue function. Clinically, "only" about a 5–10% of weight loss in overweight patients can often improve metabolic diseases such as dyslipidemia, especially hypertriglyceridemia.
- The lipid parameter most consistently improved with weight loss is the reduction in triglyceride levels, which is the lipid parameter most associated with adiposopathic mixed dyslipidemia.
- The typical mean weight loss achieved with longer term weight management pharmacotherapy may not ultimately improve HDL-C and LDL-C levels over a span of years, which is similar to the lipid effects often described with nutritional intervention and modest increases in physical activity.

Bariatric surgery[24,201]

- The effect of bariatric surgery on lipid levels is variable and dependent upon the type of bariatric surgical procedure (e.g., gastric bypass, gastric sleeve, adjustable gastric banding).
- Gastric bypass procedures generally produce greater improvements in lipid and other metabolic parameters because of greater reductions in body fat, alterations in gut and other hormones, and improvements in inflammatory factors.
- In general, the greater the fat weight loss, the greater the improvement in lipid levels.
- Lipid levels trend toward baseline the greater the length of time after the bariatric procedure.
- The Swedish Obese Subjects (SOS) Study[80,81]
  - Prospective study of 4047 patients with obesity; 2010 received bariatric surgery (ie, vertical-banded gastroplasty, gastric banding, gastric bypass) and 2037 received "conventional treatment."
  - Greater weight loss at 2 and 10 years was achieved with gastric bypass.
  - Bariatric surgery significantly improved multiple metabolic parameters, and reduced overall mortality.
  - Regarding lipids, compared with conventional therapy, bariatric surgery:
    - At both 2 and 10 years, bariatric surgery significantly reduced the incidence of hypertriglyceridemia (defined as ≥150 mg/dL).
    - At 2 years (but not 10 years), bariatric surgery significantly reduced the incidence of low HDL-C (defined as <39 mg/dL).
    - Bariatric surgery did not significantly reduce hypercholesterolemia (defined as ≥200 mg/dL) at 2 or 10 years.

IX. LIPID PHARMACOTHERAPY[1,82]

Statin Pharmacology

- In addition to evaluation and management of secondary causes of dyslipidemia and ASCVD risk factors, as well as implementation of appropriate nutrition and physical activity, lipid-altering drug therapy is often indicated.
- Unless contraindicated, moderate to high intensity statins are the first line pharmacotherapy of choice to treat elevated atherogenic cholesterol levels.
- Statin randomized clinical trials provide the most extensive evidence for the greatest magnitude of ASCVD risk reduction.
- The 2013 American College of Cardiology/American Heart Association Guideline on the Treatment of Blood Cholesterol in Adults has identified four groups of patients that may most benefit from statin therapy based upon the best clinical trial data ("statin benefit groups"):
  - Patients with clinical ASCVD.
  - Patients with primary elevations of LDL-C levels ≥190 mg/dL.
  - Patients 40 to 75 years of age with diabetes mellitus having LDL-C 70–189 mg/dL.
  - Patients without clinical ASCVD or diabetes who are 40 to 75 years of age with LDL-C 70–189 mg/dL and an estimated 10-year ASCVD risk of 7.5% or higher.
- In a meta-analysis that included statin trials, a reduction in non-HDL-C levels was associated with a reduction in ASCVD risk.[38]

- Regarding LDL-C levels (a co-lipid treatment target along with non-HDL-C levels), the Scandinavian Simvastatin Survival Study, was a secondary prevention study of 4444 patients, generally considered to be the first study to conclusively "prove" that statins not only reduce CHD morbidity and mortality, but also reduce overall all--cause mortality. In this randomized controlled clinical trial, if total cholesterol exceeded 200 mg/dL while being administered simvastatin 20 mg per day, then the simvastatin was "titrated" to 40 mg per day.[83,202]
- Randomized, controlled, clinical trials of statins generally support improved ASCVD outcomes with higher dose statins achieving an end-of-study LDL-C level of ~70 mg/dl, versus lower dose statins achieving an end-of-study LDL-C level of ~100 mg/dL.[84–87,202]
- In patients at very high ASCVD risk and mean LDL cholesterol levels of ~70 mg/dL while treated with statin therapy, evidenced-based, randomized, controlled, clinical trial data support improved ASCVD outcomes by attaining an LDL cholesterol level below 70 mg/dL (mean value ~54 mg/dL) with the addition of ezetimibe to the statin.[88]
- Multiple national and international guidelines support specific lipid treatment goals, such as LDL-C levels of < 70 or < 100 mg/dL, depending upon ASCVD risk.[1,89–94,202]

Non-statin Pharmacotherapy[1]

- Non-statin drug classes for lipid management include cholesterol absorption inhibitors, bile acid sequestrants, fibric acids, long-chain polyunsaturated omega-3 fatty acids, nicotinic acid, proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors, lomitapide, and mipomersen. Depending upon the population studied, baseline lipid levels, and whether administered with or without statins, many of these non-statin agents have randomized, controlled clinical trial evidence supporting a reduction in ASCVD (lomitapide and mipomersen do not have clinical trial evidence of a reduction on ASCVD risk).
- Clinical trials that evaluated statins in hypertriglyceridemic patients with triglycerides less than 1000 mg/dL have demonstrated statins lower triglyceride levels to a degree similar to lipid-altering agents often considered to be primarily triglyceride-lowering agents (eg, fibrates, omega-3 fatty acids).[95]
- Fibrates and prescription omega-3 fatty acids are first-line drug choices for patients with TG ≥500 mg/dL, although consideration may be given to using statin therapy as a firstline drug in patients with TG 500-999 without a history of pancreatitis.
- In patients with elevated TG (200 to 499 mg/dL) on maximum tolerated statin therapy who are at their LDL-C goal but not their non–HDL-C goal, the addition of therapies that primarily lower TG and VLDL-C (fibrates, high-dose omega-3 fatty acids) may be considered to help achieve atherogenic cholesterol goals.
- For patients not at goal levels for atherogenic cholesterol on maximally tolerated statin therapy, consideration should be given to adding non-statin lipid-altering therapy to ongoing statin therapy for further lowering of atherogenic cholesterol, as long as the patient has sufficient ASCVD risk to warrant it, and the expected treatment benefit outweighs the risk for adverse consequences.
- After implementing maximally tolerated statins, recommended combination therapies to consider for further lowering of atherogenic cholesterol include:
  - Ezetimibe 10 mg every day
  - Colesevelam 625 mg 3 tablets twice a day (or 3.75 g powder form every day or in divided doses)
  - Extended release niacin titrated to a maximum of 2000 mg daily
- Among patients on maximally tolerated statins, PCSK9 inhibitors are indicated as an adjunct to diet for the treatment of adults with heterozygous FH or clinical ASCVD, who require additional lowering of LDL-C.

Statin Safety

Statin intolerance[97]

- Statin intolerance can be defined as adverse symptoms, signs, or laboratory abnormalities attributed by the patient or provider to the statin, and in most cases, perceived by the patient to interfere unacceptably with activities of daily living (such as work/housework, or leisure-time activity), leading to a decision to stop or reduce statin therapy.
- The NLA has proposed a pragmatic working definition of statin intolerance that may be useful in assisting clinicians, researchers, insurers, and regulatory authorities.
- Statin intolerance is a clinical syndrome that may be characterized by:
  - The inability to tolerate at least 2 statins: one statin at a low or lowest starting daily dose AND another statin at any daily dose.
  - Either objectionable symptoms (real or perceived) or abnormal laboratory determinations, which are temporally related to statin treatment.
  - Reversible upon statin discontinuation, but reproducible by rechallenge with other known determinants being excluded (such as hypothyroidism, interacting drugs, concurrent illnesses, significant changes in physical activity or exercise, and underlying muscle disease).
- In the individual patient, the patient's subjective feelings, preferences, and judgment are determinative, though best aided by the evaluation and effective communication with the clinician.
- Although statins are generally well-tolerated and safe, the frequency of statin intolerance is difficult to estimate.
- When assessed by spontaneous reporting within the context of clinical trials, statin and placebo groups often

do not differ with regard to reporting of myalgias and muscle intolerance.[98] However:
  - As part of study entry criteria, many randomized statin trials excluded patients with signs and symptoms of statin intolerance.
  - No universally accepted definition of statin intolerance exists that can be used by clinicians, researchers, insurers, and regulatory authorities, although some clinical trial designs may reliably address statin intolerance.
  - No universally accepted validated instrument exists to specifically assess statin intolerance.
  - Of 42 randomized control, double-blind studies of statin therapy, only 26 reported muscle adverse experiences, only 4 reported average creatine kinase (CK) levels, and only 1 specifically queried for muscle symptoms.[98]
- Some patients may benefit from continued use of statins, if their adverse symptoms associated with statin administration are mild. Such a course is justified due to the ability of statins to prevent ASCVD.

Statin safety: muscle[99]

- The most common form of statin intolerance relates to muscle adverse experiences, including weakness, aching, stiffness, and/or pain.
- Before permanently discontinuing statins from muscle symptoms unaccompanied by substantially elevated CK levels:
  - Patients should have a thorough medical evaluation to determine other potential causes of muscle symptoms.
  - Patients should have an evaluation of their concurrent medications to determine if potential drug interactions might exist that interfere with the conjugation, metabolism, or excretion of statins, which may increase statin blood levels and thus increase the potential risk of statin adverse experiences
- No validated scale or instrument exists that is universally accepted to accurately diagnose statin-associated myalgias in clinical practice.
- From a symptomatic standpoint, statin-associated muscle complaints can be increased by acute and chronic physical activity.
- From a diagnostic standpoint, statin-associated muscle weakness, often unaccompanied by muscle pain or elevated CK levels, can present with proximal upper or lower extremity weakness.[97]
- In patients with muscle pain or weakness while on a statin, potential diagnostic testing includes CK levels, as well as diagnostic testing applicable to other common causes of muscle pain or weakness, such as thyroid stimulating hormone (to evaluate possible hyper or hypothyroidism) and sedimentation rate blood testing (to evaluate possible rheumatologic or infections causes).
  - Rhabdomyolysis can occur with statin therapy.
    - Rhabdomyolysis can have a number of different causes, in patients on or off statins.
    - Statins should be discontinued immediately in patients presenting with severe and otherwise unexplained muscle weakness and/or pain and/or marked elevations in muscle enzymes
    - If the elevations in CK are thought statin-related, then the patient should undergo an evaluation to determine if concurrent medical illnesses may have contributed to elevated statin levels (e.g., liver or kidney disease, or hypothyroidism), or possibly from drug interactions with concurrent pharmacotherapies.
  - Aldolase and myoglobin levels are not recommended.
  - If CK >50 times upper limit of normal and/or dark brown urine, then urinary myoglobin should be evaluated.
  - Other more investigational evaluations may include strength and aerobic testing, metabolic tests (magnetic resonance spectroscopy, oxygen uptake intake), and pharmacogenetic testing.
  - Electromyography and muscle biopsy may be indicated.
- From a therapeutic standpoint, patients who are initially intolerant to 1 statin can often tolerate a different statin. Other clinical approaches are to reduce the statin dose, or administer the statin fewer than 7 days a week.
- The use of supplements such as vitamin D and coenzyme Q10 do not have sufficiently consistent clinical trial evidence to allow for routine recommended use.

Statin safety: liver[100]

- Among the more common asymptomatic "intolerance" to statin therapy is elevated liver enzymes.
- One of the clinical challenges regarding the elevation in liver enzymes in patients treated with statins is that elevated liver enzymes have a number of potential causes.
- Long-term clinical trial data does not support the incidence of liver failure or liver-related death as being different when comparing statin-treated and placebo-administered groups.
- Published instances of severe liver disease due to statins are isolated to rare case reports.
- Statins are contraindicated in patients with acute liver failure or decompensated cirrhosis. However, many patients at higher ASCVD risk with milder liver dysfunction may safely be treated with statins, especially patients with uncomplicated fatty liver who have liver transaminase levels < 3 times the upper limits of normal, and no increase in alkaline phosphatase and total bilirubin, which might otherwise be suggestive of severe (obstructive) liver disease.

Statin safety: cognition[101]

- Cognition can broadly be described under 4 domains:
  - Executive function
  - Memory
  - Language
  - Visuospatial ability

- Statins are sometimes reported as contributing to mild cognitive impairment, defined as a state of cognitive dysfunction between normal cognition and dementia, with the latter being defined as cognitive dysfunction that involves 2 domains and sufficiently severe to interfere with daily activities leading to progressive loss of independence.
- Statins are also sometimes reported to have favorable effects with regard to maintaining cognition, and/or delaying dementia.
- Baseline cognitive assessment is not necessary before statin use, because objective assessments within the context of larger, controlled clinical trials have not consistently supported statins as having adverse effects upon cognition.
- If a provider encounters a patient with cognitive symptoms after starting a statin, then it may be reasonable to withhold statin administration for 1 to 2 months. If no improvement in cognition is observed after 1 to 2 months of statin discontinuation, then the clinician:
  - May wish to better focus on alternative causes of cognitive dysfunction.
  - May discuss the potential restart of the statin.

Statin safety: diabetes mellitus[102]

- Statins increase the risk for type 2 diabetes mellitus.
- Statin-treated patients are most likely to develop type 2 diabetes mellitus if they are overweight or obese, or have elevated glucose or triglyceride levels at baseline.
- Meta-analyses of statin trials indicate statin use is associated with a statistically significant 10% to 12% increased risk for the development of type 2 diabetes mellitus, with somewhat higher risk among more intensive statin regimens.
- Among patients with existing diabetes mellitus, available data suggest little to no adverse effect on glucose control among patients with type 2 diabetes mellitus, with an approximate 0.12% increase in hemoglobin A1c.[103]
- Given that statins reduce ASCVD risk, no change is recommended regarding statin use among patients at risk for ASCVD.
- Statin-treated patients should be engaged in intensive nutrition therapy, supplemented by appropriate physical activity, with a goal to avoid weight gain and prevent the onset of type 2 diabetes mellitus.
- New-onset diabetes mellitus, or deteriorating glycemic control, in patients with known diabetes mellitus should be aggressively evaluated for other potential contributors to elevated glucose levels and managed similarly to non-statin patients with type 2 diabetes mellitus.
- Statin therapy reduces ASCVD risk among patients with type 2 diabetes mellitus, with ASCVD being the most common cause of morbidity and mortality among patients with type 2 diabetes mellitus.

PCSK9 inhibitors (Alirocumab, Evolocumab)

- PCSK9 attaches to hepatic LDL receptors, and facilitates the intrahepatic degradation of LDL receptors, which are then no longer available to recycle to the liver surface to clear more LDL (and its cholesterol) from the blood. Circulating LDL-C cholesterol levels are thus increased
- Approved PCSK9 inhibitors are injectable human monoclonal antibodies, administered every 2 (and sometimes every 4) weeks. PCSK9 monoclonal antibodies attach to PCSK9, limiting its ability to bind and promote degradation of the hepatic LDL receptors
- PCSK9 inhibitors increase the number of hepatic LDL receptors, enhancing clearance of LDL and its cholesterol from the circulation.
- PCSK9 inhibitors reduce LDL cholesterol levels by 40 - 60%
- PCSK9 Inhbitors are indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous FH or clinical ASCVD, who require additional lowering of LDL-C.
- The determination of the degree of additional LDL cholesterol lowering required among patients with Heterozygous FH and clinical ASCVD is best determined by measuring lipid levels, and working with the patient to establish lipid goals.
- Clinical trials have supported PCSK9 as generally well tolerated, and effective in lowering LDL cholesterol when used in combination with statins, or as monotherapy
- The addition of PCSK9 inhbitors to statin therapy often promotes additional LDL-C lowering, and allows more patients to achieve LDL cholesterol goals, when compared to other common treatment strategies, such as doubling the statin dose, changing to a more potent statin, or adding ezetimibe[203]
- Clinical judgment best determines the maximal tolerated statin dose. The maximally tolerated statin dose for some patients may be 0 mg. In patients untreated with statin therapy, alternative non-statin lipid-altering therapies may be effective in improving dyslipidemia when used as monotherapy, or when used in combination with other non-statin therapies.[96]

X. LIPID-ALTERING DRUG INTERACTIONS[99,104]

Pharmacokinetics and pharmacodynamics

- Drug interactions can occur with disruption of the bioavailability, overall systemic exposure, and prolongation of the residence time of the drug in the blood, which in turn is dependent upon pharmacokinetic and pharmacodynamic properties relative to absorption, distribution, metabolism, and excretion.[105]
- Gastrointestinal absorption of oral medications can be influenced by the presence or absence of food or concomitant medications.

- Distribution of medications can be influenced by their lipophilicity/hydrophilicity.
- Excretion of medications can be influenced by the function of the organ responsible for excretion, such as liver or kidney.

Drug metabolism

- Drug metabolism can be influenced by disease (eg, gastrointestinal disease, liver failure, renal insufficiency), age, gender, and genetic variation (eg, polymorphisms), concomitant drugs, foods, and toxins.
- Regarding oral medications, once administered, drugs undergo first-pass metabolism (or presystemic metabolism) through phase 1 (e.g., CYP450) and phase 2 (e.g., glucuronidation) metabolism.
  - The first-pass effect takes place in the gastrointestinal lumen and gut wall and may involve bacterial enzymes as well as gastrointestinal enzymes (pancreatic and hepatic).
  - The first-pass effect also occurs in the liver.
  - Because of first-pass metabolism, only a small amount of active drug typically emerges from the liver and reaches systemic circulation, thus reducing bioavailability.
  - This first-pass effect can be mitigated by administering drugs via rectal suppository, intravenous, intramuscular, inhaled, or sublingual routes.
- Some drugs are administered as pro-drugs that require conversion into active metabolites that demonstrate pharmacologic effects.
- One of the more commonly recognized systemic enzyme systems involved with drug metabolism is the cytochrome P450 (CYP450) enzyme system.
- The most common CYP450 isoenzyme for drug metabolism is CYP450 3A4, although other isoenzymes are often important as well.

Transporters

- Most clinicians are aware of CYP450 enzyme systems involved in potential drug interactions because these enzyme systems are often described in pharmacotherapy prescribing information.
- Biologic transporters are localized in organs such as small intestine, liver, and kidney, and are critical for drug absorption and elimination due to their function in cellular influx and efflux. Thus inhibition or induction of drug transporters by concomitant drugs can also the pharmacokinetics and pharmacodynamics of drugs.

Statin drug interactions

- Statins are an illustrative example of how multiple considerations are in play when determining the potential for drug interactions.
- The organic anion transporting polypeptide-C transporter (OATP-C) is involved in metabolism of statins such as atorvastatin, lovastatin, pitavastatin, pravastatin, simvastatin, and rosuvastatin.
- Clinically, the SLCO1B1 polymorphism of OATP-C may explain >60% of the cases of myopathy observed with the simvastatin 80 mg per day dose.[106]
- Atorvastatin is an illustrative example of a statin that has many pharmacokinetic influences. Specifically, atorvastatin acid[107]:
  - Is highly lipophilic
  - Is completely absorbed from the gastrointestinal tract after oral administration.
  - Is subject to extensive first-pass metabolism in the gut wall as well as in the liver, with 12% bioavailability.
  - Is extensively metabolized in both the gut and liver by oxidation, lactonization and glucuronidation, and the metabolites are eliminated by biliary secretion and direct secretion from blood to the intestine.
  - Has a high volume of distribution of atorvastatin acid of 381 L, and plasma protein binding exceeds 98%.
  - Is a substrate for P-glycoprotein, OATP-C and H+-monocarboxylic acid cotransporter.
  - Has a renal excretion route that is of minor importance (<1%–5%) for the elimination of atorvastatin acid.
  - Undergoes metabolism by CYP450 3A4, with the formation of 2 active metabolites from the acid and the lactone forms of atorvastatin.
  - Both atorvastatin acid and its metabolites undergo glucuronidation mediated by uridine 5-diphosphoglucuronosyltransferase 1A1 and 1A3.
  - As a result of these metabolic processes, atorvastatin is subject to metabolism by CYP3A4 and cellular membrane transport by OATP-C and P-glycoprotein, with potential drug–drug interactions with potent inhibitors of these systems, such as itraconazole, certain protease inhibitors, cyclosporin, fibrates, erythromycin, and grapefruit juice.
  - Metabolism of atorvastatin can be increased with CYP3A4 inducers, such as phenobarbital, phenytoin, and rifampin. Efavirenz is a highly active antiretroviral therapy (HAART) for the treatment of a human immunodeficiency virus that is an inducer of CYP 3A4, and may diminish the effectiveness of statins such as atorvastatin.[108]
  - Gemfibrozil inhibits the phase II glucuronidation of atorvastatin, which may increase atorvastatin levels. Atorvastatin increases the bioavailability of digoxin, most probably by inhibition of P-glycoprotein.
  - The metabolism of atorvastatin suggests it is often difficult to predict the potential for drug interactions, without having data from specific drug interaction studies or clinical evidence available with a given drug.

XI. LIPOPROTEIN APHERESIS[109,110]

Definition

- Lipoprotein apheresis is a form of apheresis (eg, a dialysis-like process wherein a particular blood constituent is removed by a filtering machine, with the remainder of the blood being returned to the patient) in which LDL (and other atherogenic lipoprotein) particles are removed from the blood.

Lipoprotein apheresis clinical considerations

- Lipoprotein apheresis is efficacious in the acute removal of apolipoprotein B containing atherogenic lipoprotein particles such as LDL, VLDL, and Lp(a) and thus efficacious in lowering non–HDL-C and LDL-C levels by 60% to 80%.
- Repeated lipoprotein apheresis produces cyclical reductions in non–HDL-C and LDL-C levels.
- Dual antecubital venous access is typical for most lipopheresis systems, although an arteriovenous fistula or indwelling catheter may be required.
- Albumin, heterologous plasma, or blood product replacement is not required because the patient's own plasma and blood cells are reinfused.
- Lipoprotein apheresis is most often used for patients with high to very high LDL cholesterol levels (e.g., Familial Hypercholesterolemia) who are unable to achieve lipid treatment goals with other therapies, and includes patients who are statin-intolerant.
- The most significant potential adverse effects of lipoprotein apheresis include:
  - Hypotension, which generally occurs in ≤1% of patients.
  - Rare cases of venous catheter line infections.
  - Poor venous access resulting in possible need for arteriovenous fistulas.
- Timing of lipoprotein apheresis treatment:
  - Every 2 weeks is most often recommended for eligible patients with heterozygous FH.
  - Once-a-week treatment may be required for patients with homozygous FH.
  - For patients wherein every 2 weeks is logistically challenging (e.g., long distance to lipoprotein-apheresis center), lipoprotein apheresis treatment every 3 - 4 weeks is expected to provide clinical benefit compared to no lipoprotein apheresis.
- Approved use of lipoprotein apheresis varies between countries and payers[110]
  - In the United States, lipoprotein apheresis is approved to lower LDL-C levels. In some European countries, lipoprotein-apheresis is approved to lower both LDL-C and Lp(a) levels. In the United States, some insurances may also pay for lipoprotein apheresis reduction of Lp(a).
  - In the US, LDL-C must be greater than 160 mg/dL for patients with atherosclerotic coronary artery disease (ie, not other atherosclerotic diseases), while treated with maximum tolerated nutritional and lipid-altering pharmacotherapy.
  - In the US, LDL-C must be greater than 300 mg/dL for patients without atherosclerotic coronary artery disease.
  - Lipoprotein apheresis is also approved for focal segmental glomerulosclerosis for the purpose of treating the dyslipidemia associated with nephrotic syndrome, as well as potentially treating (and sometimes causing remission) of the nephrotic syndrome itself.[111]

Lipoprotein apheresis systems

- Two lipoprotein apheresis systems are available in the US; however, several other systems are available outside the US.

Dextran Sulfate Apo B Lipoprotein Adsorption System (Liposorber)

- Plasma is separated from cells and then passed through twin columns of dextran sulfate bound to cellulose beads. The column not in use is regenerated, allowing for greater plasma volume to be treated.
- Apo B–containing lipoproteins are selectively bound by electrostatic charge.
- The blood cells and treated plasma are returned to the patient via the blood return line.
- Requires systemic anticoagulation with heparin.
- Angiotensin-converting enzyme reduces bradykinin degradation in plasma; angiotensin-converting enzyme inhibitors promote excessive bradykinin, which may cause hypotenstion.
- This system requires patients to stop angiotensin-converting enzyme inhibitor therapy at least 24 hours before each treatment because of the possible increase in bradykinin and anaphylactoid reaction that can occur during lipoprotein apheresis.
- Patients undergoing lipoprotein-apheresis may benefit from switching from an angiotensin-converting enzyme inhibitor, to an angiotensin receptor blocker, which does not adversely affect bradykinin levels.
- Available in more than 50 centers in the United States.

Heparin extracorporeal LDL apheresis (HELP)

- Plasma is separated from cells, which is then acidified with a heparin buffer.
- Because heparin has a negative charge, and LDL particles have a positive charge, the electrostatic attraction precipitates an LDL-heparin complex, which is removed by a filter.
- The plasma is then dialyzed in a carbonate buffer to restore physiological pH and remove the high concentration of heparin.

- Both the Liposorber and HELP LDL apheresis systems require heparinization to avoid clotting in the tubing and plasma separators. Typically, heparinization for the Liposorber system is 25 units/kg body weight bolus followed by an infusion rate of 25 units/kg per hour, with adjustments to achieve the correct level of anticoagulation. For the HELP system, the heparin bolus is 35 units/kg body weight followed by an infusion rate of 1000-1500 units per hour, with adjustments, as needed. Hence, the heparin bolus for the HELP system is larger, but the heparin infusion rate may be lower depending on the weight of the patient.
- May require less time for a treatment, but has more limited capacity for plasma volume it processes (3000 mL).
- Heparin precipitation reduces fibrinogen levels by up to 50%, although acute bleeding occurs very rarely if at all.
- Bradykinin levels are not altered; therefore, angiotensin-converting enzyme inhibitors do not need to be discontinued.
- Available at less than 10 sites in the United States.

Conventional plasmapheresis (plasma exchange)

- Sometimes used for acute triglyceride reduction (reduction in VLDL and chylomicron particles).
- May be useful to relieve jaundice, xanthoma pain, and pruritus for patients with primary biliary cirrhosis having elevated lipoprotein X (Lp-X), which are particles that are:
  - Lipid complexes that form in the clinical setting of biliary obstruction and familial lecithin-cholesterol acyltransferase deficiency.
  - Rich in phospholipid and free (non-esterified) cholesterol.
  - Poor in cholesterol esters and triglycerides.
  - Composed of albumin as a main protein, and increased apolipoprotein C, with lack of apolipoprotein B.
  - Twice the size (60 nm) of normal LDL.

Evidence for clinical benefit of lipoprotein apheresis

- Randomized ASCVD outcomes studies are difficult because of ethical considerations of leaving patients with marked elevations in cholesterol untreated for many years. Thus, as opposed to other cholesterol-lowering interventions with statins for example, outcomes data with lipoprotein-apheresis are scarce, and includes:
- Hokuriku Familial Hypercholesterolemia Low-Density Lipoprotein Apheresis Study Group Study.[112]
  - Six-year safety and efficacy study of 130 ASCVD patients with heterozygous FH treated with lipid-altering pharmacotherapy or LDL apheresis combined with lipid-altering pharmacotherapy.
  - LDL apheresis plus lipid-altering pharmacotherapy reduced time-averaged LDL-C 58%; lipid-altering pharmacotherapy alone reduced LDL-C 28%.
  - LDL apheresis plus lipid-altering pharmacotherapy reduced ASCVD events by 72% compared with lipid-altering pharmacotherapy alone (incidence of 10% versus 36%, respectively).
- LDL-Apheresis Atherosclerosis Regression Study (LAARS)[113]
  - Two-year study of 42 men with hypercholesterolemia and severe ASCVD treated with simvastatin 40 mg per day or apheresis plus simvastatin 40 mg per day.
  - LDL apheresis plus simvastatin reduced time-averaged LDL-C 63%; simvastatin alone lowered LDL-C 47%.
  - No angiographic differences were found in the 2 treatment groups in mean segment diameter or minimal obstruction diameter. In the apheresis plus simvastatin group, more minor lesions disappeared compared with the simvastatin alone group.
  - The apheresis plus simvastatin group also had improved functional effects compared with the simvastatin alone group, such as increased exercise time to 0.1 mV ST-segment depression and maximum level of ST depression via bicycle exercise cardiac testing.

XII. DYSLIPIDEMIA IN CHILDREN AND ADOLESCENTS[48,114–120]

ASCVD risk for children, adolescents, and young adults <21 years of age

- Asymptomatic atherosclerotic lesions begin at an early age, especially in the presence of ASCVD risk factors.
- LDL-C, triglycerides, and low HDL-C levels correlate to the extent of vascular lesions in children and young adults.
- Vascular lesions in children can be reversed with interventions to manage and treat ASCVD risk factors, including improvement in lipid levels.

Lipid screening for children, adolescents, and young adults <21 years of age

- Targeted screening is recommended for children ≥2 years of age with any of the following:
  - One or both parents known to have hypercholesterolemia or are receiving lipid-lowering medications.
  - Family history of premature ASCVD (men <55 years of age; women <65 years of age).
  - Family history is unknown (e.g., adopted children, or unknown health history of one or both parents).
  - Moderate to high risk for premature ASCVD.
- Universal screening is recommended beginning at 10 years of age (range 9 to 11). If lipid levels are acceptable, then screening should be repeated every 5 years throughout life, with earlier screening prompted by change in ASCVD risk factors (including clinically significant weight gain), evidence of ASCVD in the patient, diagnosis of a potential

secondary cause of dyslipidemia, or onset of a premature ASCVD event in a first degree relative.

ASCVD risk assessment in children, adolescents, and young adults <21 years of age

- High ASCVD risk includes those with:
  - History of current cigarette smoking
  - BMI ≥ 97 percentile
  - High blood pressure that requires drug treatment (i.e., blood pressure > 99th percentile plus 5 mmHg)
  - Diabetes mellitus (type 1 or 2)
  - Kawasaki disease with persistent aneurysms
  - Postorthotopic heart transplant
  - Chronic renal disease
- Moderate ASCVD risk includes those with:
  - BMI in the 95th to 96th percentile
  - High blood pressure that does not require drug treatment
  - HDL- C level <40 mg/dL
  - Kawasaki disease with regressed coronary aneurysms
  - Systemic lupus
  - Juvenile rheumatoid arthritis
  - Human immunodeficiency virus infection
  - Nephrotic syndrome

Management of dyslipidemia in children, adolescents, and young adults <21 years of age

- Goal is to implement early intervention to correct dyslipidemia.
- Management should focus on lifestyle changes based on lipid-profile findings plus weight management if the BMI is ≥85th percentile in children ≥10 years of age with an LDL-C level 130 to 190 mg/dL, a negative family history of premature CVD in first-degree relatives, and no high- or moderate-level risk factors or risk condition.
- Lipid-altering pharmacotherapy should be considered in children, adolescents, and young adult patients at moderate to high risk of premature ASCVD.
- Given that the evidence linking abnormal lipid levels to premature ASCVD is strongest among those with the greatest degree of lipid abnormalities, the priority of lipid-altering pharmacotherapy should be applied to patients with severe genetic dyslipidemias (eg, FH, familial combined hyperlipidemia).

Statin therapy in children, adolescents, and young adults with dyslipidemia <21 years of age

- Statins are the drug of choice for LDL-C lowering for those > 10 years of age.
- Statins are not generally recommended before 10 years of age, unless the patient with dyslipidemia (e.g., Familial Hypercholesterolemia) has clinical ASCVD, a substantial family history of premature ASCVD, or the child has 1 or more high risk conditions or multiple ASCVD risk factors.
- Statin treatment for children < 10 years of age is based upon clinical judgment after careful review of ASCVD risk factors, current medications, medical conditions, potential benefits as well a short-and longer-term side effects of treatment.
- Treatment with a statin should be considered after a 6-month trial of lifestyle/diet management in children >10 year of age:
  - With an LDL-C > 190 mg/dL, such as children with Familial Hypercholeserolemia
  - An LDL-C level of 160-189 mg/dL with a positive family history of premature ASCVD events in first-degree relatives.
  - At least 1 high-level risk factor or risk condition or at least 2 moderate-level ASCVD risk factors or risk conditions.
- All marketed statins, except pitavastatin, are approved by the FDA for use in children with Familial Hypercholesterlemia when the LDL-C level is >190 mg/dL or >160 mg/dL with 1 or more risk factors.
- Pravastatin is indicated to treat hypercholesterolemia in those >8 years of age. Other statins (e.g., simvastatin, fluvastatin, lovastatin, atorvastatin, and rosuvastatin) are indicated to treat hypercholesterolemia in those >10 years of age.
- If a child or adolescent has a non-HDL cholesterol of ≥ 145 mg/dL, then additional follow-up and management is recommended, with lipid goals defined as non-HDL cholesterol < 145 mg/dL and LDL cholesterol < 130 mg/dL.
- Among children with FH, lipid treatment goals are to achieve an LDL cholesterol < 130 mg/dL, or if not possible, to achieve at least a 50% reduction in LDL cholesterol.

Non-statin therapy for children, adolescents, and young adults with dyslipidemia <21 years of age

- Along with lifestyle recommendations, children, adolescents, and young adults with dyslipidemia should have routine visits with the clinician to assess and evaluate for:
  - Cigarette smoking
  - Appropriate nutrition
  - Physical activity
  - Family history of ASCVD
  - Medication history, with a focus on potential drug interactions and effects of concurrent medications upon ASCVD risk factors (eg, body weight, lipids, blood pressure, glucose)

- BMI
- Blood pressure
- Lipid levels
- General blood chemistries (safety laboratory), including glucose, alanine aminotransferase (ALT), apartate aminotransferase (AST), as well as kidney assessments (e.g., urine for protein and creatinine blood tests) if kidney disease is suspected as a potential secondary cause of dyslipidemia.
- Creatine kinase should be considered in children and young adults with muscle symptoms, especially if statin therapy is being considered.
- Assessment of sexual maturation (i.e., Tanner staging)
- Assessment for child-bearing potential
- Potential need for contraception in girls and young women

- Ezetimibe and colesevelam are FDA-approved in children ≥10 years of age to lower LDL-C levels in youth with FH.
- Genetic mutations are likely present in children < 2 years of age with severely elevated triglyceride levels (e.g., >2000 mg/dL)[121]
- Very high triglyceride levels are a risk factor for pancreatitis in children and young adults
- Although not approved for youths <18 years of age, omega-3 fatty acids, fibrates and niacin may be considered to reduce the risk of pancreatitis when the triglyceride levels are ≥ 500 mg/dL.

XIII. DYSLIPIDEMIA IN SELECT POPULATIONS[48,82]

Dyslipidemia and older individuals[48,122]

- Many sentinel ASCVD outcomes trials excluded older patients (eg, >75 years of age).
- Because of a relative lack of data, the upper age limits for ASCVD, risk scores are often at or below 65,[123] 75,[124] or 80[82,125–128] years of age, depending upon the particular ASCVD risk assessment calculator.
- Total cholesterol and LDL-C levels after 65 years of age are not as strongly associated with predicted ASCVD risk, compared with younger individuals; however, those older than 65 years of age may have greater absolute ASCVD risk reduction with statin therapy.
- Limited data appear to suggest total cholesterol and LDL-C levels are poorly correlated to ASCVD after 80 years of age, with a potential inverse relationship to all-cause mortality.[129]
- Reasons for the weaker correlation of cholesterol with ASCVD in older vs younger individuals might include:
  - Patients with higher cholesterol levels (and thus more susceptible to ASCVD) may have died before reaching an older age, depleting the number of patients with higher cholesterol among the population of older adults, and thus resulting in lower mean lipid levels among older survivors.
  - Although lifelong dyslipidemia contributes to the development, promotion, and progression of atherosclerosis, clinical ASCVD events in older individuals may be more dependent upon non-lipid ASCVD risk factors that trigger plaque instability, rupture, and/or thrombosis.
  - Older individuals have increased risk of other chronic diseases, weight loss, and malnutrition, which may result in lower cholesterol levels.
  - Older individuals are at increased risk of hemorrhagic stroke, which is often reported to have an inverse association with cholesterol levels.
- The decision to initiate statin therapy in patients ≥75 years of age is based on generalization from applicable clinical trials, via a "patient-centered" approach, and includes:
  - Patient provider discussion of risks vs benefits
  - Consideration of potential drug-drug interactions and polypharmacy
  - Considerations regarding the overall health of the patient, as it applies to life expectancy and quality of life issues
  - Cost considerations
  - Patient preference

Dyslipidemia and race/ethnicity[48,122]

- Established ASCVD risk factors generally apply to all races and ethnicities.
- The predictive strength of ASCVD risk factors may differ among racial and ethnic groups.[130,131]
- Different racial and ethnic groups may have different predispositions to clinical manifestations of ASCVD, at least in part, because of a difference in the prevalence of race or ethnic-related ASCVD risk factors, as well as different genetic, environmental, and cultural influences.[202]
- In Europe:
  - The European Systematic Coronary Risk Evaluation (SCORE) ASCVD risk algorithm is specific for populations in European countries and regions. SCORE only assesses CVD death (ie, does not include nonfatal CVD events).
  - The Prospective Cardiovascular Munster (PROCAM) model is also used in Europe, and although similar to Framingham, is adjusted for the European populations.[132]
  - The QRISK is also ethnic specific (at least for the United Kingdom), and may be reliable for all of Western Europe.[126]
- Regional differences in these scoring systems may reflect differences in nutrition and environment (eg, cigarette smoking prevalence).
- ASCVD risk-prediction equations for the United States sometimes include race; however, when they do, they are mainly validated for non-Hispanic White and African American men and women between the ages of 30 and 79 years. The number of other racial and ethnic participants in the US cohorts has thus far been inadequate to

incorporate their race or ethnicity as an independent variable.

Asians[48]

- Compared with Caucasians, individuals of South Asian ancestry are at increased risk of atherosclerotic coronary heart disease.[122]
- South Asians are especially at increased risk for metabolic syndrome, insulin resistance, and adiposopathic mixed dyslipidemia[24] (sometimes called "atherogenic dyslipidemia"). South Asian individuals often have elevated triglyceride and reduced HDL-C levels, increased LDL-P with an increased prevalence of smaller, more dense LDL particles), all of which may increase ASCVD risk.[133]
- Compared with treatment of Caucasians at the same statin doses, Asians (especially well-studied in Japan) typically have increased statin levels.

African Americans[48]

- Epidemiologically, African Americans[122] are often reported to have a more favorable lipid profile compared with Caucasian Americans, including higher HDL-C levels and lower triglyceride levels.
- Clinically, African Americans also have among the highest ASCVD event rates of any US ethnic or racial group.
- African Americans have an excess prevalence of other major ASCVD risk factors, such as hypertension, left ventricular hypertrophy, obesity (women), and type 2 diabetes mellitus.
- Lp(a) levels may be higher with wider interindividual variations in African Americans compared with Caucasians.[134]

Hispanics[48]

- Hispanics[122] have an increased prevalence of elevated triglyceride and reduced HDL-C levels, and an increased risk for the development of insulin resistance.
- Compared with non-Hispanic Caucasians and African Americans, Hispanics have a disproportionate increase in triglyceride levels ≥500 mg/dL.
- An apparent "Hispanic Mortality Paradox" exists, reflecting a potential racial/ethnic disparity wherein Hispanics have a lower overall risk of mortality than non-Hispanic Whites and non-Hispanic Blacks, but higher risk of mortality than Asian Americans.[135]
- Mexican Americans reportedly have lower coronary heart disease mortality compared with European Americans.[136]

American Indians and Alaskan Natives[48]

- American Indians appear to have an increased incidence of ASCVD, possibly related to the high prevalence of diabetes mellitus, obesity, metabolic syndrome, cigarette smoking, and other ASCVD risk factors (e.g., sedentary lifestyle and low socioeconoimic status).[48,137]
- Due to high prevalence of obesity, sedentary lifestyle, metabolic syndrome, and diabetes mellitus, appropirate and early nutritional and physical activity interventions may be especially important.
- As American Indians and Alaskan Natives often have multiple ASCVD risk factors, aggressive management of multiple ASCVD risk factors is warranted, in addition to dyslipidemia.
- ASCVD risk tools are not validated for American Indians and Alaskan Natives, and may underestimate ASCVD risk in these populations.

Pima Indians

- Pima [(Akimel O'odham, or "river people)" - a small subset of American Indians located in southern Arizona and northern Mexico] have an especially high genetic prevalence of obesity, insulin resistance, type 2 diabetes mellitus, and the metabolic syndrome.
- Among Pima men older than 30 and in women older than 25 years of age, untreated total cholesterol and LDL-C levels may be lower than in Caucasians. Pima Indians without diabetes mellitus also may have lower HDL-C and higher triglyceride levels than Caucasians, both of which are worsened with obesity.[138]
- ASCVD risk among Pima Indians may not be as high as anticipated, in consideration of the high prevalence of metabolic ASCVD risk factors found in Pima Indians.[139,140]

Racial/ethnic groups and potential statin benefits[48]

- When studied in significant numbers of African American and Hispanic patients[122,141,142]:
  - Rosuvastatin reduced ASCVD risk similarly between Caucasians and non-Whites.
  - Rosuvastatin reduced ASCVD risk similarly between Blacks and Hispanics.
- When studied in Japanese patients:
  - Pravastatin 10 to 20 mg reduced ASCVD risk.[143]
  - When administered in combination with low-dose pravastatin and simvastatin, the omega-3 fatty acid eicosapentaenoic acid (EPA) reduced CHD events.[144]

Racial/ethnic groups and statin safety[48,122]

- Caucasians, African Americans, and Hispanics appear to have similar rates of adverse experiences with statin therapy, except for diabetes mellitus; African Americans and American Indians may be more likely to be diagnosed with incident diabetes mellitus than Whites.[142]

- At each dose of statins, LDL-C levels may be reduced more in Asians than Whites;[145] this is likely because of genetic differences in statin metabolism resulting in statin levels higher in Asians for a given statin dose.[145]
- The US Prescribing Information for rosuvastatin recommends that Chinese and other Asian patients use caution with administration of rosuvastatin doses exceeding 20 mg per day and recommends initating rosuvastatin therapy at 5 mg per day in patients taking niacin ≥1 g/day.

Dyslipidemia and women[48,122]

- ASCVD is the leading cause of mortality in women.[146,147]
- Many more women die of ASCVD than breast cancer.
- In the United States, the majority of ASCVD-related deaths occur in women.
- The evidence supporting lipid-altering therapy in primary and secondary prevention of ASCVD in women is more limited than for men.
- ASCVD outcomes trials usually require patients at increased risk for ASCVD, within a defined age range. From a population standpoint, at every age, men are at higher risk for ASCVD compared with women of the same age. Therefore, men have historically represented a more readily accessible patient population in ASCVD outcomes trials evaluating lipid-altering drug therapies.[148]
- The use of many investigational and approved lipid-altering pharmacotherapies are contraindicated in women who are pregnant, or at risk of pregnancy. This has limited the number of younger women as participants in ASCVD outcome trials.
- Stroke comprises a relative increased share of ASCVD risk burden in women. Protocol-directed risk assessments that do not include stroke may underestimate global ASCVD risk for women.
- Earlier ASCVD prevention trials focused on "premature" cardiovascular events. The onset of ASCVD events tends to occur approximately a decade later in women compared with men, again, leading to possible exclusion of women as participants in ASCVD outcomes trials.
- Many earlier monotherapy trials of non-statins (eg, niacin, gemfibrozil, cholestyramine) did not enroll women.
- An insufficient number of women participants in ASCVD primary prevention trials of lipid-altering drug therapies have often limited the statistical power to adequately evaluate the ASCVD outcome efficacy of lipid-altering drugs among women subgroups.
- Among patients with ASCVD, meta-analyses support statins as reducing the risk of ASCVD events equally among women and men.[149,150]
- Among patients without ASCVD, most randomized clinical trials have not reported significant reductions in ASCVD events or mortality in women, largely because of insufficient numbers resulting in lack of statistical power.
- In the Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, rosuvastatin administered to women (n=6801) with high-sensitivity C-reactive protein ≥ 2 mg/L and LDL-C levels <130 mg/dL reduced ASCVD events in women compared to placebo.[151]

Dyslipidemia and pregnancy[48]

- Preeclampsia, gestational diabetes mellitus, and/or pregnancy induced hypertension identify women at increased risk for ASCVD, which should be considered in ASCVD risk factor screening, counseling, and preventive interventions.[152]
- During early pregnancy, maternal metabolism and associated hyperphagia are mostly anabolic, increasing maternal fat stores.[153,154]
- During the third trimester, maternal metabolism becomes more catabolic, supporting fetal growth:
  - Maternal insulin resistance and peripheral adipose tissue lipolysis increases, which in turn, increases maternal lipoprotein levels, and increases the triglyceride content of VLDL, HDL, and LDL particles.
  - Maternal hepatic gluconeogenesis is increased.
  - Maternal utilization of ketones in the fasting state is preferred, freeing maternal glucose as the primary substrate for fetal energy production.
- Beyond glucose alone, women with prepregnancy diabetes mellitus and gestational diabetes mellitus have metabolic, hormonal, and inflammatory factors that affect maternal and fetal outcomes, including maternal:
  - Amino acids
  - Glycerol
  - Ketones
  - Lipids
- Increasing body fat in early pregnancy may be associated with an increased risk of:
  - Hypertriglyceridemia
  - Preeclampsia
  - Future gestational diabetes mellitus
  - Large for gestational age infants
  - Preterm delivery
  - Stillbirth
- HDL-C levels and pregnancy:
  - Lower maternal HDL-C levels in early pregnancy may be associated with an increased risk for gestational diabetes mellitus.
  - Higher maternal HDL-C levels may be associated with lower rates of preterm birth.
- Both low (<10th percentile) and high (>90th percentile) maternal total cholesterol levels are associated with preterm birth.
- Appropriate nutrition and physical activity are recommended for women with dyslipidemia who are pregnant.

- Excessive body fat during pregnancy may increase placental transport of glucose, lipids, fatty acids, and amino acids, especially in pregnant women with gestational diabetes mellitus, insulin resistance, or type 2 diabetes mellitus.
- Increased placental transport of nutrients may contribute to:
  - An increase in fetal body fat, contributing to large-for-gestational-age infants and macrosomia.
  - Epigenetic effects upon fetal stem cell fate and adversely affect postnatal biologic processes involved in substrate metabolism, and which may result in epigenetic generational transmission of increased risk for adiposopathy, dyslipidemia, obesity, diabetes mellitus, and other metabolic diseases.[155]
  - Increased risk of offspring obesity, offspring ASCVD risk factors, and offspring ASCVD premature mortality.[156]
- Statins are not indicated in pregnant women
- For pregnant women with, or at risk for potentially life-threatening triglyceride-induced pancreatitis, in addition to very low-fat, simple carbohydrate-restricted diet, lipid-altering drugs of choice include prescription omega-3 fatty acids and possibly gemfibrozil in the third trimester, which should be administered only if the potential benefit to the patient justifies the potential risk to the fetus.
- Other potential pharmacotherapies to prevent potentially life-threatening triglyceride-induced pancreatitis options include:
  - Niacin
  - Metformin
  - Insulin

Polycystic ovary syndrome[48]

- Polycystic ovary syndrome (PCOS) often occurs in premenopausal women with overweight or obesity, and is characterized by androgen excess, chronic oligo-anovulation, and enlarged ovaries.
- Women with PCOS often have increased ASCVD risk and increased ASCVD risk factors, including lipid abnormalities such as increased triglyceride, increased non–HDL-C, increased LDL-C, and decreased HDL-C levels.[157–159]
- Although total cholesterol and LDL-C may not significantly differ between PCOS women with overweight vs PCOS women with normal weight, other lipid parameters such as triglycerides and HDL-C (as well as markers of glucose metabolism) are adversely affected in PCOS women who are overweight.[160]
- As with other patients with increased ASCVD risk, women with PCOS should be treated with aggressive nutrition therapy, physical activity, and if indicated, lipid-altering drug therapy.[157]
- In addition to improving dyslipidemia, statins may lower testosterone,[161] although this may not improve menstrual regularity, spontaneous ovulation, hirsutism, or acne among women with PCOS.[162]

Menopause[48]

- Menopause is associated with increased ASCVD risk. However:
  - Women have an ASCVD risk that increases linearly with aging.[148]
  - Menopause may be a surrogate for age.[163,164]
  - Women often gain body fat and experience worsening dyslipidemia during and following the menopause transition,[165] similar to aging men.
- Some evidence supports a rise in total cholesterol, LDL-C, and apo B levels within the 1-year interval before and after the final menstrual period,[166] suggesting that in addition to aging, at least some unfavorable lipid changes occur during, and perhaps partially due to the hormone and metabolic changes that occur with menopause.[167]
- Although postmenopausal oral estrogen therapy may modestly lower LDL-C and raises HDL-C levels, oral estrogens may also increase triglycerides and high-sensitivity C-reactive protein[168–170] levels.
- When initiated years after menopause, oral hormone therapy (eg, estrogens alone or in combination with a progestin), may increase ASCVD risk and may increase the risk of stroke among women without ASCVD.[171–173]
- Postmenopausal hormone therapy should not be administered specifically to reduce ASCVD risk.

XIV. DYSLIPIDEMIA IN PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS (HIV)[48]

- HIV is an important ASCVD risk factor that should be considered equivalent to one additional ASCVD risk factor when assessing ASCVD risk, and which should be considered in the patient-centered decision-making process regarding non-pharmacologic, and pharmacologic lipid interventions.
- Improved care of HIV patients [including safer and more effective antiretroviral therapy (ART)] has increased survival among patients with HIV; however, risk for ASCVD is increasing among patients with HIV infection
- Patients with HIV infection not receiving ART are at increased risk of ASCVD, possibly due to immune-mediated factors
- Patients with HIV infection treated with ART are at increased risk of ASCVD, possibly due to immune-mediated factors, as well as the onset or worsening of insulin resistance, hyperglycemia, elevated triglyceride, and low high density lipoprotein cholesterol levels.
- Even with ART, having a CD4 (a glycoprotein found on immune cells) T cell count less than 200 cells/per cubic mm is associated with an increased risk of ASCVD.[174]

- No validated 10 year ASCVD risk score exists that specifically applies to patients with HIV infection
- Although ASCVD outcome studies are lacking in supporting the use of any lipid-altering agent in HIV infected patients, statins are considered the first line treatment for hypercholesterolemia in patients with HIV infection, keeping in mind that statins differ in their potential for drug interactions with ART (with rosuvastatin, pravastatin, and pitavastatin generally having the least potential for drug interactions)
- In the absence of clinically meaningful drug interactions, statins are generally well tolerated in patients with HIV infection, with some evidence of an increased risk of diabetes mellitus.[175]

XV. DYSLIPIDEMIA IN PATIENTS WITH INFLAMMATION[48]

- ASCVD is a leading cause of death among patients with autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus
- Existing ASCVD risk calculators inaccurately predict ASCVD risk in patients with inflammatory diseases; a need exists to validate an ASCVD risk calculator for patients having inflammatory diseases.
- The United Kingdom based QRISK2 is the only ASCVD risk calculator that incorporates rheumatoid arthritis as a variable; however, the QRISK2 is rarely used in the US to assess ASCVD risk in patients with rheumatoid arthritis.
- The Reynolds Risk Score does include the inflammatory marker of C-reactive protein (CRP). However, the Reynolds Risk Score was developed in a patient population with CRP levels predominantly much lower than found in patients with inflammatory diseases. Thus, the Reynolds Risk Score may underestimate ASCVD risk in patients with inflammatory diseases.
- Despite an overall increased risk of ASCVD, patients with rheumatoid arthritis (an equivalent to one additional ASCVD risk factor) may have lower total cholesterol and lower LDL cholesterol compared to the general population.
- LDL cholesterol levels may be decreased during an active flare of rheumatoid arthritis; thus, lipid levels are best measured when the inflammatory disease activity is better controlled and stabilized.
- Statin therapy is the treatment of choice to treat hypercholesterolemic patients with inflammatory disease.

XVI. LIPID THERAPY ADHERENCE STRATEGIES AND TEAM-BASED COLLABORATIVE CARE[48]

Improving lipid medication adherence

- The World Health Organization defines *adherence* as ''the extent to which a person's behavior—taking medications, following a diet and/or executing lifestyle changes—corresponds with agreed recommendations from a health care provider.'' *Persistence* is defined as the length of time a patient fills his or her prescriptions or follows a treatment plan.[176–178]
- Observational data have identified individual predictors of treatment adherence and nonadherence, and of persistence and nonpersistence.
- Social, demographic, and clinical factors do not always distinguish between adherent and nonadherent individuals, and therefore the exclusive use of these factors as a guide to interventions intended to optimize adherence will fail to adequately target many individuals.
- Adherence is the result of a cluster of individual, social, and environmental factors, and broad-based interventions are needed to address the complexity of these challenges.
- Although individual provider efforts are helpful, sustained improvements in adherence require systems approaches and removal of organizational barriers.
- Team-based self-management support, outreach via phone, text or automated phone messaging, electronic prescribing, lower prescription copays and less frequent prescription refills, are some of the approaches used by integrated health care systems to improve medication adherence.
- Identification of treatment non-adherence (including, but not limited to medication) and measures to facilitate adherence may require a multidisciplinary healthcare team approach, which includes the patient, and depending upon the circumstance and resources available, the physician, nurse practitioner, physician assistant, nurse, dietitian, diabetes educator, exercise specialists, office staff, social worker, community health worker, pharmacist, psychologist, and counselor, as well as patient family, friends, and caregivers.
- Measures to specifically facilitate medication adherence might include simplifying treatment regimen, provide clear education, engage patients in decision making, address perceived and real barriers of medication adherence, identify improve suboptimal health literacy, and routinely assess and evaluate adherence with every patient encounter.
- In larger healthcare systems, including accountable care organizations (ACOs), team-members may engage in systematic and continuous quality reporting and improvement to identify individuals not achieving goals and intervene (via electronic registries and lists, 'in-reach' methods such as clinic prompts, and 'outreach' methods such as regular or automated phone messaging, mail, email, or secure text messaging).
- Other health Information Technology-enabled strategies that may close lipid treatment gaps include provider-level tools such as Electronic Health Records-based decision support, alerts, and dashboards; and patient-level tools such as portals that provide connectivity to providers.

- National Committee for Quality Assurance, American Society of Health-System Pharmacists, and American Medical Association, the American College of Cardiology (ACC), American Heart Association (AHA), American Association of Cardiovascular and Pulmonary Rehabilitation, American Academy of Family Physicians, and American Nurses Association outline concepts for clinician-patient shared accountability in the achievement of performance measures.[179]
  - Patients who are more actively engaged in self-care, defined as the ability to perform the activities necessary to achieve, maintain, or promote optimal health, are more likely to successfully achieve their treatment goals
  - The general framework of shared accountability is predicated on partnerships between patients and clinicians, in which patients play an active role in setting goals, making treatment decisions, and assessing outcomes
  - Key conceptual issues for shared accountability are (a) shared goal setting, (b) shared decision making, (c) shared care planning and monitoring, including patient feedback and self-care, and (d) assessment of patients' longitudinal outcomes
  - Goals are useful, as they allow for process measures, such as treatment intensification or alteration by clinician(s) in response to elevated blood pressure levels; if the first medication choice or dose titration does not achieve the desired goal, several iterations of this process may be required
  - Defining the appropriate period of evaluation is an important technical feature of performance measures and should be meaningful from both patient and provider perspectives; performance measures must define a discrete period of measurement consistent with the actual treatment goals for the measures
  - As a principle of shared accountability, performance on these measures should be reported back to both clinicians and patients in a timely fashion to facilitate shared care management and achievement of best outcomes.
  - Thus, having lipid goals may enhance patient self-care and accountability, improve monitoring of the patient's response to treatment and clinical progress, and better allow for patient/clinician partnership in making treatment adjustments for the duration of lipid therapy.
- Those with the highest ASCVD risk provide among the greatest challenges, in that they are less likely to achieve lipid treatment goals, substantially due to the recommendations of lower non-HDL-C and LDL-C level attainment compared to patients at lower ASCVD risk.
- An LDL-C goal of <100 mg/dL is a National Quality Forum-endorsed performance measure in the treatment of more than 15 ASCVD-related diagnoses
- At the time of this writing, the decision by Healthcare Effectiveness Data and Information Set (HEDIS) to retain or retire LDL-C<100 mg/dL as a goal and performance measure remains under review.

XVII. INVESTIGATIONAL LIPID-ALTERING AGENTS IN DEVELOPMENT 2016 (Table 1)

Table 1 Brief summary of lipid-altering pharmacotherapies in development

Class of agent and mechanism of action	Name	Manufacturer	Sample references or Clinical Trials.gov Identifiers	Sentinel, reported safety/ tolerability findings	Sentinel lipid effects
Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors	Bococizumab	Pfizer (RN316)	[195]	Rare injection site reactions, with most cases being mild	>50% reduction in LDL-C and non–HDL-C levels
	ALN-PCS	Alnylam and the Medicines Company	[180,196]	Mild localized injection site reactions	Mean LDL cholesterol reduction 64%, with some degree of LDL cholesterol lowering maintained over 140 days, potentially supportive of a once-quarterly and possibly biannual subcutaneous administration

(*continued on next page*)

Table 1 (*continued*)

Class of agent and mechanism of action	Name	Manufacturer	Sample references or Clinical Trials.gov Identifiers	Sentinel, reported safety/ tolerability findings	Sentinel lipid effects
Dual modulator of adenosine triphosphate-citrate lyase and adenosine monophosphate-activated kinase	Bempedoic acid (ETC-1002)	Esperion	[181]	Possible increase in myalgia, mild increase in homocysteine and mild decrease in hemoglobin	15%–25% reduction in LDL-C levels 15%–21% reduction in non–HDL-C levels
Cholesteryl ester transfer protein (CETP) inhibitor	Anacetrapib	Merck	[182,183]	Generally well tolerated with no increase in blood pressure; drug concentration still detectable 2–4 years after last dosing	As much as 40% reduction in LDL-C As much as 150% increase in HDL-C
	TA-8995	Amgen (Dezima)	[184]	Generally well tolerated	27 - 45% reduction in LDL-C, 76 - 179% increase in HDL-C
Diacylglycerol acyltransferase-1 (DGAT-1) inhibitor	Pradigastat	Novartis (LCQ908)	[185]	Transient diarrhea and other gastrointestinal adverse experiences	Lowers triglyceride and other lipid levels, HbA1c, and body weight
Antisense Apo C3 inhibitor	Volanesorsen	Ionis Pharmaceuticals	[186]	Injection site reactions	Up to 77% reduction in triglyceride levels
Antisense inhibitor of lipoprotein (a)	ISIS-APO(a)Rx	Ionis	[197]	Mild injection site reactions	Dose dependent reduction in lipoprotein (a) up to 78%
Dialkyl ether dicarboxylic acid	Gemcabene	Gemphire Therapeutics Inc.	[187]	Generally well tolerated	Variable effects on lipid levels, depending upon baseline values and gemcabene dose administered
Peroxisome proliferator activated receptor (PPAR) delta agonist	MBX-8025	Cymabay	[188]	Possible increase in creatine kinase, mild decrease in hemoglobin, and increase in platelets	18 - 43% reduction in LDL-C levels, 18 - 41% reduction in non-HDL-C, 26 - 30% reduction in triglycerides, reduction in apoBand small LDL particles
Cholesterol absorption inhibitor	HS-25	Hisun	NCT02087917	Not reported	Not reported
Botanic extract from red yeast Chinese rice	ZueZhiKang	Beijing Peking University WBL Biotech Co. (WPU)	[189,190]		Lowers LDL cholesterol
Structural derivative of eicosapentaenoic acid	Icosabutate (PRC-4016)	Pronova Biopharm	[204]	Generally well tolerated	Reduces triglycerides
Niacin analogue	ARI-3037MO	Arisaph	NCT02250105	Not reported	Reduces triglycerides
Covalently linked niacin and eicosapentaenoic acid	CAT-2054	Catabasis	[198]	Generally well tolerated	Lowers LDL cholesterol
Docosopentoenoic acid and eicosapentaenoic acid	MAT9001	Matinas BioPharma Inc.	[191]	Not reported	Reduces triglycerides

APPENDIX A: National Lipid Association (NLA) Annual Summary of Clinical Lipidology 2016: Tables, Figures, Charts, and Hyperlinks

Section of this NLA Annual Summary	Title and links to applicable tables/figures/charts	Reference
NLA Executive Summary	Table 1. Classifications of cholesterol and triglyceride Levels in mg/dL	1
	Table 2. Treatment goals for non-HDL-C, LDL-C, and Apo B in mg/dL	1
	Table 3. Criteria for ASCVD risk assessment, treatment goals for atherogenic cholesterol, and levels at which to consider drug therapy	1
	Table 7. Major risk factors for ASCVD	1
	Table 8. Criteria for classification of ASCVD	1
	Table 9. High- or very high-risk patient groups	1
	Table 10. Sequential steps in ASCVD risk assessment	1
	Table 11. Risk indicators (other than major ASCVD risk factors) that might be considered for risk refinement	1
Genetics and Classification of Dyslipidemia	Figure 1: Clinical manifestations of primary hypertriglyceridemia (eruptive cutaneous xanthomas, lipemic plasma, lipemia retinalis, tuberous xanthomas, and palmar crease xanthomas)	7
	Table 1. Genetic classification of dyslipidemia	*
	Table 2. Genetic causes of hypolipidemias	*
Evaluation and Management of Familial Hypercholesterolemia	Table 3: Simon Broome diagnostic criteria for familial hypercholesterolemia	*
	Table 4. Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolemia	*
	Table 5. MEDPED diagnostic criteria for heterozygous familial hypercholesterolemia	*
	Table Summary Recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia	16
Secondary Causes of Dyslipidemia	Table 6. Secondary causes of dyslipidemia due to disordered metabolism or disease	*
	Table 7. Secondary causes of dyslipidemia due to drugs	*
Biomarkers and "Advanced Lipid Testing"	Table 1. Summary recommendations for measurement of inflammatory markers and advanced lipoprotein/subfraction testing in initial clinical assessment and on treatment management decisions.	25
Medical Nutrition Therapy	Table 4. Predicted lipid effects of macronutrient replacement of saturated fatty acids with polyunsaturated fatty acids, monounsaturated fatty acids, and carbohydrate (page S10)	48
	Chart 1. Nutrition Recommendations for the Management of Dyslipidemia. (page S26)	48
	Table 8. Nutritional content, characteristics and diseases/disorders/altered metabolic states that may elevate LDL-C and/or triglyceride concentrations	*
Physical Activity	Table 9. Physical exercise recommendations for improvement in lipid levels	*
	Table 10. Primary factors influencing exercise-generated weight loss and exercise training lipid/lipoprotein response	*
Obesity, Adiposopathy, Metabolic Syndrome, and Diabetes Mellitus	Table 1. Adiposopathy ("sick fat"): summary of causality and examples of anatomic, pathophysiologic, and clinical manifestations	24
	Figure 3. Adiposopathy in the fasting state and the contribution to the lipid pattern typically found with the metabolic syndrome	24
	Figure 4. Inter-relationship between adiposopathy, type 2 diabetes mellitus, dyslipidemia, and atherosclerosis	24
	Table 1. Metabolic syndrome definitions.	71
	Table 4. Examples of Endocrine and Immune Adipocyte and Adipose Tissue Factors as Potential Contributors to "Adiposopathic Dyslipidemia."	24
	Table 11. Non-weight management pharmaceuticals that that may affect body weight.	*
Statin & Non-Statin Pharmacotherapy	Table 12. Intensity of statin therapy	1
	Table 3. Focus on ASCVD risk reduction: 4 statin benefit groups	82
	Table 13. Drugs affecting lipoprotein metabolism	1

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Section of this NLA Annual Summary	Title and links to applicable tables/figures/charts	Reference
Lipid-Altering Drug Prescribing Information	Atorvastatin: http://labeling.pfizer.com/ShowLabeling.aspx?id=587	NA
	Fluvastatin: https://www.pharma.us.novartis.com/product/pi/pdf/Lescol.pdf	NA
	Lovastatin: http://www.merck.com/product/usa/pi_circulars/m/mevacor/mevacor_pi.pdf	NA
	Pitavastatin: http://www.kowapharma.com/documents/LIVALO_PI_CURRENT.pdf	NA
	Pravastatin: http://packageinserts.bms.com/pi/pi_pravachol.pdf	NA
	Rosuvastatin: http://www1.astrazeneca-us.com/pi/crestor.pdf	NA
	Simvastatin: http://www.merck.com/product/usa/pi_circulars/z/zocor/zocor_pi.pdf	NA
	Ezetimibe: http://www.merck.com/product/usa/pi_circulars/z/zetia/zetia_pi.pdf	NA
	Omega-3-acid ethyl esters (EPA and DHA): https://www.gsksource.com/gskprm/htdocs/documents/LOVAZA-PI-PIL.PDF	NA
	Icosapent ethyl (EPA only): http://www.vascepa.com/full-prescribing-information.pdf	NA
	Omega-3-carboxylic acids (EPA and DHA free fatty acid formulation): http://www1.astrazeneca-us.com/pi/epanova.pdf	NA
	Allirocumab: http://products.sanofi.us/praluent/praluent.pdf	NA
	Evolocumab: http://pi.amgen.com/united_states/repatha/repatha_pi_hcp_english.pdf	NA
	Colesevelam HCl: http://dsi.com/prescribing-information-portlet/getDocument?product=WC&inline=true	NA
	Cholestyramine: http://www.rxlist.com/questran-drug/side-effects-interactions.htm	NA
	Colestipol: http://www.rxlist.com/colestid-drug/side-effects-interactions.htm	NA
	Fenofibrate: http://www.rxlist.com/tricor-drug/side-effects-interactions.htm	NA
	Fenofibric acid: http://www.rxabbvie.com/pdf/trilipix_pi.pdf	NA
	Gemfibrozil: http://www.rxlist.com/lopid-drug/side-effects-interactions.htm	NA
	Extended-release niacin: http://www.rxabbvie.com/pdf/niaspan.pdf	NA
	Lomitapide: http://www.juxtapidremsprogram.com/_pdf/012187_JuxtapidPI_8.5x11_FIN.PDF	NA
	Mipomersen: http://www.kynamro.com/~/media/Kynamro/Files/KYNAMRO-PI.pdf	NA
Statin safety: Muscle	Table 1. Spectrum of statin-associated muscle adverse events (page S60)	205
	Table 12. Non-statin causes of elevated muscle enzymes	*
	Table 4. Diagnostic criteria for myopathy (page S65)	205
	Table 5. Indications for skeletal muscle biopsy (page S67)	205
	Figure 2. Algorithm for the evaluation of statin-associated muscle injury (page S68)	205
Statin safety: Liver	Table 1. Hy's law criteria (page S49)	205
	Table 2. Questions addressed by liver experts in the 2006 and 2014 National Lipid Association Statin Safety Task Force Reports (page S50)	205
	Table 3. Illustrative causes of elevated liver enzymes in adolescents and adults (page S52)	205
	Figure 1. Comprehensive approach to patients with elevated liver blood testing (transaminases <3 times the upper limits of normal) (page S54)	205
	Figure 2. Comprehensive approach to patients with elevated liver blood testing (transaminases >3 times the upper limits of normal) (page S55)	205
Statin safety: Cognition	Figure 1. Evaluation of the patient with cognitive symptom (page S12)	205
Statin safety: Diabetes mellitus	Table 1. Criteria for screening for prediabetes and diabetes before or concurrent with initiation of statin therapy (page S23)	205
	Table 2. Criteria for the diagnosis of prediabetes and diabetes (page S26)	205
	Table 3. Summary of clinical trial evidence for CVD event reduction in patients with diabetes (page S27)	205

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Section of this NLA Annual Summary	Title and links to applicable tables/figures/charts	Reference
Statin drug interactions	Table 13. Drug metabolism basics	*
	Table 14. Phases of drug interaction	*
	Table 15. Transporter classes	*
	Table 16. Pharmacokinetic and pharmacodynamics properties of statins	*
	Figure 1. Chemical structure of statins (page S31)	205
	Figure 2. Metabolic fate of statins (S31)	205
	Table 1. Transporters and enzymes involved in statin metabolism (S32)	205
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	Figure 3. A proposed ranking of significance with respect to area under the curve changes and drug-drug interaction possibilities (page S35)	205
	Table 12. Comparison of drug-drug interactions across all statins (page S41)	205
	Table 13. Dose limits of various statins with respect to various interacting medications (page S43)	205
	Table 14. Statin/fibrate combination therapy pharmacokinetic interactions (page S43)	205
Lipoprotein-apheresis	Table 14. Lipoprotein Apheresis	1
Dyslipidemia in children and adolescents	Table 7. Acceptable, borderline-high, and high plasma lipoprotein lipids and apolipoprotein concentrations for children and adolescents (page S29)	48
	Table 9. International Diabetes Federation's definition of the at risk group and metabolic syndrome in children and adolescents (page S30)	48
	Chart 3. Recommendations for the evaluation and management of dyslipidemia in children (S34)	48
Dyslipidemia in select populations	Chart 4. Recommendations for women's lipid health (page S44)	48
	Chart 5. Lipid recommendations for women: pregnancy and menopause (page S49)	48
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	Chart 8. Lipid recommendations for African Americans (page S66)	48
	Table 20. Waist circumference thresholds for abdominal obesity by various international organizations, based upon race and geographic location (page S69)	48
	Chart 9. Lipid recommendations for South Asians (page S72)	48
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Dyslipidemia in patients with inflammation	Chart 12. Lipid recommendations for patients with rheumatoid arthritis (page S84)	48
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	Chart 15. Lipid Recommendations for team-based collaborative care (page S100)	48

NA, not applicable
*Online NLA Resource Center.

APPENDIX B: Lipid Recommendations, Lipid Guidelines, and Atherosclerotic Cardiovascular Disease Risk Calculators

Lipid Guidelines, Recommendations, and Position Statements

- National lipid association recommendations for patient-centered management of dyslipidemia: Part-1, full report.
- National lipid association recommendations for patient-centered management of dyslipidemia: Part-2
- New cholesterol guidelines for the Management of atherosclerotic cardiovascular disease risk: a comparison of the 2013 American College of Cardiology/American Heart Association cholesterol guidelines with the 2014 National Lipid Association recommendations for the patient-centered management of dyslipidemia
- Key Aspects of the NLA Recommendations for the Patient-Centered Management of Dyslipidemia
- A lipidologist perspective of global lipid guidelines and recommendations, part 2: Lipid treatment goals
- National Institute for Health and Clinical Excellence Guidance on Lipid Modification: Cardiovascular Risk Assessment and the Modification of Blood Lipids for the Primary and Secondary Prevention of Cardiovascular disease.
- An International Atherosclerosis Society position paper: global recommendations for the management of dyslipidemia: Executive Summary.
- 2013: ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines
- American Association of Clinical Endocrinologists's Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis.
- 2012 Update of the Canadian Cardiovascular Society Guidelines for the Diagnosis and Treatment of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult
- Comprehensive risk management for the prevention of cardiovascular disease: executive summary of the Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases in Japan - 2012.
- ESC/EAS Guidelines for the management of dyslipidaemias: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS)
- National Cholesterol Education Program Adult Treatment Panel III Guidelines: Implications of recent clinical trials

Atherosclerotic Cardiovascular Disease Risk Assessment Tools and Calculators

- American College of Cardiology/American Heart Association atherosclerotic cardiovascular disease Risk Estimator
- United States National Heart, Lung, and Blood Institute Framingham Risk Score
- Reynolds Risk Score
- QRISK Risk Calculator
- Lloyd-Jones Framingham Algorithm
- Systemic Coronary Risk Estimation (SCORE)
- Prospective Cardiovascular Munster Study (PROCAM) Risk Scores (Quick Check and Health Check)
- A lipidologist perspective on global lipid guidelines and recommendations, Part 1: Lipid treatment targets and risk assessment

Journal of Clinical Lipidology Electronic Resources (accessible at www.lipid.org) 2016

E1 National Lipid Association Position Statements and Hyperlinks

- **2015 National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1: Full report.**[2]
- **2015 National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 2: (Lifestyle therapies, groups with special considerations, older patients, patients with human immune deficiency, patients with inflammation, patients with residual risk, strategies to assist with adherence, team-based collaborative care).**[48]
- **2015 Lipids and bariatric procedures part 1 of 2: Scientific statement from the National Lipid Association, American Society for Metabolic and Bariatric Surgery, and Obesity Medicine Association: FULL REPORT**
- **2014 National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1 – executive summary.**
- **2014 Statin Safey Update.**
- **2013 Obesity, adiposity, and dyslipidemia: A consensus statement from the NLA.**
- **2011 Clinical Utility of Inflammatory Markers and Advanced Lipoprotein Testing: Advice from an Expert Panel of Lipid Specialists.**
- **2011 Familial Hypercholesterolemia: Screening, Diagnosis and Management of Pediatric and Adult Patients.**
- **2008 National Lipid Association Statement Regarding Reporting of Non-HDL on Standard Laboratory Reports.**
- **2007 Report of the National Lipid Association's Safety Task Force: The Non-statins.**

- **2006 A Symposium: Report of the National Lipid Association's Statin Safety Task Force**.

E2 Other National Lipid Association documents

Lipid Clinic and CMR operations manual/ course

(https://www.lipid.org/education/courses/coding)

Coding and reimbursement

(https://www.lipid.org/practicetools/reimbursement)

E3 Links to:


Podcasts: https://www.lipid.org/aggregator/audio


Webcasts: https://www.lipid.org/aggregator/webcasts


Slide shows: https://www.lipid.org/aggregator/slideshows

Websites: https://www.lipid.org/aggregator/websites


Applications: https://www.lipid.org/aggregator/application

CME: https://www.lipid.org/aggregator/CME


Patient information: https://www.lipid.org/aggregator/patients

Disclosures

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To view the disclosures of each author and reviewer, visit www.lipid.org/2016SummaryDisclosures.

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