

Original Contribution

National Lipid Association Annual Summary of Clinical Lipidology 2015



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Guidelines

Abstract: The National Lipid Association (NLA) Annual Summary of Clinical Lipidology 2015 is a 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 and Consensus Statements. The goal is to provide clinicians an ongoing resource that translates the latest advances in medical science toward the evaluation and treatment of patients with dyslipidemia. The 2015 NLA Annual Summary of Clinical Lipidology was founded on the principles of evidence-based medicine and is generally consistent with established national and international lipid guidelines. Topics include a general discussion of the 2014 NLA Recommendations for Patient-Centered Management of Dyslipidemia, genetics, secondary causes of dyslipidemia, biomarkers and “advanced lipid testing,” medical nutrition, physical activity, obesity, pharmacotherapy, statin safety, lipid-altering drug interactions, lipoprotein apheresis, dyslipidemia in children and adolescence, dyslipidemia in older individuals, race/ethnicity, and women, health information technology and electronic medical records, as well as investigational lipid-altering drugs in development.
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I. INTRODUCTION

Principles

The 2015 NLA Annual Summary of Clinical Lipidology was first proposed in 2012, and this 2015 version is the first published issue. It 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 an individual patient because no set of recommendations or guidelines can have 100% applicability to an individual patient. Thus, evaluation and treatment decisions should be based on 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 Table and Figure Hyperlink Format

Within the document are highlighted hyperlinks that direct the reader to Appendix A, which in turn lists applicable tables and figures highlighted by hyperlinks that allow for electronic retrieval from original publications, as well as reference citation for nonelectronic retrieval of the applicable tables and figures. In an age of wide-scale availability of Internet access, computers, smartphones, and tablets, the intent is to provide a central directory of tables and figures useful for both medical science as well as the day-to-day management of patients with dyslipidemia. Providing a single Appendix that categorizes

electronic links to tables and figures, instead of reprinting the tables and figures, allows for greater access to, and more robust inclusion of sentinel tables and figures helpful to clinical lipidologists and their patients.

Review Board Charge 2015

The Review Board was charged with the construct and edits of the NLA Annual Summary of Clinical Lipidology 2015. This Review Board comprised NLA members, 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. Other NLA Resources listed at the end of this document include NLA Recommendations, NLA Position Statements, and NLA Consensus Reports. Other published and electronic NLA resources are listed as well.

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II. 2014 NLA RECOMMENDATIONS FOR PATIENT-CENTERED MANAGEMENT OF DYSLIPIDEMIA PART 1.

Lipid evaluation and management principles¹

- The NLA has recommended basic principles in the evaluation and management of dyslipidemia, for the purpose of reducing atherosclerotic cardiovascular disease (ASCVD) risk. These principles include:
 - An elevated level of atherogenic cholesterol carried by circulating apolipoprotein B (apo B)-containing lipoproteins, as reflected by non-HDL-C and low-density lipoprotein cholesterol (LDL-C), is a cause of atherosclerosis, the key underlying process contributing to most clinical ASCVD events.
 - The term *atherogenic cholesterol* is intended to reflect 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 extent that atherogenic cholesterol is reduced. This benefit is presumed to result from the lowering of atherogenic cholesterol through multiple modalities, including lifestyle and pharmacotherapy.
- 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 intervention, 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 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.
- Setting lipid treatment goals and monitoring LDL-C levels are among the most important tools in implementing a successful lipid management strategy and allows the clinician to assess patient response to therapy and identify potential barriers to patient adherence to lipid treatments (eg, adverse experiences, financial concerns).
- 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)

- Non-HDL-C is a co-primary lipid treatment target, along with LDL-C levels.

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- 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 potentially 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 changes and levels 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 (ie, only one of the two is elevated), CHD risk is more closely aligned with non-HDL-C than LDL-C.
- Possible explanations for the superiority of non-HDL-C over LDL-C for predicting ASCVD event risk include:
 - Like LDL, some triglyceride-rich lipoprotein remnants enter the arterial wall and thus contribute to the initiation and progression of atherosclerosis.
 - Non-HDL-C correlates more closely than LDL-C with apo B 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 levels)
- 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.
- In patients without elevated triglyceride levels, LDL-C may be a better predictor of ASCVD risk; therefore, both LDL-C and non-HDL-C have clinical utility in helping to set and measure achievement of lipid treatment goals.

Apolipoprotein B (apo B)

- Apo B is an optional, secondary lipid target for treatment.
- Each potentially 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.
- Apo B and non-HDL-C share the advantage that neither requires fasting for accurate assessment.

- Non-HDL-C is favored over apo B by the NLA Expert Panel because it is universally available, requires no additional expense, and because apo B has not been consistently superior to non-HDL-C in predicting ASCVD risk.
- Apo B is a potential contributor to 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 often occurs 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 necessary until the patient has been treated to his or her goal levels for atherogenic cholesterol.

Triglycerides

- An elevated triglyceride level is not a target of therapy per se, except when very high (≥ 500 mg/dL).
- When the triglyceride concentration is very high (≥ 500 mg/dL, and especially if ≥ 1000 mg/dL), reducing the concentration to <500 mg/dL to prevent pancreatitis becomes the primary goal of therapy.
- When triglycerides are between 200 and 499 mg/dL, the 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 recommended as a target of therapy per se, but the level is often raised as a consequence of efforts to improve other lipid parameters through lifestyle and 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, ileal bypass surgery, bariatric surgery) reduce ASCVD event risk.
- Lipid treatment goals are useful as means to ensure the intensity of therapy to lower atherogenic cholesterol is matched to the absolute risk for an ASCVD event.
- 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, evaluable lipid levels 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.
- If 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 patient 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).
 - Secondary ASCVD risk indicators that might be considered for risk refinement (e.g. calcium artery scoring, hs-CRP, Lp [a], microalbuminuria, etc.).

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.
- 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 (eg via use of statins) have yet to demonstrate convincing benefits from the primary outcomes of randomized, controlled trials in dialysis patients.

High ASCVD risk

- Patients at high ASCVD risk include patients with:
 - ≥ 3 major ASCVD risk factors.
 - High ASCVD risk condition, including 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 to estimate 10-year or long-term/lifetime risk for an ASCVD or atherosclerotic coronary heart (CHD) event. High risk is defined as >10% using the Adult Treatment Panel III Framingham Risk Score for hard coronary heart disease (myocardial infarction or CHD death), and >15% using the 2013 Pooled Cohort Equations for hard ASCVD (myocardial infarction, stroke, or cardiovascular disease [CVD] death) or >45% using the Framingham long-term

CVD (myocardial infarction, CHD death or stroke) risk calculation. These tools help facilitate identification of patients who may be classified as high risk in the absence of any of the high risk conditions listed previously.

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 an approximately 5% to <15% 10-year risk for an ASCVD event.
- 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).
- 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 an approximately <5% 10-year risk for an ASCVD event, and lipid-altering pharmacotherapy is generally only considered when non-HDL-C levels are \geq 190 mg/dL or LDL-C levels are >160 mg/dL.
- Quantitative risk scoring is not typically necessary for low ASCVD risk individuals.

III. GENETICS AND CLASSIFICATION OF DYSLIPIDEMIA²

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, apolipoprotein assays, and lipoprotein lipase activity.
- Diagnosis of more rare dyslipidemias can sometimes be assisted by genetic or functional testing (eg, gene sequencing, LDL receptor activity, lipoprotein lipase activity).
- The appearance of the serum can provide clues to diagnosis of genetic dyslipidemia.³

Hypolipidemias

- Just as genetic abnormalities can contribute to elevated lipoprotein and lipid levels, genetic abnormalities can also contribute to low lipoprotein and low lipid levels.

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 genetic genome, or may do custom sequencing of one or more genes. Genome-wide association studies may provide common single nucleotide polymorphisms, which are different gene sequences that code for biological mechanisms contributing to abnormal lipid levels.
- In certain countries, patients with marked elevations in LDL-C levels may 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.
- Few US research sites and testing centers perform genotyping for patients with hypercholesterolemia. However, the National Institutes of Health website, GeneTests (www.genetests.org), provides a list of laboratories that are Clinical Laboratory Improvement Amendments–certified and offer genetic testing.
- 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 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 (see FH section).
- 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 is not clear.⁴
- Example #3: A dominant form of genetic hypercholesterolemia is gain-of-function mutations of PCSK9 that can cause phenotypical familial hypercholesterolemia.⁵ 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 mutations, 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 efflux plant sterols and cholesterol 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 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.

EVALUATION AND MANAGEMENT OF FAMILIAL HYPERCHOLESTEROLEMIA⁶⁻⁹

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,¹⁰ 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.¹¹
- 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^{10,12-14}

- 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. Tendon xanthomas and xanthelasmas are pathognomonic for FH in this clinical setting, with genetic testing often, but not always, confirmatory.

Screening and genetic testing for familial hypercholesterolemia^{7,8}

- 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 specifically for FH: general principles

- In addition to high-intensity statins, 2 other lipid-altering pharmacotherapies have a labeled 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 by 50% in patients with homozygous FH on maximum tolerated lipid-lowering therapy and LDL apheresis.

- Among the more common adverse experiences with lomitapide gastrointestinal are elevations in hepatic fat and liver transaminases.
- Because of the alterations in liver transaminases and increase in hepatic fat, mipomersen and lomitapide are available only through Risk Evaluation and Mitigation Strategy programs.

Treatment options specific for heterozygous FH

- High-intensity statins are the pharmacotherapy of first choice, 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.
- If LDL-C is not sufficiently lowered with statins, then consideration should be given to adding other cholesterol-lowering drugs:
 - Ezetimibe.
 - Bile acid sequestrants.
 - Niacin.
 - LDL apheresis for FH patients with inadequate control with pharmacotherapy, or who are intolerant to statins (see discussion of Lipoprotein apheresis).

Treatment options specific for homozygous FH

- If LDL-C is not sufficiently lowered with statins, then consider adding other cholesterol-lowering drugs.
 - Ezetimibe.
 - Bile acid sequestrants.
 - Microsomal triglyceride transfer protein inhibitors (e.g., lomitapide).
 - Apo B antisense agents (e.g., mipomersen).
 - Niacin.
 - LDL apheresis.
 - Rarely, portacaval anastomosis.
 - Rarely, liver transplantation may be considered for children with homozygous FH.

IV. SECONDARY CAUSES OF DYSLIPIDEMIA^{1,15}

- Beyond genetic considerations, dyslipidemia can also be due to secondary causes.
- A “two hit phenomenon”¹⁵ 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 or from drugs that alter lipid metabolism.

V. ADDITIONAL LIPID PARAMETERS^{16–22}

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; it is a biomarker of ASCVD risk.
- HDL particles include many surface 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.
- 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, triglycerides, insulin resistance, systemic inflammation, and cigarette smoking, all of which can confound the true relationship between HDL-C levels and the risk of ASCVD.
- HDL-C levels are inversely associated with elevated triglyceride-rich lipoprotein levels, small (more dense) LDL-P, and increased atherogenic particle number. The concentration of these atherogenic lipoproteins can be quantified by measuring apo B levels.
- 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 have not been proven to reduce ASCVD risk.
 - The clinical relevance of HDL may be more dependent upon the flux of cholesterol from arterial macrophages via HDL-mediated macrophage cholesterol efflux.
 - 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 specific pharmacotherapies to increase HDL-C levels.
- For patients with adiposopathic metabolic syndrome or insulin resistance, optimal HDL particle concentration and function are best achieved by appropriate lifestyle intervention, such as cigarette smoking cessation, appropriate nutrition, and increased (vigorous) physical activity.

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. Cholesterol-laden macrophages are known as foam cells.
 - When the LDL-P is low (ie, fewer LDL particles are present in the circulation), fewer particles 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.
- 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, ASCVD risk often tracks better with LDL-P 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.
- 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 remains unclear if additional LDL-P information would 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)²³

- Lipoprotein (a) [Lp(a)] is a lipoprotein similar to LDL, whose increased levels are associated with increased ASCVD risk.
- No favorable function of Lp(a) has yet been identified.
- Lp(a) consists of an LDL molecule, 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 may lower Lp(a); however, the clinical implications are unclear^{24,25}:
 - Niacin
 - Mipomersen (apo B antisense)
 - Estrogen
 - Lipoprotein apheresis
- 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 antagonists
 - L-carnitine
 - Tamoxifen
 - Thyroxine replacement in hypothyroid patients
- Investigational agents that may lower Lp(a) levels
 - PCSK9 inhibitors
 - CETP inhibitors
 - Thyroid receptor beta subunit agonists
- In patients with low ASCVD risk, Lp(a) measurements are not recommended for routine ASCVD risk assessment.
- Among patient at low ASCVD risk, lipid treatment decisions are unlikely to be altered by use of Lp(a).

- 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”¹⁶

Biomarkers as initial assessment of ASCVD risk

- 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.”
 - Some biomarkers are potentially useful to assess initial ASCVD risk, before starting lipid-altering therapy.

Biomarkers for on-treatment assessment of ASCVD therapy

- Other biomarkers may not only be useful to assess ASCVD risk, but also to monitor the progress of therapy.
- However, 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.^{26,27}
- 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.^{28,29}

- 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).^{30–32}
- 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.³³
- 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, some clinicians may choose to monitor lipoprotein (a) during lipid-altering intervention.³⁴
- 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.
 - It is currently impossible to determine if the reduction in ASCVD risk is due to improved lipid levels or due to reduction in C-reactive protein alone.³⁵
 - 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.³⁶

VII. NUTRITION, PHYSICAL ACTIVITY, OBESITY

Medical nutrition therapy^{1,15,37}

Triglyceride-induced pancreatitis

- In patients with very high triglyceride levels and acute triglyceride-induced pancreatitis with hyperchylomicro-nemia, 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).
- Parenteral nutrition is reserved for severe cases where fasting is prolonged, and enteral nutrition is not feasible or inadequate because of persistent gastrointestinal dysfunction.³⁸
- 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 (<15% of energy consumption).

Medical nutrition therapy for dyslipidemia^{15,39}

- 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 which weight reduction is not a therapeutic intent, reduction in LDL-C can be achieved with nutritional intake of <7% of calories as saturated fatty acids, very low levels of trans-fatty acids, and dietary cholesterol not to exceed 200 mg per day.
- Even with carbohydrate-restricted nutrition 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 most 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 the latter is 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 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.
- HDL-C levels may also be affected by factors such as chronology and the energy and nutrient profile of the diet.
 - During active weight loss, especially if achieved through a fat-restricted dietary intake, HDL-C levels may transiently decrease.

- After stabilization of weight, HDL-C levels often return, or trend to baseline once weight has stabilized.
- 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 review of clinical trials of nutrition interventions indicates that a 2- to 7-kg weight loss is typical.
 - Weight loss may have widely variable effects on dyslipidemia, which depends upon the baseline lipid levels, the extent of weight loss, and how the weight loss was achieved. However, in general, 2 to 7 kg of weight loss might be expected to:
 - Reduce total cholesterol by about 9 mg/dL.
 - Initially reduce LDL-C by 4 mg/dL, with variable effects afterwards.
 - Reduce HDL-C during active weight loss by 1.2 mg/dL.
 - Increase HDL-C by 1.6 mg/dL during weight maintenance.
 - Decrease triglycerides by 6 mg/dL.
- 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.^{40–43}
- 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.⁴⁴
- More consistent reductions in LDL-C levels are achieved with greater weight reduction.
- Exercise training may decrease LDL-P, which may also represent a less atherogenic profile.⁴³
- 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, 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 clinically relevant weight loss is achieved, exercise training may improve lipid and lipoproteins parameters, even without substantial reductions in body weight.
- If measured by a standard lipid panel, 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.⁴³
- Some increase in physical activity is better than no physical activity.
 - 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.

Adherence to nutrition therapy

- Regarding nutrition intervention for the purposes of both weight loss and treating dyslipidemia, the recommended diet should be one 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 different nutritional therapies tend to wane, with different dietary 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 include appropriate education and follow-up by a health professional trained in nutrition, such as a registered dietitian or registered dietitian nutritionist.

Physical activity¹⁵

Effects of physical activity on lipid levels

- Physical activity refers to any bodily movement produced by skeletal muscles that requires energy expenditure.

- “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 elicit sustained reductions in triglyceride levels (eg, VLDL triglycerides).⁴⁵

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 reductions in resting metabolic rate, and may counter other weight-regain mechanisms.
- More intensive physical activity, such as 1 hour of daily moderate aerobic exercise, 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 intramuscular fat and visceral adipose tissue compared with caloric restriction alone.

Obesity, adiposopathy, metabolic syndrome, and diabetes mellitus^{15,26,46,47}

Obesity as a disease

- 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.
- The pathogenic increase in body fat may be caused by nutritional imbalances and/or unfavorable environmental and cultural factors as well as from genetic/epigenetic or developmental errors, infections (eg, gut microbiota), hypothalamic injury, and adverse reactions to pharmacotherapies.
- 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 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 dyslipidemia.”
- This same adiposopathic dyslipidemic pattern is 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 and metabolic abnormalities (eg, abnormalities in lipid and glucose levels, increase in 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.⁴⁸

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 as well as fatty infiltration of muscle and liver, which in turn contributes to 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.

- The totality of triglyceride-rich particles is increased (eg, VLDL, intermediate density lipoproteins, remnant lipoproteins). These triglyceride-rich lipoproteins contain 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), 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.⁴⁹
 - 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) may be an alternative measure of the pathogenic potential of an increase in body fat.
- **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.**^{50–55}

Weight management pharmacotherapy^{15,37}

- 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 dyslipidemia.

- The typical mean weight loss achieved with longer term weight management pharmacotherapy may not substantially improve HDL-C and LDL-C levels, which is similar to the lipid effects most often described with nutritional intervention and modest increases in physical activity.

Bariatric surgery¹⁵

- The effect of bariatric surgery on lipid levels is variable and dependent upon the type of bariatric surgical procedure (eg, adjustable gastric banding, gastric sleeve, gastric bypass).
- 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 since the bariatric procedure.
- The Swedish Obese Subjects (SOS) Study^{56,57}
 - 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.

VIII. LIPID PHARMACOTHERAPY^{1,58}

Statin Pharmacology

- Concomitant with lifestyle modification and management of ASCVD risk factors, lipid-altering drug therapy is often indicated.
- Unless contraindicated, the first-line pharmacotherapy for treatment of elevated atherogenic cholesterol levels is a moderate- or high-intensity statin.

- 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 proposed 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 with 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 with statins was associated with a reduction in ASCVD risk.²⁸
- 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.⁵⁹
- 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.^{60–63}
- 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.¹⁵⁴
- Multiple national and international guidelines support specific lipid treatment goals, such as LDL-C levels of <70 or 70 mg/dL, depending upon ASCVD risk. (See prior section entitled: “Summary of the 2014 NLA Recommendations for Patient-Centered Management of Dyslipidemia Part 1.)^{1,64–69}

Non-statin Pharmacotherapy¹

- Non-statin drug classes for lipid management include cholesterol absorption inhibitors, bile acid sequestrants, fibric acids, long-chain omega-3 fatty acids, and nicotinic acid. Depending upon the population studied, baseline lipid levels, and whether administered with or without statins, these non-statin agents have randomized, controlled clinical trial evidence supporting a reduction in ASCVD.

- Clinical trials that evaluated statins in hypertriglyceridemic patients have often demonstrated that statins lower triglyceride levels to a similar degree compared with lipid-altering agents often considered to be primarily triglyceride-lowering agents (eg, fibrates, omega-3 fatty acids).⁷⁰

Combination Lipid-Altering Pharmacotherapy

- For patients not achieving adequate response to statin therapy, then combining statin therapy with another lipid-altering pharmacotherapy may be appropriate.
- Another clinical situation wherein non-statin combination therapy⁷¹ may be necessary is in patients with statin intolerance, or who may have contraindications to statin therapy.

Statin Safety

Statin intolerance⁷²

- 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.⁷³ However:
 - Many randomized statin trials have excluded patients with signs and symptoms of statin intolerance, before the study.

- 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.⁷³
- 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: muscle⁷⁴

- 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—increasing statin blood levels and thus increasing the potential risk of statin adverse experiences
 - A trial of statin therapy may help define the relationship between the statin and muscle symptoms.
- Myalgias from statins can be reliably differentiated from myalgias from placebo via validated tools such as the Short-Form McGill Pain Questionnaire and Short-Form Brief Pain Inventory; however, these are rarely used in clinical practice.
- 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 as might be assessed by the Medical Research Council definition.⁷²
- In patients with muscle pain or weakness, other diagnostic testing might include CK levels.
 - 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 muscle weakness and/or pain and 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 (eg, liver or kidney disease), 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 options 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: liver⁷⁵

- 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 the failure to recognize 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.

Statin safety: cognition⁷⁶

- 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 is sufficiently severe to interfere with daily activities leading to progressive loss of independence.
- Despite the occasional reported association of statin use with mild cognitive impairment, baseline cognitive assessment is not necessary before statin use, because as a class, statins are not associated with adverse effects upon cognition.

- If a provider does encounter 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 mellitus⁷⁷

- Statins may increase the risk for type 2 diabetes mellitus; the mechanism is unknown.
- 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.¹⁵⁵
- Given that statins reduce ASCVD risk, no change is recommended to current practice regarding statin use among patients at risk for ASCVD.
- Statin-treated patients should be engaged in aggressive nutrition therapy and 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.

IX. LIPID-ALTERING DRUG INTERACTIONS⁷⁸

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.⁷⁹
- Gastrointestinal absorption of oral pharmaceuticals 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 may be influenced by disease (eg, gastrointestinal disease, liver failure, renal insufficiency), age, gender, and genetic variation (eg, polymorphisms).
- Drug metabolism may be influenced by concomitant drugs, foods, toxins, etc.
- Regarding oral pharmacotherapy, once administered, drugs undergo first-pass metabolism (or presystemic metabolism) through phase 1 and phase 2 metabolism that reduces the concentration of a drug before reaching the systemic circulation.
 - 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 may also occur in the liver and lung.
 - Because of first-pass metabolism, only a small amount of active drug typically emerges from the liver to the systemic circulation, thus reducing bioavailability.
 - This first-pass effect can be avoided by administering drugs via suppository, intravenous, intramuscular, inhaled, or sublingual routes.
- Some drugs are administered as pro-drugs that require metabolism to render 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 the prescribing information.
- What is often less recognized is the importance of biologic transporters with respect to drug metabolism and potential drug interactions.

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

cerivastatin, pravastatin, rosuvastatin, atorvastatin, lovastatin, and pitavastatin.

- Clinically, the SLCO1B1 polymorphism of OATP-C may explain >60% of the cases of myopathy observed with the simvastatin 80 mg per day dose.⁸⁰
- Atorvastatin is an illustrative example of a statin that has many pharmacokinetic influences. Specifically, atorvastatin acid⁸¹:
 - Is highly soluble and permeable.
 - 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 oral bioavailability is 12% to 14%.
 - 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 volume of distribution of atorvastatin acid is 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 of minor importance (<1%–5%) for the elimination of atorvastatin acid.
 - Undergoes metabolism by cytochrome P450 (CYP) 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, nelfinavir, ritonavir, cyclosporin, fibrates, erythromycin, and grapefruit juice.
 - An interaction with gemfibrozil seems to be mediated by inhibition of glucuronidation. 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.

X. LIPOPROTEIN APHERESIS⁸²

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 may be removed from the blood.

Lipoprotein apheresis clinical considerations

- Lipoprotein apheresis is substantially efficacious in the short term removal of 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 is required to maintain reduction in non-HDL-C and LDL-C levels and provides the best potential to reduce ASCVD risk.
- 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 is returned.
- Lipoprotein apheresis is most often used for patients with high to very high cholesterol (eg, FH) levels who are unable to achieve lipid treatment goals with other therapies, especially among patients who are statin-intolerant.
- In the United States, lipoprotein apheresis is only 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).
- The most significant potential adverse experiences 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 heterozygous FH.
 - Once-a-week treatment may be required for patients with homozygous FH.
 - For patients wherein every 2 weeks is logistically challenging (eg, distance to lipoprotein-apheresis center), once-a-month lipoprotein apheresis might be expected to provide clinical benefit compared to no lipoprotein apheresis.
- Approved use of lipoprotein apheresis
 - LDL-C must be greater than 200 mg/dL for patients with atherosclerotic coronary artery disease (ie, not other atherosclerotic diseases), on maximum tolerated nutritional and lipid-altering pharmacotherapy intervention.
 - LDL-C must be greater than 300 mg/dL for patients without atherosclerotic coronary artery disease.
 - In situations wherein vascular disease is rapidly advancing despite maximum nutrition therapy, physical activity, and pharmacotherapy, lipoprotein apheresis is sometimes approved and supported by third-party payers at LDL-C levels <200 mg/dL.

Lipoprotein apheresis systems

Dextran Sulfate Apo B Lipoprotein Adsorption System (Liposorber)

- Passes cell-free plasma through twin columns of dextran sulfate bound to cellulose beads.
- Apo B-containing lipoproteins are selectively bound by an electrostatic charge.
- Requires systemic anticoagulation with heparin.
- Angiotensin-converting enzyme reduces bradykinin degradation in plasma.
- Excess bradykinin can cause hypotension.
- Dextran Sulfate Apo B Lipoprotein Adsorption Systems 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.
- Patients undergoing lipoprotein-apheresis may benefit from switching from and angiotensin-converting enzyme inhibitor, to an angiotensin receptor blocker, which does not require medication adjustment.
- 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 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.
- Does not require systemic anticoagulation.
- 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 LP-X1. LP-X1 particles are:
 - Lipid complexes that form after prolonged biliary obstruction.
 - Rich in phospholipid and free (non-esterified) cholesterol.

- Poor in cholesterol esters and triglycerides.
- Composed of albumin as a main protein and poor in other proteins such as apo B.
- Twice the size (60 nm) of normal LDL.

Evidence for clinical benefit of lipoprotein apheresis

- Sham 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 is scarce, and includes:
 - Hokuriku Familial Hypercholesterolemia Low-Density Lipoprotein Apheresis Study Group Study.⁸³
 - 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 LDL-C 58%; lipid-altering pharmacotherapy alone reduced LDL-C 28%.
 - LDL apheresis plus lipid-altering pharmacotherapy reduced ASCVD events by 72% (incidence of 10%) compared with lipid-altering pharmacotherapy alone (incidence of 36%).
 - LDL-Apheresis Atherosclerosis Regression Study (LAARS)⁸⁴
 - 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 LDL-C 63%; simvastatin alone lowered LDL-C 47%.
 - Regarding angiographic findings:
 - No differences were found in the 2 treatment groups in mean segment diameter or minimal obstruction diameter. In the apheresis group plus simvastatin group, more minor lesions disappeared compared with the simvastatin alone group.
 - The apheresis group plus simvastatin group may have had improved functional effects compared with the simvastatin alone group, such as time to ST-segment depression and maximum level of ST depression via bicycle exercise cardiac testing.

XI. DYSLIPIDEMIA IN CHILDREN AND ADOLESCENTS⁸⁵⁻⁹¹

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

- Especially in the presence of ASCVD risk factors, asymptomatic atherosclerotic lesions begin at an early age.
- 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 any child ≥ 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 (eg, children who were adopted).
 - Moderate to high risk for premature ASCVD.
- Universal screening is recommended beginning at 9 to 11 years of age. If normal, screening should be repeated every 5 years throughout life.

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 without treatment
 - Diabetes mellitus (type 1 or 2)
 - Kawasaki disease with recurrent aneurysms
 - Postorthotopic heart transplant
 - Chronic renal disease
- Moderate ASCVD risk includes those with:
 - BMI in the 95th to 96th percentile
 - High blood pressure without 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 ≥ 85 th 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 factor 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 generally not recommended before 10 years of age, unless the patient with dyslipidemia (eg, FH) has ASCVD, a substantial family history of premature ASCVD, or the child has 1 or more high-risk conditions or multiple ASCVD risk factors.
- Treatment with a statin should be considered after a 6-month trial of lifestyle/diet management in children ≥ 10 years of age with an LDL-C ≥ 190 mg/dL, such as those with FH.
- Statins are the drug of choice for LDL-C lowering for those older than 10 years of age.
- Treatment with a statin should be considered after a 6-month trial of lifestyle/diet management in children ≥ 10 years of age with either of the following:
 - An LDL-C 160 to 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.
- Statin treatment of children <10 years of age is based upon the clinical judgment after careful review of ASCVD risk factors, current medications, medical conditions, potential benefits as well as short- and long-term side effects of treatment.
- All marketed statins, except pitavastatin, are approved by the FDA for use in children with FH when the LDL-C is >190 mg/dL or 160 mg/dL with 1 or more risk factors.
 - Pravastatin at ≥ 8 years of age.
 - All others (simvastatin, fluvastatin, lovastatin, atorvastatin and rosuvastatin) ≥ 10 years of age.

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, liver enzymes, and kidney blood testing
- Assessment of sexual maturation
- 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.
- Although not FDA-approved for use in youth < 18 years of age with a markedly elevated triglyceride level (ie, ≥ 500 mg/dL), omega-3 fatty acids, niacin, and fibric acid derivatives may be considered to prevent pancreatitis.

XII. DYSLIPIDEMIA IN SELECT POPULATIONS⁵⁸

Dyslipidemia and older individuals⁹²

ASCVD Risk in older individuals

- 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 65,⁹³ 75,⁹⁴ or 80^{58,95–98} 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.⁹⁹
- 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 often related to 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.

Clinical practice decisions

- The decision to initiate statin therapy in patients ≥ 75 years of age is based on all forms of evidence, including generalization from applicable clinical trials, via a “patient-centered” approach, and includes:
 - Benefit vs risk assessment
 - Comorbidities
 - Life expectancy
 - Quality of life considerations
 - Patient preferences
 - Tolerability of the statin (see the Statin Intolerance section)
 - Clinical judgment
 - Knowledge that continued statin therapy beyond age 75 years provides benefit in reducing ASCVD risk

Dyslipidemia and race/ethnicity⁹²

ASCVD risk assessment by race/ethnicity

- 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.^{100,101}
- 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.
- 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.¹⁰²
 - The QRISK is also ethnic specific (at least for the United Kingdom), and may be reliable for all of Western Europe.⁹⁶
- 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

- Compared with Caucasians, individuals of South Asian ancestry are at increased risk of atherosclerotic coronary heart disease.⁹²
- Asians are at increased risk for metabolic syndrome, insulin resistance, and adiposopathic dyslipidemia¹⁵ (sometimes called “atherogenic dyslipidemia”). 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.¹⁰³
- Compared with treatment of Caucasians at the same statin doses, Asians (especially well-studied in Japan) typically have increased statin levels.

African Americans

- Epidemiologically, African Americans⁹² 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 diabetes mellitus.
- Lp(a) levels may be higher with wider interindividual variations in African Americans compared with Caucasians.¹⁰⁴

Hispanics

- Hispanics⁹² 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.¹⁰⁵
- Mexican Americans reportedly have lower coronary heart disease mortality compared with European Americans.¹⁰⁶

Native Americans and Pima Indians

- In general, American Indians appear to have an increased incidence of ASCVD, possibly related to the high prevalence of diabetes mellitus and other ASCVD risk factors.^{107,108}

- Pima Indians 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.¹⁰⁹
- ASCVD risk among Pima Indians may not be as high as anticipated, based upon high prevalence of metabolic ASCVD risk factors found in Pima Indians.^{110,111}

Clinical practice decisions

Racial/ethnic groups and potential statin benefits

- When statins were studied in significant numbers of African American and Hispanic patients^{92,112,113}:
 - Rosuvastatin reduced ASCVD risk similarly between Caucasians and non-Whites.
 - Rosuvastatin reduced ASCVD risk similarly between Blacks and Hispanics.
- When statins were studied in Japanese patients:
 - Pravastatin 10 to 20 mg reduced ASCVD risk.¹¹⁴
 - When administered in combination with low-dose pravastatin and simvastatin, the omega-3 fatty acid eicosapentaenoic acid (EPA) reduced CHD events.¹¹⁵

Racial/ethnic groups and statin safety⁹²

- Caucasians, African Americans, and Hispanics appear to have similar rates of adverse experiences with statin therapy, except for diabetes mellitus, wherein African Americans and American Indians may be more likely to be diagnosed with incident diabetes mellitus than Whites.¹¹³
- At each dose of statins, LDL-C levels may be reduced more in Asians than Whites,¹¹⁶ likely because of genetic differences in statin metabolism wherein statin levels are higher for a given statin dose.¹¹⁶
- The US Prescribing Information for rosuvastatin recommends that Chinese and other Asian patients use caution with using rosuvastatin doses exceeding 20 mg per day and initiate rosuvastatin therapy at 5 mg per day in patients taking niacin ≥ 1 g/day.

Dyslipidemia and women⁹²

ASCVD risk in women

- ASCVD is the leading cause of mortality in women.^{117,118}
- 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. 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.¹¹⁹
- The use of some investigational and approved lipid-altering pharmacotherapies are contraindicated in women at risk of pregnancy (statins are pregnancy category X), thus disproportionately limiting the number of younger women as participants in ASCVD outcomes 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 in 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.^{118,119}
- 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.
- A notable exception would be the Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, wherein rosuvastatin administered to women (n=6801) with high-sensitivity C-reactive protein ≥ 2 mg/L and LDL-C levels <130 mg/dL had reduced ASCVD events compared to placebo.¹²²
- increases maternal lipoprotein levels, and increases 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 maternal triglycerides and body fat in early pregnancy may increase the risk of:
 - Preeclampsia
 - Future gestational diabetes mellitus
 - Large for gestational age infants
 - Induced preterm delivery
 - Stillbirth
- HDL-C levels and pregnancy:
 - Lower maternal HDL-C levels in early pregnancy may increase the risk for gestational diabetes mellitus.
 - Higher maternal HDL-C levels may be associated with lower rates of preterm birth.
- Both low (<10 th percentile) and high (>90 th 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 genetics that can affect stem cell fate and adversely affect postnatal biologic processes involved in substrate metabolism.
 - Increased risk of offspring obesity, offspring ASCVD risk factors, and offspring ASCVD premature mortality.¹²⁵
- Statins are not indicated in pregnant women (statins are category X).
- 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 (pregnancy category C) 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.

Dyslipidemia and pregnancy

- During early pregnancy, maternal metabolism and associated hyperphagia are mostly anabolic, increasing maternal fat stores.^{123,124}
- During the third trimester, maternal metabolism becomes more catabolic; therefore, to support fetal growth:
 - Maternal insulin resistance is increased and peripheral adipose tissue lipolysis is increased, which

- Other potential pharmacotherapies to prevent potentially life-threatening triglyceride-induced pancreatitis options include:
 - Niacin: prescription extended-release niacin is generally pregnancy category C
 - Metformin: generally pregnancy category B
 - Insulin: generally pregnancy category B or sometimes C

Polycystic ovary syndrome

- 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.^{126–128}
- 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.¹²⁹
- 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.¹²⁶
- In addition to improving dyslipidemia, statins may lower testosterone,¹³⁰ although this may not improve menstrual regularity, spontaneous ovulation, hirsutism, or acne among women with PCOS.¹³¹

Menopause

- Menopause is often believed to increase ASCVD risk. However:
 - Women have an ASCVD risk that increases linearly with aging.¹¹⁹
 - Menopause may be a surrogate for age.^{132,133}
 - Women often gain body fat and experience worsening dyslipidemia during and following the menopause transition,¹³⁴ similar to aging men.
- Although postmenopausal estrogen therapy may modestly lower LDL-C and raises HDL-C levels, estrogens may also increase triglycerides and high-sensitivity C-reactive protein^{135–137} 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.^{138–140}
- Postmenopausal hormone therapy should not be administered specifically to reduce ASCVD risk.

XIII. HEALTH INFORMATION TECHNOLOGY AND ELECTRONIC MEDICAL RECORDS: LIPID MANAGEMENT AND VALUE-BASED HEALTH CARE¹⁴¹

Overview¹⁴¹

- System barriers play a key role in lipid treatment gaps that contribute to the well-documented “quality chasm” in US health care, and to negative health and economic outcomes.
- Policymakers and payers have embarked on a “value-based health care agenda” with the primary aim to improve quality and reduce costs via incentives, accreditation, public reporting, and payment. Three principal functions frame the federal value-based health care agenda:
 - Establishment of aims and priorities for improving the quality of American health care (or the “National Quality Strategy”)
 - Identification and endorsement of quality metrics
 - Measurement and improvement of quality
- Improvement of health care delivery is best achieved within health care systems and models accountable for the health of an entire population of patients (ie, via population management). Fundamental to population management is a health information technology (HIT) infrastructure capable of measuring and reporting performance, and supporting quality improvement processes. Treatment of dyslipidemia is well-suited for a value-based health care agenda because:
 - The diagnosis and treatment of dyslipidemia has a major impact on health and economic outcomes for ASCVD, the number 1 cause of morbidity and mortality of both men and women.
 - Large numbers of patient populations are eligible for lipid-altering therapy.
 - Lipid-altering therapy is cost effective in reducing ASCVD risk.
 - Treatment of dyslipidemia can be measured by well-defined performance metrics, allowing for longitudinal tracking.

Quality aims and priorities related to lipid management¹⁴¹

- The National Quality Strategy was established by the Department of Health and Human Services in response to the Affordable Care Act (initially passed as law in 2010), and has 3 broad aims and 6 priorities for improving American health care.
- Among these is promotion of the most effective prevention and treatment practices for CVD, and the development and spread of new care delivery models. Improving lipid treatment within organized care systems is fully aligned with this strategy.

Identification and endorsement of quality measures related to lipid control

- To achieve the aims and priorities established by the National Quality Strategy, quality must be measurable and measured.¹⁴¹
- In a multistep process sponsored by the Centers for Medicare & Medicaid Services and the Agency for Healthcare Research and Quality:
 - Research identifies evidence of the need for improvement.
 - Measure developers provide test measures.
 - The National Quality Forum (a nonprofit, nonpartisan public service organization) then endorses measures based on specific criteria and that has endorsed 19 process and outcome measures related to lipid control across the spectrum of patients with cardiovascular disease or risk.
- Two key legislative acts have incentivized health systems, hospitals, and eligible professionals to use HIT to report quality measures, including those for lipid control:
 - The American Recovery and Reinvestment Act
 - Health Information Technology for Economic and Clinical Health Act
- Under these acts, those who engage in “meaningful use” of electronic health records, which includes quality reporting, are eligible for incentive payments from Centers for Medicare & Medicaid Services and commercial payers.
- Purchasers, quality oversight groups and certification boards are also engaged in quality measurement, especially of individual providers. For instance, health plans have their own quality measures, termed the Healthcare Effectiveness Data and Information Set (or HEDIS measures), which are developed by the National Committee for Quality Assurance.

Improving lipid treatment quality

- Even when tied to incentives, quality reporting and benchmarking are often insufficient to sustain performance improvement.¹⁴¹
- Specific interventions must be applied to close the quality improvement cycle, which can be facilitated by HIT and electronic tools. HIT interventions can be categorized by the principal end-user (ie, by the provider), the patient, and/or by system-wide teams.

Provider HIT tools

- Provider HIT tools for lipid management include computerized decision support in the form of alerts,

guideline and/or medication support, and risk calculators. Smartforms that link computerized decision support to computerized physician order entry and e-prescribing interfaces makes these interventions more “actionable.” Barriers include negative physician attitudes toward guidelines, alert “fatigue,” workflow interruptions, and lack of linkage to “action” tools. Electronic Health Records may provide a point-of-care tool that identifies cardiovascular registry patients with lipid care gaps and connects the provider to a “smart set” of orders for statin therapy, a follow up lipid panel, printable patient education, and web-based decision support. Quality dashboards allow providers to track outcomes in real-time.

Patient-level HIT tools

- Patient-level HIT tools for improving lipid outcomes include personal health records and portals, web-based education and risk factor monitoring, televideo conferencing, and mobile technologies. Secure websites allow insured members to view their own lipid panels, view their “personal action plan” and securely exchange messages with their providers. Current data show improved LDL screening and control. These data provide strong evidence that patient-level HIT interventions provide significant leverage for closing lipid treatment gaps, with more patients achieving treatment goals.

System-level HIT tools

- System-level HIT tools for lipid management include monitoring by non-physicians of databases and registries for care gaps, followed by outreach via phone, mail, e-mail, or an electronic device, with varying degrees of primary physician involvement. Large, integrated health care systems have systematized data-based monitoring of lipid care gaps, outreach by multidisciplinary care teams and/or pharmacists, and “in-reach” by receptionists who remind visiting patients to undergo lipid testing in response to electronic “prompts.”

Improving lipid medication adherence: where individual and system factors overlap

- 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.¹⁴¹

- 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 only using these to guide interventions for improving adherence fails to target many.
- 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 being used by integrated health care systems to improve medication adherence.

XIV. INVESTIGATIONAL LIPID-ALTERING AGENTS IN DEVELOPMENT 2015 (Table 1)

Table 1 Brief summary of lipid-altering pharmacotherapies in development

Class of agent and mechanism of action	Name	Manufacturer	Sample references and/or Clinical Trials.gov Identifiers	Sentinel, reported safety/tolerability findings	Sentinel lipid effects
Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors	Alirocumab	Regeneron/Sanofi	142,143	Rare injection site reactions, with most cases being mild	>50% reduction in LDL-C and non-HDL-C levels
	Evolocumab	Amgen	144-146		
	Bococizumab	Pfizer (RN316)	NCT01243151		
	LY3015014	Lilly	NCT01426412		
	ALN-PCS	Alnylam and the Medicines Company	147		
Dual modulator of adenosine triphosphate-citrate lyase and adenosine monophosphate-activated kinase	ETC-1002	Esperion	148	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	149,150	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
	Evacetrapib	Lilly	151	Generally well tolerated with no increase in blood pressure	
Diacylglycerol acyltransferase-1 (DGAT-1) inhibitor	Pradigastat	Novartis (LCQ908)	NCT01514461*	Transient diarrhea and other gastrointestinal adverse experiences	Lowers triglyceride and other lipid levels, HbA1c, and body weight
Antisense Apo C3 inhibitor	Isis-APO CIII Rx	Isis	†	Injection site reactions	Up to 77% reduction in triglyceride levels
Botanic extract from red yeast Chinese rice with multiple components, some having statin-like activity	ZueZhiKang	Beijing Peking University WBL Biotech Co. (WPU)	152,153 NCT01327014	156	Lowers cholesterol

(continued on next page)

Table 1 (continued)

Class of agent and mechanism of action	Name	Manufacturer	Sample references and/or Clinical Trials.gov Identifiers	Sentinel, reported safety/ tolerability findings	Sentinel lipid effects
Structurally enhanced omega-3 fatty acid	Icosabutate (PRC-4016)	Pronova Biopharm	NCT01972178	Not reported	May reduce triglyceride and have other lipid effects
Niacin analogue	ARI-3037MO	Arisaph	NCT02250105	Not reported	May reduce triglyceride and have other lipid effects

*Abstract: <https://www.lipid.org/util/eposters/PDF/107.pdf>. Lise Kjems, Charles Daniel Meyers, Tom Thuren. Diacylglycerol Acyltransferase 1 (DGAT1) Inhibition as a Metabolic Regulator: Clinical Benefits of Pradigastat in Obese Patients With Type 2 Diabetes. Poster 107 presented at 2014 NLA Annual Scientific Sessions, Orlando, Florida, May 1-4, 2014.

†Abstract: Vickie Alexander, Trish Novak, Nicholas Viney, John Su, Jennifer Burkey, Walter Singleton, Richard Geary, Isis Pharmaceuticals, Inc, Carlsbad, CA, USA. An Antisense Inhibitor of Apolipoprotein C-III Lowers Fasting Plasma Apolipoprotein C-III and Triglyceride Concentrations in Healthy Volunteers. ACC Moderated Poster Contributions. McCormick Place South, Hall A, Sunday, March 25, 2012, 9:30 a.m.-10:30. E1685JACC March 27, 2012 Volume 59, Issue 13. a.m. Session Title: Prevention: Clinical: Current Research in Lipidology Abstract Category: 9. Prevention: Clinical Presentation Number: 1190-529.

APPENDIX A: National Lipid Association (NLA) Annual Summary of Clinical Lipidology 2015: Tables, Figures, and Hyperlinks

Section of this NLA Annual Summary	Table/figure number and title description as found in the original publication and hyperlink	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	
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	Table 10. Sequential steps in ASCVD risk assessment	1	
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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		8	
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	*	
Medical Nutrition Therapy	Table 8. Nutritional content, characteristics and diseases/disorders/ altered metabolic states that may elevate LDL-C and/or triglyceride concentrations	*	

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	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	15
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	Table 11. Non-weight management pharmaceuticals that that may affect body weight.	*
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Statin & Non-Statin Pharmacotherapy	Table 3. Focus on ASCVD risk reduction: 4 statin benefit groups	58
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Lipid-Altering Drug Prescribing Information	Atorvastatin: http://labeling.pfizer.com/ShowLabeling.aspx?id=587	NA
	Simvastatin: http://www.merck.com/product/usa/pi_circulars/z/zocor/zocor_pi.pdf	NA
	Pravastatin: http://packageinserts.bms.com/pi/pi_pravachol.pdf	NA
	Fluvastatin: https://www.pharma.us.novartis.com/product/pi/pdf/Lescol.pdf	NA
	Mevacor: 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
	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
	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
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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	

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	Figure 2. Comprehensive approach to patients with elevated liver blood testing (transaminases >3 times the upper limits of normal) (page S55)	74	
	Figure 1. Evaluation of the patient with cognitive symptom (page S12)	74	
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	Statin safety: Diabetes mellitus	Table 1. Criteria for screening for prediabetes and diabetes before or concurrent with initiation of statin therapy (page S23)	74
		Table 2. Criteria for the diagnosis of prediabetes and diabetes (page S26)	74
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	Table 1. National Quality Forum-endorsed lipid measures	141	
	Table 4. Determinants of adherence/non-adherence and persistence/poor persistence	141	

NA, not applicable

*Online NLA Resource Center.

Journal of Clinical Lipidology Electronic Resources
(accessible at www.lipid.org) 2015

E1 National Lipid Association Position Statements and Hyperlinks

[2014 National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1 – executive summary.](#)

[2014 Statin Safety 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/practicetools/operations_manual)

Coding and reimbursement

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

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To view the disclosures of each author and reviewer, visit www.lipid.org/2015compendiumdisclosures.

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