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National Lipid Association Recommendations - Part 2

National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 2

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Adherence;
Team-based care

Abstract: An Expert Panel convened by the National Lipid Association previously developed a consensus set of recommendations for the patient-centered management of dyslipidemia in clinical medicine (part 1). These were guided by the principle that reducing elevated levels of atherogenic cholesterol (non–high-density lipoprotein cholesterol and low-density lipoprotein cholesterol) reduces the risk for atherosclerotic cardiovascular disease. This document represents a continuation of the National Lipid Association recommendations developed by a diverse panel of experts who examined the evidence base and provided recommendations regarding the following topics: (1) lifestyle therapies; (2) groups with special considerations, including children and adolescents, women, older patients, certain ethnic and racial groups, patients infected with human immunodeficiency virus, patients with rheumatoid arthritis, and patients with residual risk despite statin and lifestyle therapies; and (3) strategies to improve patient outcomes by increasing adherence and using team-based collaborative care.

Introduction

In 2014, the National Lipid Association (NLA) convened an Expert Panel to develop a consensus set of recommendations for the patient-centered management of dyslipidemia (Part 1).[1] The evidence base used was derived from randomized controlled trials (RCTs), meta-analyses of results from RCTs, and review of results from observational, genetic, metabolic, and mechanistic studies. Based on the totality of evidence, the Part 1 NLA Recommendations for Patient-Centered Management of Dyslipidemia laid out several conclusions and core principles.

1. An elevated level of cholesterol carried by circulating apolipoprotein (apo) B-containing lipoproteins (non-high-density lipoprotein cholesterol [non-HDL-C] and low-density lipoprotein cholesterol [LDL-C], termed *atherogenic cholesterol*) is a root cause of atherosclerosis, the key underlying process contributing to most clinical atherosclerotic cardiovascular disease (ASCVD) events;
2. Reducing elevated levels of atherogenic cholesterol will lower ASCVD risk in proportion to the extent that atherogenic cholesterol is reduced;
3. The intensity of risk-reduction therapy should generally be adjusted to the patient's absolute risk for an ASCVD event;
4. Atherosclerosis is a process that often begins early in life and progresses for decades before resulting in a clinical ASCVD event. Therefore, both intermediate-term and long-term/lifetime risk should be considered when assessing the potential benefits and hazards of risk-reduction therapies;
5. For patients in whom lipid-lowering drug therapy is indicated, statin treatment is the primary modality for reducing ASCVD risk;
6. Treatment goals and periodic monitoring of atherogenic cholesterol levels (non-HDL-C and LDL-C) are important tools in the implementation of a successful treatment strategy. These aid the clinician in assessing the adequacy of treatment and facilitate active participation by the patient through feedback and reinforcement of the beneficial effects of lifestyle and pharmaceutical therapies; and
7. Non-lipid ASCVD risk factors should also be managed appropriately, particularly high blood pressure, cigarette smoking, and diabetes mellitus.

The NLA Part 1 Recommendations emphasize the importance of taking a *patient-centered* approach in counseling patients about the benefits and hazards of lifestyle and drug therapies. Using the principle of shared decision making, the patient should be an active participant in the process, engaging with the clinician in a dialogue about the objectives and potential benefits of therapy, as well as risks, side effects, and costs. The initial step is a determination of the patient's risk for an ASCVD event (Table 1).[1] Lifestyle counseling is a key element of preventive efforts at all levels of risk, and dietary adjuncts may be used to enhance atherogenic cholesterol reduction. If lifestyle therapies, including dietary adjuncts, are insufficient to achieve desired levels of atherogenic cholesterol, evidence-based drug therapy, particularly moderate- to high-intensity statin therapy should be considered. If goal levels of atherogenic cholesterol are not achieved with maximally tolerated statin therapy, combining a statin with a second (and sometimes a third) agent may be considered for selected patients. Alternative strategies may be needed for patients who are statin intolerant, or who prefer not to use statin therapy. Lastly, regular patient and lipid follow-up is warranted to assess adherence and adequacy of the atherogenic cholesterol responses to therapy.

NLA Part 2 recommendations

The creation of the NLA Part 2 Recommendations for Patient-Centered Management of Dyslipidemia was intended to expand upon the NLA Part 1 Recommendations in areas where clinicians may desire additional guidance, particularly where the evidence base is less robust or is

Table 1 NLA Part 1 Recommendations for Patient-Centered Management of Dyslipidemia–Criteria for ASCVD risk assessment, treatment goals for atherogenic cholesterol, and levels at which to consider drug therapy

		Treatment goal	Consider drug therapy
Risk category	Criteria	Non–HDL-C, mg/dL LDL-C, mg/dL	Non–HDL-C, mg/dL LDL-C, mg/dL
Low	• 0–1 major ASCVD risk factors • Consider other risk indicators, if known	<130 <100	≥190 ≥160
Moderate	• 2 major ASCVD risk factors • Consider quantitative risk scoring • Consider other risk indicators*	<130 <100	≥160 ≥130
High	• ≥3 major ASCVD risk factors • Diabetes mellitus (type 1 or 2)† ○ 0–1 other major ASCVD risk factors and ○ No evidence of end-organ damage • Chronic kidney disease stage 3B or 4‡ • LDL-C of ≥190 mg/dL (severe hypercholesterolemia)§ • Quantitative risk score reaching the high-risk threshold‖	<130 <100	≥130 ≥100
Very high	• ASCVD • Diabetes mellitus (type 1 or 2) ○ ≥2 other major ASCVD risk factors or ○ Evidence of end-organ damage¶	<100 <70	≥100 ≥70

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

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

Taken from Jacobson TA, et al. *J Clin Lipidol*. 2015;9:129–169.[1]

*For those at moderate risk, additional testing may be considered for some patients to assist with decisions about risk stratification.

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

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

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

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

¶End-organ damage indicated by increased albumin-to-creatinine ratio (≥30 mg/g), CKD (eGFR, <60 mL/min/1.73 m^2), or retinopathy.

lacking results from RCTs on clinical ASCVD events to guide clinical decisions. Based on feedback from NLA members and other important stakeholders, several major content areas were identified for inclusion.

1. Lifestyle therapies–nutrition and exercise/physical activity;
2. Groups with special considerations that span the lifespan from children to seniors and from pregnancy to menopause;
3. Ethnic groups including Hispanics/Latinos, African Americans (AAs), South Asians (SAs), and American Indians (AIs)/Alaska Natives (ANs);
4. Groups with increased ASCVD risk, including patients with human immunodeficiency virus (HIV), rheumatologic disease, and those with high residual risk despite statin and lifestyle therapies; and
5. Strategies to improve patient outcomes centered on improving adherence and maximizing team-based collaborative care.

NLA Part 2 represents a continuation of previous NLA recommendations developed by a diverse and interdisciplinary panel of experts. The process began with appointment of an executive Steering Committee. Section Chairs and Expert Panel members with expertise in core topic

Table 2 NLA Part 2 Recommendations for Patient-Centered Management of Dyslipidemia–Expert Panel

NLA expert panel steering committee members
Terry A. Jacobson, MD, FNLA, *Chair*; Kevin C. Maki, PhD, CLS, FNLA; Carl Orringer, MD, FNLA; Peter Jones, MD, FNLA

I. Lifestyle therapies section
Nutrition
Penny Kris-Etherton, PhD, RDN, CLS, FNLA, *Co-Chair*; Geeta Sikand, MA, RDN, CLS, FNLA, *Co-Chair*; Kevin C. Maki, PhD, CLS, FNLA, *Co-Chair*; Julie Bolick, MS, RDN, CLS, FNLA; Mary R. Dicklin, PhD; Carol Kirkpatrick, PhD, RDN, CLS, FNLA; Katherine Rhodes, PhD, RDN; Nancy T. Smith, MS, RDN, CDE, CLS
Exercise
Ralph La Forge, MSc, FNLA, *Chair*; Kevin C. Maki, PhD, FNLA

II. The lifespan—children to seniors section
Children and adolescents
Stephen Daniels, MD, PhD, FNLA, *Co-Chair*; Don Wilson, MD, FNLA, *Co-Chair*; Piers Blackett, MD, FNLA; Sarah DeFerranti, MD; Samuel Gidding MD, FNLA; Rae-Ellen W. Kavey, MD, MPH; Brian McCrindle, MD; Catherine McNeal, MD, PhD, FNLA; Elaine Urbina, MD
Women's health
Pamela Morris, MD, FNLA, *Chair*
From pregnancy to menopause
Robert Wild, MD, MPH, PhD, FNLA, NCMP, *Chair*; Thomas Dayspring, MD, FNLA, NCMP; James A. Underberg, MS, MD, FNLA
Older patients
Carl Orringer, MD, FNLA, *Co-Chair*; Scott Grundy, MD, PhD, FNLA, *Co-Chair*; Joyce Ross, MSN, CRNP, FNLA

III. Ethnic and racial groups section
Hispanics/Latinos
Martha Daviglus, MD, PhD, *Chair*; J Antonio G. Lopez, MD, FNLA; Amber Pirzada, MD; Carlos Jose Rodriguez, MD, MPH, FACC
African Americans
Keith Ferdinand, MD, FNLA, *Chair*
South Asians
Kris Vijay, MD, FNLA, *Co-Chair*; Prakash Deedwania, MD, *Co-Chair*
American Indians/Alaska Natives
Kevin C. Maki, PhD, FNLA, *Co-Chair*; Ralph La Forge, MSc, FNLA, *Co-Chair*

IV. High-risk conditions and residual risk section
HIV-infected persons
Judith Aberg, MD, *Chair*; Carl J. Fichtenbaum, MD; Joel E. Gallant, MD; Michael A. Horberg, MD; Christopher T. Longenecker, MD; Merle Myerson, MD, FNLA; E. Turner Overton, MD
Patients with rheumatoid arthritis
Katherine Liao, MD, MPH, *Chair*; Jonathon S. Coblyn, MD; Jeffrey Curtis, MD, MS, MPH; Jorge Plutzky, MD, FNLA; Daniel Solomon, MD, MPH
Patients with residual risk despite statin and lifestyle therapy
Peter Jones, MD, FNLA, *Co-Chair*; James McKenney, PharmD, FNLA, *Co-Chair*

V. Improving patient outcomes section
Patient adherence
Joyce Ross, MSN, CRNP, FNLA, *Co-Chair*; Lynne Braun, PhD, CNP, FNLA, *Co-Chair*
Team-based collaborative care
Lynne Braun, PhD, CNP, FNLA, *Co-Chair*; Matthew Ito, PharmD, FNLA, *Co-Chair*; Joyce Ross, MSN, CRNP, FNLA, *Co-Chair*

VI. Additional general panel members
Harold Bays, MD, FNLA; W. Virgil Brown, MD, FNLA

HIV, human immunodeficiency virus; NLA, National Lipid Association.

areas were identified and approved by the Steering Committee (Table 2). After an initial draft of the consensus recommendations was compiled, this was made available to the public for an open comment period. Input was solicited from stakeholders, including the general public, NLA members, other professional societies, and governmental agencies. Comments and suggestions were then collated for adjudication by the NLA Expert Panel members, and final recommendations were presented to the NLA Board for approval.

Table 3 Grading of the strength of recommendations and quality of evidence

Evidence grading: strength of recommendation*	
Grade	Strength of recommendation
A	**Strong recommendation** There is high certainty based on the evidence that the net benefit† is substantial
B	**Moderate recommendation** There is moderate certainty based on the evidence that the net benefit is moderate to substantial, or there is high certainty that the net benefit is moderate
C	**Weak recommendation** There is at least moderate certainty based on the evidence that there is a small net benefit
D	**Recommend against** There is at least moderate certainty based on the evidence that it has no net benefit or that the risks/harms outweigh benefits
E	**Expert opinion** There is insufficient evidence or evidence is unclear or conflicting, but this is what the expert panel recommends
N	**No recommendation for or against** There is insufficient evidence or evidence is unclear or conflicting

Evidence grading: quality of evidence	
Type of evidence	Quality rating‡
Well-designed, well-executed RCTs that adequately represent populations to which the results are applied and directly assess effects on health outcomes Well-conducted meta-analyses of such studies Highly certain about the estimate of effect; further research is unlikely to change our confidence in the estimate of effect	High
RCTs with minor limitations affecting confidence in, or applicability of, the results Well-designed, well-executed nonrandomized controlled studies and well-designed, well-executed observational studies Well-conducted meta-analyses of such studies Moderately certain about the estimate of effect; further research may have an impact on our confidence in the estimate of effect and may change the estimate	Moderate
RCTs with major limitations Nonrandomized controlled studies and observational studies with major limitations affecting confidence in, or applicability of, the results Uncontrolled clinical observations without an appropriate comparison group (eg, case series, case reports) Physiological studies in humans Meta-analyses of such studies Low certainty about the estimate of effect; further research is likely to have an impact on our confidence in the estimate of effect and is likely to change the estimate	Low

RCT, randomized controlled trial.

This was the system used in the new American Heart Association/American College of Cardiology cholesterol guidelines[3] that were published in the 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults Report from the Panel members appointed to the Eighth Joint National Committee.[3]

*The system was adapted as a hybrid of the National Heart Lung and Blood Institutes (NHLBI) rating System (NHLBI cardiovascular-based methodology) used in thè new American Heart Association/American College of Cardiology cholesterol guidelines[3] and adapted from the original GRADE system of evidence rating.[4]

†Net benefit is defined as benefits minus risks/harms of the service/intervention.

‡The evidence quality rating system used in this guideline was developed by the National Heart Lung, and Blood Institute's (NHLBI's) Evidence-Based Methodology Lead (with input from NHLBI staff, external methodology team, and guideline panels and work groups) for use by all the NHLBI cardiovascular disease guideline panels and work groups during this project. As a result, it includes the evidence quality rating for many types of studies, including studies that were not used in this guideline.

Permission to reuse table granted from the American Medical Association.[3]

Taken from Jacobson TA, et al. *J Clin Lipidol*. 2015;9:129–169.[1] Originally published in James PA, et al. *JAMA*. 2014;311:507–520 and Stone NJ, et al. *J Am Coll Cardiol*. 2014;63(25 Pt B):2889–2934.[2,3]

The NLA Expert Panel graded the recommendations using an adapted grading system from both the National Heart, Lung, and Blood Institute's Evidence-Based Methodology Team[2,3] and the Grading of Recommendations Assessment, Development and Evaluation system of evidence rating (Table 3).[4] For each recommendation, the

strength of the recommendation was assigned, with consideration given to the "net benefit" after taking into account potential benefits and risks or harms associated with the service or intervention. The quality of the evidence rating was determined using the rating system developed by the National Heart, Lung, and Blood Institute's Evidence-Based Methodology Panel, as published in the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults.[3]

Lifestyle therapies

Lifestyle therapies are central to dyslipidemia management and should be advised for all patients, whether or not drug therapy is also prescribed. As outlined in Part 1 of the NLA Recommendations for Patient-Centered Management of Dyslipidemia,[1] a trial of lifestyle therapies should be attempted prior to use of drug therapy for most patients. Exceptions include patients at very high or high risk for whom clinicians may wish to simultaneously begin lifestyle and drug therapies.

Targets of lifestyle therapies and rationale for their use

The targets of lifestyle therapies will principally be levels of atherogenic cholesterol, which include LDL-C and non-HDL-C. The non-HDL-C concentration is comprised mainly of LDL-C and very low-density lipoprotein cholesterol (VLDL-C) levels. VLDL-C concentration is highly correlated with the circulating level of triglycerides (TG). The TG level per se is not a recommended target of therapy, except when very high (≥500 mg/dL). In these patients, lowering the TG concentration to <500 mg/dL is the primary objective of therapy to reduce the risk of acute pancreatitis. When the TG level is < 500 mg/dL, attaining goal levels of atherogenic cholesterol is the main objective of therapy. High-density lipoprotein cholesterol (HDL-C) is not a target of therapy, although low HDL-C is a strong predictor of ASCVD event risk. Lifestyle changes that lower levels of atherogenic cholesterol often alter HDL-C, but the clinical relevance of these changes is uncertain at present. Additional targets of lifestyle interventions include excess adiposity for those who are overweight or obese, and other ASCVD risk factors, such as elevated blood pressure, hyperglycemia (and diabetes), and smoking. The focus of the evidence summarized below is on the influence of lifestyle interventions on lipoprotein lipid levels, but clinicians should be aware that changes in other risk factors contribute to ASCVD risk.[1]

Limited evidence is available from randomized clinical trials to assess the impacts of lifestyle therapies on ASCVD event risk. However, evidence from epidemiologic studies consistently supports a strong relationship between circulating levels of atherogenic cholesterol and ASCVD event risk.[1,5,6] In particular, studies of genetic variants that influence LDL-C and VLDL-C levels show that even relatively small differences in these lipoprotein lipid levels are associated with changes in ASCVD event risk.[7–9] Moreover, the differences in ASCVD risk for a given difference in atherogenic cholesterol level produced by genetic variants is larger than would be predicted from RCTs of lipid-altering drug therapies.[7,8,10,11] In RCTs, each reduction of 1% in LDL-C or non-HDL-C is associated with a 1% reduction in coronary heart disease (CHD) event risk over a period of ~5 years.[12,13] Genetic variants that alter LDL-C have a stronger association with CHD event risk than would be predicted based on RCT results, generally showing that each 1% difference in LDL-C induced by genetic variants is associated with a 2–3% difference in CHD risk.[10,11] These findings are consistent with the hypothesis that relatively small differences in levels of atherogenic cholesterol have important impacts on ASCVD risk if maintained over an extended period. They also suggest that results from intervention studies lasting only ~5 years likely underestimate the potential benefit of decades-long exposure to lower levels of atherogenic lipoprotein cholesterol levels.

Genetic variants that alter VLDL-C, without affecting LDL-C, are also associated with differences in ASCVD event risk. The magnitude of the differences observed with genetically induced differences in VLDL-C are at least as large as those associated with differences in LDL-C for a given mg/dL difference.[9,14] For example, in the Copenhagen Heart Studies, each 38.7 mg/dL (1 mmol/L) difference in LDL-C was associated with a 47% difference in CHD event risk. However, each 38.7 mg/dL (1 mmol/L) difference in VLDL-C (referred to as remnant cholesterol by the investigators) was associated with a CHD risk difference of 182%.[9] These findings are consistent with a causal role for VLDL-C (or some variable closely correlated with VLDL-C) in ASCVD event risk, and support the importance of both LDL-C and non-HDL-C (the sum of LDL-C and VLDL-C) as targets of therapy.

In addition to strong and consistent associations in observational studies between levels of atherogenic cholesterol and ASCVD event risk, the diet and lifestyle patterns recommended based on their ability to lower levels of atherogenic cholesterol in RCTs have also been associated with lower ASCVD risk in observational studies.[15–17] These findings are almost certainly explained in part by associations with major ASCVD risk factors, such as lipoprotein lipid and blood pressure levels. However, the recommended lifestyle patterns have also been linked with potentially favorable differences in emerging and non-traditional ASCVD risk factors, including markers of insulin resistance, inflammation, thrombogenicity, and oxidative stress.[18] Therefore, clinicians should be aware that effective lifestyle therapies elicit changes in biochemical parameters with potential clinical relevance beyond those that are typically measured in clinical practice.

Counseling on implementation of lifestyle changes

Patients with dyslipidemia, metabolic syndrome, overweight or obesity should be referred for lifestyle modification counseling whenever possible. A registered dietitian nutritionist plays an important role in counseling the patient to develop and implement an individualized cardioprotective eating plan (i.e., medical nutrition therapy [MNT] for dyslipidemia). Other health professionals, such as an exercise specialist, behavioral health specialist, social worker and/or psychologist, also are important in achieving physical activity/exercise goals, stress management, identification and management of triggers for unhealthy eating patterns, and tobacco cessation.

General principles for a healthy lifestyle

The 2010 Dietary Guidelines for Americans (DGA) present general principles for a healthy lifestyle.[19] They emphasize a balance between energy intake and expenditure to maintain a healthy body weight. This includes controlling energy intake to avoid weight gain and assist with weight loss in overweight/obese persons, maintaining adequate physical activity, and minimizing time spent in sedentary behaviors as also recommended by the American College of Sports Medicine[20] and the American Council on Exercise.[21] The DGA also emphasize avoiding excessive sodium intake, limiting consumption of energy from saturated fats, *trans* fats, added sugars, refined grains, and for adults who choose to consume alcohol, to do so in moderation. The DGA emphasize consuming fruits and vegetables; nuts, peas and legumes; whole grains; lean sources of protein; low-fat or fat-free dairy products; seafood; and liquid vegetable oils. Recommended macronutrient ranges for adults are 45–65% of energy from carbohydrate, 10–35% from protein, and 20–35% of energy from fat. As of this writing, the 2015 DGA had not yet been released, but the 2015 Dietary Guidelines Advisory Committee's (DGAC) Scientific Report recommended removal of the upper limit for dietary fat to allow greater flexibility, particularly with regard to reducing intakes of cholesterol-raising (12–16 carbon saturated and *trans* unsaturated) fatty acids and refined grains and sugars.[22] In place of these dietary components, greater emphasis is placed on increasing consumption of foods containing unsaturated fatty acids, such as nuts and liquid vegetable oils.[22]

Lifestyle therapies for dyslipidemia management

The NLA Expert Panel recommends lifestyle therapies as an integral component of treatment plans for management of dyslipidemia and ASCVD event risk reduction at all levels of risk. For lowering levels of atherogenic cholesterol, the main features include a cardioprotective dietary pattern low in cholesterol-raising fatty acids (<7% of energy from saturated fatty acids and minimal intake of *trans* unsaturated fatty acids) and dietary cholesterol (<200 mg/day), as well as regular physical activity (at least 150 min per week of moderate or higher intensity activity). Dietary adjuncts, including plant sterols/stanols and viscous fibers, may be used to enhance the reductions in atherogenic cholesterol. Energy restriction and further increases in physical activity are recommended for overweight or obese patients for whom weight loss and additional reductions in atherogenic cholesterol levels are desired. These lifestyle interventions should be implemented within the general principles outlined above from the 2010 DGA. Reviews of the evidence in support of specific recommendations and additional details about their implementation are outlined below.

Nutrition

Dietary patterns to reduce risk of ASCVD

The focus of much contemporary nutrition research is on dietary patterns because they represent the totality of the diet, including the myriad of combinations and quantities of foods and nutrients that are consumed.[23] There is evidence that particular dietary patterns, as well as specific nutrients (and also physical activity), play significant roles in the prevention and treatment of ASCVD by beneficially modifying major ASCVD risk factors, particularly lipoprotein lipids and blood pressure.[24]

Recommended dietary patterns share many characteristics. For example, the 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk[24] made the following recommendation, which is similar to other recommended diets (described below):

> Advise adults who would benefit from LDL-C lowering to consume a dietary pattern that emphasizes intake of vegetables, fruits and whole grains; includes low-fat dairy products, poultry, fish, legumes, non-tropical vegetable oils and nuts; and limits intakes of sweets, sugar-sweetened beverages and red meats. The dietary patterns that are recommended and representative of these foods/food groups are the DASH dietary pattern, the USDA Food Pattern, or the AHA diet. These recommended dietary patterns provide 5–6% of calories from saturated fat and are low in trans fats.

Dietary Approaches to Stop Hypertension (DASH) dietary patterns

The DASH dietary pattern emphasizes consumption of vegetables, fruits, and low-fat milk and dairy products; includes whole grains, poultry, seafood, and nuts; and is lower in sodium, red and processed meats, sweets, and sugar-containing beverages (e.g., soda, juice drinks). The DASH dietary pattern assessed in the initial DASH RCTs provides approximately 27% of calories from total fat (6% saturated fatty acids, 13% monounsaturated fatty acids [MUFA], 8% polyunsaturated fatty acids [PUFA]), 58% of calories from carbohydrate, and 15% of calories from

protein.[25,26] Two DASH dietary pattern variations include replacing 10% of total energy from carbohydrate with either protein or unsaturated fat.[27]

United States Department of Agriculture (USDA) food patterns

The USDA food patterns recommend daily amounts of foods from the 5 major food groups (vegetables, fruits, grains, dairy products, and protein foods).[19] The patterns include an allowance for liquid vegetable oils (and spreads made from liquid vegetable oils) and limitations on the quantity of calories consumed from solid fats and added sugars.

AHA diet patterns

The AHA diet patterns[24,28] recommend balancing energy intake and physical activity to achieve and maintain a healthy body weight; consuming a diet rich in vegetables and fruits; choosing whole-grain, high-fiber foods; consuming fish, especially oily fish, at least twice a week; and limiting intake of saturated fat, *trans* (partially hydrogenated) fat, and cholesterol by choosing lean meats and non-meat alternatives and fat-free (skim) or low-fat (1% fat) dairy products. The AHA diet patterns further recommend minimizing intake of beverages and foods with added sugars and salt, and suggest that, if alcohol is consumed, this should be done in moderation (and only by adults of legal drinking age).

The 2015 DGAC Scientific Report

The 2015 DGAC[23] evaluated 3 dietary patterns, all of which have been associated with health benefits. These are the healthy US.-style pattern, the healthy Mediterranean-style pattern, and the healthy vegetarian pattern. These have similar food-based characteristics to those defined by the 2013 AHA/ACC Guideline on Lifestyle Management and, compared to the average American diet, are higher in vegetables, fruits, and whole grains; low- or non-fat dairy; seafood, legumes, and nuts; moderate in alcohol (for adults); lower in red and processed meats; and low in sugar-sweetened foods/drinks and refined grains. The Committee specified that: "A healthy diet can be achieved in multiple ways and preferably with a wide variety of foods and beverages. Optimal nutrition can be attained with many dietary patterns and a single dietary pattern or approach or prescription is unnecessary."

In addition, food-based recommendations for a traditional Mediterranean diet (from both Greece and Spain) were presented, which underscores the fact that this dietary pattern encompasses a wide range in cultures and food production practices in countries that border the Mediterranean Sea. Thus, the "Mediterranean diet" is not one "standard" eating pattern. Nonetheless, as is the case for the dietary patterns summarized previously, it emphasizes consumption of vegetables, fruits and nuts, and whole grains. A unique attribute is a focus on olive oil. Small amounts of meats and cheese are included routinely.

It should also be noted that there are several Asian dietary patterns, such as the traditional Japanese and Okinawan diets that have been associated with a low risk of CHD. However, there is limited information available about the composition of Asian diets, and evidence of their health benefits compared with other recommended dietary patterns also is limited. Despite this, the recommended food-based dietary patterns can be applied to a healthy Asian eating pattern.

Vegetarian and semi-vegetarian dietary patterns

There are various vegetarian dietary patterns including: an ovo-vegetarian diet that includes eggs; a lacto-vegetarian diet, which includes dairy products; a vegan diet, which is free of all meats, eggs and dairy products; a raw vegan diet, which includes only fresh and uncooked foods; a macrobiotic diet (pesco-vegetarian) that includes fish, but no other meats; and a semi-vegetarian diet, which occasionally includes meats; as well as combinations of the above. The therapeutic vegetarian dietary patterns most studied are the portfolio diet[29]; a very-low-fat vegetarian diet, such as the Ornish Plan with $<10\%$ of energy from fat[30,31]; and low-fat vegan diet plans.[32,33]

Associations of dietary patterns with ASCVD risk

DASH dietary pattern and USDA food pattern

The recommended dietary patterns were based on the precept of reducing chronic disease risk (including ASCVD risk) and promoting health. Two papers reported the health benefits associated with different dietary patterns in several large cohorts (Multiethnic Cohort, National Institutes of Health-American Association of Retired Persons Diet and Health Study, and the Women's Health Initiative Observational Study).[34–36] In both reports, the dietary patterns evaluated were the Healthy Eating Index 2010 (representative of the USDA dietary pattern), the Alternative Healthy Eating Index 2010 (representative of the AHA dietary pattern), the Mediterranean-style dietary pattern, and the DASH dietary pattern. The healthy eating indexes used in these studies were based on the 2010 DGA, with adaptations made based on dietary patterns consistently associated with lower risk of chronic diseases. The Mediterranean-style dietary pattern is an adaptation of the traditional Mediterranean diet defined by Trichopoulou et al.[37]

Harmon et al.[35] found that higher diet quality scores on each of the indexes were associated with 11 to 26% lower risks of mortality from all causes, as well as cardiovascular and cancer mortality for both men and women. In the report by Liese et al.,[36] in women, high diet quality was associated with an 18 to 26% lower risk of all-cause mortality, a 19 to 28% lower risk of cardiovascular mortality, and an 11 to 23% lower risk of cancer mortality. In men, the risk reductions associated with high diet quality were 17 to 25% for all-cause mortality, 14 to 26% for cardiovascular mortality, and 19 to 24% for cancer mortality. Similar findings have been reported recently in the Southern Community Cohort

Study of low socioeconomic status AAs.[38] Participants with the healthiest diets (in the top one-fifth of the Healthy Eating Index 2010 score) had approximately 20% lower risk of total mortality, and death from cancer and CVD were lower compared with individuals consuming the unhealthiest (bottom-fifth) diets. These studies provide evidence that a variety of healthy dietary patterns (albeit patterns that share many common foods and nutrient profiles) confer health benefits in diverse cohorts.

In other analyses of the health effects of the DASH-style dietary pattern, results have consistently shown associations with lower risks for CVD. For example, in the Nurses' Health Study, Fung et al.[39] reported that, in the highest quintile of the DASH dietary score, there was a significant decrease in relative risk (RR) of CHD by 24% and stroke by 18%. In the Third National Health and Nutrition Examination Survey (NHANES), Parikh et al.[40] reported that consumption of a DASH-like diet was associated with a significantly lower mortality from all causes (31%) and decreased risk of stroke (89%) in adults with hypertension.

In an analysis of NHANES 2007–2010 data of 11,296 men and women using the 2005 Healthy Eating Index scores, consumption of AHA Heart-Check Food Certification Program-certifiable foods was positively associated with diet quality, and inversely associated with cardiometabolic risk factors.[41] Compared to the lowest quartile of diet quality score, the highest quartile score was associated with lower frequencies of obesity (26%), elevated waist circumference (24%), and metabolic syndrome (24%).

Mediterranean-style dietary pattern

Several meta-analyses of epidemiologic studies have reported that consumption of a Mediterranean-style diet is associated with reduced risk for total and cardiovascular mortality.[42–45] In a very large meta-analysis of 18 cohorts with greater than 4 million subjects, a 2-point increase in the Mediterranean diet adherence score (score range was from 0 [minimal adherence] to 18 [maximal adherence]) was associated with an 8% reduction in overall mortality, a 10% reduction in CVD events, and a 4% reduction in neoplastic disease.[44] In an analysis of 81,722 women in the Nurses' Health Study, Chiuve et al.[46] reported that women in the highest quintile for the Mediterranean diet score had a 40% reduction in sudden cardiac death compared to women in the lowest quintile.

In a meta-analysis of 15 prospective and cross-sectional studies and 35 clinical trials with 534,906 participants, the Mediterranean diet was highly inversely associated with the metabolic syndrome (log-hazard ratio −0.69, 95% confidence interval [CI]: −1.24 to −1.16).[47] Also, there were favorable associations of the Mediterranean diet on criteria for the metabolic syndrome, including a smaller waist circumference (−0.42 cm), higher HDL-C (1.17 mg/dL), lower TG (−6.14 mg/dL), lower systolic (−2.35 mm Hg) and diastolic (−1.58 mm Hg) blood pressures, and lower fasting glucose (−3.89 mg/dL).

PREvención con DIeta MEDiterránea (PREDIMED) was a multicenter RCT conducted in Spain that evaluated the efficacy of advice to follow a Mediterranean diet on the primary prevention of CVD.[48] A total 7447 participants, 55 to 80 years of age, with type 2 diabetes or with 3 or more CVD risk factors (hypertension, hypercholesterolemia, family history of heart disease, tobacco use, or overweight/obesity) were randomized to: (1) advice to follow a low(er)-fat diet; (2) a Mediterranean diet supplemented with extra-virgin olive oil (1 L/week/family; 50 g/day per participant); or (3) a Mediterranean diet supplemented with tree nuts (30 g/day: 15 g walnuts, 7.5 g almonds, 7.5 g hazelnuts). After 4.8 years, there was a 30% reduction in the primary endpoint, which was rate of major cardiovascular events (myocardial infarction [MI] stroke, or death from cardiovascular causes) in each of the Mediterranean diet groups.

The Lyon Diet Heart Study,[49] an RCT conducted in France, evaluated the effects of a Mediterranean-style diet vs a "prudent Western-style diet" on secondary prevention of MI over 104 weeks. The Mediterranean-style diet was lower in saturated fat and higher in α-linolenic acid (ALA) from a canola oil–based margarine. Subjects in the Mediterranean-style diet group were advised to consume more bread, root vegetables, green vegetables, and fish; less meat; to eat fruit every day; and to replace butter and cream in the diet, which was facilitated by provision of a canola oil-based margarine. The Mediterranean-style diet treatment group had 50% to 70% lower risk of recurrent cardiac events, major secondary events, and hospitalizations, despite no changes in blood lipids/lipoproteins and similar body mass index (BMI) and blood pressure compared to the control group.

Vegetarian diet

In a systematic review and meta-analysis of 8 observational studies (183,321 participants) that evaluated clinical outcomes associated with a vegetarian diet compared to a non-vegetarian diet, Kwok et al.[50] reported that, for ischemic heart disease, the associations of a vegetarian diet with lower risk for ischemic heart disease compared to non-vegetarian controls, or the general population, in the Seventh Day Adventist studies was RR 0.60, 95% CI 0.43–0.80 and in the non-Seventh Day Adventist studies was RR 0.84, 95% CI 0.74–0.96. Key et al.[51] reported that, compared with regular meat eaters, mortality from ischemic heart disease was 20% lower in occasional meat eaters, 34% lower in individuals who ate fish but did not eat meat, 34% lower in lacto-ovo-vegetarians, and 26% lower in vegans.

Limitations of observational evidence

Several dietary patterns have been associated with reduced risk for ASCVD. These dietary patterns share many attributes because of an emphasis on plant foods and lean proteins, as well as low intakes of saturated and *trans* fatty acids compared with the average American diet.

However, it should be noted that the average American diet has changed over time (data below for 1971–1974 from: Centers for Disease Control and Prevention [CDC] 2004[52] and data from 2011–2012 from: USDA 2014[53]). Results from the NHANES surveys show that mean dietary protein intake has remained relatively stable at ~15–16% of energy. Mean energy from dietary fat has declined from 36–37% of energy in 1971–1974 to 33.8% of energy in 2011–2012, with saturated fatty acid intake declining from 13–14% of energy to 10.9% over that time. *Trans* fatty acid consumption has also declined, particularly after 2006 when *trans* fatty acid content was required to be on the Nutrition Facts label. A report from the US. Food and Drug Administration (FDA) estimated that average US consumption of industrially produced *trans* fatty acids decreased from about 2.0% of energy in the late 1990s to about 0.6% of energy in 2010.[54] The decline in the energy contribution of dietary fats has been accompanied by an increase in the percentage of energy from carbohydrate from 42–45% (1971–1974) to 48.6% (2011–2012). However, because mean energy intake has increased, the total average daily consumption of dietary fat per person has been relatively stable (69.0 g/day for women and 96.2 g/day for men), while carbohydrate intake has increased from 175 g/day in 1971–1974 to 228 g/day in 2011–2012 for women. Corresponding values for men are 260 and 305 g/day, respectively.

With some exceptions, such as the results from the PREDIMED and Lyon-Diet Heart studies, little clinical trial evidence from cardiovascular outcomes trials is available from, which to fully evaluate the possible risks and benefits of these dietary patterns. It is also difficult to determine the potential for bias and confounding because dietary patterns are often associated with other lifestyle factors.[55] Nevertheless, the results from observational studies are reasonably consistent across studies, and biologically plausible, given what is known about the effects of such dietary patterns on major ASCVD risk factors from RCTs that have compared them with dietary patterns more similar to the average American diet, particularly for serum lipids and blood pressure.[15–17]

NLA Expert Panel recommendations–dietary patterns

Several dietary patterns have been associated with reduced risk for ASCVD. These dietary patterns share many attributes, with an emphasis on plant foods and lean sources of protein. Compared with an average American/Western diet, these dietary patterns are lower in saturated fats, *trans* fats, and cholesterol. The NLA Expert Panel recommends any of these healthy dietary patterns for lowering elevated levels of atherogenic cholesterol (LDL-C and non-HDL-C). However, the dietary pattern recommended should be individualized based on the patient's specific dyslipidemia. Also, patient preferences and cultural considerations are important for guiding decisions about recommendations to maximize dietary adherence. Nutritional counseling and follow-up/monitoring by a registered dietitian nutritionist are recommended whenever possible to individualize patients' cardioprotective dietary patterns and to promote long-term dietary adherence.

Replacements for saturated and *trans* fatty acids in the diet

The dietary patterns reviewed previously are lower in saturated and *trans* fatty acids compared to the average American diet. This is important for dyslipidemia management because these are the dietary components that have the greatest adverse effect on atherogenic cholesterol levels.

Table 4 shows the predicted effects of replacing 5% of energy from saturated fatty acids with a matched quantity of energy from PUFA, MUFA, and carbohydrates, based on results from controlled feeding trials.[24] Values are shown for LDL-C, TG, and HDL-C. Effects on VLDL-C are estimated by dividing the predicted change in TG by 5. Accordingly, based on the data shown in Table 4, the predicted changes in non-HDL-C, approximated as the sum of changes in LDL-C and estimated VLDL-C (TG/5), associated with substitution of 5% of energy from saturated fatty acids with PUFA, MUFA and carbohydrate are −9.4, −6.0, and −4.1 mg/dL, respectively.

Like saturated fats, *trans* fatty acid consumption increases levels of atherogenic cholesterol, with each 1% of

Table 4 Predicted effects of macronutrient replacement of dietary saturated fatty acids with PUFA, MUFA, and carbohydrate on lipoprotein lipids based on results from controlled feeding trials*

Dietary component	Predicted effects* on lipoprotein lipids of replacing 5% of energy from saturated fatty acids with 5% of energy from the specified dietary component, mg/dL		
	LDL-C	TG	HDL-C
PUFA	−9.0	−2.0	−1.0
MUFA	−6.5	+1.0	−6.0
Carbohydrate	−6.0	+9.5	−2.0

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; TG, triglyceride.

*Results are summarized from controlled feeding trials of subjects with average-to-mildly dyslipidemic baseline levels of lipoprotein lipids. Effects may be more pronounced in those with higher baseline values.

Source: Adapted from Eckel RH, et al. *J Am Coll Cardiol*. 2014;63(25 Pt B):2960–2984.[24]

energy from *trans* fatty acids raising LDL-C by ~1.5 mg/dL compared with carbohydrate and, to a somewhat greater extent, compared with MUFA and PUFA.[24] As previously discussed, intake of *trans* fatty acids in the average American diet has declined in recent years from ~2.0% of energy to 0.6% of energy.[54] Further reductions are expected due to recent actions by the FDA to remove industrially produced *trans* fatty acids from the list of foods Generally Recognized as Safe. For patients who consume greater than average quantities of foods that may contain *trans* fatty acids, such as some cookies, pastries, biscuits, crackers, deep-fried foods, microwaved popcorn, and frozen dinners, dietary advice that emphasizes the recommended food categories and food patterns discussed previously will minimize *trans* fatty acid consumption.

Selected results from randomized controlled feeding trials

OmniHeart was a randomized, controlled feeding trial that evaluated the effects of 3 variants of the DASH dietary pattern on lipoprotein lipids and blood pressure in subjects with pre-hypertension and stage I hypertension.[27] After baseline measurements were collected with subjects consuming their habitual diets (similar to the average American diet), 3 experimental diets were compared in a randomized order: 1) a high-carbohydrate, low-saturated fat DASH diet with 58% of energy from carbohydrate, 27% from fat (6% from saturated fatty acids) and 15% from protein; 2) a higher protein diet where 10% of the energy from carbohydrate was replaced with mixed-source protein; and 3) an unsaturated fat diet where 10% of energy from carbohydrate was replaced with unsaturated fats (8% from MUFA and 2% from PUFA). Baseline values and changes in lipoprotein lipids are shown in Table 5.[27] Atherogenic cholesterol levels were reduced on all 3 DASH diet variants compared with habitual intake. Changes in LDL-C and non-HDL-C levels were significantly greater during the higher protein (−14.2 and −17.3 mg/dL, respectively) and higher unsaturated fat (−13.1 and −15.1 mg/dL, respectively) diets than during the higher carbohydrate diet (−11.6 and −11.0 mg/dL, respectively). These results suggest that a diet low in saturated fatty acids that emphasizes carbohydrates, proteins, or unsaturated fats will improve the lipid profile, but that emphasis on proteins and unsaturated fats may elicit the most favorable effects on levels of LDL-C and non-HDL-C.

Liquid vegetable oils are a major dietary source of unsaturated fatty acids. However, some vegetable oils are higher in MUFA, such as canola, high-oleic safflower, and olive oils, while others are higher in PUFA, such as corn and safflower oils. Consequently, consumers and clinicians should understand the effects of different vegetable oils on lipoprotein lipid levels. A controlled feeding study conducted by Maki et al.[56] evaluated the effects of a PUFA-rich corn oil and a MUFA-rich extra-virgin olive oil (4 tablespoons/day were incorporated into foods) as part of a weight maintenance diet (34% of energy from fat, ~8% from saturated fatty acids) on lipids and lipoproteins in men and women with elevated LDL-C. Consumption of the corn oil diet reduced LDL-C by 10.9% compared to subjects' baseline (average American) diets, which was significantly greater than the reduction of 3.5% with extra-virgin olive oil. Results were similar for non-HDL-C, with a significantly greater mean reduction of 9.3% with corn oil vs 1.6% with extra-virgin olive oil. The HDL-C responses were similar between treatments; however, there was a smaller increase in TG on the corn oil (3.5%) vs the extra-virgin olive oil (13.0%) diet. These results are generally consistent with those from other studies,[57,58] and support the view that greater reductions in atherogenic cholesterol levels should be expected when saturated fatty acids are replaced with PUFA (omega-6) compared to MUFA (omega-9).[59] However, it should be noted that other factors, such as the higher plant sterol content of the corn oil, may have also contributed to the lipoprotein lipid changes observed in the study by Maki et al.[56]

Summary–replacements for saturated fatty acids

The NLA Expert Panel recommends consuming a diet that is low in saturated fatty acids (<7% of energy) for those in need of atherogenic cholesterol lowering.

Table 5 Changes from baseline lipoprotein lipid levels by diet in OmniHeart

	Diet (% energy from carbohydrate/protein/fat)			
	Habitual baseline diet (various)	Carbohydrate diet (58/15/27)	Protein diet (48/25/27)	Unsaturated fat diet (48/15/37)
Lipid	Mean, mg/dL	Mean or median change from baseline, mg/dL		
LDL-C	129	−11.6[a]	−14.2[b]	−13.1[a,b]
Non-HDL-C	154	−11.0[a]	−17.3[b]	−15.1[b]
HDL-C	50	−1.4[a]	−2.6[b]	−0.3[c]
TG	102	0.1[a]	−16.4[b]	−9.3[c]

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.
Different letters in a row denote statistically significant differences in response, $P < .05$.
Source: Adapted from Appel LJ, et al. *JAMA*. 2005;294:2455–2464.[27]

Replacing saturated fats with unsaturated fats, proteins, or carbohydrates lowers levels of atherogenic cholesterol, although replacement with unsaturated fats and proteins elicit greater reductions than carbohydrate. Unsaturated fat intake can be increased by incorporating liquid vegetable oils and oil-rich foods, such as nuts and liquid vegetable oil spreads, into the diet. PUFA (mainly omega-6) produce greater reductions in atherogenic cholesterol levels than MUFA (omega-9).

Dietary cholesterol

The 2010 US Dietary Guidelines recommended that dietary cholesterol be <300 mg per day for healthy individuals ages 2 years and older.[19] In the 2006 Diet and Lifestyle Revision,[28] the AHA recommended <300 mg per day and, in 2011, the AHA recommended <150 mg per day for the prevention of CVD in women.[60] The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III recommended <200 mg/day of cholesterol as part of the Therapeutic Lifestyle Changes diet.[12] More recently, the 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk did not make a recommendation for dietary cholesterol because the panel concluded that there was "insufficient evidence to determine whether lowering dietary cholesterol reduces LDL-C".[24] The 2015 DGAC did not recommend continuation of the recommended limit of dietary cholesterol to <300 mg per day because "available evidence shows no appreciable relationship between consumption of dietary cholesterol and serum cholesterol".[23] Thus, the usefulness of limiting dietary cholesterol intake for the US population, and for those with elevated levels of atherogenic cholesterol, has become controversial. The available evidence was reviewed carefully by the NLA Expert Panel.

Effects of dietary cholesterol on total cholesterol (total-C) and LDL-C levels

The effects of dietary cholesterol on circulating levels of LDL-C and total-C (and to a lesser extent, non-HDL-C) have been evaluated in a large number of studies. Results of the effects of dietary cholesterol on serum total-C and LDL-C have been evaluated in 6 meta-analyses.[61-66] In aggregate, these included data from 438 studies; 424 in subjects with normolipidemia and 14 in participants with dyslipidemia. An increase of 100 mg/day in dietary cholesterol was reported to increase total-C approximately 2 to 3 mg/dL.[63,64,66] Hopkins[61] evaluated results from 27 studies in which controlled diets were supplied by a metabolic kitchen, and reported that the increase in serum total-C produced by a given change in dietary cholesterol is non-linear and dependent on the baseline level of dietary cholesterol. Accordingly, the increase in serum total-C predicted for an increment of 100 mg/day in dietary cholesterol would be progressively less with higher baseline levels of cholesterol intake.

Weggemans et al.[66] completed a meta-analysis of results from 17 studies involving 556 subjects in which diets differed only in the amount of dietary cholesterol or number of eggs (with yolks) fed over periods of at least 14 days and for which lipoprotein lipid values were reported. They reported that an addition of 100 mg/day of dietary cholesterol would be predicted to increase total-C by 2.17 mg/dL, LDL-C by 1.93 mg/dL, and HDL-C by 0.31 mg/dL, resulting in a small increment in the total-C:HDL-C ratio of 0.02. These values align closely with those reported by Clarke et al.[63] from an analysis of data reported in 395 dietary solid food experiments. It should be noted that the clinical importance of the increase in HDL-C observed with increasing dietary cholesterol is uncertain.

A more recent systematic review and meta-analysis of 40 studies (17 cohort studies with 19 publications and 19 trials with 21 publications) was published by Berger et al.[67] In the review of 17 of the 19 trials, dietary cholesterol (intervention cholesterol intake was 501 to 1415 mg/day and 0 to 415 mg/day in the control conditions) significantly increased both serum total-C (11.2 mg/dL) and LDL-C (6.7 mg/dL). When the intervention intake levels were greater than 900 mg/day, there were no longer statistically significant increases in LDL-C. In this review, dietary cholesterol also increased HDL-C (3.2 mg/dL). Similar to the Hopkins results,[61] the increases in total-C and LDL-C were greatest when the baseline dietary cholesterol intake was the lowest.

Ginsberg et al.[68] conducted a controlled feeding study in which 4 dietary conditions were evaluated, each for 8 weeks with washouts between treatments, in 20 young, healthy men. This trial was chosen as an illustrative example of the effects of dietary cholesterol because it was a well-designed dietary intervention with controlled feeding that allowed evaluation of dose-response, and included measurements of lipoprotein lipids by ultracentrifugation, the reference standard. In this trial, average total-C and LDL-C increased by 1.47 mg/dL and 1.38 mg/dL, respectively, for each 100 mg/day increase in dietary cholesterol. HDL-C also increased by 0.29 mg/dL per 100 mg/day of dietary cholesterol, while VLDL-C and TG levels did not change. The apo B concentration rose by 1.19 mg per 100 mg/day increase in dietary cholesterol, and the change in apo B correlated significantly with the change in LDL-C. While these results are consistent with the view that an increase in dietary cholesterol modestly raises levels of atherogenic cholesterol (and lipoprotein particles), it should be noted that the responses varied widely, with 3 subjects showing a decrease in total-C with increasing cholesterol intake and some subjects displaying more than twice the mean response.

Variation in responses to dietary cholesterol

Griffin and Lichtenstein reviewed results from studies on the effects of dietary cholesterol and lipoprotein lipids

published between 2003 and 2013.[69] They concluded the following:

> Within the context of current levels of dietary cholesterol intake, the effect on plasma lipid concentrations, with primary interest in LDL-C cholesterol concentrations, is modest and appears to be limited to population subgroups. In these cases, restrictions in dietary cholesterol intake are likely warranted. The biological determinants of inter-individual variability remain a relatively understudied area.

The interpretation of the NLA Expert Panel is that the available data are consistent with the conclusion that dietary cholesterol has modest effects to increase total-C and LDL-C levels on average, although there are hypo- and hyper-responders in the population. Unfortunately, at present, there is no widely available and inexpensive method for clinical use to predict who is likely to experience a change in atherogenic cholesterol (or not) in response to changes in dietary cholesterol intake. The effects of other dietary constituents, particularly saturated and unsaturated fatty acids, on circulating levels of atherogenic cholesterol are generally larger and more predictable than that of dietary cholesterol. For most individuals, restricting saturated fat intake to <7% of energy, while following any of the recommended dietary patterns, will result in lower dietary cholesterol consumption, because saturated fats and cholesterol are both present in many foods (e.g., fatty cuts of meats, processed meats, full-fat dairy foods). However, some popular foods are particularly high in cholesterol, but not in saturated fatty acids, including eggs, shrimp and other shellfish, and some organ meats (which are commonly consumed in some regions of the United States).[70]

Observational evidence for dietary cholesterol or egg consumption and ASCVD risk

The authors of a meta-analysis of 16 prospective cohort studies with follow-up times ranging from 5.8 to 20.0 years reported that, in comparison with those who ate egg less than once per week, individuals who ate egg once per day or more did not have significantly higher risks of overall CVD, ischemic heart disease, or stroke.[71] The pooled hazard ratios (HRs) (95% CI) were 0.96 (0.88, 1.05) for overall CVD, 0.97 (0.86, 1.09) for ischemic heart disease, and 0.93 (0.81, 1.07) for stroke. The HR for ischemic heart disease mortality was 0.98 (0.77, 1.24) and for stroke mortality was 0.92 (0.56, 1.50). Thus, egg consumption was not associated with the risk of CVD and cardiac mortality in the general population. A more recent systematic review and meta-analysis of 17 cohort studies with 361,923 subjects reported that dietary cholesterol intake was not significantly associated with incidence of coronary artery disease, ischemic stroke, or hemorrhagic stroke.[67] The authors noted, however that the cohort studies reviewed were heterogeneous and lacked methodological rigor, which limited definitive conclusions being made about dietary cholesterol and ASCVD outcomes.

The authors of a review of 8 large prospective cohort studies (17 reports, including 9 for CHD and 8 for stroke) and a meta-analysis (3,081,269 person years and 5847 cases of incident CHD) reported an increased risk of CHD in a subgroup analysis of individuals with diabetes comparing the highest with the lowest categories of egg consumption of 1.54 (1.14 to 2.09; $P = .01$).[72] The association of egg consumption with increased CHD risk in those with diabetes may be a reflection of the cholesterol content of eggs (approximately 186 mg per single large egg yolk). Among 5672 women with type 2 diabetes in the Nurses' Health Study, higher consumption of dietary cholesterol was associated with increased risk of CVD.[73] Each increase of 200 mg cholesterol/1000 kcal was associated with a 37% increased risk of CVD, which was a composite of fatal CHD, nonfatal MI, and stroke (Tanasescu 2014). In a prospective cohort study of 37,851 men and 80,842 women in the Health Professionals Follow-up Study, higher egg consumption was associated with an increased risk of CHD only among those subjects with diabetes.[74] Men with diabetes consuming 1 egg or more daily had double the risk of CHD compared to those consuming 1 egg or less each week; women with diabetes consuming 1 egg or more daily had 1.49 times the risk of CHD than those consuming 1 egg or less per week.[74]

In summary, the observational evidence suggests that egg and dietary cholesterol consumption are not consistently associated with increased ASCVD risk, with the possible exception of increased risk in those with diabetes mellitus. Mechanisms to potentially explain differences in risk among those with and without diabetes are uncertain. Observational studies are subject to various types of bias and confounding,[55] including intercorrelations between types of foods consumed (e.g., a correlation between consumption of eggs and processed breakfast meats) and displacement effects (higher egg consumption may be associated with lower consumption of other foods), thus such evidence must be interpreted with caution. Accordingly, the conclusions of the NLA Expert Panel regarding dietary cholesterol intake for dyslipidemia management are based mainly on the results from well-controlled RCTs designed to evaluate the effects of dietary cholesterol on levels of atherogenic cholesterol.

Conclusions from review of evidence on dietary cholesterol and ASCVD risk

Results from well-controlled RCTs indicate that dietary cholesterol has modest effects to raise levels of total-C, LDL-C, and HDL-C. The increase in HDL-C associated with increased dietary cholesterol is of uncertain clinical importance. Hyper- and hypo-responders to dietary cholesterol exist, with some individuals showing little or no increases in atherogenic cholesterol levels in response to greater intake of dietary cholesterol and others showing responses well above the average. The biological determinants of inter-individual variability are understudied, and presently no inexpensive and widely available methods are

available for identifying those who are likely to be hyper- or hypo-responders. In controlled feeding RCTs, each 100 mg/day of dietary cholesterol raises LDL-C by an average of ~1.9 mg/dL. Observational data have consistently reported no association between dietary cholesterol or egg consumption (a large contributor to dietary cholesterol intake) and ASCVD risk in the general population, but suggest that there may be increased ASCVD risk associated with greater cholesterol and egg consumption in those with diabetes mellitus. The NLA Expert Panel recommendations are, therefore, based mainly on results from controlled-feeding RCTs showing modest effects of dietary cholesterol to raise total-C and LDL-C, while recognizing that other dietary factors (saturated fatty acids, *trans* fatty acids, MUFA and PUFA) more reliably and predictably influence levels of atherogenic cholesterol.

Weight loss

Effects of weight loss on lipoprotein lipids

Results from systematic reviews of RCTs indicate that clinically meaningful changes in CVD risk indicators are associated with a loss of at least 2.5 kg or 3% of body weight.[75,76] A weight loss of 5 to 8 kg that is sustained results in a mean LDL-C reduction of approximately 5 mg/dL and a mean increase in HDL-C of between 2 and 3 mg/dL.[76] In addition, a 3 kg weight loss is expected to decrease TG by at least 15 mg/dL.[76] However, clinicians should be aware that there is marked variation in the lipid/lipoprotein responses to weight loss. In addition, all of the major lipoprotein lipid variables (LDL-C, VLDL-C, TG, and HDL-C) typically decrease during active weight loss.[75,76] The values above reflect the effects observed after lower and stable levels of body weight and adiposity have been established.[76] Favorable changes in lipoprotein lipids are unlikely to be sustained unless a reduced weight is maintained. Therefore, the critically important consideration for all lipoprotein changes is weight loss maintenance. Behaviors associated with successful maintenance of a reduced body weight include high levels of physical activity (discussed in detail in the section on exercise/physical activity); eating breakfast regularly; self-monitoring of weight; and maintaining consistent, calorie controlled eating patterns across weekdays and weekends.[77]

LDL-C values decline with weight loss on average, but the response tends to be larger in younger subjects, and may be blunted in older individuals.[78,79] However, the TG and VLDL-C reductions appear to be similar among younger and older individuals. The relationship between age and lipoprotein lipid responses to weight loss is understudied and should be pursued in future research. Among lipoprotein lipid parameters, TG levels (and VLDL-C, which is highly correlated with the TG concentration) appear to respond most readily to weight loss.[75] Higher baseline values and larger weight loss are associated with greater TG lowering.[75] In addition, lower carbohydrate diets during weight loss and weight maintenance have been shown to lower TG more than higher carbohydrate diets.[75] Loss of at least 3% of body weight also produces favorable changes in other ASCVD risk indicators, including blood pressure, glycemia, and insulin resistance.[75]

Effects of macronutrient distribution on weight loss and metabolic parameters

Many studies have been conducted to identify which dietary approach is most successful in promoting long-term weight loss and weight loss maintenance. It is clear that losses of body weight and fat will occur with a variety of macronutrient distributions, as long as they reduce energy intake below energy expenditure.[80] Several dietary patterns, such as Mediterranean-style, DASH, USDA, and vegetarian diets can be tailored to personal and cultural food preferences and appropriate calorie needs for weight control.[23,24]

The ideal macronutrient composition for weight reducing diets and weight loss maintenance is the source of much controversy and may differ among individuals for a variety of physiological and behavioral reasons. The consensus view of the NLA Expert Panel is that there is suggestive evidence that partially replacing carbohydrate (especially refined starches and sugars, thus, also reducing dietary glycemic load) with higher protein foods may be beneficial to enhance weight loss and weight loss maintenance. This may be due, in part, to the effects of protein, compared with carbohydrate, to enhance satiety, induce a greater thermic effect of food, and to favor maintenance of fat-free mass.[81–84]

In a review of the influence of protein intake on weight loss and weight maintenance, Westerterp-Plantenga and colleagues[82] concluded:

> …evidence shows that a relatively high protein intake sustains weight maintenance by (a) favoring regain of fat free mass at the cost of fat at a similar physical activity level, (b) reducing the energy efficiency with respect to the body mass regained, and (c) increasing satiety.

Wycherley et al.[84] evaluated the effects of energy-restricted high-protein, low-fat diets (25–35% energy from protein, ≤30% of energy from fat) with standard-protein, low-fat diets (12–18% of energy from protein, ≤30% of energy from fat). Twenty-four trials that included 1063 individuals satisfied the search criteria. The higher protein diets elicited greater decreases in body weight (0.79 kg), fat mass (0.87 kg), and TG (20.4 mg/dL), and smaller reductions in resting energy expenditure (596 kJ/day [142.4 kcal/day]) and fat-free mass (0.43 kg). The authors concluded that a higher protein weight loss diet provides modest benefits for reducing body weight, as well as TG, by attenuating reductions in fat-free mass and resting energy expenditure. The degree to which these differences can be attributed to increased protein vs lower carbohydrate intake (and hence reduced glycemic load) is uncertain, and both may be important contributors.

In the largest trial completed to date on the effects of diet composition on weight loss maintenance, Larsen et al.[85] randomly assigned a group of 773 adults who had lost at least 8% of body weight to 5 diet groups to assess effects of protein intake and glycemic index on weight loss maintenance. The groups included a control diet with intermediate levels of protein and glycemic index with the remaining subjects assigned to lower and higher protein and lower or higher glycemic index in a 2 x 2 factorial manner. Targeted differences were 12% of energy between the lower and higher protein groups, and 15 glycemic index units for the lower and higher glycemic index groups. In an intention-to-treat analysis, the weight regain over 26 weeks was 0.93 kg less in the groups assigned to a high-protein diet than in those assigned to a low-protein diet, and 0.95 kg less in the groups assigned to a low-glycemic-index diet than in those assigned to a high-glycemic-index diet. The group that received the combination of a higher protein and lower glycemic index diet had the least weight regain (showing a small mean additional weight loss) of the 5 treatment arms, and also had the highest rate of study completion. The authors concluded that a diet with a moderately higher protein content (average intake 22–23% of energy during the intervention) and reduced glycemic index (56–57 units) improved the maintenance of weight loss, and may thus have advantages for weight regain prevention.

The NLA Expert Panel acknowledges that additional research is needed to more clearly define effective dietary strategies for enhancing adherence to hypocaloric diets, and preventing weight regain after weight loss interventions.[80,86] However, based on the evidence discussed herein, the NLA Expert Panel consensus view is that eating patterns that contain a moderate quantity of carbohydrate, lower glycemic index and load, and higher protein, have been associated with modest benefits regarding weight loss and maintenance.[82,84,85] Furthermore, the Expert Panel also strongly believes that additional research is needed to more clearly define effective dietary strategies for enhancing adherence to hypocaloric diets and preventing weight regain after weight loss interventions.[80,86]

Importance of lifestyle counseling and ongoing support

The Preventing Overweight Using Novel Dietary Strategies trial randomly assigned 811 overweight or obese subjects to 1 of 4 dietary conditions that emphasized different macronutrient distributions.[80] Participants were offered regular individual and group counseling sessions. After 6 months and 2 years of the intervention, the groups did not differ with regard to changes from baseline body weight. However, the number of sessions attended was a strong predictor of weight loss at the 2-year timepoint in all groups, with each additional session attended associated with a 0.2 kg greater loss of body weight. This illustrates the importance of lifestyle counseling and ongoing support to maximize success with weight loss interventions.

Dietary adjuncts for lowering atherogenic cholesterol

If a diet based on a cardioprotective dietary pattern that is low in cholesterol-raising fatty acids and cholesterol plus regular physical activity and weight loss, if overweight or obese is insufficient to attain atherogenic cholesterol goals, clinicians may consider the use of dietary adjuncts to enhance the effects of other lifestyle interventions. The NLA Expert Panel consensus view is that there was sufficient evidence to recommend consideration of the use of supplemental plant sterols/stanols (~2 g/day) and viscous fibers (5–10 g/day from foods and/or supplemental sources) to enhance reductions in levels of atherogenic cholesterol. Consumption of greater quantities of viscous fiber (10 to 25 g/day) as was recommended by the NCEP ATP III[12] will generally result in greater atherogenic cholesterol lowering; however, attaining this level of consumption is challenging. As is the case for other lifestyle interventions, recommendations are based primarily on results from RCTs demonstrating reductions in atherogenic cholesterol levels. ASCVD event trials are not available for these interventions, which prevents a full evaluation of the potential benefits and risks with their use.

Effects of plant (phyto) sterols/stanols on lipoprotein lipids

Phytosterols (PS), a term used to refer to both plant sterols and plant stanols, are compounds that naturally occur in foods of plant origin, particularly vegetable oils, nuts, seeds, and grain products. The typical diet consumed in the United States provides approximately 200–400 mg/day and the amount of PS consumed daily in a vegan diet is roughly twice that amount. There is a large evidence base supporting the LDL-C-lowering effect of PS, which has been summarized in multiple meta-analyses. The meta-analyses conducted by Law et al.[87] and Katan et al.[88] were the first to examine the effects of PS on cholesterol levels. Both showed that consumption of 2 g/day of stanols or sterols lowered LDL-C by 5–10%. Follow-up meta-analyses by Demonty et al.[89] and AbuMweis et al.[90] confirmed these findings and concluded that, with an increasing dose of PS, the LDL-C-lowering effect increases, but this plateaus at doses above ~3 g/day.

More recently Musa-Veloso et al.[91] conducted the largest meta-analysis on PS consumption, which included 114 trials representing 182 trial arms and evaluating LDL-C lowering dose-response effects separately for plant sterols and plant stanols. The range of PS intake was 0.2–9.0 g/day; however, there were only 4 studies with a PS intake >4.0 g/day. The authors concluded that at a dosage <3 g/day, effects of plant sterols and stanols are comparable.

The lipid-lowering efficacy of PS-fortified products (both free plant sterols and stanols and their esterified forms) has been demonstrated in different population

subgroups, including adults with type 2 diabetes mellitus, metabolic syndrome, and familial hypercholesterolemia (FH).[92–94] Atherogenic cholesterol lowering with plant sterols and stanols has been demonstrated in children with FH,[95] although an insufficient body of evidence is available from which to draw firm conclusions about the efficacy of PS for reducing atherogenic cholesterol levels in those with FH.

The efficacy of PS for lowering atherogenic cholesterol levels in various food and beverage formulations was examined by Demonty et al.[89] who reviewed studies that compared fat vs non-fat foods, dairy vs nondairy, liquid vs solid foods, and free or esterified PS. There were no significant differences in response to plant sterols vs stanols, fat-based vs non-fat-based food formats, and dairy vs nondairy foods at intake levels ≤2 g/day. It is possible (and theoretically likely) consumption of PS multiple times per day results in greater efficacy than a single intake.[89] If taken in a single dose, the efficacy of PS appears to be greatest when consumed during or shortly after a meal, preferably a large enough meal that bile flow is triggered. There also appears to be an effect of baseline LDL-C concentration on the magnitude of the absolute decrease in LDL-C concentration, with larger reductions in LDL-C among individuals with higher baseline levels.[89] However, when expressed as a percentage of the baseline value, LDL-C reductions are similar across a wide range of baseline LDL-C values.[88]

In addition to the well-established effects of PS to produce LDL-C-lowering, there also is some evidence that PS reduce TG concentrations. In a meta-analysis of 12 RCTs, PS intake in the range of 1.6 to 2.5 g/day produced a modest TG-lowering effect of about 6%.[96] More recent data reviewed by Rideout et al.[97] indicate that PS supplementation results in a variable TG-lowering response ranging from 0.8 to 28%. The evidence supports the view that individuals with elevated TG (≥150 mg/dL) have a greater TG-lowering response to PS (11–28%) than subjects with normal plasma TG concentrations (0.8–7%).[97]

Mechanisms of action of PS

One mechanism by which PS lowers LDL-C is reducing intestinal cholesterol absorption by competing with cholesterol for limited space in mixed micelles.[98] This makes less cholesterol available to the enterocytes for transport via Niemann-Pick C1-Like 1 transporters. A second mechanism is that an increase in the intracellular level of PS in the enterocytes triggers an up-regulation of adenosine triphosphate-binding cassette transporter (ABC) G5 and ABCG8 that move sterols (including cholesterol) out of the enterocytes and into the intestinal lumen.[98] The net result of these actions is to reduce hepatic cholesterol content, which then results in an up-regulation of hepatic LDL receptors that remove apo B-containing lipoproteins from the blood, thus lowering the blood cholesterol concentration, particularly LDL-C.[98]

Safety of supplemental PS consumption

The safety of PS has been reviewed by several regulatory agencies. The US FDA classifies PS as having Generally Recognized as Safe status. Furthermore, the FDA has authorized a health claim stating that consuming foods that include plant sterols/stanols (at least 0.75 g/serving) may reduce the risk of CHD. Potential health concerns have been raised related to elevated PS concentrations following the intake of PS-enriched foods in those with homozygous phytosterolemia (also known as sitosterolemia), a rare autosomal recessive genetic disorder.[99] Average PS concentrations in individuals consuming PS-fortified margarine-type spreads range from 0.6 to 2.0 mg/dL.[88] However, patients with phytosterolemia are unable to effectively clear absorbed PS from the blood and tissues due to defects in the ABCG5 and/or ABCG8 sterol transporters. This causes PS concentrations to increase to levels that are often 20–45 times typical values.[100,101] The disorder occurs in about 1 in 5 million people and CVD risk is severe in these patients due to premature atherosclerosis.[88] Heterozygous phytosterolemia is much more common, occurring in ~1 in 500 people. Individuals with heterozygous phytosterolemia appear clinically and biochemically normal, with normal to only a slight increase in plasma PS concentrations and moderate hypercholesterolemia.[102] Although few studies have examined the effects of PS consumption in this subgroup, individuals with heterozygosity for an ABCG8 mutation appear to respond to a PS challenge similarly to individuals without phytosterolemia.[103,104]

The connection between high circulating PS concentrations and premature CHD has led to investigations of the association between lower circulating PS concentrations and CHD risk. To date, the findings have not supported a clear link between circulating PS concentrations in the normal range and the development of CVD.[105] Genser et al.[106] conducted a meta-analysis specifically examining the impact of increased serum concentrations of PS on CVD risk. The analysis included 17 studies involving 11,182 participants reporting either risk ratios of CVD in relation to PS concentrations (8 studies) or standardized mean differences in PS concentrations between CVD cases and controls (15 studies). The authors concluded that there is no relationship between serum concentrations of PS and CVD risk over a 3-fold difference in serum plant sterol concentrations.[106] Measurement of circulating PS concentrations in clinical practice is generally limited to the diagnosis of phytosterolemia.[107]

Another concern that has been raised about plant sterols is that they reduce the absorption of some fat-soluble vitamins. Randomized trials have demonstrated that PS consumption lowers blood concentrations of β-carotene by about 25%, concentrations of α-carotene by 10%, and concentrations of vitamin E by 8%.[87] In part, this is likely due to reduced absorption of carotenoids; lower concentrations of vitamin E are most likely due to reduced concentrations of its main lipoprotein carrier, LDL. After the decrease in total-C induced by PS was corrected for, a statistically significant reduction

remained only for β-carotene (between 8% and 19%). Eating more fruits and vegetables would likely counter the decreased carotenoid absorption. The blood concentrations of vitamin D and vitamin A are unaffected by PS.[108–111] There also does not appear to be any influence on vitamin K-dependent clotting factors or prothrombin time.

Effects of viscous dietary fibers on lipoprotein lipids

Dietary fibers are plant substances that are resistant to digestion in the small intestine.[112] Fibers are classified in various ways, including solubility in water, viscosity, and fermentability by colonic microbiota. Viscous fibers, including pectins, gums, mucilages and some hemicelluloses, have gelling properties in the gastrointestinal tract, and their consumption has been associated with reductions in total-C, LDL-C, and non-HDL-C.[113–115] Commonly consumed food sources of viscous fibers include oats, barley and legumes (e.g., lentils, lima beans, kidney beans), as well as fruits, including apples, pears, plums and citrus fruits,[70] and vegetables, including broccoli, Brussels sprouts, carrots, and green peas. Supplemental forms of viscous fibers are also available as fiber laxative products (e.g., those that contain psyllium seed husk and methylcellulose).

Well-controlled RCTs evaluating the effects of consuming viscous fibers on lipoprotein lipids have consistently shown reductions in total-C and LDL-C. Brown et al.[116] completed a meta-analysis of 66 RCTs to evaluate the lipoprotein lipid effects of viscous fibers from oat products (beta-glucan), psyllium, pectin, and guar gum. Statistically significant reductions in total-C and LDL-C were observed for each of the 4 fiber types, with no significant changes observed for TG or HDL-C concentrations. The pooled effects for all fibers per gram of daily consumption for all studies were reductions of 1.1 mg/dL for both total-C and LDL-C. Accordingly, intakes in the range of 5–10 g/day would be expected to lower mean total-C and LDL-C levels by 5.5 to 11.0 mg/dL. A more recent meta-analysis of 28 RCTs evaluating the effects of oat beta-glucan on lipoprotein lipids found that, in studies where 3.0–12.4 g/day were provided, mean total-C and LDL-C levels were reduced relative to control by 9.7 and 11.6 mg/dL, respectively.[117] TG and HDL-C levels were not significantly altered.

Few data exist from which to evaluate determinants of the atherogenic cholesterol responses to viscous dietary fiber consumption. Fibers that create greater viscosity in the intestinal lumen will tend to have a greater cholesterol-lowering effect.[115,118] Some forms of processing that may occur during the production of dietary fiber concentrates and extracts will lower the molecular weight of the fiber, which will reduce their viscosity and potentially interfere with the hypocholesterolemic effects.[117] Therefore, if a fiber supplement is to be used, it is ideal to confirm that when mixed with water and allowed to sit for several minutes a viscous gel-like solution is formed.

Mechanisms of action of viscous dietary fibers

Viscous dietary fibers may act through several mechanisms to affect lipoprotein metabolism.[119] The main proposed mechanisms relate to trapping of cholesterol and bile acids in the small intestine, resulting in reduced absorption/reabsorption.[119] The net result of these actions is to reduce hepatic cholesterol content, which triggers an up-regulation of hepatic LDL receptors that remove apo B-containing lipoproteins from the blood, thus lowering the blood cholesterol concentration, particularly LDL-C.[119]

Safety of viscous fiber consumption

Few safety concerns are associated with increased viscous fiber consumption. If viscous fiber supplements such as fiber laxatives are used, it is critical to consume adequate fluid as directed on the product label to avoid intestinal blockage (a rare occurrence). The supplement should be mixed and consumed immediately, before significant thickening has occurred, to avoid choking. There is a theoretical concern that viscous fiber supplements may reduce carotenoid absorption. Regular consumption of fruits and vegetables should help to counteract this potential effect.[120]

Summary of the anticipated effects of recommended dietary interventions on LDL-C and non-HDL-C

A rule of thumb for clinicians to use in predicting the effects of the recommended dietary interventions is that each should be expected to reduce LDL-C (and non-HDL-C) by 3–7%, or ∼5% on average. Expected results based on RCTs of practical dietary interventions in free-living individuals suggest that the LDL-C lowering would be:

- Diet low in saturated and *trans* fatty acids and cholesterol: 5 to 10%
- Loss of 5% of body weight: 3 to 5%
- 2 g/day PS or 7.5 g/day viscous fiber: 4 to 10%
- Total: 12 to 25%

Combining any 2 of the interventions recommended would be expected to reduce LDL-C by 6 to 19%. The portfolio diet approach, which combines PS, viscous fibers, soy, and almonds has been shown to reduce LDL-C by ∼30% with controlled feeding, but the reduction was less (∼15%) when subjects were free-living.[121,122] If maintained over an extended period, each 1% reduction in LDL-C is expected to reduce CHD risk by 2–3%, based on results from genetic variants that alter atherogenic cholesterol levels.[7,11] Thus, a modest reduction of as little as 6% in LDL-C, maintained over an extended period, could reduce CHD risk by 12–18%, whereas a reduction of 15% by combining dietary interventions could potentially reduce CHD risk by 30–45%.

PS and viscous fiber may be used in combination, but there are few studies that have administered them together to investigate their combined influences on atherogenic cholesterol. Both PS and viscous fibers reduce atherogenic cholesterol, in part, by reducing cholesterol absorption.[98,119] Viscous fibers also lower bile acid re-absorption.[119] Therefore, there is uncertainty regarding whether their effects are fully additive. PS products should not be used in combination with a cholesterol absorption inhibitor drug (ezetimibe) because both work through interference with cholesterol absorption and the addition of PS to ezetimibe therapy did not have an incremental effect on the LDL-C response.[123]

Long-chain omega-3 fatty acids

The long-chain polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), both derived from marine sources, as well as the essential fatty acid, ALA, derived from plant sources, have been of scientific interest for decades. The history of the marine-derived omega-3 fatty acids dates back to the first studies conducted with Greenland Eskimos that reported that a low death rate from CHD was associated with a very high intake of seafood (around 400 g/day).[124,125] Recommendations for EPA and DHA are based on epidemiological and RCTs of both primary and secondary prevention of CVD and have evaluated both fish/seafood and omega-3 fatty acid supplements/fortified foods. The recommendation for ALA is based on the precept of meeting nutrient adequacy.

Evidence from prospective observational studies and some randomized clinical trials suggests that, compared with little or no intake, consumption of 250 to 550 mg/day of EPA and DHA is associated with a 36% lower risk of CHD death and reduced total mortality by 17% (summarized by Mozaffarian and Rimm[126]). Harris et al.[127] conducted a pooled analysis of observational studies and reported that the highest (approximately 566 mg/day) vs lowest intake of EPA + DHA was associated with approximately a 37% reduction in CHD mortality. These collective analyses formed the basis for the current dietary recommendations for EPA and DHA for the primary prevention of coronary disease.

The 2010 DGA recommended 250 mg/day of EPA and DHA[19] and the Academy of Nutrition and Dietetics recommends 500 mg/day.[128] The DGAC 2010 concluded:[19]

> "Moderate evidence shows that consumption of two servings of seafood per week (4 oz per serving), which provide an average of 250 mg per day of long-chain n-3 fatty acids, is associated with reduced cardiac mortality from CHD or sudden death in persons with and without CVD. An increase in seafood intake to two servings per week at 4 oz per serving is advised for high-risk (those with CVD) and average-risk persons, especially as the first presentation of CVD (MI, stroke) is frequently fatal or disabling. The quantity and frequency of seafood consumption is important, but the type of seafood (those providing at least 250 mg of long-chain n-3 fatty acids per day) also is critical."[19]

The recommendation for increased seafood intake can be met by consuming both farm-raised and wild-caught seafood, because, as a result of current aquaculture practices, they now contain approximately the same amounts of omega-3 fatty acids.[23]

The AHA issued 2020 Impact Goals to improve the cardiovascular health of all Americans, which included a primary dietary recommendation for fish: ≥ two 3.5-oz. servings per week (preferably oily fish).[129]

Secondary prevention

For secondary prevention of CHD, Harris et al.[130] noted that there have been 9 large randomized trials with omega-3 fatty acid supplements, of which 4 reported positive (favorable) results,[131–134] 4 were neutral,[135–138] and 1 study was negative (i.e., suggested an adverse effect).[139] The positive trials were conducted between the 1980s through the early 2000s and showed that EPA and DHA intakes between 0.85 and 1.8 g/day were associated with reduced risk for CVD events. The trials with neutral results were reported between 2010 and 2012 and provided 376 to 840 mg/day of EPA and DHA. Five systematic reviews and meta-analyses have been conducted evaluating omega-3 long-chain PUFA intake for the secondary prevention of CHD. Two of these meta-analyses were published before 2010[140,141] and reported evidence of benefits in patients with existing CHD; however, the 3 meta-analyses published after 2010 did not report benefits.[142–144] The Rizos et al.[144] meta-analysis has been criticized because the authors used a critical value for declaring statistical significance of 0.006 to account for multiple comparisons instead of the traditional P value of 0.05. As noted by Harris,[145] "Without this statistical maneuver, their data led to the conclusion that fish oil supplementation significantly reduced risk for cardiac death by 9% [RR of 0.91; 95% CI 0.85–0.98; $P = .01$]."

Several possible reasons for the lack of an effect in the most recent trials have been put forth.[145] First, it may be that EPA and DHA are not effective, although there is considerable evidence that argues against this possibility. Second, increased consumer awareness of the benefits of fish and fish oil have increased background intakes and an additional 1 g of supplemental omega-3 fatty acids daily may not confer any further benefit. Notably, no measures of omega-3 status, such as plasma or red blood cell levels of omega-3, were included in most of the large-scale trials. Thus, it is not possible to determine whether a subset of patients with low omega-3 status might have benefitted. Third, in more recent clinical trials of higher risk subjects, standards of medical care were different from those in earlier decades, resulting in large percentages of study

participants taking other therapies, such as statins, antiplatelet agents, beta-blockers, and drugs that influence the renin-angiotensin axis. As discussed by Rizos et al.,[144] demonstrating benefits with a low dosage of EPA + DHA (median intake of 1.0 g/day omega-3 acid ethyl esters) when added to these cardioprotective therapies may not be possible.

Mechanisms for ASCVD benefits of long-chain omega-3 fatty acids

Long-chain omega-3 fatty acids may influence ASCVD event risk through a number of mechanisms, including altering susceptibility to ventricular arrhythmia, lowering heart rate and blood pressure, and reducing platelet activation and inflammation.[126] The dose-response characteristics for these various effects have not been fully explored, and the relative importance of these mechanisms in different population subgroups may vary. At higher levels of intake, omega-3 fatty acids lower levels of TG and VLDL-C.

Heart failure

Nestel et al.[146] noted that there may be a benefit for use of omega-3 fatty acid supplements as an adjunct to heart failure therapy. Results of the Gruppo Italiano per lo Studio della Sopravvivenza (GISSI)-Prevenzione Trial[147] showed that there was a substantially larger benefit for sudden cardiac death reductions with EPA and DHA supplementation in patients with ejection fractions <40% compared with those >50% (58% reduction vs 11% reduction, $P = .0003$). In the GISSI-Heart Failure Trial, patients with functional Class II to IV heart failure who were randomized to 1 g/day of EPA and DHA ethyl esters for 3.9 years had an absolute 9% reduction in mortality or hospital admission ($P = .04$). In a subsequent review, Marchioli and Levantesi[148] reported that in 100 heart failure patients, treatment with 1 g/day omega-3 fatty acid supplements was associated with prevention of 1.8 deaths and 1.7 cardiovascular hospitalizations. Moreover, in the GISSI-Heart Failure Trial, baseline plasma phospholipid EPA levels were inversely related to total mortality.[149] The National Heart Foundation of Australia concluded that there is modest support for 1 g/day of omega-3 PUFA in addition to standard therapy for patients with heart failure.[146]

ALA

In a systematic review and meta-analysis of 27 studies, Pan et al.[150] reported an inverse association between ALA intake and total CVD risk. They found a 14% higher incidence in total events in the lowest vs highest tertile of dietary ALA intake and biomarker levels (combined). In the dietary ALA studies, there was a 10% reduction in risk when comparing those with the highest vs those with the lowest tertiles of intake. Each 1 g/day increment of ALA intake is associated with a 10% lower risk of CHD death. This epidemiologic evidence needs to be corroborated with clinical studies that evaluate the effects of ALA on primary prevention of CVD events. The 2010 DGA recommendation for ALA intake was 0.6 to 1.2% of energy, which may lower CVD risk; however, evidence was insufficient to warrant a greater intake.[19]

Dietary considerations for management of hypertriglyceridemia

Part 1 of the NLA Recommendations for Patient-Centered Management of Dyslipidemia endorses non-HDL-C and LDL-C as targets of therapy.[1] Currently, TG is not a specific target for therapy except when levels are ≥500 mg/dL. When the TG concentration is ≥500 mg/dL—and especially if ≥1000 mg/dL—reducing risk of pancreatitis by lowering of TG to <500 mg/dL becomes the primary goal of therapy. For patients with hypertriglyceridemia who have borderline high to high TG (range: 150 to 499 mg/dL), the primary objective of therapy is to reduce risk for an ASCVD event by lowering levels of atherogenic cholesterol (non-HDL-C and LDL-C). The predominant lipoprotein transporter of TG in the blood is VLDL, and the circulating level of TG is highly correlated with VLDL-C, a component of non-HDL-C (non-HDL-C is mainly comprised of LDL-C and VLDL-C).

Non-dietary secondary causes of hypertriglyceridemia, such as medications and disease conditions, including uncontrolled diabetes, hypothyroidism, and renal disease, should be identified and treated where applicable (Refer to Part 1 of the NLA recommendations[1]). Elevated TG (and VLDL-C) reflect multifactorial metabolic imbalances derived from the interaction of genetic and environmental factors and are highly responsive to lifestyle practices.[151–154]

The 2011 AHA Scientific Statement on TG and CVD[152] provides a comprehensive review of the epidemiology, pathophysiology, etiology, special populations and treatment for hypertriglyceridemia, and proposes a practical algorithm for screening and management of elevated TG levels (Fig. 1 adapted[152]). This evidence-based analysis yielded the following conclusion on nutrition and TG management:

> Overall, optimization of nutrition–related practices can result in a marked triglyceride-lowering effect that ranges between 20% and 50%. These practices include weight loss, reducing simple carbohydrates at the expense of increasing dietary fiber, eliminating industrial-produced trans fatty acids, restricting fructose and saturated fatty acids, implementing a Mediterranean-style diet, and consuming marine derived omega-3 PUFA. Dietary practices or factors that are associated with elevated triglycerides levels include excess body weight, especially visceral adiposity; simple carbohydrates, including added sugars and fructose; a high glycemic load; and alcohol.

The NLA has provided practical information for physicians to give patients regarding approaches to reduce TG (Supplemental Figure 1).[155]

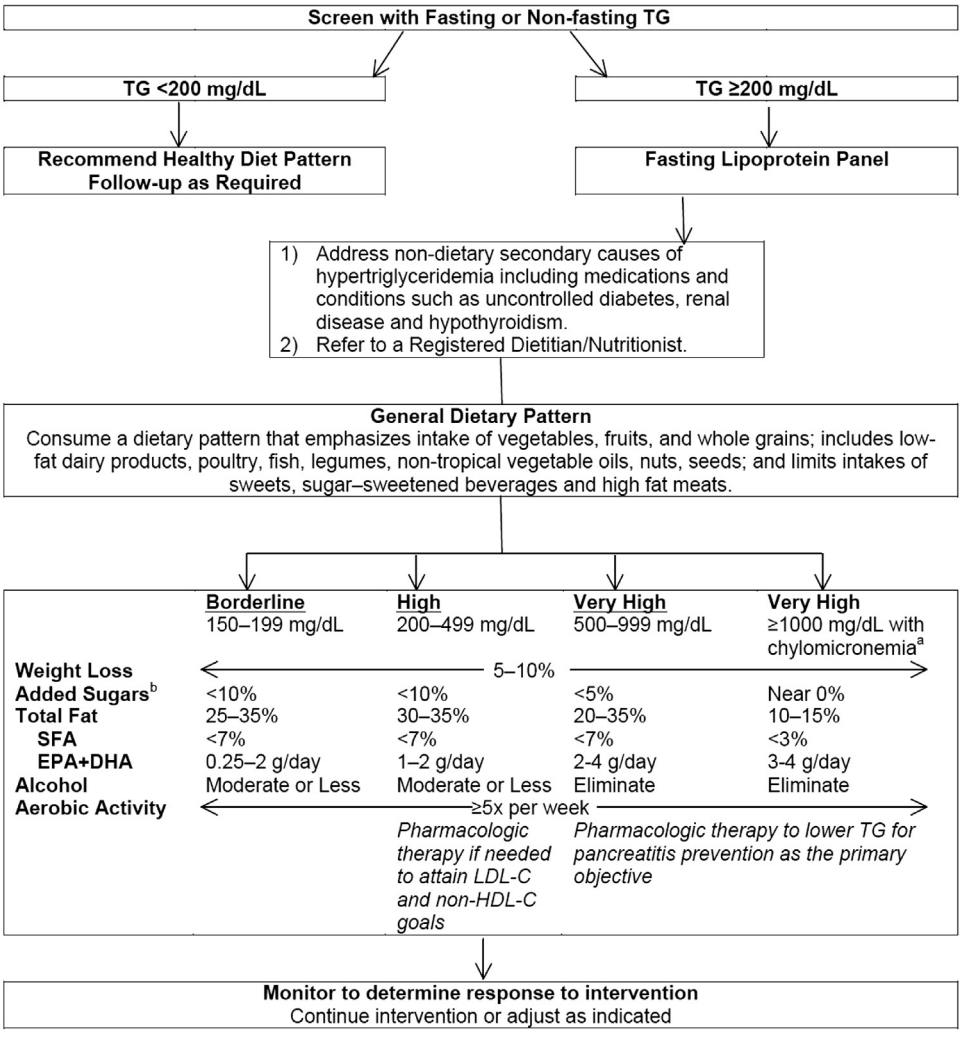

Figure 1 Clinical algorithm for screening and management of elevated TG. Adapted from Miller M, et al. *Circulation*. 2011;123:2292–2333.[152] [a]Special consideration for patients with initial TG ≥1000 mg/dL and chylomicronemia: recheck lipids in 2 weeks. When TG <500 mg/dL, diet may gradually be liberalized with monitoring. [b]In addition to added sugars, some foods and beverages that are high in naturally occurring sugars, for example, honey and fruit juices, should be limited. EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; SFA, saturated fatty acids; TG, triglyceride.

Weight loss

The magnitude of reduction in TG is related to magnitude of weight loss, but even a small (3–5%) reduction in body weight can lower TG.[152,156] As noted by Miller et al.,[152] a 5–10% weight loss would be expected to lower TG by approximately 20%. A strong association has been demonstrated between TG and weight, elevated BMI, and visceral fat.

Mediterranean-style dietary pattern

While the optimal macronutrient distribution for lowering TG is not established and likely depends on the individual, the Mediterranean-style dietary pattern has been shown to consistently produce a TG-lowering effect.[152] The various definitions of the Mediterranean diet used in studies limits comparisons, but in general, a Mediterranean-style dietary pattern includes an emphasis on plant-based foods, including fruits, vegetables, whole grain cereals, legumes, nuts and seeds, along with small amounts of dairy, fish and seafood, animal protein and eggs; wine in moderation and mainly with meals; and often a greater proportion of total fat, typically from olive oil. Red meat, processed meats, and simple and refined carbohydrates are limited.[157] The 2011 AHA Scientific Statement on TG and CVD[152] concluded that a Mediterranean-style dietary pattern is associated with an approximate 10–15% reduction in TG compared with a low-fat diet.

Macronutrient distribution

A high-carbohydrate/low-fat diet that is high in refined starches and simple carbohydrates is not beneficial for the management of elevated TG (200–500 mg/dL) and, thus, is not recommended. The Institute of Medicine's Panel on Macronutrients reported that for every 5% decrease in total fat, TG level is predicted to increase by 6%, which may be

attributable to the higher carbohydrate content of lower fat diets.[158] Partial replacement of refined grains and added sugars with fiber-rich whole grains and other complex carbohydrate foods, such as legumes, will often lower the TG concentration. The preferred dietary substitutes for refined grains and added sugars are foods high in unsaturated fats, protein, and fiber-rich whole grains, nuts, seeds and legumes. It is important, however, to understand that carbohydrates from less refined sources, such as brown rice and whole-grain bread, can also raise the TG concentration.

Alcohol

There is a J-shaped relationship between alcohol intake and TG level. In some individuals, low alcohol consumption may be associated with decreased TG.[159–161] High alcohol intake is associated with TG elevation, especially in the presence of obesity.[162] Patients with hypertriglyceridemia that is affected by alcohol should be advised to reduce or eliminate alcohol. In those with very high TG (≥500 mg/dL), complete abstinence of alcohol is generally recommended to reduce the likelihood of pancreatitis.[152,159,162]

Long-chain omega-3 fatty acids

The lipid-altering effects of EPA + DHA are very similar to those observed with fibrate medications. RCTs of the effects of fibrates on ASCVD event risk have shown mixed results, but subgroups with elevated TG, especially if accompanied by low HDL-C, have consistently shown risk reduction.[163,164] Thus, it is possible that therapeutic dosages of long-chain omega-3 fatty acids (2.0 to 4.0 g/day) might lower ASCVD event risk in patients with elevated TG or elevated TG plus low HDL-C. A subgroup analysis of participants in the Japan EPA Lipid Intervention Study (JELIS) with TG ≥150 mg/dL plus HDL-C <40 mg/dL suggested that the reduction in CVD event risk with EPA ethyl esters (1.8 g/day) was larger in this subset (53%) than in the overall study sample (19%).[165] Two ASCVD outcomes trials are currently underway to assess the influence of prescription omega-3 products on CVD outcomes in patients with hypertriglyceridemia despite statin therapy (Reduce Cardiovascular Events in High Risk Patients With Hypertriglyceridemia and on Statin [REDUCE-IT] is registered at ClinicalTrials.gov as NCT01492361 and STatin Residual Risk Reduction With EpaNova in HiGh CV Risk PatienTs With Hypertriglyceridemia [STRENGTH] is registered as NCT02104817).[166,167]

Intakes of 2.0 to 4.0 g/day of long-chain omega-3 fatty acids are generally required to achieve significant (>15%) TG-lowering effects.[153] As noted by Pirillo and Catapano,[168] there is little evidence of clinically relevant efficacy at dosages <1 g/day. The TG-lowering effect observed at recommended intakes (200 to 500 mg/day) for primary prevention of coronary disease ranges from 3.1% to 7.2%.[168] With higher intakes of EPA and DHA (2.0 to 4.0 g/day), the TG-lowering effect ranges from 20% to 35% and even up to 45% in individuals with very high TG (≥500 mg/dL).[168] The percentage reduction in TG with therapeutic dosages of EPA + DHA increases in a non-linear fashion with higher baseline TG concentrations.[169–172]

Omega-3 fatty acid preparations containing EPA and DHA may increase LDL-C by up to 49% in patients with very high TG (the range is +17% to +49%), although little or no increase is typically observed in patients with mixed dyslipidemia. Wei et al.[173] conducted a meta-analysis to evaluate and compare the effects of EPA and DHA on lipoprotein lipids. Randomized placebo-controlled trials of monotherapy with EPA (n = 10), DHA (n = 17), or EPA vs DHA (n = 6) were identified. Compared with placebo, DHA raised LDL-C 7.23 mg/dL (95% CI 3.98–10.5), whereas EPA non-significantly reduced LDL-C. In direct comparison studies, DHA raised LDL-C 4.63 mg/dL (95% CI 2.15–7.10) more than EPA. Both EPA and DHA reduced TG, with a slightly greater reduction by DHA in direct comparison studies. DHA also raised HDL-C (4.49 mg/dL; 95% CI 3.50–5.48) compared with placebo, whereas EPA did not. The authors concluded that both EPA and DHA lower TG, but that the two fatty acids have divergent effects on LDL-C and HDL-C. This conclusion is consistent with that from a review of 22 studies published by Jacobson et al.,[174] 6 of which directly compared EPA with DHA, 12 studied DHA alone, and 4 studied EPA alone.

Prescription EPA and EPA + DHA concentrates have been approved in ethyl ester and carboxylic acid forms (discussed in Harris et al.[130] and Ballantyne et al.[175]). Presently, these are indicated for the treatment of very high TG (≥500 mg/dL). A cautionary note is that the EPA and DHA ethyl esters may not be absorbed well on an empty stomach or when consumed with a low-fat meal.[176] Omega-3 fatty acid preparations in other forms (e.g., fish oil, algae oil, krill oil) are sold as dietary supplements (reviewed by Skulas-Ray et al.[177]). The National Heart Foundation of Australia has affirmed that omega-3 fatty acids are a means for TG lowering with the caveat that they may augment the anti-platelet effects of combination therapy with aspirin and other anti-platelet drugs.[146] Use of supplemental long-chain omega-3 fatty acids at therapeutic dosages (2.0 to 4.0 g/day), whether taken as prescription drugs or dietary supplements, should be done under the supervision of a qualified clinician.

Dietary recommendations for management of patients with very high TG (≥500 mg/dL)

For individuals with very high TG (≥500 mg/dL), nutrition therapy will differ from the management of TG <500 mg/dL (Fig. 1).[152] Plasma TG are mainly transported in plasma by 2 distinct classes of lipoproteins: 1) chylomicrons produced and absorbed in the gastrointestinal tract; and 2) VLDL synthesized in the liver. In healthy individuals, chylomicron particles quickly transfer TG to the peripheral tissues and are removed from plasma within

Table 6 Nutrition therapy for very high TG (≥500 mg/dL)/chylomicron clearing[12]

Temporarily limit total fat to 10%–15% calories (typically 20–40 g/day) during chylomicron clearing
Avoid alcohol
Avoid refined starches and partially replace with high fiber, whole grain foods
Avoid added sugars, limit fruit; no fruit juice or sugary beverages
Spread calories and carbohydrates evenly through the day
Limit calories if weight loss is indicated
If extra calories are needed, add medium chain TG oil and increase gradually
Exercise 30–60 min most days
Adjust diabetes medications as appropriate to maintain glycemic control
Once chylomicron particles have been cleared and TGs are <500 mg/dL, gradually advance dietary fat to tolerance

TG, triglyceride.

a few hours. In normotriglyceridemic patients, nearly all of the TG in fasting plasma is carried by lipoproteins other than chylomicron particles. When fasting TG are ≥500 mg/dL, and particularly when ≥750 mg/dL, fasting chylomicronemia is often present. At very high fasting TG levels, especially if ≥1000 mg/dL, restriction of dietary fat to less than 15% total energy intake (usually <20–40 g daily; 40 g is 15% of energy for a 2400 kcal diet) is recommended to reduce the formation of chylomicron particles. This restriction is temporary while chylomicron particles are cleared, except for patients with lipoprotein lipase deficiency. Table 6 summarizes recommendations for lifestyle therapies in patients with very high TG (≥500 mg/dL).[12]

Patients with very high TG should also adhere to other dietary and lifestyle recommendations to reduce endogenous TG synthesis, including reducing consumption of sugars, refined grains, and alcohol (complete alcohol abstinence is recommended for those with very high TG), and engaging in moderate or higher intensity aerobic activity ≥5 days per week. Medium chain TG oil may provide additional calories during the initial chylomicron-clearing phase because medium chain TG are directly absorbed into portal circulation, and, thus, do not induce chylomicron synthesis.[178,179] Patients on very-low fat diets (<15% of energy) over an extended period may benefit from consuming a source of essential fatty acids (walnut or sunflower oil), as well as fat-soluble vitamin supplements.[154]

When TG have decreased to <500 mg/dL, for most individuals without lipoprotein lipase deficiency, dietary fat intake may be liberalized with monitoring of the TG response. Monitoring TG responses to changes in food intake helps patients to learn their particular dietary sensitivities.

Additional dietary considerations for lowering ASCVD risk

In addition to the core considerations for management of dyslipidemia and associated ASCVD risk described above, the NLA Expert Panel concluded that additional topics warranted comment and consideration by clinicians. These are described below.

Whole grains and dietary fibers

Consumption of whole grains, including rye, oats, barley, and whole wheat, is associated with a reduced risk of ASCVD events including CHD and stroke, as well as reduced risk for the development of type 2 diabetes mellitus.[17] There is no standard definition of whole grains; however, whole grains generally include the bran, germ, and endosperm.[17] The bran component contains soluble and insoluble dietary fibers, B vitamins, minerals, flavonoids, and tocopherols, whereas the germ fraction contains fatty acids, antioxidants, and phytochemicals, and the endosperm is comprised primarily of starch (carbohydrate polysaccharides) and storage proteins. The AHA issued 2020 Impact Goals to improve the cardiovascular health of all Americans and included a recommendation to consume ≥3 1-oz.-equivalent servings of fiber-rich whole grains per day.[129] The NLA Expert Panel endorses this recommendation.

Nuts, seeds, and legumes

Since the early 1990s, numerous observational studies and controlled clinical trials have shown consistent associations between consumption of nuts, seeds, and legumes with lower ASCVD event risk and an improved ASCVD risk factor profile (reviewed by Griel and Kris-Etherton[180] and Ros et al.[181]). The AHA's 2020 Impact Goals to improve the cardiovascular health of all Americans included a recommendation to consume ≥4 servings per week of nuts, seeds, and legumes.[129] The NLA Expert Panel endorses this recommendation, with particular emphasis on nut consumption.

The NLA Expert Panel consensus view was that the evidence was particularly strong and consistent for nut consumption as a predictor of favorable cardiovascular health outcomes. In a pooled analysis of 4 early prospective studies (Adventist Health Study,[182] Nurses' Health Study,[183] Iowa Women's Health Study,[184] Physicians' Health Study[185]) that evaluated nut consumption and CHD incidence, there was a 37% reduction in multivariable-adjusted risk of fatal CHD[186] when the highest (≥4 servings/week) vs the lowest frequency of nut intake was compared (0.63; 95% CI 0.51 to 0.83). All

studies reported a dose-response relationship between nut consumption and reduced CHD mortality rates.

More recently, in a systematic review and meta-analysis of 25 observational studies and 2 clinical trial reports with 501,791 individuals,[187] nut consumption was inversely associated with incidence of fatal ischemic heart disease (6 studies; 6749 events; RR per 4 weekly 28.4-g servings: 0.76; 95% CI 0.69–0.84; I^2 = 28%), nonfatal ischemic heart disease (4 studies; 2101 events; RR: 0.78; 0.67–0.92; I^2 = 0%), and diabetes (6 studies; 13,308 events; RR: 0.87; 0.81–0.94; I^2 = 22%), but not stroke (4 studies; 5544 events). In this study, individuals from the United States, Spain, Finland, China, Greece, Costa Rica and Japan were studied. Thus, the favorable associations between nut consumption and risk for fatal and nonfatal ischemic heart disease are present in many countries with a wide range of risk profiles and background diets.

As mentioned previously, the PREDIMED RCT[48] randomized participants to receive: (1) a low(er)-fat diet (37% calories from fat); (2) a Mediterranean diet with extra-virgin olive oil (EVOO) (1 L/week/family; 50 g/day per participant); or (3) a Mediterranean diet with tree nuts (30 g/day: 15 g walnuts, 7.5 g almonds, 7.5 g hazelnuts). After 4.8 years, there was a 30% reduction in the primary endpoint, which was rate of major cardiovascular events (MI, stroke, or death from cardiovascular causes) in both Mediterranean diet groups. These results are, therefore, concordant with those from observational studies and suggest that a Mediterranean-style dietary pattern rich in nuts is associated with lower ASCVD event risk.

The NLA Expert Panel consensus includes a recommendation to consume ≥4 servings/week of nuts (including the legume, peanuts) to reduce risk of ASCVD. One serving of nuts is 1 oz. Nuts should be incorporated as part of a cardioprotective dietary pattern that also ideally includes seeds and legumes. For diet planning purposes, nuts may be considered a plant protein food as well as a source of unsaturated fatty acids.

Soy protein

Many RCTs have assessed the effects of soy protein on serum lipoprotein lipids, with emphasis on LDL-C. In the early clinical studies, in which animal protein was almost entirely replaced with soy protein, significantly reduced plasma cholesterol levels were observed in both healthy young women[188] and hypercholesterolemic patients.[189] Subsequent investigations of the cholesterol-lowering effects of soy protein were examined in a 1995 review that showed consumption of 47 g soy protein/day reduced serum total-C by 9.3%, LDL-C by 12.9%, and TG by 10.5%, while increasing HDL-C by 2.4%.[190] This analysis provided the basis for the FDA health claim for soy, which states: “Diets low in saturated fat and cholesterol that include 25 g of soy protein a day may reduce the risk of heart disease.”

Despite the evidence in support of this health claim, more recent meta-analyses have reexamined the effects of soy on the lipid profile and reported substantially smaller effects.[191,192] The AHA Soy Science Advisory Panel reported results from a meta-analysis that showed a mean LDL-C reduction of 3% with soy protein interventions from results in 22 randomized trials.[193] This panel also concluded that soy had no effect on HDL-C, TG, lipoprotein (a) [Lp(a)], or blood pressure.

The evidently smaller LDL-C-lowering effect of soy in recent studies prompted concern regarding the heart-health claim previously allowed for soy products. In response, Jenkins et al.[194] reviewed the evidence in an attempt to estimate the intrinsic and extrinsic (displacement) potential of soy for reducing LDL-C to assess whether the heart health claim for soy continues to be justified. The intrinsic effect of soy was derived from a meta-analysis using soy studies (20–133 g/day soy protein). The extrinsic effect of soy in displacing foods higher in saturated fat and cholesterol was estimated using predictive equations for LDL-C and NHANES III population survey data with the substitution of 13 to 58 g/day soy protein for animal protein foods. Their results suggested that soy protein consumption of approximately 30 g/day may have an intrinsic effect of reducing serum LDL-C by approximately 4% to 5% and may displace animal products rich in saturated fat and cholesterol to reduce LDL-C values by an additional 4% to 5%. Taken together, the estimated LDL-C reduction attributable to both the intrinsic and extrinsic effects of soy protein foods range from 7.9% to 10.3%.

The conclusions of Jenkins and colleagues[194] were confirmed in the 2011 meta-analysis by Anderson et al.[195], which also sought to reexamine the effects of soy protein on lipids and lipoproteins. This analysis included 20 parallel-design studies (981 control and 954 soy-treated subjects) and 23 crossover studies (970 control and 970 soy-treated subjects). Soy protein intake ranged from 15 to 50 g/day, with a mean intake of ~30 g/day. Soy protein intake was associated with an LDL-C reduction of 5.5% in parallel studies and 4.2% in crossover studies. In studies that presented baseline data, hypercholesterolemic individuals experienced significantly greater reductions in LDL-C compared to individuals with normal cholesterol levels. In parallel studies, HDL-C values were 3.2% higher with soy vs control, and fasting TG levels were 10.7% lower for soy vs control. The duration of treatment necessary to produce maximal effects on LDL-C was 8 weeks. The authors also examined whether the delivery form influenced the lipoprotein lipid response to soy protein consumption from studies where soy protein was consumed in water or another beverage (n = 27), in soy milk or yogurt (n = 9), or in other food forms (n = 11), such as soy nuts, tofu, or muffins. No association between food form and reduction in LDL-C was reported.

The mechanisms responsible for the effects of soy protein consumption on LDL-C remain unclear. Maki et al.[196] evaluated the effects of 25 g/day of a very low isoflavone soy protein preparation (1 mg aglycone equivalent/g protein) on lipoprotein lipids in men and

women with hypercholesterolemia (baseline LDL-C ~134 mg/dL) who had a demonstrated response to a bile acid sequestrant drug (colesevelam) to assess the possible roles of binding with bile acids and cholesterol on the cholesterol-lowering effect. Compared to a milk protein control, significant reductions were observed for non-HDL-C (6.9%), TG (13.7%), and apo B (7.3%) with the soy protein preparation. A near-significant reduction of 5.0% was observed for LDL-C ($P = .08$). No significant differences between the treatments were observed for fecal excretion of bile acids or cholesterol. Therefore, these results suggest that the lipid-altering effects of soy are not attributable to trapping of bile acids or cholesterol, or to effects of isoflavones (because this study used a very low isoflavone preparation). Additional research is needed to more clearly define the mechanisms by which soy protein influences lipoprotein metabolism.

The existing FDA-approved health claim for soy and heart disease requires that each food with the health claim on its label contain at least 6.25 g of soy protein, based on the need for 25 g of soy protein to show significant lowering of serum total-C and LDL-C levels. Soy foods that meet the 6.25 g level include 4 oz. of whole soybeans, 8 oz. of soy milk, 3.5 oz. soy flour, 8 oz. textured soy protein, 4 oz. tofu, and 4 oz. tempeh.

In summary, soy protein lowers LDL-C via intrinsic and extrinsic effects. When incorporated in a cardioprotective diet as a substitute for foods high in saturated fat, there is an LDL-C-lowering effect that is due to both decreasing saturated fat and increasing soy protein. Soy protein foods are one source of plant protein among others (e.g., nuts, legumes) that can be included in a cardioprotective eating pattern.

Probiotics

Probiotics are live microorganisms that can confer beneficial effects on the host.[197] There is emerging evidence that certain bacterial strains reduce blood cholesterol levels (reviewed in DiRienzo[198] and Ettinger et al.[199]). The genera *Lactobacillus* and *Bifidobacterium* are a significant proportion of probiotic cultures in functional foods; however, certain *Bacillus* and *Enterococcus* strains may also be incorporated into probiotic products.[200]

In a meta-analysis of 13 controlled trials of 485 participants with normal or high cholesterol levels who were treated with probiotics, total-C decreased 6.40 mg/dL, LDL-C decreased 4.90 mg/dL, and TG decreased 3.95 mg/dL.[201] An earlier meta-analysis of 6 intervention studies reported similar lipid and lipoprotein effects.[202] In a more recent review of 26 clinical studies,[198] a significant LDL-C-lowering effect was reported for 4 probiotic strains: *Lactobacillus reuteri NCIMB* 30242 (8.9–11.6%), *Enterococcus faecium* (5%), and the combination of *Lactobacillus acidophilus* La5 and *Bifidobacterium lactis* Bb12 (0–7.5%).

There are several proposed LDL-C-lowering mechanisms of probiotics: 1) sequestering of cholesterol in the gut by incorporation into cellular membranes[203,204]; 2) conversion of cholesterol to coprostanol, which is excreted in the feces[204]; and 3) production of bile salt hyrolases that deconjugate bile acids, interfering with incorporation of cholesterol into mixed micelles; and possibly through an effect of deconjugated bile acids to stabilize ABC sterol transporters that move cholesterol and other sterols out of enterocytes.[205,206]

At present, the evidence base is too limited to make a recommendation regarding the use of probiotic products as dietary adjuncts to lower atherogenic cholesterol levels. However, the available data appear promising and suggest that additional research is warranted to further evaluate this class of products.

Effects of coconut oil on lipoprotein lipids

Despite being comprised of approximately 65% cholesterol-raising (12–16 carbon saturated) fatty acids,[207,208] coconut oil, and particularly "virgin" coconut oil, has gained popularity among some consumers because of purported health benefits. However, the claims made for virgin coconut oil, or coconut oil in general, are not supported by a robust scientific evidence base. There are few published studies in humans that have examined the effect of coconut oil or virgin coconut oil on lipids/lipoproteins, and all were conducted outside the United States.

One RCT was a well-controlled feeding study conducted in Malaysia with a group of 45 healthy subjects who consumed diets in a crossover fashion with 30% of energy from fat, two-thirds of which was provided by 1 of 3 test fats: palm oil, olive oil, or coconut oil.[209] The 3 diets differed only in the type of test fat incorporated, and intakes of cholesterol-raising saturated fatty acids (12 to 16 carbon) during the 3 diets were 10.7% (palm oil), 5.2% (olive oil), and 17.0% (coconut oil). Compared to the olive oil diet, the coconut oil diet increased mean levels of total-C (6.5%) and LDL-C (7.8%), while also raising HDL-C to a similar degree (7.0%). Values were intermediate between the olive and coconut oil conditions during the palm oil diet, with levels of total-C, LDL-C, and HDL-C raised by 3.4%, 4.6%, and 2.3%, respectively, compared with the olive oil diet. These findings are similar to the effects predicted based on the differences in the fatty acid compositions of the 3 test fats. Therefore, the results of this study illustrate that the saturated fatty acids in coconut oil increase total-C, LDL-C, and HDL-C. The increase in HDL-C is of uncertain clinical relevance, but the increase in LDL-C would be expected to have an adverse effect on ASCVD risk.

After reviewing the limited available evidence, the NLA Expert Panel consensus view is that, if coconut oil is used as part of a daily eating plan and/or in food preparation, it is recommended that it be used within the context of a healthy dietary pattern. One tablespoon of coconut oil contains 11.7 g of saturated fat and 1 tablespoon of virgin coconut oil contains 13.6 g of saturated fat.[70] Either would, therefore, contribute a significant portion of the recommended total daily saturated fat limit of <7% of energy (15.5 g/day of saturated fat would constitute 7%

of energy on a 2000 kcal/day diet). Therefore, if coconut oil and virgin coconut oil are incorporated into a healthy dietary pattern, this must be done sparingly by patients who would benefit from reductions in atherogenic cholesterol (LDL-C and non-HDL-C).

Role of the registered dietitian nutritionist in the management of dyslipidemia

Four systematic reviews[210–213] conducted from 1995 to 2014 and 7 research trials[214–220] conducted from 2011 to 2014 have been completed to assess the effectiveness of MNT guided by dietitian(s) for ASCVD risk factor modification. The results support the conclusion that multiple visits with a dietitian (nutritionist) can result in improvements in LDL-C, TG, and metabolic syndrome criteria.[221–231] Five studies conducted abroad (in China, Greece, Korea, Malaysia, Japan) refer to nutrition professionals as "dietitians" rather than as "registered dietitian nutritionists" or "registered dietitians".[216–220] Of note, is that the studies conducted in the United States used the "registered dietitian" credential because it was only recently replaced by the "registered dietitian nutritionist" credential in 2014 by the Academy of Nutrition and Dietetics. In this document, "registered dietitian nutritionist" is used synonymously for "registered dietitian" as well as "dietitian."

McCoin et al.[213] systematically reviewed the lipid profile changes in 8 studies conducted between 1991 and 2006 that met the criteria for MNT interventions provided by a registered dietitian nutritionist, with the MNT provided for 6 weeks to 6 months. Interventions resulted in significant decreases in total-C (6–13%) and LDL-C (7–15%). TG and HDL-C changes were mixed.[213] Authors of a systematic Cochrane review of 9 studies[212] concluded that MNT by a registered dietitian nutritionist is recommended for treating patients with disorders of lipid metabolism and other CHD risk factors. On the basis of this review, the Academy of Nutrition and Dietetics Expert Panel on Disorders of Lipid Metabolism recommended that the registered dietitian nutritionist should provide multiple visits for MNT (3 to 6 visits) over 8 to 12 weeks to improve a patient's lipid profile. Two studies reported that the magnitude of LDL-C reduction was greater with additional visits or time spent with the registered dietitian nutritionist.[212] There is no evidence to support an adverse effect of MNT for dyslipidemia management on quality of life, and some evidence is suggestive of a favorable effect of MNT on patients' sense of well being.[232,233]

Taken together, these data strongly indicate that MNT provided by a registered dietitian nutritionist is effective for improving lipid/lipoprotein profiles and cardiometabolic risk factors and may favorably affect quality of life. Overall, MNT provided by a registered dietitian nutritionist resulted in improved LDL-C, TG, HDL-C, glycemia, and body weight status. Several studies[212–220] also reported reductions in waist circumference, BMI, body fat, and improved dietary intakes (energy, saturated fat, and fiber).

See Chart 1 for the Nutrition Recommendations.

Exercise/physical activity

Considerable evidence from population studies links higher levels of physical activity and cardiorespiratory fitness with reduced risk for ASCVD events. Physical activity has a number of beneficial effects on risk factors for ASCVD. In addition to effects on lipids and lipoproteins summarized below, increasing physical activity and cardiorespiratory fitness in previously sedentary people has been associated with improvements in blood pressure, insulin resistance, and hemostasis.[234–237]

Exercise training in the absence of a change in adiposity has effects to reduce the circulating TG concentration and modestly raise the level of HDL-C.[238] If the volume of exercise is sufficient to lower body fat, this will typically enhance these changes, while also resulting in a modest to moderate reduction in the LDL-C concentration.[238,239]

The magnitudes of changes in lipid and lipoprotein levels depend on a number of variables (see below) beyond the type, frequency, intensity, and duration of physical activity. These factors are important for clinicians to be aware of because they may influence, or interact with, the effects of exercise and contribute to variability in responses.

- Gender and menopausal status
- Race/ethnicity
- Nature and severity of the lipid/lipoprotein disorder
- Accompanying changes in diet (including alcohol intake)
- Changes in body fat
- Plasma volume changes
- Genetic factors (e.g., apo E and C isoforms)
- Seasonal and diurnal changes in lipoprotein lipid levels

Quality and quantity of physical activity required to generate favorable lipid and lipoprotein changes

In order to reduce LDL-C, the quantity of physical activity needed is consistent with recommendations for long-term weight control (200–300 min/week of moderate intensity physical activity or ≥2000 kcal/week), which may be accumulated in repeated bouts of exercise of at least 10 min each.[20] Use of well-engineered pedometers for recording walking step counts has been successfully employed in outpatient clinic settings as a means of tracking activity for managing dyslipidemia and promoting weight loss. In general, the amount of walking required to produce weight loss is ≥40,000 steps/week (beyond steps/activities of daily living), which is approximately equivalent to 2000 kcal/week energy expenditure (based on ~2000 steps/mile and ~100 kcal gross energy cost/mile).[21,240]

The recommendations for accumulating sufficient physical activity to lower body fat and LDL-C differ from the more general public health guidelines.[241] The CDC public health guidelines recommend that all healthy adults aged 18 to 65 years should engage in moderate intensity aerobic (cardiorespiratory endurance) physical activity for a minimum of 30 min

Chart 1 Nutrition recommendations

Recommendations	Strength	Quality
The NLA Expert Panel supports a cardioprotective eating pattern for the management of dyslipidemia and overall cardiovascular health that includes <7% of energy from saturated fat, with minimal intake of *trans* fatty acids to lower levels of atherogenic cholesterol (LDL-C and non-HDL-C).	A	Moderate
The cardioprotective eating pattern should limit cholesterol intake to <200 mg/day to lower levels of atherogenic cholesterol (LDL-C and non-HDL-C).	B	Moderate
There are individuals who are hyper-responders to dietary cholesterol because of genetic or other reasons. For known or suspected hyper-responders, further reduction in dietary cholesterol beyond the <200 mg/day that is recommended as part of the cardioprotective eating pattern for the management of dyslipidemia may be considered. Consumption of very low intakes of dietary cholesterol (near 0 mg/day) may be helpful for such individuals.	B	Low
The NLA Expert Panel recommends any of the following healthy dietary patterns, including an emphasis on a variety of plant foods and lean sources of protein for managing dyslipidemia: DASH, USDA (healthy US-style), AHA, Mediterranean-style, and vegetarian/vegan. However, the dietary pattern should be individualized based on the patient's specific dyslipidemia. Also, patients' cultural and food preferences are important for guiding food selection to maximize dietary adherence. Nutritional counseling and follow-up/monitoring by a registered dietitian nutritionist is recommended whenever possible to individualize a patient's dietary pattern. Nutrition therapy should be included in those with other medical conditions, including diabetes.	A	Moderate
If alcohol is consumed as part of a healthy dietary pattern, this should be in moderation (≤7 drinks per week for women and ≤14 drinks per week for men; consumed in a non-binge pattern). One drink is equivalent to 12 oz. beer, 5 oz. wine, or 1.5 oz. distilled spirits.	A	Moderate
Dietary saturated fat may be partially replaced with unsaturated fats (mono- and polyunsaturated fats), as well as proteins, to reach a goal of <7% of energy from saturated fats. This can be achieved, in part, by incorporating foods high in unsaturated fats, such as liquid vegetable oils and vegetable oil spreads, nuts and seeds, as well as lean protein foods, such as legumes, seafood, lean meats, and non- or low-fat dairy products, into the diet as replacements for foods high in saturated fats.	A	Moderate
Weight loss of 5-10% body weight is generally recommended for overweight or obese individuals to lower atherogenic lipoprotein lipids and improve other ASCVD risk factors. A variety of dietary approaches can be implemented for weight loss. Any dietary approach will result in weight loss if energy intake is reduced. An energy-reduced healthy dietary pattern that meets nutrient needs is recommended for patients who are overweight or obese. Several healthy dietary patterns, such as the Mediterranean-style, DASH, USDA, and vegetarian diets, can be tailored to personal and cultural food preferences and appropriate calorie needs for weight control.	A	Moderate
Eating patterns that contain a moderate quantity of carbohydrate, lower glycemic index and load, and higher protein, have been associated with modest benefits for weight loss and maintenance.	C	Low
Plant sterols and stanols (~2 g/day) are recommended for cholesterol lowering, as well as viscous fibers (5 to 10 g/day or even greater, if acceptable to the patient), as adjuncts to other lifestyle changes. However, individuals with phytosterolemia (sitosterolemia) should avoid foods that are fortified with stanols and sterols.	B	Moderate
For patients with TG levels ≥150 mg/dL, lifestyle therapy is indicated, including weight loss, if overweight or obese, physical activity, and restriction of alcohol, and sugars and refined starches. Partial replacement of sugars and refined starches with a combination of unsaturated fats, proteins, and high-fiber foods may help to reduce TG and non-HDL-C concentrations.	A	Moderate
For patients with TG levels ≥1000 mg/dL (and selected patients with TG 500-999 mg/dL), a low-fat diet (<15% of energy) and alcohol abstinence are recommended initially to minimize chylomicronemia. In patients with hypertriglyceridemia and diabetes, dietary carbohydrate should not be substantially increased to avoid worsening glycemia when reducing fat intake. Medium chain TG oil may be used as a source of energy that will not induce chylomicron production. For patients without lipoprotein lipase deficiency, dietary fat may be liberalized with monitoring of the TG response once the TG concentration is <500 mg/dL.	B	Moderate
Therapeutic dosages of EPA + DHA for TG reduction are 2.0 to 4.0 g/day. Use of these dosages of long-chain omega-3 fatty acids for TG-lowering should be done only under the supervision of a qualified clinician. Clinicians are encouraged to educate patients on the importance of the amount of EPA + DHA in each capsule of dietary supplement or prescription products, and to take the appropriate number of capsules daily to achieve therapeutic levels. At present, prescription forms of EPA and EPA + DHA concentrates are only indicated for treatment of very high TG (≥500 mg/dL) to reduce the risk of pancreatitis.	B	Moderate

(*continued on next page*)

Chart 1 (*continued*)

Recommendations	Strength	Quality
For primary and secondary prevention of ASCVD, consuming ≥2 servings/week of fish/seafood (preferably oily) is recommended. One serving is equal to 3.5 to 4 oz. and should ideally not be prepared using deep-frying.	A	Moderate
For patients with known ASCVD, suggestive, but not conclusive, evidence from RCTs is available for a benefit of long-chain omega-3 fatty acid supplementation at ~1 g/day EPA + DHA on cardiac mortality, but not non-fatal ASCVD events. EPA + DHA supplements may be considered for such patients, especially those who do not consume the recommended intakes of EPA + DHA from dietary sources.	C	Low
For patients with heart failure, 1 g/day of EPA + DHA is recommended as an adjunct to heart failure therapy.	A	Moderate
An ALA intake of 0.6 to 1.2% of energy is recommended.	A	Moderate
Consumption of at least three 1-oz. equivalent servings per day of fiber-rich whole grains is recommended.	A	Moderate
Consumption of ≥4 servings/week (1 oz. per serving) of nuts (including the legume, peanuts) is recommended, because nut consumption has been consistently associated with reduced ASCVD risk. Nuts may be included in the diet as a protein food and as a source of healthy fat (predominantly unsaturated fatty acids).	A	Moderate
Soy protein foods are one source of plant protein, among others (e.g., nuts, legumes), that may be used as a substitute for protein foods high in saturated fat as part of a cardioprotective eating pattern.	B	Moderate
Nutrition education/MNT by a registered dietitian nutritionist with follow-up and monitoring are recommended to promote long-term dietary adherence. Clinicians should, when feasible, refer patients to a registered dietitian nutritionist for MNT to individualize a cardioprotective dietary pattern and promote successful lifestyle modifications.	A	Moderate

on 5 days each week (i.e., ≥150 min per week), or vigorous intensity aerobic physical activity for a minimum of 20 min on 3 days each week. Combinations of moderate and vigorous intensity activity may be performed to meet this recommendation. The weekly volume of physical activity required to lower LDL-C and body weight is greater, i.e., ≥2000 kcal/week, which generally requires 200–300 min/week of moderate or higher intensity physical activity.[6,20] This greater amount of physical activity necessary for reducing LDL-C was also recommended by the 2008 Physical Activity Guidelines Advisory Committee.[242] Thus, for management of body weight and LDL-C, the recommendations are as follow:

- Primary activity: aerobic exercise
- Intensity: 40–75% aerobic capacity (oxygen uptake reserve)
- Frequency: 5 or more days a week
- Duration: 30–60 min per session
- 200–300 min/week of moderate or higher intensity physical activity (≥2000 kcal/week).

Type of physical activity

Aerobic exercise is the preferred mode of physical activity in nearly all consensus guidelines that cover exercise and dyslipidemia. This is because there is significantly greater energy expenditure in dynamic aerobic exercise, compared with resistance exercise training, and this appears to be a necessary component of the lipid-altering effects of exercise training, and more likely to produce reductions in adiposity.[236] However, resistance exercise can, and should, play a supportive role to help maintain strength, balance, and bone health.[236] There is a dose-response effect of physical activity required for significant weight loss, with 250–300 min or more per week of moderate aerobic exercise being near optimum.[20,243]

Exercise and TG

The circulating TG level frequently declines with exercise training to a degree that depends upon several factors, including baseline value, exercise energy expenditure, and how soon TG values are measured after the last exercise session. Higher baseline values, greater energy expenditure and measurement closer to the time of the last exercise bout are all associated with larger reductions. In intervention trials, fasting TG have been lowered by 4 to 37% (approximate median reduction of 24%).[244] TG generally decline immediately after a session of high-volume endurance exercise, and remain lower for up to 48 hours after the session. The magnitudes of the decreases in plasma TG concentration after a single exercise session before and after training are similar, i.e., 15 to 50%. These observations suggest that chronic exercise, if not accompanied by reduced adiposity, does not have a sustained effect on the plasma TG concentration beyond that attributed to the repeated effects of acute exercise; hence exercise should be performed on a regular and uninterrupted basis to maintain a lower TG concentration.[245] Changes in TG are highly correlated with changes in VLDL-C concentration.[9,151] Thus, exercise training can help to lower the atherogenic cholesterol level by reducing VLDL-C, one of the two main components of non-HDL-C (non-HDL-C is mainly comprised of LDL-C and VLDL-C).

Elevated postprandial TG levels are associated with reduced HDL-C; an increase in the generation of small, dense LDL particles[246]; impaired endothelial function[247]; and is postulated to increase atherosclerotic plaque

formation.[248] Over the past 15 years, there has been extensive research supporting the finding that sufficient exercise completed 1 to 12 hours before a fat-rich meal will reduce postprandial lipemia by 25 to 40%.[249–251] The suppression of postprandial TG can last up to 36 hours after a significant bout of exercise, e.g., ≥400 kcal of exercise or ~4 miles of walking. Some investigators report that women may be more responsive to reducing postprandial TG with exercise than men.[252] Higher intensity exercise (>60% of maximum aerobic capacity) appears to be more effective for reducing postprandial TG than moderate intensity exercise, even when matched for the same total energy expenditure.[253]

Exercise and HDL-C

There is a marked variability of HDL-C response between individuals, with a small 3 to 5% increase in HDL-C on average having been observed after training, albeit with a range of results from −5 to +25%.[254,255] The HDL-C response appears to be influenced by baseline HDL-C, gender, training volume, and, to a lesser degree, training intensity.[255] In general, there are greater HDL-C responses to exercise training in those who have relatively low HDL-C and high TG levels.[254] Average TG levels are higher and HDL-C levels lower in men compared to women,[256], which may help to explain the larger mean HDL-C response to exercise training in men.[255]

The amount of aerobic exercise needed to produce significant HDL-C changes is estimated at ~1000 to 1500 kcal/week (i.e., ~7 to 14 miles/week of walking or jogging).[257,258] Resistance training may also generate increases in HDL-C. There are reports that 6 to 9 weeks of resistance training (8 to 10 exercises, 3 times/week) can significantly increase HDL-C 4 to 9% in men and women.[259,260] Moreover, the HDL-C response to exercise training is under considerable genetic influence, with underlying genetic polymorphisms (e.g., lipoprotein lipase and hepatic lipase) explaining up to 50% of the variation in HDL-C.[261,262]

LDL-C response to physical activity

Exercise programs have the best chance of reducing LDL-C when there is associated body fat reduction.[24,238,263,264] Most studies evaluating the total-C and/or LDL-C response to exercise training have found minimal to moderate decreases with sufficient exercise volume. Many studies have used an insufficient volume of exercise or energy expenditure, or failed to account for the effects of other variables such as changes in fat mass, plasma volume, dietary habits, or seasonal variation in cholesterol and lipoproteins. When changes in LDL-C and total-C have been reported, they are often associated with exercise training programs in which participants expended considerable more than 1200 kcal/week.[263] Endurance exercise programs producing this level of caloric expenditure most effective at lowering total-C and LDL-C in previously untrained individuals, since trained individuals do not seem to respond, even with extreme increases in training volume.[263] On average, the volume of exercise training associated with body fat loss (200–300 min per week of moderate intensity activity) will reduce LDL-C by 4 to 7%.[263,264] The LDL-C response to exercise training appears to be greatest with higher baseline LDL-C, greater total energy expenditure of the exercise program, and more loss of fat mass.[242,263,265,266]

Few controlled exercise trials have been conducted in subjects with dyslipidemia, with most evaluating individuals with normal or modestly elevated TG and/or LDL-C. An often-quoted meta-analysis (of 13 studies) found a non-significant decrease of <1% in LDL-C, independent of changes in body weight.[267] This analysis included a wide range of training modalities (running, swimming, stationary cycling, dance) and an average training stimulus of ~40 min/session, 3.9 times a week at the higher end of the range of what is considered moderate intensity exercise. This volume of exercise, ~1600 to 1800 kcal/week, is insufficient by current recommendations (≥2000 kcal/week) to demonstrate meaningful reductions in LDL-C.

See Chart 2 for the Exercise/physical activity Recommendations.

Chart 2 Exercise/physical activity recommendations

Recommendations	Strength	Quality
The recommended minimal quantity of exercise for supporting cardiovascular health and improving the lipid profile (lowering TG and sometimes raising HDL-C) is 150 min per week of moderate to higher intensity aerobic activity. This level of physical activity is consistent with public health recommendations.	A	High
To enhance the effects on TG and HDL-C, and produce reductions in LDL-C, as well as loss of body fat and weight, ≥2000 kcal per week of energy expenditure (generally 200 to 300 min per week) of moderate or higher intensity physical activity is recommended.	B	Moderate
Resistance exercise is also recommended to play a supportive role in maintaining strength, balance, and bone density.	B	Moderate

The lifespan–children to seniors

Children and adolescents

Lipid abnormalities and increased lifetime risk of ASCVD

Although ASCVD events rarely occur in children, the risk factors and risk behaviors that accelerate development of ASCVD are present in childhood.[268–270] In pathology

studies, there is a striking increase in both severity and extent of atherosclerosis as age and the number of risk factors increase.[271] The presence and intensity of risk factors are highly correlated with the extent and severity of atherosclerosis. The combined impact of multiple risk factors is exponentially greater than individual factors alone.[271] Furthermore, risk factors measured in childhood and adolescence are better predictors of the severity of atherosclerosis than risk factors measured in young adults.[272]

Observational data from individuals with genetic mutations that alter atherogenic cholesterol (LDL-C and non-HDL-C) over a lifetime provide the best evidence relating dyslipidemia to future probability of ASCVD. Genetic traits characterized by lifelong elevation of atherogenic cholesterol are associated with increased age-adjusted rates of ASCVD related events,[273] while those with genetically low levels of atherogenic cholesterol are associated with few events and longer life expectancy.[11,274] What is not known is whether achieving the same level of lipid lowering with medications over decades will offer the same protective effects as observed in individuals with lifelong lower cholesterol levels secondary to a genetic mutation.[275]

Expected lipid values in children and adolescents

Cholesterol levels, including LDL-C and non-HDL-C, are low at birth, increase in the first two years of life, peak prior to adolescence and decline during adolescence.[276] The expected values for LDL-C, non-HDL-C and apo B in children <19 years of age are lower than those in adults.[277,278] Table 7 lists acceptable, borderline-high and high values for children and adolescents.[279]

Genetic and acquired conditions associated with abnormal lipid levels

Present from birth, FH is associated with accelerated atherosclerosis and early ASCVD events.[280] Despite its prevalence and the availability of effective treatment options, FH is underdiagnosed and undertreated in both children and adults in the United States and worldwide.[281,282]

Youth with FH and other genetic forms of dyslipidemia often have severe alterations in blood lipids and incur the highest risk for CVD in early adulthood, yet rarely have signs or symptoms. This highlights the need for lipid screening. Affected children can be detected in families with premature ASCVD when a reliable family history is available. Often, however, the family history is unavailable, incomplete or inaccurate.[283]

In addition to genetic forms of dyslipidemia, acquired forms commonly occur in children who are overweight or obese, insulin resistant, and those with moderate to high risk conditions (Table 8).

Clustering of risk factors in youth greatly accelerates atherosclerosis.[271] Among the most prevalent risk combinations are the use of cigarettes with one other risk factor, obesity associated with insulin resistance, elevated TG levels, reduced HDL-C levels, and elevated blood pressure. The increasing prevalence of obesity in childhood, which is often continued into adult life, is associated with the same obesity-related risk factor clustering seen in adults. In 2007, the International Diabetes Federation launched a new definition to identify children and adolescents with the metabolic syndrome (Table 9).[284]

Risk factor tracking from childhood to adulthood

Elevated levels of cholesterol present during childhood track moderately well as children mature into adults.[285] Correlation is strongest for the highest and lowest levels of LDL-C. The strongest association of elevated LDL-C levels with ASCVD risk is evident in children with FH. Some genetic dyslipidemias require additional risk factors, such as obesity and insulin resistance, for full expression.

Table 7 Acceptable, borderline-high, and high plasma lipoprotein lipids and apolipoprotein concentrations for children and adolescents

Category	Low, mg/dL*	Acceptable, mg/dL	Borderline-High, mg/dL	High, mg/dL*
TC	—	<170	170–199	≥200
LDL cholesterol	—	<110	110–129	≥130
Non–HDL cholesterol	—	<120	120–144	≥145
Apolipoprotein B	—	<90	90–109	≥110
Triglycerides				
0–9 y	—	<75	75–99	≥100
10–19 y	—	<90	90–129	≥130
HDL cholesterol	<40	>45	40–45	—
Apolipoprotein A-1	<115	>120	115–120	—

Values far plasma lipid and lipoprotein levels are from the NCEP Expert Panel on Cholesterol Levels in Children. Non-HDL cholesterol values from the Bogalusa Heart Study are equivalent to the NCEP Pediatric Panel cut points for LDL cholesterol. Values for plasma apolipoprotein B and apolipoprotein A-1 are from the National Health and Nutrition Examination Survey III. Note that values shown are in mg/dL; to convert to SI units, divide the results for TC, LDL cholesterol, HDL cholesterol, and non-HDL cholesterol by 38.6; for triglycerides, divide by 88.6.

*Low cut points for HDL cholesterol and apolipoprotein A-1 represent approximately the 10th percentile. The cut points for high and borderline-high represent approximately the 95th and 75th percentiles, respectively.

Taken from: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. *Pediatrics*. 2011;128(Suppl 5):S213–256.[279] Permission to reprint was obtained.

Table 8 Major risk factors and conditions in children and adolescents

Criteria	Moderate risk	High risk
Body mass index	≥95th percentile–96th percentile	≥97th percentile
Hypertension	High blood pressure without medication	High blood pressure with medication
Cigarette smoking	—	Current smoker
HDL-C	<40 mg/dL	—
Predisposing medical conditions	Kawasaki disease with regressed coronary aneurysms	Kawasaki disease with current coronary aneurysms
	Chronic inflammatory disease*	Type I and II diabetes mellitus
	HIV infection	Postorthotopic heart transplant
	Nephrotic syndrome	Chronic kidney disease/end-stage renal disease/ postrenal transplant

HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus.
*Systemic lupus erythematous, rheumatoid arthritis.

Therefore, complete phenotypic expression may be delayed until adulthood.

Lowering LDL-C and diminished lifetime risk of ASCVD

Although there is ample evidence that the lesions of atherosclerosis may begin in childhood, ASCVD is rarely symptomatic during the first 4–5 decades of life.[286] In adults, efforts to lower atherogenic cholesterol and other risk factors have resulted in substantial reduction in ASCVD-related morbidity and mortality.[287] Despite this success, ASCVD remains a leading cause of morbidity and mortality in the adult population. Reducing risk factors with a healthy diet and lifestyle is the primary intervention in youth. However, for those at high risk due either to genetics and/or lifestyle, many have advocated for earlier identification and treatment with the aim of providing more effective primary prevention,[288–290] including reduction of all risk factors.[291]

Recent publications using genome-wide analysis have demonstrated many alleles that profoundly affect ASCVD risk by their association with lifelong atherogenic

Table 9 International Diabetes Federation's definition of the at risk group and metabolic syndrome in children and adolescents

Age group (years)	Obesity (WC)	Triglycerides	HDL-C	Blood pressure	Glucose
6–<10†	≥90th percentile				
10–<16	≥90th percentile or adult cut-off if lower	≥1.7 mmol/L (≥150 mg/dL)	<1.03 mmol/L (<40 mg/dL)	Systolic BP ≥130 or diastolic BP ≥85 mm Hg	FPG ≥5.6 mmol/L (100 mg/dL)‡ or known T2DM
16+(Adult criteria)	WC ≥94 cm for Europid males and ≥80 cm for Europid females, with ethnic-specific values for other groups*	≥1.7 mmol/L (≥150 mg/dL) or specific treatment for high triglycerides	<1.03 mmol/L (<40 mg/dL) in males and <1.29 mmol/L (<50 mg/dL) in females, or specific treatment for low HDL	Systolic BP ≥130 or diastolic BP ≥85 mm Hg or treatment of previously diagnosed hypertension	FPG ≥5.6 mmol/L (100 mg/dL)‡ or known T2DM

BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; IDF, International Diabetes Federation; T2DM, type 2 diabetes mellitus; WC, waist circumference.

Diagnosing the metabolic syndrome requires the presence of central obesity plus any two of the other four factors.

*For those of South and South-East Asian, Japanese, and ethnic South and Central American origin, the cutoffs should be ≥90 cm for men, and ≥80 cm for women. The IDF Consensus group recognise that there are ethnic, gender and age differences but research is still needed on outcomes to establish risk.

†Metabolic syndrome cannot be diagnosed, but further measurements should be made if there is a family history of metabolic syndrome, T2DM, dyslipidemia, cardiovascular disease, hypertension and/or obesity.

‡For clinical purposes, but not for diagnosing the MetS, if FPG 5.6–6.9 mmol/L (100–125 mg/dL) and not known to have diabetes, an oral glucose tolerance test should be performed.

Taken from: Zimmet P, et al.; IDF Consensus Group. *Pediatr Diabetes*. 2007;8:299–306.[284] Permission to reprint was obtained.

cholesterol levels that are higher or lower than the general population.[274,292–294] Individuals with hypobetalipoproteinemia, whose lifelong LDL-C levels may be as low as 10–15 mg/dL, have normal growth, development and increased longevity.[295] Proprotein convertase subtilisin kexin type 9 (PCSK9) variants resulting in more subtle LDL-C lifetime lowering to approximately 100 mg/dL have shown substantial reduction in ASCVD risk as well.[11] Polymorphisms in Niemann-Pick C1-like 1 protein also result in lower lifetime levels of LDL-C and reduced ASCVD risk.[7,8] Genetic mutations that result in altered concentrations of TG and TG-rich lipoproteins, such as variants in lipoprotein lipase, apo C3, and apo A5, are also associated with increased or reduced ASCVD risk, depending on the direction of the lipid changes.[9,294,296–298]

Importantly, there is no evidence to suggest that moderately lower LDL-C levels, such as those that occur in some genetic mutations, are harmful. Lowering plasma cholesterol does not decrease intracellular cholesterol levels, which are maintained by an efficient LDL receptor homeostatic mechanism.[299] In healthy newborns when brain growth is most rapid, umbilical cord LDL-C levels are <40 mg/dL, only rising to levels of approximately 100 mg/dL by 2 years of age.[300] Long-term safety data in youth receiving lipid-lowering medication, however, are lacking, and evidence from RCTs is based on relatively small sample sizes.

Lipid screening

Who to screen

Screening should be performed in children 2–18 years of age: 1) in whom one or both biological parents are known to have hypercholesterolemia or are receiving lipid-lowering medications; 2) who have a family history of premature ASCVD in an expanded first-degree pedigree in men <55 or women <65 years of age; and 3) whose family history is unknown (e.g., children who were adopted) (Table 8). In addition, universal screening of all children, regardless of general health or the presence or absence of CVD risk factors, is recommended once between 9 and 11 years of age, with repeat lipid screening at 20 years of age, or earlier if dyslipidemia is present. The NLA Recommendations for the Patient-Centered Management of Dyslipidemia–Part 1 defined adults as individuals ≥20 years of age.[1]

Age of screening

Targeted screening based on family history and presentation should begin at 2 years of age. For universal screening, 10 years of age (9–11) is the optimal time for initial lipid testing, with repeat screening at 20 years of age, or earlier if dyslipidemia is present. Lipid testing during scheduled clinic visits, such as with childhood immunizations and well child visits as recommended by the current American Academy of Pediatrics (AAP) well child schedule (Bright Futures), present other opportunities for screening.[301]

Role of family history and risk factors in ASCVD risk assessment

Risk evaluation should include a family history of early ASCVD in all first-degree relatives. A family history of premature ASCVD represents the net effect of genetic, biochemical, behavioral, and environmental components. However, reliance on family history alone as a basis for lipid screening fails to identify as many as 30–60% of children and adolescents with elevated levels of cholesterol.[302–304] Despite its limitations, the presence of a positive family history (i.e., a parent, sibling, aunt, uncle or grandparent with a history of treated angina, MI, percutaneous coronary artery catheter intervention procedure, coronary artery bypass grafting, stroke, or sudden cardiac death before 55 years of age in a male or 65 years of age in a female) has been consistently found to increase baseline risk for ASCVD. Detection of a positive family history and/or risk factors should lead to evaluation of all family members, especially the biologic parents, for ASCVD risk factors. The family history should be updated regularly as a part of routine pediatric care.

Risk factors and conditions

Children should be regularly screened for major risk factors and conditions associated with increased ASCVD risk. Validated methods for risk factor scoring are not available for patients <20 years of age.

Normal and abnormal lipid values and children

The AAP[305] and AHA[306] have established cut points for plasma lipids, lipoproteins, and apolipoproteins (Table 7).[279] These population-derived values in children vary from the values defined by the NLA for adults,[1] the latter derived from observational studies and ASCVD outcomes of RCTs as levels that provide optimum cardiovascular health. Although comparable outcome data are not available for children, studies are needed to help determine whether such levels might provide optimum cardiovascular health for children >2 years of age.

The use of age-appropriate lipid percentiles during childhood and adolescent growth and development is supported by the tracking of lipids from youth to adulthood. Evidence from adult studies that non-HDL-C is a better independent predictor of ASCVD than LDL-C, is supported by pediatric data as well.[307,308]

LDL-C and/or non-HDL-C goals for children

Although long-term outcome data are lacking, the case for managing children and adolescents based on their percentiles is strengthened by Mendelian randomization studies showing that lower levels of LDL-C and non-HDL-C may be more advantageous for cardiovascular health, especially if maintained over a lifetime.[11,275] Use of percentile-based norms is consistent

with cut points for the metabolic syndrome adopted by the International Diabetes Federation (Table 9).[284] Consequently, percentile-based cut points are recommended and should be considered as the upper limits for valid therapeutic goal ranges for managing children and adolescents.[279]

Testing methods

Use of measured fasting total-C, HDL-C, and TG allows calculation of LDL-C, which equals the total-C – [HDL-C + TG/5]. Non-HDL-C, an estimate of the cholesterol content of all atherogenic lipoprotein particles, is simply total-C minus HDL-C in fasting or non-fasting blood. A non-fasting blood sample is often more practical and efficient for calculation of non-HDL-C. If the non-HDL-C level is ≥145 mg/dL (95th percentile), then additional follow-up is recommended. Two fasting lipid profiles should be obtained and the results averaged for evaluation of the risk related to apo B-containing lipoproteins.

Blood samples can be drawn by venipuncture or finger stick, the latter often preferred by children. If available, point of care lipid testing has proven reliable and correlates well with standard laboratory results.[309–311]

Routine measurement of Lp(a), apo B, apo A1, and lipoprotein subclasses and their sizes by advanced lipoprotein analysis is not recommended at this time, but may be helpful in selected cases. Lp(a) may be useful in the assessment of children with a strong family history of vascular disease as well as stroke, both hemorrhagic and ischemic.[312] In individuals with FH, Lp(a) has increasingly been recognized as a risk accelerator and can be useful in assessing risk in addition to non-HDL-C and LDL-C levels.

Selective screening and cascade screening

Prior guidelines focused on selective screening of children with a family history of hypercholesterolemia and/or premature CHD.[313,314] A 2007 United States Preventive Services Task Force Report concluded that "inaccurate and incomplete family history reporting makes it neither sensitive nor specific enough to use as a predictive screening tool for childhood dyslipidemia".[283] Therefore, although a detailed family history should always be performed, a family history alone is inadequate as an indication for screening.

Screening the family of an affected FH patient by systematically identifying first-degree relatives, i.e., cascade screening, is recommended to enhance detection of individuals at risk for FH. Reverse cascade screening, i.e., screening all first-degree relatives of a child identified with FH, is also recommended. The adults are at greater short term risk than the child. Although less evidence exists for cascade (and reverse cascade) screening in other dyslipidemias with strong genetic components such as elevated levels of Lp(a) and familial combined hyperlipidemia, it is a reasonable consideration when these conditions are identified in a first-degree relative.

Adverse effects of screening

Recommendations for any screening program should depend on assessment of benefits and harms, and whether there are overall health gains.[315] The case for screening children for dyslipidemia appears justified by the benefits of early education of families with respect to adoption of healthy lifestyles and the potential of offsetting early atherosclerosis.[316,317] The prevention of premature cardiovascular death in youth is best established in FH; the LDL-C lowering efficacy and safety of treatment with statins has been demonstrated in children after age 8 for pravastatin but after age 10 for other approved statins.[318] The benefit of lipid-lowering therapy is less clear for other lipid disorders.

Although the cost of universal screening is unknown, the current and projected human and fiscal costs of premature ASCVD are substantial.[319] The cost-effectiveness of FH screening based on targeted screening has been estimated in Holland.[320] Screening family members of a proband was shown to be effective in the United Kingdom by increasing the detection rate and cost savings on long-term health[321] and in Australia.[322] The cost effectiveness of reverse cholesterol screening has also been shown.[323]

There is no evidence of harm from a child being labeled as a result of disclosure of inherited ASCVD risk factors,[324] although there are potential hazards of unsupervised and overly restrictive diets.[279,325] There have been no adverse psychosocial effects identified during dietary treatment for hypercholesterolemia.[326] With recent health insurance reforms, the potential issues related to future insurability have hopefully been negated.

Lifestyle interventions

Diet and other lifestyle interventions have been shown to be modestly effective in lowering LDL-C in children and adolescents. A diet that has a total fat content of 25–30% of calories, saturated fat content of ≤7% of calories and dietary cholesterol <200 mg/day is beneficial in lowering LDL-C and non-HDL-C. This diet has no adverse effects, including no adverse effects on growth and development.[279]

Dietary adjuncts, such as plant stanols or sterol esters and viscous fibers can enhance LDL-C lowering, particularly in children with FH.[95,327] Long-term data are lacking on the safety and efficacy of plant stanols and sterol esters in children and adolescents.

In children with elevated TGs, a diet that includes reduction of refined carbohydrates and sugars, along with a reduction of saturated fat is recommended.[279] When overweight/obesity is present, a decrease of total calories is recommended as part of weight management using multicomponent interventions.[328] Increased physical activity, including increased moderate or higher intensity physical activity of at least 60 minutes per day is also important.

The implementation of these dietary management strategies should, when feasible, be guided by a registered dietitian nutritionist. There is limited evidence on the effectiveness of diet and lifestyle interventions in improving intermediate or surrogate markers of atherosclerosis, such as carotid intima-media thickness or endothelial function, although obesity is associated with higher carotid intima-media thickness in children.[329]

Pharmacotherapy

There is evidence from clinical trials on children age 10 and above that pharmacologic treatment to lower atherogenic cholesterol is safe, effective and improves carotid intima-media thickness. Most of the available evidence focuses on the relatively short-term use of statins.[316] There is some evidence to support the use of bile acid sequestering agents for lowering LDL-C in children and adolescents.[330,331] There is limited evidence on the safety and efficacy of cholesterol absorption inhibitor in children and adolescents.[332]

The risks of pharmacologic treatment for elevated LDL-C or non HDL-C in children appear to be low and quite similar to the short-term risks in adults. In general, high intensity statin therapy has not been studied in children and adolescents and the longest duration studies have only been 2 years. Thus, the long-term safety of cholesterol-lowering agents is not specifically known for children and adolescents.

The major adverse event for statins is the risk of myositis and potentially for rhabdomyolysis.[333,334] The extent of these side effects in the pediatric population is unknown, given the limited frequency and duration of statin use in children, the lack of concomitant or underlying diseases, and the use of multiple drug therapies. Muscle symptoms should be monitored in pediatric patients who are treated with a statin, following a baseline (pretreatment) fasting glucose or glycated hemoglobin measurement for those with diabetes risk factors, as well as measurement of liver enzymes and creatine kinase.[279] The NLA updated its statin safety recommendations in 2014, which offer useful guidance for management of adult and pediatric patients with statins.[334] The primary adverse events for bile acid sequestering agents are gastrointestinal. These side effects can often be managed with increased dietary fiber and fluid consumption. There has been increasing risk for type 2 diabetes mellitus in adolescents indicating that adult risk for statin-associated diabetes should also be considered in children, especially in those with diabetes risk factors.[335]

Target level of lipids for lifestyle intervention and pharmacologic treatment

The evidence supports that children age 8 years and above are potential candidates for pharmacologic treatment for lipid lowering. There is not a strong evidence base to determine at what level of LDL-C or non-HDL-C treatment with a pharmacologic agent should be considered. There is also inadequate evidence regarding target levels for treatment goals. Those with LDL-C $\geq$190 mg/dL are quite likely to have heterozygous FH with an elevated lifetime risk for ASCVD.

The National Heart, Lung, and Blood Institute's Expert Panel considered the evidence regarding risk for increased progression of atherosclerotic lesions associated with multiple risk factors. This led to an algorithm based on additional risk factors for children and adolescents age 10 and older with LDL-C $\geq$160 but $<$190 mg/dL and with LDL-C $\geq$130 but $<$160 mg/dL. This algorithm is presented in Figure 2.[279] Decisions on target levels during treatment are a matter of clinical judgment and can be based on the percentiles for LDL-C and non-HDL-C presented in Table 7.[279]

This NLA Expert Panel recommends *upper limits* for therapeutic atherogenic cholesterol goal ranges for managing children and adolescents of 144 mg/dL for non-HDL-C and 129 mg/dL for LDL-C. However, in patients with FH for whom these targets are unachievable, an atherogenic cholesterol reduction of 50% should be the target.[286] The NLA has also endorsed the FH guidance from the International FH Foundation.[337]

When pharmacologic treatment is initiated, it is important to continue lifestyle-based treatment because this combination is probably more effective than medication alone and may allow for use of a lower dosage of medication.

At present, there are no clinically useful tests with, which to monitor the effectiveness of statin therapy, other than following the LDL-C and/or non-HDL-C levels. Surrogate testing for atherosclerosis progression, such as carotid intima media thickness or coronary artery calcium (CAC), is not recommended at this time, because they are regarded as investigational modalities.

See Chart 3 for the Recommendations for Children and Adolescents.

Women's health

Management of dyslipidemia in women

Management of dyslipidemia in women requires consideration of gender-specific differences in cardiovascular risk, strengths and weaknesses of the available scientific evidence base, and the potential risks and benefits of lipid-lowering therapies. The most recent data available indicate that while the gap is narrowing, more women than men continue to die annually from CVD.[256] Heart disease remains the leading killer of women. After MI, women are more likely than men to develop heart failure or die within 5 years of the event. Women have a higher risk for stroke than men, with a lifetime risk for initial stroke at 55–75 years of age of 20–21% for women vs 14–17% for men.[338] Women account for nearly 60% of deaths due to stroke in the United States. Before the age of 75 years, men experience a higher proportion of events attributable to CHD, while women experience a higher proportion of events attributable to stroke.[339]

Despite the importance of ASCVD as a health concern for women, they have historically been under-represented

Chart 3 Recommendations for children and adolescents

Recommendations	Strength	Quality
Universal lipid screening of all children, regardless of general health or the presence or absence of ASCVD risk factors, is recommended between 9-11 years of age, with repeat lipid screening at 20 years of age, or earlier if dyslipidemia is present.	E	Low
If a child or adolescent patient is screened and has a fasting or non-fasting non-HDL-C level ≥145 mg/dL, then additional follow-up is recommended. Two fasting lipid profiles should be obtained and the results averaged for evaluation of the most appropriate course of action.	E	Low
Children at least 2 years of age with the following characteristics should be screened for dyslipidemia: • One or both biological parents are known to have hypercholesterolemia, or are receiving lipid-lowering medications • Have a family history of premature ASCVD in an expanded first degree pedigree (i.e., to include not only parents and siblings, but also aunts, uncles, and grandparents) in men <55 or women <65 years of age • Consideration should also be given to screening for those in whom family history is unknown (e.g., adopted)	B	Moderate
Children should be regularly screened for major risk factors and conditions associated with increased ASCVD risk, but there are no validated methods for risk factor scoring in patients <20 years of age.	B	Moderate
Decisions on target levels during treatment are a matter of clinical judgment, but age-appropriate, percentile-based cutpoints from the 2011 Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: National Heart, Lung, and Blood Institute should be considered as the *upper limits* for therapeutic atherogenic cholesterol goal ranges for managing children and adolescents: • Non-HDL-C: 144 mg/dL • LDL-C: 129 mg/dL	E	Low
Cascade screening and reverse cascade screening are recommended to enhance detection of individuals at risk for FH.	B	Moderate
An alternate treatment goal for pediatric FH patients in whom it may not be possible to achieve an LDL-C level of <130 mg/dL, is a 50% reduction in LDL-C.	E	Low
Diet and other lifestyle interventions, including increased physical activity and weight management when overweight/obesity is present, are recommended for lowering elevated LDL-C, non-HDL-C, and TG in children and adolescents. Dietary management strategies should be guided by a registered dietitian nutritionist whenever feasible.	A	High
Children ≥8 years of age are potential candidates for pharmacologic treatment for lipid lowering. The following treatment plans can be considered: • Administer pharmacologic agents, primarily statins, when LDL-C level is ≥190 mg/dL and/or non-HDL-C is ≥220 mg/dL. • Consider additional risk factors in addition to elevated LDL-C and/or non-HDL-C and follow the treatment algorithm from the 2011 Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: National Heart, Lung, and Blood Institute.	B	Moderate
Statins and bile acid sequestrants are pharmacologic agents with evidence for efficacy and safety in children and adolescents. There is limited evidence on the safety and efficacy of cholesterol absorption inhibitors in children and adolescents.	B	Moderate
Consideration should be given to measurement of pretreatment fasting glucose or glycated hemoglobin levels, liver enzymes, and creatine kinase in pediatric patients for whom a statin is prescribed.	E	Low
Potential side effects with lipid-altering pharmacotherapy should be monitored in pediatric patients according to the recommendations from the respective 2014 NLA statin safety task force.	B	Moderate

in RCTs of lipid-lowering therapies. In those statin trials that have included women, there have been no gender-specific differences in the observed lipid responses to statin therapy, with similar reductions in total-C, LDL-C, and TG, and increases in HDL-C among men and women.[340,341] In studies of primary prevention of ASCVD there has not been adequate statistical power to draw firm conclusions from subgroup analyses by gender. Similarly, no individual secondary prevention trials of lipid-lowering therapies have been adequately powered to reliably detect gender-specific differences in effect. A recent review, however, demonstrated that there has been significant improvement in the recruitment of women for statin RCTs from 1990 to 2010.[342] In the 1990's, statin RCTs of >500 participants included only 18.6% women (95% CI 16.31–21.13%). By the first decade of the 2000's similar-sized trials included, on average, 31.46% women (95% CI 29.45–32.52%). Although the available data are limited, the prevalence, morbidity, and mortality of ASCVD in women make it imperative to consider approaches to lipid management while the evidence base expands.

Primary ASCVD prevention in women

Although women without previous ASCVD are at lower absolute short- to intermediate-term event risk compared to men for a given age, lifetime risk is higher among women, in part due to longer life expectancy.[256] Approximately 70% of MIs in the United States are first events, and approximately 15% of these will be fatal during hospitalization.[343] However, nearly 50% of sudden cardiac deaths occur outside a hospital and these patients will not have an opportunity for prevention of recurrent events. Clearly, primary prevention strategies are critical to reduce mortality and morbidity for both at-risk women and men.

The lower age-adjusted incidence of ASCVD events in women compared to men requires that lipid-lowering RCTs include a large sample size of women to make valid gender-specific comparisons, and to extend age limits through the ninth decade of life. The Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) primary prevention trial included 6801 women and 11,001 men with high-sensitivity C-reactive protein (hs-CRP) ≥2.0 mg/dL and LDL-C ≤130 mg/dL randomized to rosuvastatin 20 mg vs placebo.[344,345] The primary endpoint was a composite of MI, stroke, hospitalization for unstable angina, arterial revascularization, or ASCVD death. The absolute rates of the primary endpoint in the rosuvastatin and placebo groups were lower in women compared to men, even though women tended to be older and had more ASCVD risk factors than men. However, the proportional reduction in the primary endpoint with rosuvastatin was similar and statistically significant in both women (HR 0.54; 95% CI 0.37–0.80; $P = .002$) and men (HR 0.58; 95% CI 0.45–0.73; $P < .001$).

In an accompanying meta-analysis, authors of the JUPITER gender-specific analysis also considered data from earlier primary prevention trials with subgroup analyses in women, including the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid Lowering Trial (ALLHAT-LLT), the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA), and the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) trial, as well as data from the primary prevention patients in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) and the Heart Protection Study (HPS).[345–351] Compared with placebo, statin therapy significantly reduced CVD events in women by about one-third (summary RR 0.63; 95% CI 0.49–0.82; $P < .001$; P for heterogeneity = 0.56) in exclusively primary prevention trials (AFCAPS/TexCAPS, MEGA, and JUPITER). When trials that included predominantly primary prevention (ASCOT-LLA and ALLHAT-LLT) were analyzed together with the exclusively primary prevention trials, the summary RR for CVD events was higher and not statistically significant (0.79; 95% CI 0.59–1.05; $P = .11$; P for heterogeneity = 0.053). The summary RR was not materially altered by the inclusion of data from HPS and PROSPER, although it was significantly different from unity (0.82; 95% CI 0.69–0.98; $P = .03$). The summary RR for total mortality was similar when the 3 exclusively primary prevention trials (n = 13,154 women, 216 deaths) were considered (0.78; 95% CI 0.53–1.15; $P = .21$) and with the inclusion of data from predominantly primary prevention trials, but did not achieve statistical significance. HPS and PROSPER did not report sex-specific mortality data in the primary prevention arms.

In view of the relatively small numbers of women previously participating in primary prevention trials, several other meta-analyses have also been conducted to examine a possible interaction between gender and the effects of lipid-lowering therapies on ASCVD outcomes, and have reported similar results.[352–359] The first meta-analysis conducted by the Cholesterol Treatment Trialists' (CTT) Collaboration included individual participant data from 14 statin RCTs with 21,575 women (24%).[352] None of the trials included in the analysis were exclusively primary prevention trials, although 46% of patients had no established ASCVD. The number of events in women was smaller (1441) compared to the number in men (6316), but there was a statistically significant reduction in major coronary events in both women (RR 0.82; 95% CI 0.73–0.93) and men (RR 0.76; 95% CI 0.72–0.80) without heterogeneity of effect by gender ($\chi^2_1 = 2.6$; $P = .1$). There was also a statistically significant reduction in major vascular events that was similar in women and men. The relative reductions in the incidence rates for major coronary and vascular events were similar among participants with previous history of MI or other CHD and those without pre-existing CHD. A separate gender-specific analysis of primary prevention patients was not provided.

Another analysis from the CTT Collaboration examined 26 statin RCTs that included 45,495 women in primary and secondary prevention trials.[355] Women had a lower baseline ASCVD event rate compared to men, but experienced a 17% (99% CI 10–24%, $P < .0001$) reduction in major vascular events per 1 mmol (39 mg/dL) reduction in LDL-C compared to a 23% (99% CI 20–26%) reduction per 1 mmol in men. A separate gender-specific analysis in exclusively primary prevention trials was not reported, however, the benefit of statin therapy was similar in both primary and secondary prevention patients in all participants. In both of these CTT meta-analyses, the point estimates for men and women have been similar, suggesting that any gender-related differences in event reduction with statin therapy, if present, are small.

Most recently, the CTT Collaborators conducted a meta-analysis of 27 primary and secondary prevention RCTs with 174,249 participants (46,675 [27%] women) to examine gender differences in the efficacy and safety of statin therapy.[357] The risk of major vascular events in the

control groups was lower among women (3.0% per year) compared with men (4.4% per year) in these trials. However, after adjusting for non-gender-related differences in baseline characteristics, there was no heterogeneity by gender in the proportional effects of statin therapy in women (RR 0.84; 99% CI 0.78–0.91; $P < .0001$) and men (RR 0.78; 99% CI 0.75–0.81; $P < .0001$; heterogeneity unadjusted $P = .021$, adjusted for baseline characteristics, P for interaction = .331) (Fig. 3).[357] The proportional reductions in major vascular events (CHD, stroke and revascularization) in individuals with no known history of vascular disease was somewhat greater in men (RR 0.72; 99% CI 0.66–0.80) than in women (RR 0.85; 99% CI 0.72–1.00; heterogeneity unadjusted $P = .033$, adjusted $P = .023$) (Fig. 3).[357] However, it is difficult to interpret this finding because there is a relatively large element of clinical judgment and regional variation in revascularization procedures.

Another recent study examined gender differences in the effect of atorvastatin on lipids and cardiovascular outcomes from the Incremental Decrease in End Points Through Aggressive Lipid Lowering trial, the Treating to New Targets (TNT) trial, the Stroke and Prevention by Aggressive Reduction in Cholesterol Levels trial, the Collaborative Atorvastatin Diabetes Study (CARDS), ASCOT, and the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN).[360] In all studies combined, there were 30,000 men and 9173 women. Major cardiovascular events occurred in 3083 (10.3%) men and 823 (9.0%) women. Lipid changes were similar between genders, and major cardiovascular events were associated with quintiles of on-treatment LDL-C in both men and women. LDL-C was also a significant predictor of risk for stroke in women, but not in men.

Thus, the available primary prevention data support the conclusion that women and men of comparable ASCVD risk experience similar reductions in events and all-cause mortality when treated with statin therapy, particularly when adjusted for age and comorbidities. Therefore, women without ASCVD should undergo ASCVD risk assessment and the intensity of lipid-lowering therapy

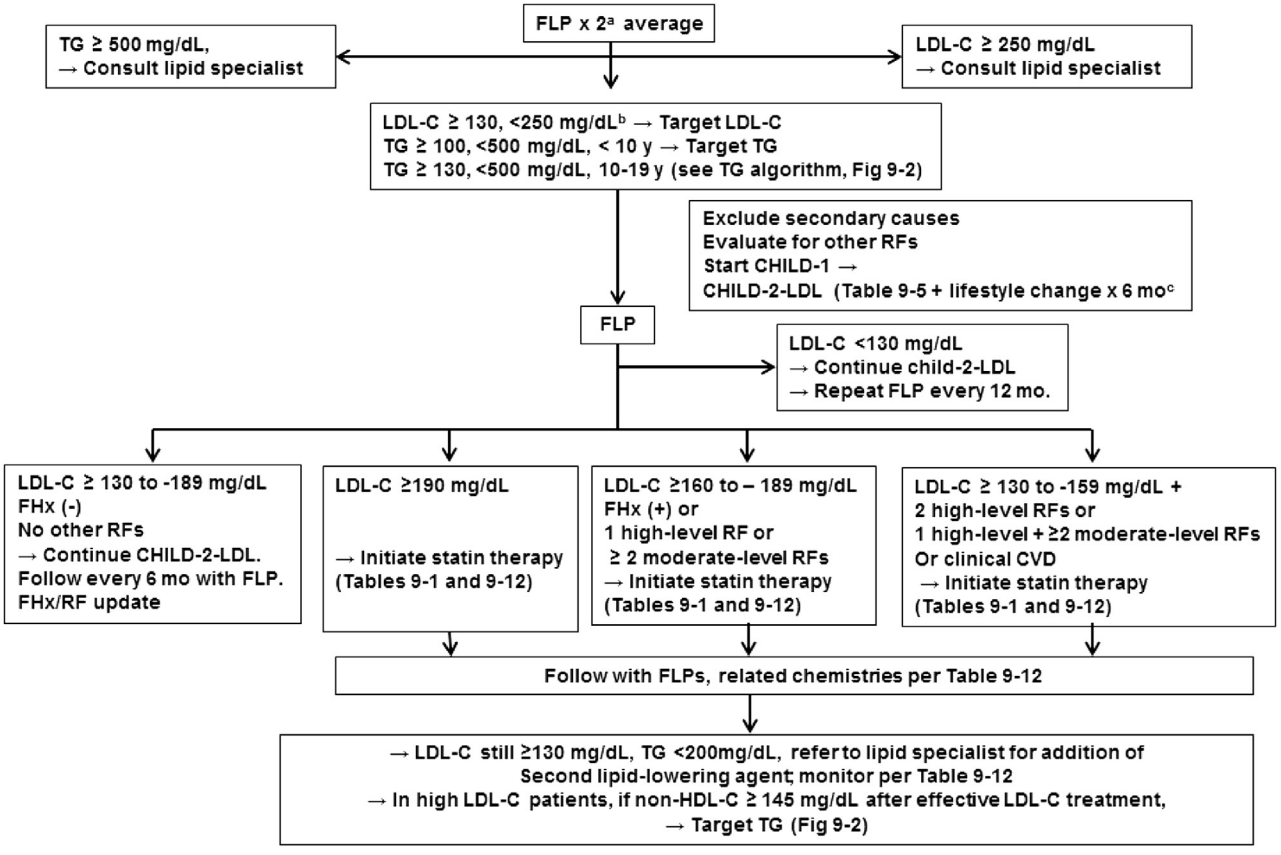

Figure 2 Dyslipidemia algorithm targeting LDL-C from the 2011 Expert Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Dyslipidemia algorithm: target LDL cholesterol. Values are in mg/dL. To convert to SI unit, divide results for TC, LDL-C, HDL-C, and non–HDL-C by 38.6; for triglycerides, divide by 88.6. [a]Obtain FLPs at least 2 weeks but no more than 3 months apart. [b]Per Table 9-9 (in the original publication from which this figure was taken), use of drug therapy is limited to children aged 10 years and older with defined risk profiles. [c]In a child with an LDL-C level of >190 mg/dL and other risk factors, a trial of the CHILD-2-LDL may be abbreviated. CVD, cardiovascular disease; FHx, family history; FLP, fasting lipid profile; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RF, risk factor; TG, triglyceride. Taken from: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. *Pediatrics.* 2011;128 Suppl 5:S213–S256.[279] Permission to reprint was obtained.

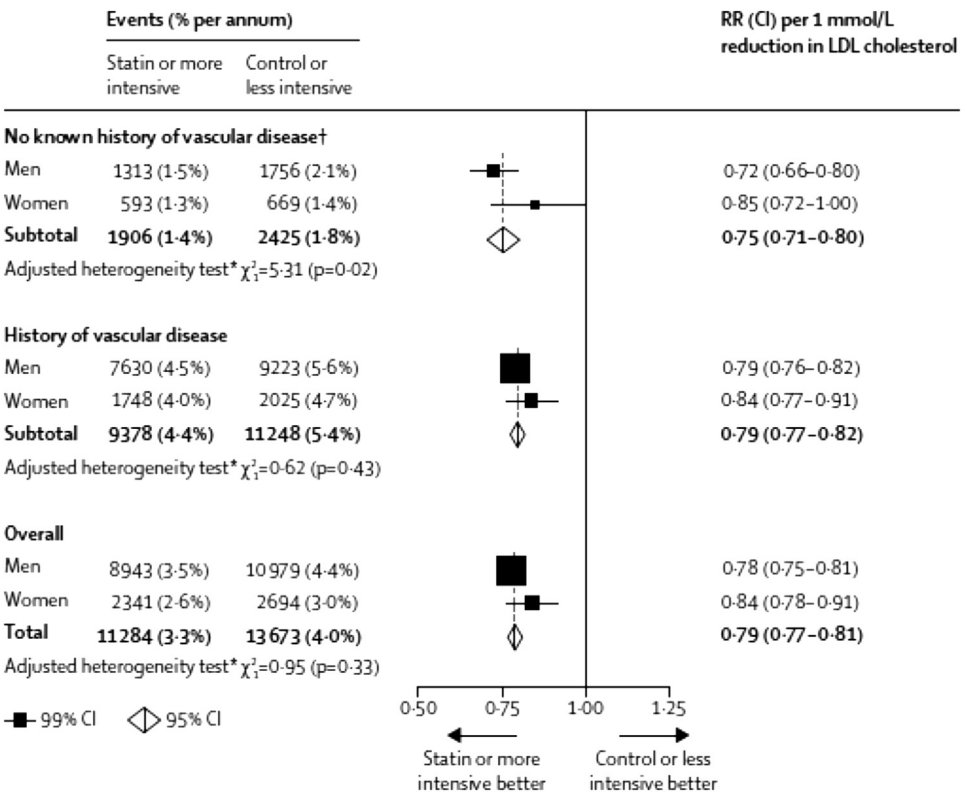

Figure 3 Meta-analysis of effects of statin on cardiovascular disease in primary and secondary prevention of women and men. Effects on major vascular events per 1-0 mmol/L reduction in LDL cholesterol, subdivided by history of vascular disease and sex. *Adjusted heterogeneity test calculated from a Cox model that corrects for nonsex differences between women and men (appendix pp 12–14; this appendix is in the original publication from which this figure was taken). †Results for men with no known history of vascular disease included 189 vs 264 first major vascular events from participants recruited into WOSCOPS in which information on previous stroke was not available. CI, confidence interval; RR, rate ratio. Taken from Cholesterol Treatment Trialists' (CTT) Collaboration, et al. *Lancet*. 2015;385:1397–1405.[357] Permission to reprint was obtained.

should be matched to the level of risk, similar to assessment and treatment of men, as described in the NLA Recommendations for the Patient-Centered Management of Dyslipidemia–Part 1.[1]

Use of risk calculators in primary prevention in women

The Expert Panel of the NLA Recommendations for the Patient-Centered Management of Dyslipidemia–Part 1 recommended quantitative risk scoring as an option for patients with 2 major ASCVD risk factors, in the absence of any high or very high risk conditions, to facilitate treatment decisions.[1] Thresholds recommended for high risk categorization were ≥10-year risk for a hard CHD event using NCEP ATP III Framingham, ≥15% 10-year risk for a hard ASCVD event using the 2013 ACC/AHA Pooled Cohort Equations, and ≥45% risk for CVD using Framingham long-term, 30-year risk. An examination by Cavanaugh-Hussey et al.[361] of the online ATP III risk calculator, in which the investigators entered data into the online tool for men and women in 5-year intervals from ages 30 to 75 years with varying risk factors, demonstrated that few women exceeded the treatment thresholds set by the ATP III guidelines and thus few qualified for intensive ASCVD prevention, regardless of risk factor burden. The 2013 ACC/AHA Pooled Cohort Equations differ from the earlier ATP III Risk Calculator because they include 1) diabetes as a risk indicator, 2) fatal and nonfatal stroke as endpoints, and 3) sex- and race-specific equations for non-Hispanic white (NHW) and AA women and men.[362,363] These changes have important implications for risk assessment for women, because stroke constitutes a greater proportion of ASCVD events in women, and often occurs earlier in life than for men. However, clinicians should be aware that the Pooled Cohort Equations have been shown to overestimate risk in some analyses.[364–367] Additional studies in which these equations are applied to different, more contemporary cohorts, are needed to further examine the potential for overestimation of risk.

The Reynolds Risk Score has been found, in some analyses, to improve the accuracy of ASCVD risk assessment in women.[368] It incorporates family history, hs-CRP, and glycated hemoglobin, as well traditional risk factors.[368] However, in a recent analysis of calibration and discrimination among multiple cardiovascular risk scores in the Multi-Ethnic Study of Atherosclerosis (MESA) population, the Framingham Risk Score and

Pooled Cohort Equations overestimated cardiovascular events in women by 8 to 67%, while the Reynolds Risk Score underestimated risk by 21%.[367] Due to these challenges in ASCVD risk assessment, some experts have recommended calculation of a patient's risk by multiple algorithms when considering initiation of statin therapy in both women and men.[369]

Secondary ASCVD prevention in women

The CTT Collaborators' 2015 meta-analysis evaluating gender-specific effects of statin therapy observed no heterogeneity by gender in the proportional effects of statin therapy overall in women and men after adjusting for non-gender related differences in baseline characteristics.[357] The proportional reductions in major vascular events in participants with a definite history of ASCVD were similar among women compared to men (heterogeneity unadjusted $P = .098$, adjusted $P = .431$) (Fig. 3).[357] Results demonstrated that, for each 1 mmol/L reduction in LDL-C, statin therapy reduced major vascular events by about 20%, major coronary events by 25%, coronary revascularizations by 25%, and ischemic stroke by just under 20%, and that these proportional reductions were similar in men and women, even though women had lower absolute cardiovascular risk. Non-gender related differences in baseline characteristics (e.g., differences in average age between men and women) accounted for any apparent differences between women and men in the magnitude of proportional reductions achieved with statin therapy.

In a meta-analysis by Kostis et al.[358] that included 40,275 women from 18 primary and secondary prevention RCTs with gender-specific outcomes, a statistically significant decrease in the primary endpoint was observed among women in both primary and secondary prevention. Although the benefit was more pronounced in secondary prevention trials (odds ratio [OR] 0.78; 95% CI 0.72–0.91; $P < .0001$) than in primary prevention trials (OR 0.85; 95% CI 0.75–0.98; $P = .0209$), the difference was not statistically significant (P for interaction = .3397). Consistent with findings from the most recent CTT meta-analysis,[357] there was a statistically significant benefit of statin therapy at all levels of risk in women, with a more pronounced benefit in low-risk groups (Fig. 4).[358] Statistically significant reductions in stroke (OR 0.74; 95% CI 0.55–0.99; $P = .0396$) and CHD events (OR 0.78; 95% CI 0.67–0.94; $P = .0090$) were also observed for women (Fig. 5).[358] All-cause mortality was lower with statin therapy in both men and women without significant interaction by gender (P for interaction = .4457).

The results summarized above support the conclusion that women with manifest ASCVD benefit from statin therapy. As outlined in the NLA Recommendations for the Patient-Centered Management of Dyslipidemia–Part 1,[1] statin therapy should be a consideration for patients at very high risk of either gender, even if the pre-treatment levels of atherogenic cholesterol are below the treatment goals. Results from recent trials in which additional benefit has been observed when atherogenic cholesterol levels have been lowered to values well below treatment goal thresholds further support this conclusion.[370–372]

Lipid-altering therapy in women with diabetes

Diabetes type 1 and type 2 increase the risk for ASCVD in both men and women compared to individuals without diabetes.[373] A meta-analysis of 37 prospective, multinational studies demonstrated that the RR for fatal CHD associated with diabetes is nearly 50% higher in women (RR 3.5; 95% CI 2.7–4.5) than it is in men (RR 2.06; 95% CI 1.81–2.34) after adjustment for major coronary risk factors, although the absolute ASCVD risk may remain lower in women with diabetes compared to men with diabetes.[374] Clinical trials in patients with diabetes[375–377] and subgroup analyses of patients with diabetes in larger trials[378–381] have demonstrated significant effects of lipid-lowering therapy (primarily statins) on CVD outcomes. The 3 statin outcome trials exclusively in patients with diabetes (CARDS, the German Diabetes and Dialysis Study, and ASPEN) included a total of 1898 women (32–46% of total participants) but no gender-specific outcomes analyses were reported. The CTT meta-analysis of 14 statin RCTs with 18,686 patients with diabetes (6165 women) demonstrated a 9% proportional reduction in all-cause mortality (RR 0.91; 99% CI 0.82–1.01; $P = .02$) and a 13% reduction in vascular mortality (RR 0.87; 99% CI 0.76–1.00; $P = .008$) for each 1 mmol/L reduction in LDL-C.[382] Although the number of events was lower in women (833) than in men (2414), the proportionate reduction in risk was similar (women: RR 0.81; 95% CI 0.67–0.97 vs men: RR 0.78; 95% CI 0.71–0.86) and there was no heterogeneity by gender ($\chi^2 = 0.1$; P for interaction = .7).

Women with diabetes type 1 or type 2 are considered to be at high to very high risk for an ASCVD event, depending on the presence of ASCVD or the presence of additional major risk factors. Moderate to high intensity statin therapy should be considered for these at-risk women matching intensity of therapy to the level of ASCVD risk.

Non-statin lipid-lowering therapy in women

There is limited gender-specific evidence for the benefit of non-statin drugs in the prevention of ASCVD events. The available clinical trial outcomes evidence for use of non-statins in women, and gaps in the evidence, are summarized below.

Bile acid sequestrants

The only outcomes trial of bile acid sequestrants has been the Lipid Research Clinics Coronary Primary Prevention Trial.[383,384] The Lipid Research Clinics Coronary Primary Prevention Trial was a multicenter, randomized double-blind study that examined the efficacy of the bile acid sequestrant, cholestyramine, for reducing

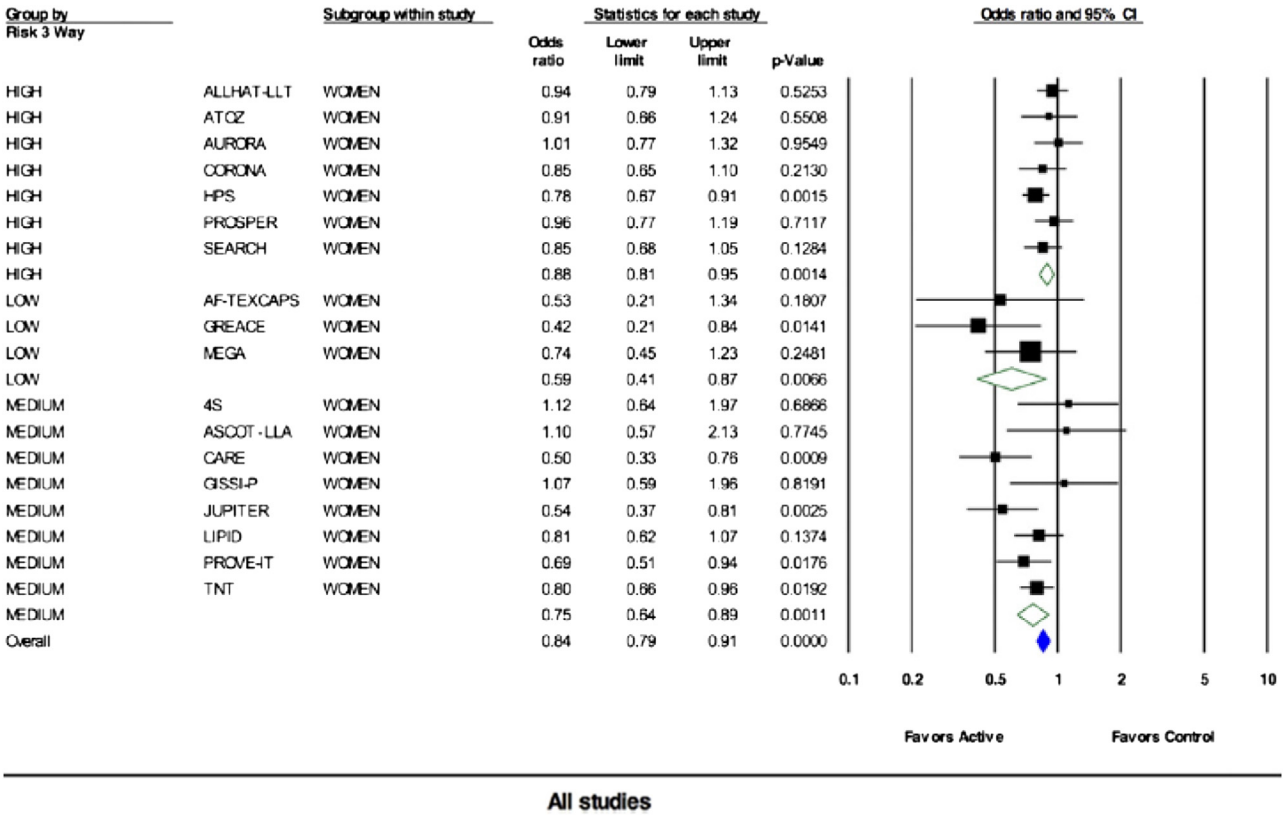

Figure 4 Meta-analysis of benefit of statin therapy in primary prevention according to level of risk in women. Forest plot for the primary event by level of risk participants in each study in women. Solid squares represent the odds ratios in individual trials and have a size proportional to the inverse of variance. Horizontal lines, diamonds, and squares denote the 95% confidence intervals (CIs) for individual trials and summary statistics. Pooled estimates were computed from a random effects model. Taken from: Kostis WJ, et al. *J Am Coll Cardiol*. 2012;59:572–582.[358] Permission to reprint was obtained.

risk of CHD. It included 3806 asymptomatic middle-aged men, and did not enroll any women.

Cholesterol absorption inhibitor

The Study of Heart and Renal Protection evaluated simvastatin 20 mg and ezetimibe 10 mg vs placebo in 9270 patients (3470 women, 37%) with chronic kidney disease (3023 on dialysis and 6247 non-dialysis dependent).[385] Treatment with simvastatin and ezetimibe produced a 17% proportional reduction in major atherosclerotic events compared to placebo (RR 0.83; 95% CI 0.74–0.94; log-rank $P = .0021$). Although the point estimates were nearly identical in men and women, there were a smaller number of events in women (324) compared to men (821) with wider CIs for women that crossed the line of unity.

In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), 18,144 patients (approximately 24% women) with acute coronary syndrome <10 days were randomized to simvastatin 40 mg daily plus ezetimibe 10 mg or placebo.[370] The primary outcome endpoint was a composite of cardiovascular death, MI, hospital admission for unstable angina, coronary revascularization (≥30 days after randomization), or stroke. Combination therapy with simvastatin and ezetimibe was associated with a statistically significant 10% relative reduction in the primary endpoint (HR 0.90; 95% CI 0.84–0.97; $P = .003$) compared to simvastatin alone. Gender was pre-specified for subgroup analysis. Women trended toward greater benefit compared to men, and although CIs were wider than in men, they did not cross the line of unity. For men, the CIs were tighter, but crossed unity. However, this gender difference (i.e., treatment by gender interaction) did not achieve statistical significance.

Niacin

The earliest large RCT of niacin, the Coronary Drug Project, included 1119 patients (men only) with prior history of electrocardiogram-documented MI randomized to niacin and 2789 randomized to placebo.[386] With a mean follow-up of 15 years, nearly 9 years after termination of the trial, mortality in the niacin group was 11% lower than in the placebo group (52.0 vs 58.2%; $P = .0004$). The HDL-Atherosclerosis Treatment Study was an angiographic trial of 160 patients (21 women) with known CHD who were randomized to 1 of 4 treatment groups: simvastatin plus niacin, antioxidants, simvastatin–niacin plus antioxidants, or placebo.[387] Endpoints included angiographic evidence of a change in coronary stenosis and the

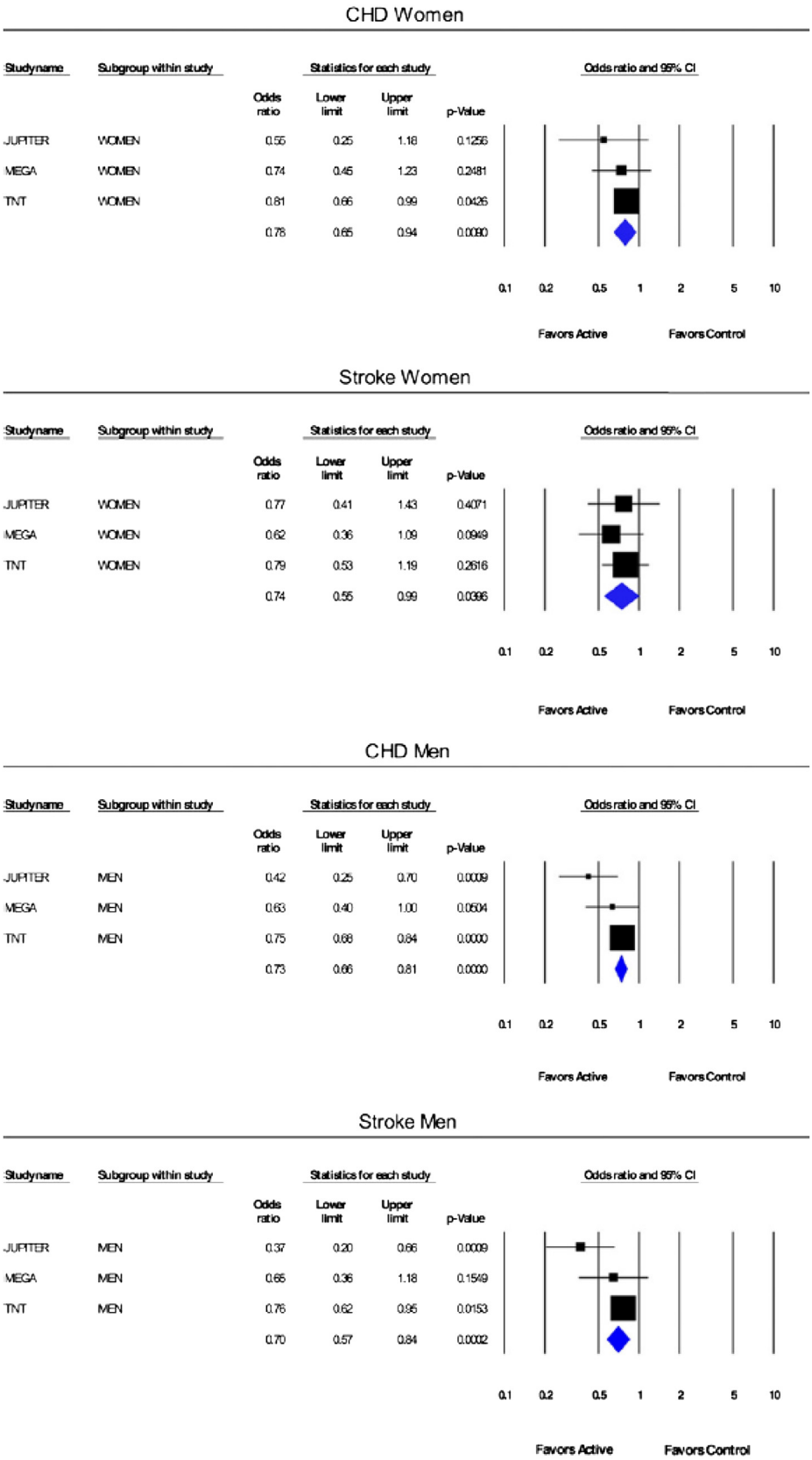

Figure 5 Meta-analysis of sex-specific coronary heart disease (CHD) and stroke outcomes. Forest plots for CHD event and for stroke in women and men. Solid squares represent the odds ratios in individual trials and have a size proportional to the inverse of variance. Horizontal lines, diamonds, and squares denote the 95% confidence intervals (CIs) for individual trials and summary statistics. Pooled estimates were computed from a random effects model. Taken from: Kostis WJ, et al. *J Am Coll Cardiol*. 2012;59:572–582.[358] Permission to reprint was obtained.

occurrence of a first cardiovascular event (death, MI, stroke, or revascularization), but the trial was not powered to detect a significant difference in clinical outcomes. The average stenosis progressed by 3.9% with placebo, 1.8% with antioxidants ($P = .16$ for the comparison with the placebo group), and 0.7% with simvastatin–niacin plus antioxidants ($P = .004$) and regressed by 0.4% with simvastatin–niacin alone ($P < .001$). The frequency of the clinical end point was 24% with placebo, 3% with simvastatin–niacin alone, 21% in the antioxidant therapy group, and 14% in the group given simvastatin–niacin plus antioxidants. The number of women included in this study was small and no gender-specific analysis of outcomes was reported.

In the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) study, 3414 patients (14.8% women) with established ASCVD were randomized to extended-release niacin 1500 to 2000 mg per day or matching placebo.[388] All patients received simvastatin, 40 to 80 mg per day plus ezetimibe 10 mg per day, if needed, to maintain an LDL-C level of 40 to 80 mg/dL. The primary end point was the first event of the composite of death from CHD, nonfatal MI, ischemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization. Following a 36-month follow-up, the trial was terminated due to lack of clinical benefit from the addition of extended-release niacin to statin therapy. There was no heterogeneity by gender ($P = .75$) but the small number of women resulted in wider CIs.

The Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) was a large trial conducted in 25,763 patients with established vascular disease (4444 women, 17.3%).[389] Participants were randomly assigned to receive 2 g of extended-release niacin and 40 mg of laropiprant or a matching placebo daily. The primary outcome was the first major vascular event (nonfatal MI, CHD death, stroke, or arterial revascularization). Women randomized to niacin and laropiprant had an excess of events compared to those randomized to placebo with a trend toward harm compared to a trend toward benefit in men, but this gender difference was not statistically significant (χ^2 3.21, $P = .07$).

Fibrates

Gemfibrozil has shown benefits in both primary and secondary prevention of CHD events when administered as monotherapy in patients with dyslipidemia, but RCTs have included only men. The Helsinki Heart Study was a primary prevention trial with gemfibrozil in 4081 asymptomatic middle-aged men with elevated levels of non-HDL-C.[390] Cardiac endpoints were reduced by 34% (95% CI 8.2–52.6; $P < .02$) in patients randomized to gemfibrozil compared to placebo. In the Veterans Affairs High-Density Lipoprotein Intervention Trial, 2531 men with a history of CHD, low HDL-C levels, and low LDL-C levels were randomly assigned to gemfibrozil 1200 mg/day or matching placebo.[391] CHD events were reduced with gemfibrozil by 11% for every 5 mg/dL (0.13-mmol/L) increase in HDL-C ($P = .02$). There are no available trials of gemfibrozil as monotherapy or in combination with statins that have included women. However, because current guidelines recommend fenofibrate as the preferred fibrate for patients with hypertriglyceridemia or mixed dyslipidemia due to the potential for adverse effects when statins are combined with gemfibrozil, the lack of evidence in women is likely of little consequence.

Two large RCTs of fenofibrate have included women as well as men. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study included 9795 participants 50–75 years of age with type 2 diabetes mellitus and not taking statin therapy at study entry.[392] Approximately 22% of patients had pre-existing ASCVD and 3657 (37.3%) of study participants were women. Patients were randomly assigned to micronized fenofibrate 200 mg daily or matching placebo; however, over the follow-up period of 5 years, more patients allocated to placebo (17%) than fenofibrate (8%; $P < .0001$) initiated combination therapy, primarily with statins. The primary outcome was CHD events (CHD death or non-fatal MI); the outcome for pre-specified subgroup analyses including gender was total cardiovascular events (composite endpoint of cardiovascular death, MI, stroke, and coronary and carotid revascularization). The reductions in total-C and LDL-C with fenofibrate therapy were greater in women than in men ($P < .001$). Men and women experienced similar increases in HDL-C and reductions in TGs. There was an 11% relative reduction in the primary endpoint of coronary events in all participants (men and women) allocated to fenofibrate, but this difference did not achieve statistical significance (HR 0.89; 95% CI 0.75–1.05; $P = .16$). Women had a statistically significant 18.9% relative reduction in the pre-specified secondary endpoint of total cardiovascular events (9.5% for placebo vs 7.7% for fenofibrate; $P = .04$), but the study was not adequately powered for gender-specific analysis and CIs were wide.[392] There was no significant treatment by gender interaction (P for interaction = .3). When analyses were adjusted for on-trial statin uptake (drop-in) and covariates (including ethnicity, age, diabetes duration, BMI, waist-to-hip ratio, systolic and diastolic blood pressures, smoking, prior CVD, prior coronary revascularization, hypertension, microvascular disease, baseline total-C, LDL-C, HDL-C, creatinine, homocysteine, dyslipidemia, microalbuminuria, macroalbuminuria, use of metformin, and use of sulfonylurea), allocation to fenofibrate reduced total CVD events in women by 30% (95% CI 8–46%; $P = .008$). There was no statistical evidence of heterogeneity of effect by gender (P for interaction = .17). There were no significant gender-specific differences in adverse effects of treatment with fenofibrate, including cancer incidence, rhabdomyolysis, pancreatitis, pulmonary embolism, or progression to end stage renal disease requiring dialysis.[393]

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial included both primary and secondary prevention patients (women 1694, men 3824) with type 2 diabetes (glycated hemoglobin ≥7.5%), LDL-C 60–180 mg/dL, HDL-C <55 mg/dL for women and blacks, HDL-C <50 mg/dL for all other groups, and TG <750 mg/dL if patients were not on lipid-lowering therapy or <400 mg/dL if they were on therapy.[394] Participants were randomized to simvastatin plus fenofibrate 160 mg or placebo and followed for a period of 4.7 years for the primary outcome, and 5.0 years for all-cause death. The primary outcome was the first occurrence of a major ASCVD event (nonfatal MI, nonfatal stroke, or death from cardiovascular causes). Secondary outcomes included the combination of the primary outcome plus revascularization or hospitalization for congestive heart failure; a combination of a fatal coronary event, nonfatal MI, or unstable angina; nonfatal MI; fatal or nonfatal stroke; nonfatal stroke; death from any cause; death from cardiovascular causes; and hospitalization or death due to heart failure. There was no statistical difference between study groups in the primary endpoint of major ASCVD event ($P = .32$) or with respect to any secondary outcome. There was a possible interaction according to lipid subgroup, with a possible benefit for patients with both a high baseline TG level and a low baseline level of HDL-C (P for interaction = .057). Of concern, gender-specific analyses suggested heterogeneity in treatment effect according to sex, with a benefit for men and possible harm for women (P for interaction = .01).[393] However, no heterogeneity by gender was observed in the subset with high TG and low HDL-C. As noted above, no gender-specific safety signal was observed in the larger FIELD trial of fenofibrate in patients with diabetes, so the significance of the treatment by gender interaction in ACCORD is of uncertain clinical relevance.

Omega-3 fatty acids/fish oil

JELIS evaluated the effects of statin plus highly purified EPA ethyl ester 1800 mg daily (600 mg three times a day after meals) or usual care (no EPA) in 18,645 Japanese primary and secondary prevention patients.[134] The study sample was predominantly women (n = 12,789, approximately 68%) and the trial examined the incremental benefit of EPA added to low-dose statin therapy (dosage was due to ethnic differences in the susceptibility to statin effects). The primary endpoint was CHD events, including sudden cardiac death, fatal and non-fatal MI, and other non-fatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting. At the mean follow-up of 4.6 years, 262 (2.8%) patients in the EPA group experienced the primary endpoint compared to 324 (3.5%) patients who did not receive EPA—a 19% relative reduction in major coronary events ($P = .011$). Unstable angina and non-fatal coronary events were also significantly reduced in the EPA group, but sudden cardiac death and CHD death did not differ between groups. In primary prevention patients with no history of coronary artery disease, EPA treatment reduced major coronary events by 18%, but this difference did not achieve statistical significance ($P = .132$). There was no heterogeneity by gender for the relative reduction in the occurrence of CHD event, although women had a lower absolute risk of events compared to men.

Non-statin recommendations

In general, the recommendations for the use of non-statin drug therapy for the management of dyslipidemia in women are the same as those outlined in the NLA Recommendations for the Patient-Centered Management of Dyslipidemia–Part 1[1]: "Nonstatin drug therapy (cholesterol absorption inhibitors, bile acid sequestrants, fibric acids, long-chain omega-3 fatty acid concentrates, and nicotinic acid) may be considered for patients with contraindications for, or intolerance to, statin therapy" with the following special considerations for women. Although clinical outcomes data for the use of bile acid sequestrants in women are lacking, results from RCTs enrolling both men and women report that bile acid sequestrants reduce atherogenic cholesterol levels in both men and women to a similar degree. Furthermore there has been no evidence of gender-specific harm associated with the use of this class of medication.

Women treated with niacin and laropiprant in HPS2-THRIVE had an excess of events and a trend toward harm, compared with men.[389] However, clinicians might consider niacin when other agents are not options for women with elevated levels of atherogenic cholesterol, based on the hypothesis that niacin might lower risk in those with residual elevation in non-HDL-C with or without concomitant statin therapy. Because levels of atherogenic cholesterol were low in the AIM-HIGH and HPS2-THRIVE trials prior to initiation of niacin therapy, the hypothesis that adding niacin to statin therapy in those with residual elevation in atherogenic cholesterol levels has not been adequately tested.

Fenofibrate is the preferred fibrate for use in women with severe hypertriglyceridemia for prevention of pancreatitis, although gender-specific evidence is limited and the benefit for cardiovascular risk reduction is uncertain.[393] Fenofibrate might also be considered for those with elevated TG and non-HDL-C, particularly in patients with low HDL-C and/or diabetes mellitus (because of microvascular benefits[392,395]). Prescription dosages of omega-3 fatty acids may be used in women for management of severe hypertriglyceridemia for prevention of pancreatitis.[134] The benefit of omega-3 fatty acid therapy for ASCVD prevention in a US population has not yet been established.

Gender differences in adverse events of lipid-lowering therapy

Adverse events of lipid-lowering therapy are commonly reported and often lead to discontinuation in health care settings,[396,397] but as with RCT evidence for benefits of lipid-lowering therapy in women, there is a paucity of

available data for evaluation of gender-specific differences in adverse events. Meta-analyses have shown no evidence for an increase in non-cardiovascular mortality, specifically no increase in cancer, associated with statin therapy in women.[340,351,352,355,357]

In the TNT trial, 23.5% (n = 1902) of the 8099 patients enrolled were women.[398] Significant gender differences in the baseline patient characteristics were noted. Women were older, had a higher BMI, had more hypertension and diabetes, were more symptomatic with angina, had a lower estimated glomerular filtration rate, and had higher levels of total-C, TG, and HDL-C. Rates of myalgia were slightly higher among women than men in TNT, but similar between treatment groups for both women and men. Discontinuations due to statin-related adverse events in both the high and low intensity groups were higher in women than in men, but the overall rates were low. Persistent elevations in hepatic transaminases were more frequent in women than men assigned to atorvastatin 80 mg (2.6% women, 0.9% men).

In JUPITER, women (n = 6801) were significantly older, more likely to have hypertension and the metabolic syndrome, and had a higher BMI and lower estimated glomerular filtration rate compared to men (n = 11,001) (all differences $P < .001$).[345] Gender-specific comparisons were provided for a number of adverse events in rosuvastatin and placebo groups. The rates of muscle-related adverse events were similar among women and men regardless of assignment to statin or placebo. Both women and men experienced a small but statistically significant increase in glycated hemoglobin ($P < .0001$). There was a higher incidence of physician-reported diabetes in women treated with rosuvastatin vs placebo (HR 1.49; 95% CI 1.11–2.01; $P = .008$). There was, however, no heterogeneity by gender for new diabetes (P for interaction = .16). There were no gender-specific differences in any serious adverse event, rhabdomyolysis, cancer, transaminase elevation >3 times the upper limit of normal on consecutive visits, or hemorrhagic stroke. The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial that included 21.9% (n = 911) women demonstrated no statistically significant gender differences in premature discontinuation of statin therapy, increases in hepatic transaminases, elevated creatine kinase levels, or myalgias/myositis.[399] Compared to men (n = 3251), women were older, more likely to have diabetes or hypertension, and had a higher incidence of history of congestive heart failure. In the CTT analysis of the safety and efficacy of statins by gender, women were older compared to men (mean age 65.1 vs 61.8 years) and had a higher prevalence of hypertension (60.0 vs 47.5%) and of diabetes (23.6 vs 17.8%).[357]

In the study of atorvastatin by Hsue et al.,[360], which examined results from the Incremental Decrease in End Points Through Aggressive Lipid Lowering trial, TNT, the Stroke and Prevention by Aggressive Reduction in Cholesterol Levels trial, CARDS, ASCOT, and ASPEN, in 4 of the 6 trials, discontinuation rates due to adverse events were higher in women than in men, but only 1 trial reported a significant treatment by gender interaction. Rates of myalgia were higher in women than men in both the statin and placebo groups.

It has been estimated that women tend to be at 1.5–1.7 times greater risk for clinically significant adverse drug reactions compared to men.[400,401] Gender differences in body fat, muscle mass, quantities of cytochrome P450 (CYP450) metabolic enzymes, coenzyme Q10 levels, pain perception and reporting of adverse reactions, and underlying genetic factors (polymorphisms associated with CYP450 isoenzymes, drug transporters, or myocyte metabolism) may all play a role in the increased frequencies of adverse drug effects reported by women.[401] Women with ASCVD or at high ASCVD risk are likely to be older with more comorbidities, which may play a role in slowing statin metabolism and clearance. Polypharmacy in elderly women, particularly with drugs known to be metabolized via the CYP450 enzyme system, can lead to drug-drug interactions and increased systemic exposure to statins with resulting adverse events.

In summary, clinicians should be particularly aware of the potential for elevated adverse events with taking statins in women, particularly glucose elevations and myalgia, which may be due to differences in age, comorbidities, BMI and body fat, muscle mass, and polypharmacy. Further study of genetic polymorphisms will provide insight into gender-specific differences in statin-related drug reactions.

See Chart 4 for the Recommendations for Women's Health.

From pregnancy to menopause

In general, preventing ASCVD requires the practice of universal principles common to both genders, however the diagnosis and treatment of lipid disorders in women poses some unique challenges. The clinical lipidologist needs to view lipids from the perspective of ASCVD prevention throughout a woman's lifespan. The fact that clinical ASCVD (particularly CHD) events occur an average of 10 years later in women compared to men has created an unfortunate misconception that prevention is less of a concern for women. The clinical lipidologist must have a working knowledge of issues important in managing primary and secondary dyslipidemias in women. Of particular concern are women with genetic dyslipidemias, lipids during pregnancy, women with polycystic ovarian syndrome (PCOS), the use of contraception, and lipid changes during menopause with and without the use of sex hormone therapy (HT).

Pregnancy

Detection, management, and treatment of dyslipidemia in pregnancy

Average values of total-C, LDL-C, HDL-C, and TG measured in 8700 women (mean ± standard deviation age

Chart 4 Recommendations for women's health

Recommendations	Strength	Quality
In general, women should be treated according to the NLA Recommendations for Patient-Centered Management of Dyslipidemia – Part 1[1] with the following special considerations.	A	High
First-line cholesterol-lowering drug therapy, unless contraindicated, is moderate- to high-intensity statin. The statin dosage may be increased or the patient switched to a more efficacious agent, if goal levels of atherogenic cholesterol are not achieved. Statin therapy should be a consideration for patients at very high risk (i.e., ASCVD or diabetes mellitus with ≥2 major ASCVD risk factors), even if the pre-treatment levels of atherogenic cholesterol are below the treatment goals.	A	High
Non-statin drug therapy with cholesterol absorption inhibitor, bile acid sequestrant, fibric acid, nicotinic acid, or long-chain omega-3 fatty acid concentrates (the latter currently indicated only for very high TG) may be considered for women with contraindications for, or intolerance to, statin therapy, or in combination with statin therapy for patients who need additional lowering of atherogenic cholesterol to achieve treatment goals.	A	High
Women taking statins may be at increased risk for certain adverse events, particularly myalgia. Variations between men and women observed in clinical studies of statin-related myalgia incidence may have been related to differences in age, comorbidities, body composition, and polypharmacy.	B	Low

of 29.5 ± 5.8 years) without cardiovascular co-morbidities, and who did not develop gestational diabetes or preeclampsia as they were followed before, during, and after pregnancy are shown in Figure 6.[402] A steady rise throughout pregnancy occurs in the major lipoprotein lipids, and these levels peak near term. The lipid changes favor the availability of fuel for fetal development and also reflect increasing insulin resistance for the mother as pregnancy progresses through term. In uncomplicated or "normal" pregnancies, neither total-C nor TG exceeds 250 mg/dL at any time during pregnancy.

The cholesterol and TG responses shown in Figure 7 are from a population that also included women with complicated pregnancies, such as hypertension and preeclampsia.[403] As in the normal pregnancy population, the values for total-C and TG rose to term. However average values were near or exceeded 300 mg/dL in this analysis.[403] TG levels exceeding 250 mg/dL are associated with pregnancy complications, including pregnancy-induced-hypertension, preeclampsia, gestational diabetes, and large for gestational age babies.[404] When values exceed 250 mg/dL, this should alert that an obstetrical complication is more likely and the woman may have had pre-pregnancy dyslipidemia.

Optimum strategies for detection and treatment of dyslipidemia in pregnancy

Many women have significant undiscovered dyslipidemia before pregnancy, and this is often associated with conditions that put them at risk for obstetrical and fetal complications. The AAP/American College of Obstetricians and Gynecologists Guidelines for Perinatal Care has no set lipid screening recommendations, however they do suggest that lipid assessment should be performed at the annual visit for all age groups.[405] By current guidelines,

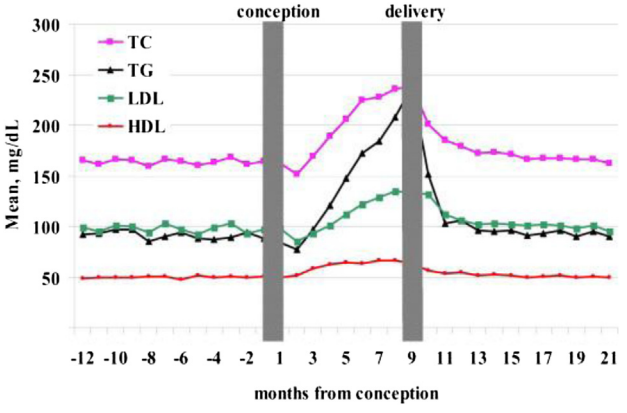

Figure 6 Lipid values in normal pregnancies (n = 8700). HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceride. Taken from Wiznitzer A, et al. *Am J Obstet Gynecol*. 2009;201:482.e1–e8.[402] Permission to reprint was obtained.

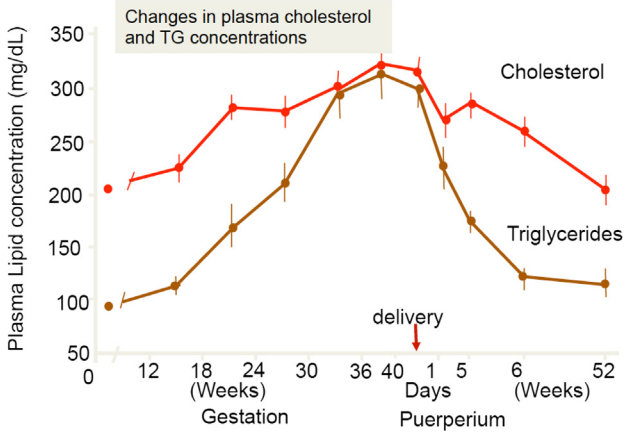

Figure 7 Pregnancy lipids and lipoproteins in normal and complicated pregnancies. TG, triglyceride. Taken from Potter JM, Nestel PJ. *Am J Obstet Gynecol*. 1979;133:165.[403] Permission to reprint was obtained.

patients with the following risk factors should be screened for gestational diabetes at the first prenatal visit: 1) BMI ≥30 kg/m^2, 2) personal history of gestational diabetes, or 3) known impaired glucose metabolism (e.g., prediabetes).[405]

The best time to screen for dyslipidemia is prior to pregnancy. When that has not occurred, lipid values may be collected with other routine laboratory tests once pregnancy is diagnosed, and monitored during the pregnancy if values are elevated. Follow-up should be performed routinely after the pregnancy is over, usually by the 6-week postpartum visit. Women who experience complications of pregnancy, or who gain excessive weight before or during pregnancy are more likely to have abnormal lipid profiles.[406] These risk factors should be queried in the diagnosis and management of dyslipidemia.

Evaluation of hypertriglyceridemia in pregnancy

Evaluation and classification of hypertriglyceridemia in a woman preparing for pregnancy, or when she is pregnant, are not different from such evaluation in the non-pregnant woman (Table 10). As noted previously, a TG elevation by the third trimester of pregnancy is to be expected.

Women with gestational diabetes and/or preeclampsia during pregnancy often have abnormal TG levels before they become pregnant. TG values in women with gestational diabetes may exceed 300 mg/dL and levels become higher as pregnancy progresses. A common reason for hypertriglyceridemia is poorly controlled or undiscovered diabetes mellitus. Most women with gestational diabetes have glucose intolerance that begins early in pregnancy. Some have type 2 diabetes mellitus that was unrecognized prior to pregnancy, and about 10% have circulating islet cell antibodies and/or HLA DR3 or DR4 and are at increased risk for type 1 diabetes mellitus post-delivery.[407,408]

Treatment and monitoring of dyslipidemia associated with pregnancy

Appropriate diet, weight management, and exercise always apply with regard to health management during pregnancy. For women on lipid-lowering medication prior to pregnancy, all, except bile acid sequestrants, are currently recommended to be stopped in preparation for pregnancy.[409,410] Table 11 provides the classification of approved lipid-lowering agents that had previously been used by the FDA.[411] The FDA has classified statins as category X; however, as of June 30, 2015, the FDA mandated new labeling changes (see below).[411] These changes should provide better guidance for clinicians as to the risk/benefit for use in pregnant women, lactating women, and women with reproductive potential. The new labeling changes will be used immediately for all new submissions for prescription drugs and biological agents. Previously approved drugs will switch to the new labeling gradually.

Controlling glycemia is central to managing TG elevations in women with gestational diabetes or diabetes present prior to pregnancy. Very high TG (≥500 mg/dL, with risk for pancreatitis) may be treated with diet/lifestyle management plus omega-3-fatty acids and/or with fenofibrate or gemfibrozil early in the second trimester based on clinical judgment (class C medication).[412] It is

Table 10 Evaluation of hypertriglyceridemia

- Medical history
  - Personal and family history of high TG, diabetes, pancreatitis, thyroid issues
  - Medicinal history, prescription, supplements
    - Antipsychotics, alpha interferon, beta-blockers, bile acid sequestrants, hormones, protease inhibitors, retinoids, thiazides, steroids
- Lifestyle issues: alcohol use, smoking, activity status
  - Laboratory testing
    - Renal function including urine protein
    - Thyroid function
    - Liver enzymes
    - Fasting glucose, glycated hemoglobin
- Physical examination
  - BMI and waist size
  - Blood pressure
  - Skin examination (xanthomata, acanthosis nigricans)

BMI, body mass index; TG, triglyceride.

Table 11 Lipid-lowering agents and pregnancy categories*

Lipid-lowering class or agent	Pregnancy category†
Statins	X
Lomitapide	X
Fibrates	C
Ezetimibe	C
Niacin	C
Cholestyramine	C
Omega-3 fatty acids	C
Colesevelam	B
Mipomersen	B

*These categories were removed from drug labeling per the new Food and Drug Administration labeling guidance effective June 30, 2015, and instead drug labeling will include a summary of the risks of using a drug during pregnancy and lactation, discussion of data supporting that summary, and relevant information to assist health care providers in treatment decisions for pregnancy (8.1), lactation (8.2), and females and males of reproductive potential.[411]

†Categories previously established by the Food and Drug Administration to indicate the potential of a drug to cause birth defects if used during pregnancy: B, animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women; C, animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; and X, studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

recommended that, at a minimum, lipids should be monitored every trimester, or within 6 weeks of an intervention to evaluate for compliance, response, and drug/dose adjustment. Women who have high TG, pregnancy-induced-hypertension, preeclampsia, gestational diabetes, and/or albuminuria during their pregnancy need to be evaluated for residual cardiometabolic risk post-pregnancy. Hypercholesterolemia during pregnancy, especially in women with FH, may be treated with bile acid sequestrants. Colesevelam is preferred because it is category B. Women with FH may also be treated with LDL apheresis.

Pregnancy and FH

Patients with FH have elevated levels of total-C, non-HDL-C and LDL-C, and an increased risk of premature atherosclerosis.[413] The increase in atherogenic lipoproteins that occurs during pregnancy may exacerbate this risk. Total-C and LDL-C have been observed to progressively rise during pregnancy in individuals with and without FH.[414] Women with FH exhibit a greater rise in LDL-C during pregnancy than those without FH.[409]

Despite high circulating levels of atherogenic lipoproteins in FH patients, data from several studies do not support an association between maternal lipid levels and maternal or perinatal outcomes.[404] In addition, FH pregnancy outcome studies have not shown an increased risk of preterm delivery, infant low birth weight, or congenital malformations as compared to women without FH.[415] There is a theoretical risk related to repetitive discontinuations of statin therapy in FH patients who have multiple pregnancies. However, results from registry analyses do not support this hypothesis.[415] There is no consistent evidence indicating that the incidence of adverse cardiovascular outcomes in those with FH is related to the gender of their FH parent.[416]

The United Kingdom National Institute of Care Excellence, the NLA Expert Panel on Familial Hypercholesterolemia, and the International Familial Hypercholesterolemia Foundation have provided recommendations that emphasize several principles.[337,413,417] Women with FH who wish to conceive should generally stop statin and other systemically absorbed lipid drug therapy a minimum of one month, and possibly as long as 3 months, prior to attempted conception[337,413,417] (opinion only). Theoretically water soluble statins have less risk. Women who conceive while on a systemically absorbed lipid drug should be advised to immediately stop the medication, although the likelihood of fetal complications in such patients is low. These patients should undergo an appropriate fetal assessment, and typically not re-start lipid drug therapy until they have completed lactation. LDL apheresis may be considered during pregnancy in homozygous FH patients, or in those heterozygous FH patients with ASCVD. Results from several small cohort studies suggest that this procedure is safe and effective in pregnant FH patients.[418,419]

Adolescent and adult female FH patients should be counseled about the need for appropriate birth control when statins are prescribed. When contraception is advised for female FH patients, low estrogen-containing oral agents, intra-uterine devices and barrier techniques are the preferred methods.[337] Intra-uterine devices and barrier techniques are preferable for those older than 35 years of age.[337]

Most women with FH should not be treated with drug therapy during pregnancy. However, those with ASCVD or homozygous FH may require pharmacotherapy. Among currently available lipid drugs, only bile acid sequestrants and mipomersen are considered to be reasonable therapeutic options (pregnancy class B on the old FDA classification system). Mipomersen is FDA-approved only for those with homozygous FH. The efficacy and safety of PCSK9 inhibitors during pregnancy has not been determined. Based upon the complexities of clinical decision-making in pregnant FH patients, referral to a clinical lipidologist is recommended.

Recommendations for women with dyslipidemia who are breast feeding

Appropriate heart healthy diets and exercise should be continued following pregnancy during breast feeding, and if weight loss is needed, a nutrition consultation with a registered dietitian nutritionist is advised. Patients with FH can receive bile acid sequestrants (colesevelam), and drug therapy for severe hypertriglyceridemia may be continued (as described in the previous section for pregnancy). For women with high TG, it is advisable to avoid estrogenic oral contraception, even with late breast feeding. As a modifiable behavior, lactation may favorably affect women's future risk for cardiovascular and metabolic diseases.[420] In the Nurse's Health Study there was a 23% lower incidence of MI in women in their 60s if they had breast fed.[421] In the Women's Health Initiative observational study, among postmenopausal women, increased duration of lactation earlier in life was associated with lower prevalence of hypertension, diabetes, hyperlipidemia, and ASCVD.[422] About 1 of 3 women will ovulate with prolonged breast feeding and therefore women should be advised to use contraception throughout the breast feeding period.

Long term ASCVD implications of complications in pregnancy

Dyslipidemia, obesity, and/or presence of the metabolic syndrome or diabetes mellitus before pregnancy, high risk status such as PCOS,[423] as well as hypertension during pregnancy are important for future ASCVD risk. Preeclampsia and pregnancy-induced-hypertension are not only associated with post-pregnancy cardiovascular risk factors such as hypertension, dyslipidemia, and obesity for the mother, but have also been linked to epigenetic factors influencing subsequent infant health.[424] Much evidence exists to suggest that developmental programming by pathologies during pregnancy influences both fetal development and future cardiometabolic risk of the fetus and the mother.[425,426]

PCOS

PCOS affects 7–22% of reproductive-age women. Understanding how to diagnose and treat PCOS is important to the clinical lipidologist.[427] Women with PCOS are at increased risk for metabolic syndrome, diabetes mellitus, and complications of pregnancy,[423] as well as endometrial cancer.[428] Nearly all women with PCOS have insulin resistance and this is aggravated by obesity and pregnancy. They are also at greater risk for obstetrical complications even if they have not developed overt metabolic syndrome.[423]

Criteria for diagnosis of PCOS

The term PCOS emanates from the characteristic morphology of the ovary (polycystic ovary), which is referred to as a string of pearl sign. This occurs because many follicles are 'suspended' in similar stages of development usually, although not always, arranged around the perimeter of the ovary. The follicles surround an endocrinologically active inner stroma that secretes androgens. There are several standard sets of criteria for diagnosis of PCOS—the most widely used are the Rotterdam criteria (Table 12[427]).[429] The Rotterdam PCOS criteria are based upon the presence of at least 2 of the following: androgen excess (measured in the blood or clinically in the form of hirsutism, acne, and/or androgenic alopecia), ovulatory dysfunction, and/or the presence of polycystic ovaries assessed by vaginal probe ultrasound.[429] The Androgen Excess Society insists that some form of androgen excess is necessary for the diagnosis of PCOS.[427] The spectrum of the condition can include persons mildly to severely affected with androgen excess, sometimes bordering on severe virilization. Women with PCOS frequently have dyslipidemia and/or the metabolic syndrome at any age, including at the onset of menses and throughout the adolescent years.

Table 12 Criteria for diagnosis of PCOS

Criteria	NIH 1990, "classic"	Rotterdam, 2003	AE-PCOS
Oligomenorrhea*	+	+/−	+/−
Clinical or biochemical hyperandrogenism†	+	+/−	+/−
Polycystic ovaries on ultrasound‡	+/−	+/−	+

AE-PCOS, Androgen Excess and PCOS society; NIH, National Institutes of Health; PCOS, polycystic ovarian syndrome.

NIH, both oligomenorrhea and clinical/biochemical hyperandrogenism; Rotterdam, any 2 of the previously mentioned criteria; AE-PCOS, presence of clinical and/or biochemical hyperandrogenism and 1 other criterion.

*8 or fewer menses per year.

†Acne, or hirsutism, or androgenic alopecia.

‡Ovarian volume >10 mL and/or >12 follicles <9 mm in at least 1 ovary.

Adapted from: Wild RA, et al. *J Clin Endocrinol Metab*. 2010;95:2038–2049.[427] Permission to reprint was obtained.

Screening for associated dyslipidemia in PCOS

This NLA Expert Panel recommends that all patients with PCOS, regardless of age should undergo initial lipid and diabetes screening, typically with fasting glucose or glycated hemoglobin.[430] The panel also recommends more frequent follow-up screening (at least every 2 years) if initial values are normal, because women with PCOS are at increased risk for dyslipidemia as they age. For those with dyslipidemia, we recommend that the lipid targets should be both non-HDL-C and LDL-C, as discussed in Part 1 of the NLA Recommendations for the Patient-Centered Management of Dyslipidemia.[1] As is the case for other conditions associated with increased risk for ASCVD, the accuracy of risk assessment using prediction equations is uncertain for women with PCOS, but, in general, the approach to risk stratification and atherogenic cholesterol treatment goals for women with PCOS should be the same as described for all patients with dyslipidemia in the NLA Part 1 Recommendations.[1]

Treatment of dyslipidemia in PCOS

Therapeutic management of dyslipidemia in PCOS should be focused on reversing all components of the metabolic syndrome through diet, exercise, and medication, if needed.[431] Metformin is frequently used to improve insulin sensitivity and is low cost, and relatively safe. However, metformin is not first line therapy for ovulation induction in PCOS women who desire pregnancy.[432] First-line therapy for ovulation induction through reducing insulin resistance is lifestyle modification. Weight loss should be targeted in all overweight/obese women with PCOS.[432,433] All lipid-lowering medications, including statins, have been used in women with PCOS, to treat the demonstrated lipid disturbances. However, it is necessary to educate women on the importance of pregnancy avoidance with some lipid lowering agents (Table 11).[411]

Unique challenges for women with PCOS

Therapy for PCOS is complicated because of several patient concerns, including: cosmetic–to reduce unwanted hair growth that, for some, is debilitating; menstrual control–to improve fertility and to reduce endometrial cancer risk; and metabolic–to control or prevent diabetes and to lower ASCVD risk.

The standard medication used to control menses, reduce endometrial and ovarian cancer risk, and reduce hirsutism is the combined oral contraceptive (COC). The more estrogenic oral contraceptives are effective for hirsutism control. Spironolactone may be used concomitantly because of its ability to reduce 5-alpha reductase, which is responsible for converting circulating testosterone into the more potent locally active dihydrotestosterone. The major risk associated with COC use is thrombotic, and therefore these agents should not be used in women

≥35 years of age who smoke because of additive stroke and MI risk. Persons with a family history positive for thrombotic disorder should be evaluated for genetic risk factors prior to using oral contraceptives.

In general, the dyslipidemia of PCOS is a result of insulin resistance. The HDL-C level is often reduced, hepatic TG production is increased, and there is often a predominance of small, dense LDL particles, particularly when a woman with PCOS is obese. Depending upon, which COC is used, the TG level may increase (sometimes to more than 500 mg/dL), HDL-C may increase, and calculated LDL-C may decrease.[432]

Lipid changes with different forms of contraception

COC can have estrogenic, progestational, androgenic, anti-estrogenic, and anti-androgenic effects. All formulations reduce risk for endometrial and ovarian cancer.[435] The major risk associated with their use is thrombotic, including venous and arterial events. Women with comorbidities, older age, and, most importantly, current smokers, are at greater risk for cardiovascular events.[434] There are 2 types of estrogen (ethinyl-estradiol and mestranol) used in the United States. Different doses of estrogen within the COC are available and a higher dose carries greater risk.[435] Most contain ≤35 μg of ethinyl-estradiol and there are multiple types of progestin in the COCs available today.

The estrogen contained in COC will frequently increase TG and HDL-C, and lower LDL-C.[436] Androgenic progestins (such as norgestrel and levonorgestrel) can raise LDL-C and lower HDL-C. The other progestational agents are usually lipid neutral. COCs with low dose norethindrone can lower LDL-C and raise HDL-C. Desogestrel (third generation) raises HDL-C and lowers LDL-C. The more estrogen a COC contains, the greater TG raising-effect it will generally have; these agents may cause severe hypertriglyceridemia in women with high baseline TG.[437] Transdermal or vaginal contraceptives (estrogen plus progestin) do not have a lower thrombotic risk in comparison to COC, but transdermal contraceptives are less prone to producing clinically important elevations in TG concentration.[438,439]

Implantable and injectable progestin forms of contraception are very efficacious for preventing pregnancy and are used especially for women at risk of noncompliance.[440] Progestin only-containing oral contraceptives are available and may be used if estrogenic preparations are contraindicated. They are, however, associated with greater risk for breakthrough bleeding and are not as effective for contraceptive purposes.

Lipid changes during menopause

The natural changes in lipids and apolipoproteins in women transitioning through the menopause years are shown in Figure 8.[441] Both LDL-C and apo B increase in the few years prior to menopausal symptoms, peak, and then plateau. HDL-C tends to decrease after menopause. The changes that occur are presumed to be related in part to declining ovarian estradiol production, although shifts in body composition, body fat distribution and other age-related physiologic changes are also likely contributors.[441,442] It is important to note that the absolute risk for ASCVD increases substantially during the menopause transition for women. Women with abnormal risk factors prior to menopause are more likely to have these factors worsen. In particular, the prevalence of metabolic syndrome increases and changes in body fat distribution occur, shifting toward a pattern of greater central and intra-abdominal adipose storage.[443,444]

Current recommendations for menopausal sex HT

Menopausal sex HT is primarily indicated to control menopause-related quality of life issues. It should not be prescribed for prevention or treatment of vascular diseases. Because sex HT increases risk for thrombosis, there is a black box warning on oral estrogen preparations for women with known coronary artery disease, thromboembolic disorders, or who have had a cerebrovascular accident. When a woman is identified as a potential candidate for sex HT for quality of life improvement due to moderate-to-severe menopausal symptoms, appropriate risk stratification is an important tool for minimizing future risk.[445]

Results from the Women's Health Initiative Trial suggest that women at higher risk for ASCVD events (e.g., dyslipidemia or presence of the metabolic syndrome) are more likely to have even higher risk when they take oral menopausal sex HT (Table 13).[445] This appears to be due to increased intravascular thrombotic activity and is evident in the first year of therapy. In general, prescribing the lowest effective dose of sex HT is recommended, but doses lower than 0.3 mg of oral conjugated estrogen given at night will not control hot flashes for most women. This dose is, however, protective against bone loss.[446] Transdermal or vaginal delivery may be associated with fewer adverse events than the oral route.[447] Vaginal and transdermal preparations also have smaller effects on clotting factors, lipid metabolism, inflammatory biomarkers, and sex hormone-binding globulin synthesis. Results from observational studies, although limited in number, suggest that transdermal delivery may be associated with less risk of venous thromboembolism and stroke than oral estrogen.[448]

See Chart 5 for the Recommendations for Pregnancy to Menopause.

Older patients

According to the World Health Organization, most developed countries have accepted the chronological age of 65 years as the definition of "elderly".[449] Statistical data from the AHA and American Stroke Association indicate that about 80% of people who die from CVD are ≥65 years of age. Among those who are 60–79 years of age, 69.1% and 67.9% of men and women, respectively, have CVD (CHD, heart failure, stroke or hypertension, and some with a combination of these). Among those ≥80 years of age, the figures are 84.7% and 85.9% of

Chart 5 Recommendations for pregnancy to menopause

Recommendations	Strength	Quality
Women should be screened for dyslipidemia before pregnancy or as part of the routine obstetrical laboratory examination.	E	Low
For women taking lipid-lowering medications prior to pregnancy, all, except bile acid sequestrants, should be stopped when the woman becomes pregnant, or is trying to become pregnant.	B	Moderate
Women should be educated on the importance of pregnancy avoidance when lipid-altering therapies other than bile acid sequestrants are used.	A	Moderate
Total-C and TG levels in women with normal pregnancies should not exceed 250 mg/dL. If they do, the clinician should consider and evaluate preexisting or acquired medical or obstetrical conditions, including hypothyroidism, chronic kidney disease, liver disease, uncontrolled diabetes mellitus, or preeclampsia.	A	Moderate
Hypercholesterolemia during pregnancy and breast feeding, especially in women with FH, may be treated with bile acid sequestrants.	B	Low
Women with FH may be treated with LDL apheresis during pregnancy and breast feeding.	A	Low
Very high TG (≥500 mg/dL) may be treated during pregnancy with diet/lifestyle management plus prescription omega-3 fatty acids; fenofibrate or gemfibrozil may be administered beginning early in the second trimester, based on clinical judgment. These agents may be used during breast feeding.	B	Low
PCOS is a high-risk condition for dyslipidemia, metabolic syndrome, and obstetrical complications of preeclampsia, hypertension, diabetes, and premature delivery. All patients with PCOS, regardless of age, should undergo initial lipid and diabetes screening and more frequent follow-up screening is recommended, even if initial values are normal.	A	Moderate
The approach to risk stratification and atherogenic cholesterol treatment goals for women with PCOS should be the same as described for all patients with dyslipidemia in the NLA Recommendations for Patient-Centered Management of Dyslipidemia – Part 1 (Jacobson 2015).	A	Moderate
Therapeutic management of dyslipidemia in PCOS should focus on diet, exercise, and lipid-lowering medication, if needed. Use of metformin should also be considered to lower TG and reduce insulin resistance.	A	Moderate
Contraceptive choice impacts dyslipidemia. COC should generally not be used by women ≥35 years of age who smoke because of additive stroke and MI risk.	A	High
Sex HT should not be used for prevention or treatment of ASCVD.	A	High
Menopausal sex HT is an option for treatment of significant menopause symptoms during menopause transition for women at minimal risk for ASCVD.	A	Moderate

men and women, respectively. CHD accounts for ~47.7% and stroke ~16.4% of deaths attributable to CVD. The average age of first heart attack is 65.0 years in men and 71.8 years in women, and nearly 70% of first strokes are in patients ≥65 years of age.[256]

ASCVD risk assessment in older patients

All current scoring systems that assess ASCVD risk reflect the progressive increase in absolute risk that occurs with advancing age, likely reflecting an age-related increase in atherosclerotic plaque burden. However, population norms often do not apply to individual patients. Application of average risk scores for age to specific patients may lead to miscalculation of risk and inappropriate consideration of drug therapy.[450] The ACC/AHA Pooled Cohort Risk Equation[3] was applied for ASCVD risk assessment to 4854 Rotterdam Study participants with a mean age of 65 years.[366] Using ≥7.5% 10-year risk as the threshold for consideration of initiation of moderate or high intensity statin therapy, 96.4% of men and 65.8% of women were potential candidates for such therapy. In this population the average predicted vs observed cumulative incidence of ASCVD events was 21.5% vs 12.7% for men and 11.6% vs 7.9% in women, reflecting poor calibration of risk in this European sample.[366]

A 1999 AHA Scientific Statement on ASCVD Risk Assessment suggested that when risk scoring is used to adjust the intensity of risk factor management in elderly patients, RR estimates, which eliminate the age factor and focus on the major risk factors, might be more useful than absolute risk estimates.[450] This approach allows providers to risk stratify and compare patients of the same age and select those at highest RR for the most aggressive treatment strategies.[450] Results from some studies suggest that serum lipids partially lose their predictive power for relative ASCVD risk prediction in the elderly.[451] A variety of reasons exist for this, including the increased number of co-morbidities among patients of advanced age.

In another study of Rotterdam study participants, 2028 patients underwent electron beam tomographic imaging of the epicardial coronary arteries and CAC scores were reported using Agatston's method.[452] During a mean follow-up of 9.2 years there were 135 hard coronary events. Subjects were classified into low (<10%), intermediate (10–20%) and high (>20%) 10-year coronary risk using a Framingham refitted risk model. The model was extended by CAC and reclassification percentages were calculated. Reclassification into high or low risk categories was greatest in those classified as intermediate risk. A total of 52% of men and women were

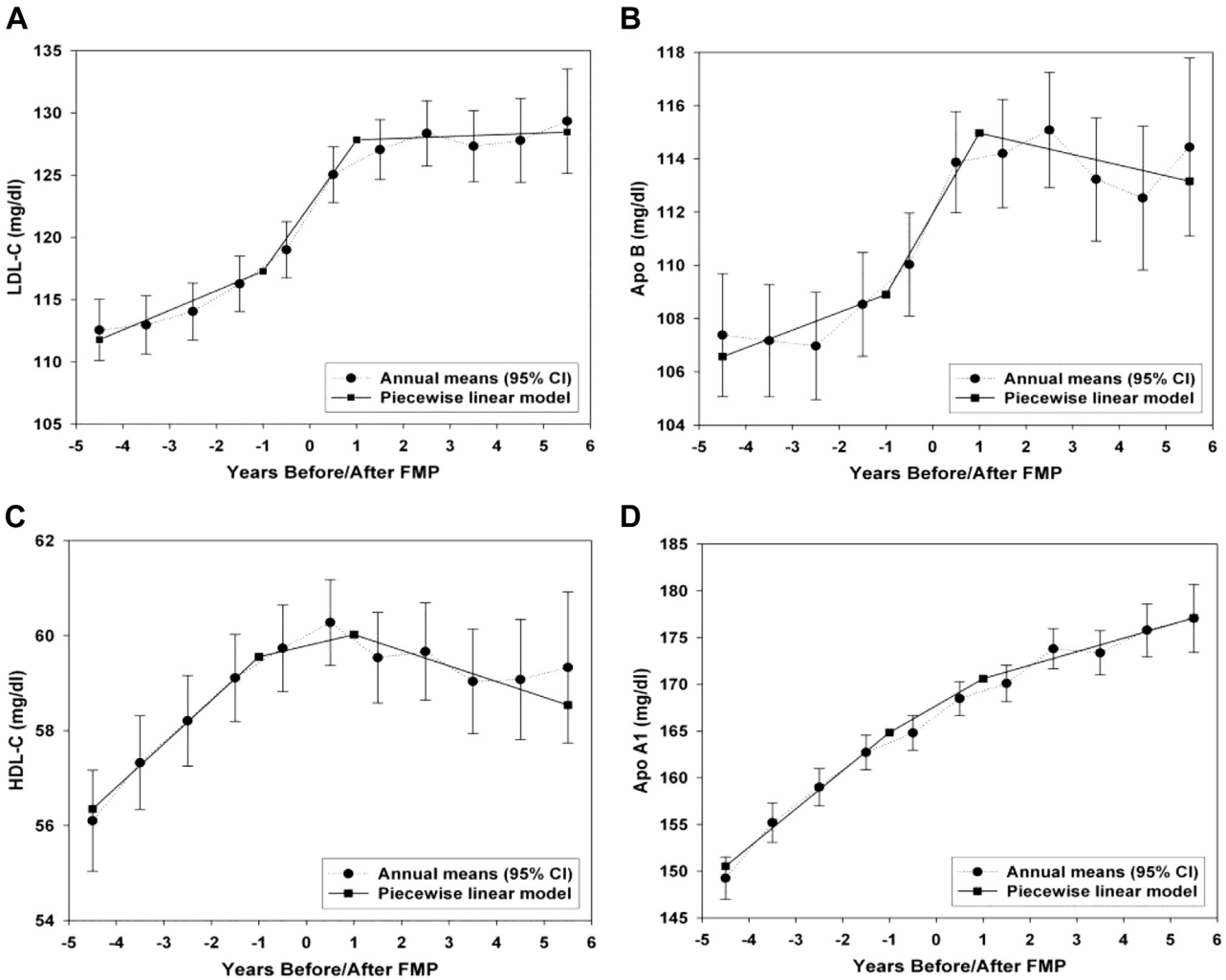

Figure 8 Patterns of LDL-C (A), apo B (B), HDL-C (C), and apo A1 (D) among women in menopausal transition in the Study of Women's Health Across the Nation. apo, apolipoprotein; CI, confidence interval; FMP, final menstrual period; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Taken from Matthews KA, et al. *J Am Coll Cardiol*. 2009;54:2366–2373.[441] Permission to reprint was obtained.

reclassified into either higher or lower risk categories based upon their CAC score. Empirically derived CAC cutoffs at, which subjects were reclassified into either high or low risk categories were 615 and 50 Agatston units, respectively.[452]

CAC is reported to be present in >50% of middle-aged US residents, and the probability of CAC is >90% by age 70 years.[453–456] Although measurement of CAC provides a more accurate means of CHD risk assessment than the use of traditional risk factor-based algorithms, the cost of the test, lack of widespread availability, and absence of studies linking results with outcomes is a limiting factor in its implementation in older patients. Nevertheless, when such testing is available it may be a valuable addition to CHD risk assessment, particularly in older patients.

Value of statin therapy in older patients

The CTT Collaboration meta-analysis of data from 26 randomized controlled primary and secondary prevention trials of statin therapy in 170,000 subjects examined the RR of fatal or non-fatal MI, percutaneous coronary intervention or bypass grafting, stroke and new cancer diagnosis, and included subgroup analyses of those ≤65, >65 to ≤75, and >75 years of age.[355] The latter two groups included 4032 and 885 subjects respectively, comparing either statin therapy or more intensive statin therapy vs control or less intensive statin therapy. The RR for those >65 to ≤75 years of age was 0.78 (95% CI 0.74–0.83) and for those >75 years of age was 0.84 (95% CI 0.73–0.97). No significant effects on cancer incidence or cancer death were observed.[355]

Secondary prevention studies

Lipid-lowering therapy in older patients is a valuable adjunct to secondary prevention of ASCVD. Few studies have specifically addressed the use of lipid-lowering therapy in older patients, although many statin studies have included subjects between the ages of 65 and 75, and have demonstrated similar relative risk reduction (RRR) in older and younger individuals. One study that specifically focused on

Table 13 CHD risk in the Women Health Initiative hormone therapy trials (estrogen plus progestin and estrogen alone) according to baseline levels of biomarkers

Biomarker	Odds ratio (95% CI) for hormone therapy effect	*P* for interaction
LDL-C (mg/dL)		
<130	0.66 (0.34–1.27)	.03
≥130	1.46 (1.02–2.10)	
LDL-C/HDL-C ratio		
<2.5	0.60 (0.34–1.06)	.002
≥2.5	1.73 (1.18–2.53)	
hs-CRP (mg/dL)		
<2.0	1.01 (0.63–1.62)	.16
≥2.0	1.58 (1.05–2.39)	
Metabolic syndrome	2.26 (1.26–4.07)	.03
No metabolic syndrome	0.97 (0.58–1.61)	

CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol.
Adapted from: Wild RA, Manson JE. *Semin Reprod Med*. 2014;32:433–437.[445] Permission to reprint was obtained.

older subjects was PROSPER that enrolled men and women 70–82 years of age with a history of, or risk factors for, vascular disease. A meta-analysis of 19,569 subjects aged 65–82 years from 9 secondary statin RCTs showed RRRs and absolute risk reductions (ARRs) of 22% and 3.1%, respectively, in all-cause mortality, 30% and 2.6% in CHD mortality, 26% and 2.3% in non-fatal MIs, and 30% RRR in need for revascularization (ARR was not reported).[457,458]

A 25%/1.7% RRR/ARR in stroke risk was also reported in this meta-analysis (Table 14).[458] However, in studies that reported stroke risk, it was favorable only in the Long-Term Intervention with Pravastatin and the Cholesterol and Recurrent Events studies. It was not reported separately in the Scandinavian Simvastatin Survival Study, HPS, PROVE IT study, and the Study Assessing Goals in the Elderly. The RRR for stroke was not significantly different with statin vs placebo in the TNT study and PROSPER.[458]

Primary prevention studies

Results from a meta-analysis of 8 statin primary prevention trials in individuals ≥65 years of age including AFCAPS/TexCAPS; ALLHAT; ASCOT-LLA; CARDS; JUPITER; MEGA; and PROSPER are shown in Figure 9.[459] This analysis included 24,674 subjects (42.7% female; mean ± standard deviation age 73 ± 2.9 years and follow up 3.5 ± 1.5 years), treated with statin therapy vs placebo, and examined the incidence of all cause death, cardiovascular death, MI, stroke, and new cancer onset. Statin therapy was associated with an RR for MI of 0.61 (95% CI 0.43–0.85; $P = .003$). Stroke incidence in ASCOT-LLA, CARDS, JUPITER, MEGA and PROSPER had an RR favoring statin therapy of 0.76 (95% CI 0.63–0.93; $P = .006$). PROSPER did not demonstrate RRR (1.03; 95% CI 0.73–1.45), and the Forest plots showed that the RRR crossed the line of identity in ASCOT-LLA (0.80; 0.58–1.11) and CARDS (0.60; 0.30–1.19), indicating that stroke benefit was limited to JUPITER and MEGA. The RRR was similar for most studies, but not all of the original trials were powered to evaluate stroke alone. There was no difference in the risk of all cause death, cardiovascular death, or cancer incidence.[459]

Statin safety in older patients

Biases in reporting side effects

Although there have been no definite signals in RCTs to suggest a higher incidence of side effects in older vs younger populations treated with statins, the use of RCTs for this purpose has limitations. Observational studies often report a higher incidence of side effects than RCTs. Patients entering RCTs and experiencing side effects during run-in periods, or exhibiting conditions that predispose to side effects are often excluded. Validated inquiry instruments that assess for harm may not be employed. Other issues including definition of adverse events, selective reporting of outcomes, and publication bias may affect the reported incidence of side effects.[335]

Myalgia

It is generally reported that older individuals have a higher incidence of statin-associated myalgia than younger patients.[460–463] It is unclear whether this is related to decreasing muscle mass that occurs during aging; polypharmacy, common among older patients that increases the risk for drug-drug interaction; a loss in the function of drug metabolizing enzymes; or a combination of these factors.[463] Results from a study based on the Understanding Statin Use in America and Gaps in Education Internet survey showed more muscle side effects in older patients, and that older patients were more likely to discontinue a statin due to muscle side effects.[464]

Diabetes

As reviewed in the NLA Task Force on Statin Safety – 2014 Update, clinical trial data, including meta-analyses, suggest a modest, but statistically significant increase in the incidence of new-onset type 2 diabetes with statin vs no statin use and with use of higher vs lower intensity statin use.[356] However, because of the well-established benefits for ASCVD risk reduction with statin use, there have been no recommendations to change clinical practice with regard to statin use other than recommending the measurement of glycated hemoglobin or fasting glucose in patients at elevated risk for diabetes. In JUPITER, which included patients with a median (interquartile range) age of 66.0 (60.0–71.0) years, patients with at least 1 major diabetes risk factor were at higher risk for developing diabetes than patients without a major diabetes risk factor. However, the cardiovascular and mortality benefits exceeded the

Table 14 ASCVD risk reduction with statin therapy in older adults from secondary prevention statin trials

Trial (ref)	Intervention	Age Subgroup (n)	All-Cause Death RRR%/ARR%	CHD Death RRR%/ARR%	CHD Events RRR%/ARR%	Stroke RRR%/ARR%	Comment
4S[53]	S20–40 vs PL	65–70 (1021)	34/6.2*	43/6.0	34/13.3 33/7.1†	NR	↓CV admissions by 21%
LIPID[54]	P40 vs PL	65–75 (3514)	21/4.5	24/2.9*	26/3.3	12/1.3	
CARE[55]	P40 vs PL	65–75 (1283)	NR	45/4.5	32/9* 39/6.7‡	40/2.9	32% RRR/5.2% ARR for PCI/CABG
HPS[56]	S40 vs PL	70–80 (5806)	NR	NR	18/5.1‡	NR	9.2% ARR in primary end point in patients 75–80 y (n = 1263)
PROSPER[57]	P40 vs PL	70–82 (5804)	NS	24/0.9	19/2.1‡	NS	25% ↑ cancer risk with P40
PROVE-IT TIMI 22[58]	A80 vs P40	≥70 (634)	NR	NR	40/8 LDL-C <70 vs LDL-C ≥70 mg/dL (in death/MI/UAP*)	NR	AE rate similar to young
TNT[59]	A80 vs A10	65–75 (3809)	NS	NS	19/2.3* (A80 vs A10)	21/0.9-NS	↑LFTs w A80 vs A10
SAGE[60]	A80 vs P40	65–85 (893)	67/2.7	67/0.9 based on 8 deaths	29/3.1‡ (P = .11)	Too few to compare	↑LFTs w A80 vs P40
Meta-analysis[61]		65–82 (19,569)	22/3.1*	30/2.6	17/2.1‡ 26/2.3 NFMI	25/1.7	30%↓PCI/CABG

A, atorvastatin; AE, adverse events; ARR, absolute risk reduction; CABG, coronary artery bypass grafting; CARE, The Cholesterol and Recurrent Events; CHD, coronary heart disease; CV, cardiovascular; HPS, Heart Protection Study; LDL-C, low-density lipoprotein cholesterol; LIPID, Long-Term Intervention with Pravastatin in Ischaemic Disease; LFTs, liver function tests; Ml, myocardial infarction; NFMI, nonfatal myocardial infarction; NR, not reported; NS, not significant; P, pravastatin; PCI, percutaneous coronary intervention; PL, placebo; PROSPER, PROspective Study of Pravastatin in the Elderly at Risk; PROVE IT-TIMI 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22; S, simvastatin; w, with; RRR, relative risk reduction; SAGE, Study Assessing Goals in the Elderly; TNT, Treating New Targets; UAP, unstable angina. The reference numbers in this table refer to the reference numbering from the original publication.

*Primary end point.

†NFMI.

‡Death or NFMI.

Taken from Fleg JL, et al. *Circulation*. 2013;128:2422–2446.[458] Permission to reprint was obtained.

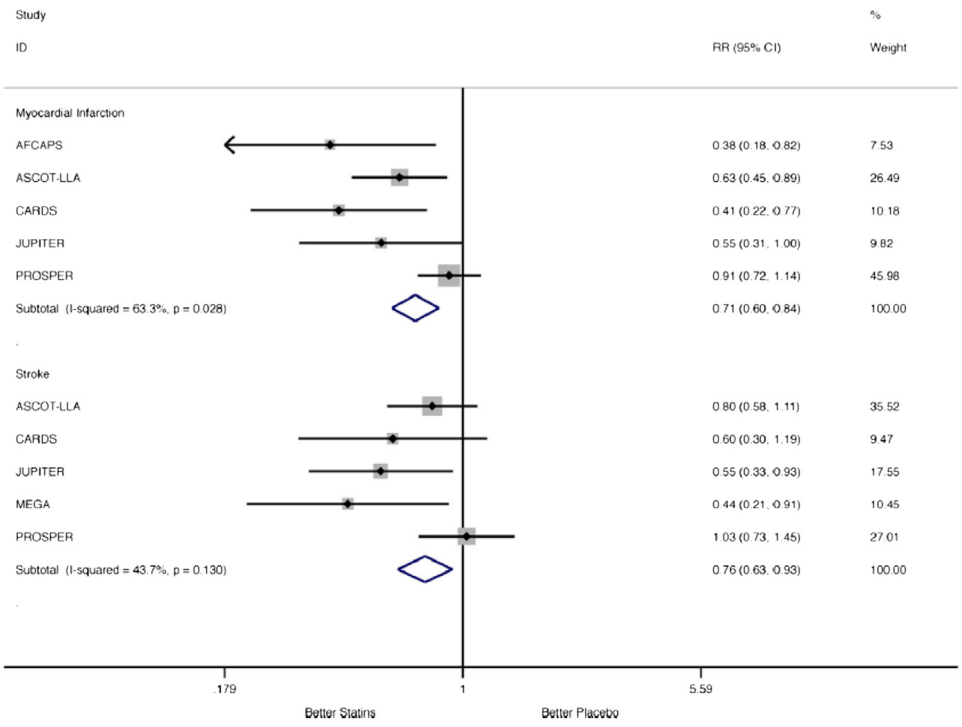

Figure 9 Relative risk (RR) for myocardial infarction and stroke from randomized trials comparing statins vs placebo in older subjects without established cardiovascular disease. Gray squares represent RRs in trials. The 95% confidence intervals (CIs) for individual trials are denoted by lines and those for the pooled RRs by open diamonds. Meta-analysis is performed by fixed effects model. AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT, Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial; ASCOT-LLA, Angio-Scandinavian Cardiac Outcomes Trial Lipid-lowering Arm; CARDS, Collaborative Atrovastatin Diabetes Study; JUPITER, Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk. Taken from Savarese G, et al. *J Am Coll Cardiol*. 2013;62:2090–2099.[459] Permission to reprint was obtained.

diabetes hazard in all patients, including those at high risk for developing diabetes.[344,465] Because the incidence of diabetes increases with age, periodic glucose monitoring, and when appropriate, glycated hemoglobin measurement, should be performed when administering statins to older patients.

Cognitive dysfunction

There have been case reports of patients noting cognitive dysfunction during the course of statin therapy. The NLA Task Force on Statin Safety – 2014 Update defined cognitive dysfunction as impairment in any of 4 domains, including executive function, memory, language and visuospatial ability.[466] Mild cognitive impairment was defined as a state of cognitive dysfunction between normal cognition and dementia, the latter of which is defined as cognitive dysfunction involving 2 domains and is sufficiently severe to interfere with activities of daily living associated with progressive loss of independence. Clinically, it is especially important to differentiate a potential medication side effect causing cognitive impairment from other causes of dementia in older patients, including Alzheimer's disease; frontoparietal dementia; Parkinson's disease; Lewy body dementia; infectious processes; inflammatory, vascular or metabolic disorders; and depression.

The following perspective on statins and cognition was put forth by the NLA Task Force on Statin Safety: 1) a baseline cognitive assessment does not need to be performed prior to initiation of statin therapy (strength of recommendation: expert opinion; quality of evidence: low); 2) statins as a class are not associated with adverse effects on cognition (strength of recommendation: strong; quality of evidence: low to moderate); and 3) in patients who report cognitive symptoms after beginning a statin, cognitive testing should be performed, other potential contributors should be ruled out, and the risk of stopping the statin should be assessed.[466] The provider may consider stopping the statin to assess the reversibility of symptoms, lowering the dose, or switching to an alternative statin. If the statin is switched, consideration may be given to starting a statin that is less likely to penetrate the brain, including pravastatin or rosuvastatin (strength of recommendation: expert opinion; quality of evidence: low).[466]

Polypharmacy and drug-drug interactions

Polypharmacy, defined as the concurrent use of 5 or more medications, is common in older patients, and is likely contributed to by changes in absorption, bioavailability, and volume of distribution. Multiple pathways of altered metabolism have been described in statin drug-drug

interactions; the CYP3A4 and CYP2C9 pathways are most commonly implicated. In addition, single-nucleotide polymorphisms in organic anion transporter 1B1, encoded by the soluble carrier organic anion transporter 1B1 gene; in breast cancer-related protein, encoded by the ABC subfamily G2 gene; and in the p-glycoprotein transporter, alter the movement of statins in and out of cells and may be an additional cause of statin-related drug interactions. Reduced muscle mass in older patients may also predispose to muscle-related side effects. It has been suggested that older patients on polypharmacy regimens be regularly evaluated for drug-drug-interactions and that medication reconciliation be carefully performed at each clinic visit. Providers should have access to references that provide a comprehensive listing of statin therapies and common drug-drug interactions.[463]

Recommendations for lipid management in older patients in other major guideline documents

The 2013 ACC/AHA Guideline for the Treatment of Blood Cholesterol includes different treatment regimens for individuals >75 years of age compared to those who are younger. Moderate intensity statin therapy is recommended for secondary prevention in those >75 years of age vs high intensity in those who are younger. In primary prevention, the ACC/AHA guidelines recommend the use of the Pooled Cohort Risk Equations to inform statin treatment decisions and the use of provider-patient discussion in which the pros and cons of statin therapy are discussed.[3] No specific recommendation is made for the intensity of statin therapy in primary prevention for those >75 years of age.

The International Atherosclerosis Society Guidelines recommend for persons >65 years of age the use of short-term (10-year) Framingham risk scoring (recalibrated for country) to estimate CHD risk, and then elevation of the estimated value by 1/3 to estimate total ASCVD risk. The guideline suggests that statin therapy should be used in those whose risk is estimated to be moderately-high or high, but that decisions about the use of drug therapy should be made while considering the pros and cons of polypharmacy, drug-drug interactions, and cost.[6]

The European Atherosclerosis Society/European Society of Cardiology Guidelines advocate for elderly patients that statin therapy generally be given for secondary prevention in the same manner as in younger patients (class 1, level of evidence B). However, because of co-morbidities and altered pharmacokinetics, therapy should be started at a low dosage and the dosage should be titrated to achieve target lipid levels that are the same as for younger patients (class 1, level of evidence C). They also recommend statin therapy for primary prevention in those with 1 or more additional risk factors, aside from age (class IIb, level of evidence B).[467]

The Canadian Cardiovascular Society Guidelines recommend statin therapy without specific upper age cut-offs for secondary prevention of ASCVD. For primary prevention, 10-year Framingham risk scoring is advocated for men ages 40–75 years and for women ages 50–75 years. Because the Framingham model is not well validated in those >75 years of age, clinical judgment regarding the use of drug therapy should be used.[468]

In secondary prevention, the National Institute of Care and Health Excellence Clinical Guideline from the United Kingdom recommends the use of high intensity statin (i.e., atorvastatin 80 mg), but a lower dosage may be considered in those with potential drug interactions, high risk of adverse effects, or patient preference. For primary prevention in those individuals up to age 84 years, the provider should discuss the benefits of lifestyle modification and optimize the management of all other modifiable ASCVD risk factors, followed by a repeat assessment of risk factors. If lifestyle modification is ineffective or inappropriate, a moderate intensity statin (i.e., atorvastatin 20 mg) is advised for those with a ≥10% 10-year ASCVD risk using the QRISK2 assessment tool.[469] In the QRISK2 tool, ASCVD includes CHD (angina and MI), stroke, and transient ischemic attack, but not peripheral arterial disease. It has been validated in populations ranging from 30–84 years of age.[469]

Summary of recommendations for lipid management from the 2015 NLA Expert Panel on older patients

Secondary and very high risk prevention (ASCVD or type 1 or 2 diabetes mellitus with ≥2 major ASCVD risk factors or evidence of end organ damage)

Consistent with the NLA Recommendations for the Patient-Centered Management of Dyslipidemia–Part 1,[1] the Expert Panel recommends consideration of moderate or high intensity statin therapy for those individuals age ≥65 to ≤75 years of age with ASCVD or diabetes mellitus. Secondary prevention patients who are >75 to <80 years of age may be treated with similar regimens after a careful consideration of the risk-benefit ratio of such therapy. In those ≥80 years of age, moderate intensity statin therapy should be considered based upon a provider-patient discussion of the risks and benefits of such therapy, consideration of drug-drug interactions, polypharmacy, concomitant medical conditions including frailty, cost considerations and patient preference. With regard to the use of combination therapy, IMPROVE-IT identified individuals (mean age 64 years) who suffered an acute coronary syndrome as being more likely to benefit from simvastatin-ezetimibe combination therapy than from simvastatin monotherapy.[370] In those older than age 65 years, the ASCVD event rate with combination simvastatin-ezetimibe therapy was 36.4% vs 39.9% on simvastatin monotherapy, for an absolute risk reduction of 3.5%.

Primary prevention

Primary prevention strategies in those 65–79 years of age should be managed in accordance with the NLA Recommendations for the Patient-Centered Management of Dyslipidemia–Part 1.[1] An individualized approach should be taken to lifestyle change recommendations in

older patients who are overweight or obese. Being overweight has been shown to protect against mortality in some elderly individuals.[470] Therefore, promoting weight loss in the elderly is not broadly recommended. However, recent RCTs have shown that supervised, moderate calorie restriction in combination with regular physical exercise in obese older adults did not increase mortality risk and may be beneficial for reducing metabolic complications.[470] An approach that takes into consideration the older patient's life expectancy, chronic comorbidities, functional status, personal motivation, and social support is recommended. In patients age 80 or older, recommendations about the advisability of weight loss should be individualized based upon clinical judgment.

Although the NLA Recommendations state that risk calculators such as the ACC/AHA Pooled Cohort Risk Calculator or the ATP III Framingham Risk Calculator can be used in select individuals with 2 risk factors, this approach in older patients has significant limitations. As most men >60 years of age and women >70 years of age are candidates for a risk-benefit discussion about statin therapy, using the ACC/AHA recommended cutpoints for the Pooled Cohort Risk Equations, there is a risk for over-treatment in this population. An application of the 2013 ACC/AHA Risk Assessment Working Group Guidelines to NHANES data from 2005 to 2010 indicated that the number of adults who would be eligible for statin therapy would increase by 12.8 million, due mostly to an increase among older adults without CVD.[471] Among adults between the ages of 60 and 75 years without CVD and not receiving statin therapy, the percentage that would be eligible for statin therapy would increase from 30.4% to 87.4% among men and from 21.2% to 53.6% among women.

The threshold recommended by the NLA for classification of high risk using the Pooled Cohort Equations is ≥15% 10-year risk for a hard ASCVD event (MI, stroke, or death from CHD or stroke), and using the ATP III Framingham Risk Calculator, a high risk cutpoint of ≥10% 10-year risk for a hard CHD event (MI or CHD death) is recommended.[1] Providing the older, statin-eligible patient with easy to understand concepts such as the number needed to treat to prevent an ASCVD event vs the number needed to harm for a statin-related side effect may allow patients to make more informed decisions about taking long-term statin therapy.[472]

For lipid management in primary prevention, non-HDL-C and LDL-C goals of <130 mg/L and <100 mg/dL are appropriate targets. Those who are unable to achieve these atherogenic cholesterol goals after a minimum 3–6 month trial on lifestyle modification should engage in a patient-provider discussion about the pros and cons of drug therapy and be recommended, whenever feasible, moderate intensity statin therapy. In those patients ≥65 years of age in whom the decision regarding the use of drug therapy remains in question, it is reasonable to recommend moderate intensity statin therapy in those with 1 or more major ASCVD risk factor aside from age, those with additional risk factors whose risk exceeds 15% on the Pooled Risk Calculator or 10% on the ATP III Framingham Risk Calculator. In those situations in which additional objective information is deemed necessary, CAC scoring may be considered for those willing to incur the cost of the test, as a score of zero in asymptomatic patients may suggest that non-pharmacologic approaches to atherogenic cholesterol reduction are a reasonable option.[473,474]

For those ≥80 years of age with atherogenic lipoproteins above the stated goals, a provider-patient discussion of the risks and benefits of statin therapy, consideration of drug-drug interactions, polypharmacy, concomitant medical conditions including frailty, cost considerations, and patient preference should be undertaken. If statin intolerance is the primary issue, consideration should be given to the use of alternate statin regimens such as low intensity statin therapy or non-daily moderate intensity statin therapy, low dose statin combination therapy with ezetimibe, bile acid sequestrants, or niacin, or non-statin monotherapy (i.e., ezetimibe or bile acid sequestrant) or their combination. Of note, these recommendations are less evidence based than using moderate to high intensity statin daily therapy. In general, we recommend that providers try to achieve at least a 30% LDL-C reduction.

ASCVD prevention using appropriate lifestyle and lipid-related pharmacological therapy should remain an important health care priority in our older population, a group that carries the largest proportional burden of these diseases. Evidence-based, empathetic shared decision-making will help to facilitate the optimal preventive strategy for the care of these patients.

See Chart 6 for the Recommendations for Older Patients.

Ethnic and racial groups

Hispanics/Latinos

Hispanics/Latinos are the largest and one of the fastest growing minority populations in the United States, and represent diverse cultures, backgrounds, and exposures. ASCVD is one of the leading causes of mortality among Hispanics/Latinos,[256] and similar associations of major ASCVD risk factors with adverse ASCVD outcomes have been reported among Hispanic/Latino adults compared to NHWs.[475]

Prevalence of hypercholesterolemia among diverse US Hispanics/Latinos

NHANES 2009–2012 data show that prevalence of total-C ≥200 mg/dL and of LDL-C ≥130 mg/dL are higher among Hispanic men compared to NHW men, and slightly lower for Hispanic women vs NHW women (Table 15).[256] As shown in Table 16, the mean level of LDL-C was higher among Hispanic men vs NHW men, and the mean level of HDL-C was lower and mean TG was higher for both

Chart 6 Recommendations for older patients

Recommendations	Strength	Quality
Primary prevention strategies in patients 65-79 years of age should be managed in accordance with the NLA Recommendations for the Patient-Centered Management of Dyslipidemia-Part 1.[1]	A	High
For patients age ≥65 to <80 years of age with ASCVD or diabetes mellitus, moderate or high intensity statin therapy should be considered after a careful consideration of the risk-benefit ratio.	A	High
For secondary prevention in patients ≥80 years of age, moderate intensity statin therapy should be considered based upon a provider-patient discussion of the risks and benefits of such therapy, consideration of drug-drug interactions, polypharmacy, concomitant medical conditions including frailty, cost considerations, and patient preference.	B	Moderate
Risk calculators such as the ACC/AHA Pooled Cohort Risk calculator or the ATP III Framingham Risk Calculator can be used in select older individuals with one additional risk factor to further assess risk, using the thresholds for high risk of ≥15% 10-year risk for a hard ASCVD event (MI, stroke, or death from CHD or stroke) with the Pooled Cohort Equations, and ≥10% 10-year risk for a hard CHD event (MI or CHD death) using the ATP III Framingham risk calculator. However, these risk calculators have several limitations for use in older patients, since advanced age is often the predominate driver of increased ASCVD risk, and this may result in overtreatment of lower risk older individuals.	E	Low
Older, primary prevention patients who are statin-eligible should undergo a patient-centered discussion with their provider about the risks and benefits of statin therapy so that they can make a more informed decision about taking statins over the long term.	E	Low
If the older primary prevention patient is unable to achieve atherogenic cholesterol goals after a minimum 3-6 month trial on lifestyle modification, the provider should discuss the pros and cons of drug therapy and, if feasible, prescribe moderate intensity statin therapy, particularly for patients with one or more ASCVD risk factor aside from age, with risk exceeding the high risk threshold using the Pooled Risk Equation or ATP III Framingham Risk Calculator.	E	Moderate
CAC scoring may be useful to further assess risk in older patients for whom questions remain about whether to prescribe drug therapy.	E	Low
If statin intolerance is an issue, consideration should be given to the use of alternate statin regimens such as low intensity statin therapy or non-daily moderate intensity statin therapy, low dose statin combination therapy with ezetimibe, bile acid sequestrants, or niacin, or non-statin monotherapy (i.e., ezetimibe or bile acid sequestrant) or their combination, with a goal of at least a 30% reduction in LDL-C.	B	Moderate

Hispanic men and women compared to NHW men and women (Table 16).[256]

The Hispanic Community Health Study/Study of Latinos (HCHS/SOL), the largest study of diverse Hispanic/Latino individuals to date, has yielded comprehensive data on the prevalence of hypercholesterolemia and dyslipidemia among Hispanic/Latino groups in the United States.[476] Among HCHS/SOL participants, 51.7% of men and 36.9% of women, respectively, had hypercholesterolemia (defined comprehensively as total-C ≥240 mg/dL, HDL-C <40 mg/dL, LDL-C ≥160 mg/dL, or receiving lipid-lowering treatment). Prevalence of hypercholesterolemia ranged from 47.6% among men of Dominican background to 54.9% among men of Central American background. Mean total-C and LDL-C levels were 195.8 mg/dL and 122.0 mg/dL among men overall, and were highest among men of Central American background (201.5 mg/dL and 125.3 mg/dL, respectively).[476] Among women, hypercholesterolemia prevalence ranged from 31.4% (South American background) to 41.0% (Puerto Rican background). Overall mean total-C and LDL-C levels among women were 195.1 mg/dL and 119.0 mg/dL, respectively, and were both highest among those of Cuban background (199.4 mg/dL and 124.2 mg/dL).[476]

A subsequent report by Rodriguez et al.[477] found that among HCHS/SOL participants, the prevalence of any dyslipidemia was 65% overall and ranged from 57.7% among participants of Dominican background to 69.8% among those of Cuban background. Lower educational attainment and Spanish language preference were associated with higher prevalence of any dyslipidemia.[477] Overall, 14.1%, 36.0%, and 14.8% of HCHS/SOL participants had high levels of total-C (≥240 mg/dL), LDL-C (≥130 mg/dL), and TG (≥200 mg/dL), respectively, and 41.4% had low HDL-C levels (defined as <40 mg/dL for men and <50 mg/dL for women). Prevalence of mixed dyslipidemia (defined as presence of both elevated TG and low-HDL-C) was 10.7% overall, and ranged from 5.4% among Dominican participants to 12.7% among Central American participants. Studies have suggested that this mixed pattern–indicating higher CVD risk regardless of LDL-C level–may be more common among Hispanics compared to NHWs.[478] Among participants of the Northern Manhattan Study, Hispanics had lower mean HDL-C (43.9 mg/dL), and higher mean TG (146.5 mg/dL) and TG:HDL-C ratio (3.9) compared to non-Hispanic blacks (NHBs) and NHWs.[479] A recent study based on electronic health data for 169,430 racially diverse patients from California reported that among men, age-standardized rates of low

Table 15 Prevalence of high total-C and LDL-C and low HDL-C according to race/ethnicity and sex from the 2015 AHA heart disease and stroke statistics

Population Group	Prevalence of Total Cholesterol ≥200 mg/dL, 2012 Age ≥20 y	Prevalence of Total Cholesterol ≥240 mg/dL, 2012 Age ≥20 y	Prevalence of LDL Cholesterol ≥130 mg/dL, 2012 Age ≥20 y	Prevalence of HDL Cholesterol <40 mg/dL, 2012 Age ≥20 y
Both sexes, n (%)*	100,100,000 (42.8)	30,900,000 (13.1)	73,500,000 (31.7)	44,600,000 (19.9)
Males, n (%)*	45,300,000 (40.4)	13,000,000 (11.6)	34,900,000 (31.0)	32,400,000 (28.9)
Females, n (%)*	54,830,000 (44.9)	17,900,000 (14.4)	38,600,000 (32.0)	12,200,000 (10.4)
NH white males, %	39.9	11.5	29.4	28.7
NH white females, %	45.9	15.3	32.0	10.2
NH black males, %	37.4	8.8	30.7	20.0
NH black females, %	40.7	10.9	33.6	10.3
Hispanic males, %	46.2	14.8	38.8	33.8
Hispanic females, %	43.4	13.7	31.8	12.8

HDL, high-density lipoprotein; LDL, low-density lipoprotein; NH, non-Hispanic.

Prevalence of total cholesterol ≥200 mg/dL includes people with total cholesterol ≥240 mg/dL. In adults, levels of 200 to 239 mg/dL are considered borderline high. Levels of ≥240 mg/dL are considered high.

*Total data for total cholesterol are for Americans ≥20 years of age. Data for LDL cholesterol, HDL cholesterol, and all racial/ethnic groups are age adjusted for age ≥20 years.

Source for total cholesterol ≥200 mg/dL, ≥240 mg/dL, LDL, and HDL: National Health and Nutrition Examination Survey (2009–2012), National Center for Health Statistics, and National Heart, Lung, and Blood Institute. Estimates from National Health and Nutrition Examination Survey 2009 to 2012 (National Center for Health Statistics) were applied to 2012 population estimates.

Taken from: Mozaffarian D, et al. *Circulation*. 2015;131:e29–e322.[256] Permission to reprint was obtained.

HDL-C (men <40 mg/dL and women <50 mg/dL) were highest among Mexican patients (47.8%), who also had among the highest prevalence (55.9%) of elevated TG levels (≥150 mg/dL).[480] Among women, prevalence of high TG levels was greatest among Mexicans (45.4%), and prevalence of low HDL-C (50.9%) was higher in Mexicans than in all other groups except Asian Indians.[480] Furthermore, in MESA, compared to whites, Hispanic participants had higher age-sex adjusted odds of having combined hyperlipidemia (defined as age-sex specific LDL-C and TG levels in the 75th percentile or higher based on a mostly white reference population) (OR 1.48; 95% CI 1.04–2.11).[481] This association was no longer significant after adjustment for BMI, suggesting that obesity may at least partly explain the increased risk for dyslipidemia among Hispanic participants.[481] Taken together these studies suggest the need to screen Hispanic/Latino individuals for mixed dyslipidemia subtypes, particularly to identify those without elevated LDL-C levels who nonetheless may be at high ASCVD risk.

An examination of the prevalence of non-HDL-C by Gardner et al.[482] found that among NHANES III (1988–1994) participants, mean non-HDL-C levels were lower among Mexican American women ≥25 years of age compared to NHWs in this age bracket (150 mg/dL vs 155 mg/dL); non-HDL-C levels among Mexican American and NHW men were similar (160 mg/dL vs 162 mg/dL).[482] However, an analysis of data from NHANES 2005–2010 showed that after adjustment for age and sex, Hispanic participants were more likely than other racial/ethnic groups to have normal LDL-C and high non-HDL-C levels (defined according to the NCEP ATP III guidelines[12]).[483] The discordance between LDL-C and non-HDL-C concentrations is particularly important in assessing residual risk for ASCVD, and clinicians should be aware of the increased possibility of this discordance in Hispanic/Latino patients. More recently, in the HCHS/SOL study, 38.2% of men and 31.5% of women were reported to have high non-HDL-C (i.e., ≥160 mg/dL); prevalence of high non-HDL-C was greatest among

Table 16 Mean levels of LDL-C, HDL-C, and TG for adults aged ≥20 years according to race and/or ethnicity and sex from the 2015 AHA heart disease and stroke statistics[256]

	Non-Hispanic White		Hispanic	
Lipid	Men	Women	Men	Women
LDL-C, mg/dL	113.8	116.8	120.1	114.8
HDL-C, mg/dL	47.7	58.5	45.4	54.3
TG, mg/dL	117.7	104.0	134.7	109.7

AHA, American Heart Association; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

those of Cuban background (43.3% among men and women combined).[477]

Hypercholesterolemia awareness, treatment, and control among US Hispanics/Latinos

According to NHANES 2011–2012 data,[256] rates of cholesterol screening are lower among Hispanic/Latino adults compared to all other major racial/ethnic groups in the United States. About 55% of Hispanic men and 64% of Hispanic women reported having been told by a doctor that their cholesterol was high and having had their cholesterol levels checked in the past 5 years (compared to about 71% and 73% of NHW men and women, respectively).[256] In NHANES 2009–2010, prevalence frequencies for awareness, treatment, and control of high LDL-C were 46.4%, 77.8%, and, 63.5%, respectively, among Hispanic participants (vs. 65.3%, 70.2%, and 67.2%, respectively among NHWs).[484] In MESA, rates of treatment and control of dyslipidemia were lower among Hispanic men and women compared to NHWs, although the prevalence of dyslipidemia was similar. Dyslipidemia treatment rates were 39.4% and 50% among Hispanic men and women, respectively. Of those treated, 68.5% and 74.5% of Hispanic men and women, respectively, had met treatment goals.[485] Another report from MESA found that compared to NHWs, Hispanic participants with similar levels of CVD risk factors were less likely to receive lipid-lowering treatment (prevalence ratio 0.75; 95% CI 0.61–0.91) although findings were attenuated and lost statistical significance with adjustment for socioeconomic status, particularly health insurance.[486]

Use of Framingham Risk Score and other cardiovascular risk assessment criteria in Hispanic/Latino adults

A report from the San Antonio Heart Study found that CVD risk scores derived from Framingham Study risk equations were higher among Mexican American men and women compared to NHWs.[487] A subsequent study by D'Agostino et al.[488] examined the validity of the Framingham coronary disease risk prediction scores among 6 racially/ethnically diverse cohorts, including 8713 Hispanic men from the Puerto Rico Heart Health Program. The authors concluded that among Hispanic men, the Framingham Risk Score systematically overestimated 5-year CHD risk compared to observed CHD event rates (*c*-statistics: 0.69 vs 0.79 for white men from the Framingham Heart Study); however, this was improved by recalibration of the model using data on mean CVD risk factor levels and CHD incidence from the Puerto Rico Heart Health Program cohort (*c*-statistic: 0.72).[488] More recently, Hurley et al.[489] examined the ability of Framingham risk factors to predict CVD death in Mexican Americans compared to NHWs using data from NHANES III (1988–1994) linked with the National Death Index. They reported that survival models based on Framingham risk factors were similarly calibrated when models were developed separately within each racial/ethnic group, and the ability of these models to discriminate between individuals who experienced CVD death from those who did not was also similar (*c*-statistic was 0.8126 for NHWs and 0.7854 for Mexican Americans).[489] DeFilippis et al.[490] examined the association of the Framingham Risk Score and the Reynolds Risk Score with incidence and progression of CAC using data from MESA. They reported that the Framingham Risk Score and Reynolds Risk Score predicted incident CAC similarly across racial/ethnic groups; both scores predicted significantly greater progression of CAC among white participants compared to Hispanic, AA, and Chinese participants.[490] Further research is required to validate existing risk prediction scores and/or develop new prediction tools for use among Hispanics/Latinos residing in the United States using current data on risk factor prevalence and CVD incidence among diverse Hispanic/Latino groups. Globorisk is a novel CVD risk prediction tool that can be recalibrated for application in different countries, including Mexico, with routinely available information.[491]

Association of lipid measures with ASCVD outcomes among Hispanic/Latino individuals

High cholesterol was associated with increased risk of both CVD mortality and all-cause mortality among Mexican American adults who participated in the San Antonio Heart Study.[475] In analyses adjusted for age, sex, socioeconomic status, and other CVD risk factors, the RR of CVD mortality and all-cause mortality associated with total-C levels >240 mg/dL (vs 160–240 mg/dL) were 2.1 (95% CI 1.0–4.6) and 1.6 (95% CI 1.0–2.6), respectively, among Mexican American participants (corresponding RRs among NHWs were 2.4 [95% CI 0.8–6.8] and 1.4 [95% CI 0.7–2.8]).[475] The authors concluded that cholesterol and other major CVD risk factors were important predictors of mortality among Mexican Americans.[475] However, in a multiethnic cohort of Medicare recipients ages 65 and older residing in Northern Manhattan (including 1054 Hispanic adults primarily of Dominican origin), plasma total-C, LDL-C, and HDL-C were not associated with all-cause mortality or with self-reported heart disease among Hispanic adults.[492] An analysis from the Northern Manhattan study also found no associations of HDL-C and TG levels with risk of MI among Hispanic participants over an average 8.9 years of follow-up.[479] However, each 1-unit increase in the TG:HDL-C ratio (examined as a continuous variable) was associated with 8% increased risk of MI in Hispanics, although no association was found in analyses with TG:HDL-C as a categorical variable (using the cut-point of TG:HDL-C >2).[479] The authors suggested that this cut-point may be unsuitable for use in Hispanics/Latinos, but cautioned that further research is required.[479]

Several studies have examined associations of lipid levels with measures of subclinical atherosclerosis. Sacco et al.[493] reported that in the Northern Manhattan Stroke Study, increasing LDL-C levels were associated with higher maximum internal carotid artery plaque thickness among Hispanic participants free of stroke (but not among

NHWs or NHBs). Another report from the same study found that despite lower prevalence of carotid plaque among Hispanic participants compared to NHWs and NHBs, there was no evidence that the effect of lipid levels (total-C, LDL-C, non-HDL-C, apo B, and total-C:HDL-C and LDL-C:HDL-C ratios) on carotid plaque differed among Hispanics compared to other racial/ethnic groups (i.e., no significant interactions were found).[494] Among MESA participants, those who had combined hyperlipidemia (LDL-C ≥160 mg/dL and TG ≥150 mg/dL) or hypercholesterolemia (LDL-C ≥160 mg/dL and TG <150 mg/dL) had increased risk of prevalent CAC compared to participants with normal lipid levels (RRs for combined hyperlipidemia and hypercholesterolemia were 1.22 [95% CI 1.08–1.38] and 1.22 [95% CI 1.11–1.34], respectively).[495] Combined hyperlipidemia or hypercholesterolemia was also associated with increased common carotid intima media thickness and internal carotid intima media thickness, compared to normal lipid levels.[495] No significant interactions between lipid levels and race were seen for any of the outcomes, which the authors suggested could possibly be due to inadequate power.[495] These findings underscore the need for further research to examine whether the impact of specific lipid parameters on the atherosclerotic process differs by race/ethnicity, given the increasing diversification of the US population.

It should be noted that most of the abovementioned studies have involved limited Hispanic/Latino background groups and thus, these findings may not be generalizable to the diverse, heterogeneous US Hispanic/Latino population. In the HCHS/SOL study, high cholesterol level (serum total-C ≥240 mg/dL or use of cholesterol-lowering medication) was associated with higher age-adjusted odds of prevalent self-reported CHD (among both men and women) and stroke (women only).[476] However, these associations were attenuated and lost significance with additional adjustment for other CVD risk factors, socioeconomic status, Hispanic background group, and acculturation-related factors (with the exception of the association of high cholesterol with CHD among women).[476] At this time there is no evidence to indicate that there is a substantial difference between Hispanics/Latinos and NHWs for the associations of atherogenic cholesterol with risk. Thus, at present, no differences in LDL-C and non-HDL-C treatment goals for Hispanics/Latinos are recommended.

Use of cholesterol-lowering medications among US Hispanic/Latino adults

Clinical trial research on effectiveness and safety of statins has largely focused on white populations, with little data on diverse Hispanic/Latino individuals. To address the scarce data in this population group, the Study Assessing Rosuvastatin in Hispanic Population investigated the effects of rosuvastatin and atorvastatin among 696 Hispanic individuals ≥18 years of age (mean age 57.9 years) who had an LDL-C level in the range of 130–300 mg/dL, TG <400 mg/dL, and a 10-year CHD risk ≥10% based on criteria described by the NCEP.[496] Both statins were associated with reductions in total-C, non-HDL-C, LDL-C, and apo B concentrations. The adverse events were mild/moderate in nature, and there were no cases of clinically relevant increases in serum creatine kinase, myopathy, or rhabdomyolysis.[496]

JUPITER, a randomized double-blind placebo-controlled trial, investigated the effectiveness of rosuvastatin in the primary prevention of MI, stroke, hospitalization for unstable angina, arterial revascularization, and CVD death among persons with LDL-C <130 mg/dL and hs-CRP ≥2.0 mg/L.[497] Among Hispanic participants (n = 2261) rosuvastatin therapy was associated with 42% lower risk of the primary endpoint (non-fatal or fatal CVD), which was similar to the reduction observed in NHWs (HRs were 0.58 [95% CI 0.25–1.39] among Hispanics and 0.55 [95% CI 0.43–0.69] among NHWs).[497] Rates of adverse events were, in general, lower among Hispanic participants compared to NHWs.[497] Despite a higher prevalence of type 2 diabetes mellitus among Hispanics,[256] there was no significant difference in cases of new-onset diabetes with statin treatment for Hispanics compared with NHWs in JUPITER ($P = .41$), and tests for heterogeneity between diabetes mellitus by race/ethnicity and statin treatment were not significant.

ALLHAT-LLT examined the effect of pravastatin vs usual care on reducing all-cause mortality in 10,355 individuals ≥55 years of age (23% Hispanic, 38% black) who had LDL-C levels of 120–189 mg/dL (100–129 mg/dL among those with history of CHD), TG <350 mg/dL, and who had hypertension and at least 1 other CVD risk factor.[347] Although pravastatin therapy was associated with lower total-C and LDL-C levels at 4 years of follow-up compared to usual care, all-cause mortality and CHD event rates did not differ significantly between the pravastatin and usual care groups (all-cause mortality: RR 0.99 [95% CI 0.89–1.11]; fatal/non-fatal CHD events: RR 0.91 [95% CI 0.79–1.04]). Analyses examining whether these findings varied by race were limited to blacks vs non-blacks and outcomes among Hispanic participants were not reported separately.[347] Thus, rigorous primary and secondary prevention clinical trials and post-marketing studies of new and existing lipid-lowering agents inclusive of sufficient numbers of diverse Hispanic/Latino adults are required to generate convincing evidence on the effectiveness and safety of such medications in this population group. However, the results to date indicate that there are no clear differences in responsiveness among Hispanics/Latinos with regard to the lipid effects of statins or the risk reduction associated with statin therapy.

Novel lipid measures among US Hispanic/Latino individuals

Although Lp(a) levels have been shown to vary by race/ethnicity, studies that have included Hispanic/Latino

participants have yielded conflicting results. In the San Antonio Heart Study, Mexican American men and women had significantly lower Lp(a) levels compared to NHW men and women (men: 10.4 vs 16.3 mg/dL; women: 11.5 vs 16.4 mg/dL).[498] A report based on data from NHANES III also found that mean Lp(a) levels were lower among Mexican American participants compared to NHWs and NHBs (14.9 vs 20.3 and 43.4 mg/dL, respectively).[499] Conversely, Kamboh et al.[500] reported that in the San Luis Valley Diabetes Study, Lp(a) levels were significantly higher in Hispanic men free of diabetes compared to NHWs (men: 13.2 vs 8.7 mg/dL, $P < .003$; women: 11.1 vs 10.3 mg/dL). Both JUPITER and MESA demonstrated no meaningful differences in Lp(a) levels between Hispanic and NHW participants.[501,502] Findings from MESA suggested that a Lp(a) cut-point of 50 mg/dL, which is consistent with the NLA Recommendations for the Patient-Centered Management of Dyslipidemia–Part 1,[1] rather than the commonly used 30 mg/dL, was better at identifying Hispanic individuals at high CHD risk. Among Hispanics, the HR for incident CHD associated with Lp(a) ≥50 mg/dL was 2.37 (95% CI 1.17–4.78), whereas HR associated with Lp(a) ≥30 mg/dL was 1.46 (95% CI 0.78–2.75).[502]

Further research on prevalence of adverse levels of various novel lipid measures among diverse Hispanic/Latino groups, mean levels by age, sex, and Hispanic background, and associations with CVD endpoints is required for valid evidence-based statements to be made about which of these measures (and cut-points) can be used to identify high risk Hispanic/Latino individuals.

Conclusions

ASCVD is one of the leading causes of mortality among Hispanics/Latinos.[256] Similar associations of major ASCVD risk factors with adverse ASCVD outcomes have been reported among Hispanic/Latino adults compared to NHWs. However, it should be recognized that, as a group, the lipid profile in Hispanic Americans is characterized by higher TG and lower HDL-C levels, resulting in higher non-HDL-C concentration and more frequent discordance between LDL-C and non-HDL-C levels. At this time, there is no evidence to suggest a need for different treatment goals, or a difference in responsiveness to lipid-lowering therapy, among Hispanics/Latinos compared to other ethnic groups. Therefore the recommendations put forth by the NLA's Patient-Centered Management of Dyslipidemia–Part 1[1] are generally recommended for patients of Hispanic/Latino ethnicity. Calibrated equations are needed to more accurately predict risk among Hispanics/Latinos, because some equations such as Framingham, appear to overestimate risk.

See Chart 7 for the Recommendations for Hispanics/Latinos.

Chart 7 Recommendations for Hispanics/Latinos

Recommendations	Strength	Quality
In general, patients of Hispanic/Latino ethnicity should be treated according to the NLA Recommendations for Patient-Centered Management of Dyslipidemia – Part 1[1] with the following special considerations.	A	High
Clinicians should be aware that Hispanics/Latinos in the United States are a diverse population group tracing their ancestry to Mexico, the Caribbean (Puerto Rico, Cuba, and the Dominican Republic), Central America (El Salvador and Guatemala), and South America. ASCVD risk factor burden varies widely among individuals of Hispanic/Latino descent, depending on their country of origin.	A	High
Hispanics/Latinos tend to have a greater prevalence of high TG and low HDL-C than NHWs, leading to higher levels of non-HDL-C, and an increased likelihood for discordance between LDL-C and non-HDL-C concentrations. LDL-C levels tend to be higher in Hispanic men compared with NHW men.	A	Moderate
Hispanics/Latinos have higher prevalence of type 2 diabetes mellitus, obesity, and metabolic syndrome compared to NHWs, particularly among women.	A	Moderate
Some cardiovascular risk equations (e.g., Framingham equations) may overestimate risk in Hispanic/Latino individuals.	B	Moderate

African Americans (AAs)

ASCVD in AAs: a high risk population

Since the 1980's, the United States has made substantial progress in improving overall health and reducing ASCVD, but racial/ethnic and socioeconomic disparities in health still persist.[503] AAs, also referred to as NHBs or blacks in the present document, have higher rates of CVD, including CHD and stroke, and CVD mortality than do Caucasians (whites).[504] These differences continue to contribute significantly to AAs having a reduced life expectancy compared to whites.[504] Moreover, AAs have higher levels of several major risk factors, most notably obesity (especially in females), arterial hypertension, type 2 diabetes mellitus, chronic kidney disease (CKD), and multiple risk factor status (Table 17).[256] Unfortunately, AAs often are underdiagnosed and undertreated for CVD risks, and they may present to the health care system late in their disease course, frequently at the time of a CVD event.[504] Hypertension is a powerful contributor to the increased CVD risk in AAs, with earlier onset and more severe blood pressure elevation, leading to increased target organ damage including left ventricular hypertrophy, heart failure, stroke, CKD and end stage renal disease,

Table 17 Prevalence of ASCVD and risk factors according to race/ethnicity from the 2015 AHA heart disease and stroke statistics

Diseases and Risk Factors	Both Sexes	Whites		Blacks		Hispanics/Latinos		Asians: Both Sexes	American Indian/Alaska Native; Both Sexes
		Males	Females	Males	Females	Males	Females		
Smoking									
Prevalence, 2013[*]	43.4 M (17.9%)	21.7%	18.7%	21.1%	15.0%	16.6%	6.7%	9.5%	21.0%
PA[†]									
Prevalence, 2013, %[*]	20.9	22.7		17.7		16.6		18.2	16.6
Overweight and obesity									
Prevalence, 2012									
Overweight and obesity, BMI >25.0 kg/m^2[‡]	159.2 M (68.5%)	72.7%	61.2%	69.4%	81.9%	80.1%	76.3%	N/A	N/A
Obesity, BMI >30.0 kg/m^2[‡]	81.8 M (35.2%)	34.2%	32.5%	37.9%	57.5%	38.4%	42.9%	10.8%[*]	46.5%[*]
Blood cholesterol									
Prevalence, 2012									
Total cholesterol >200 mg/dL[‡]	100.1 M (42.8%)	39.9%	45.9%	37.4%	40.7%	46.2%	43.4%	N/A	N/A
Total cholesterol >240 mg/dL[‡]	30.9 M (13.1%)	11.5%	15.3%	8.8%	10.9%	14.8%	13.7%	N/A	N/A
LDL cholesterol >130 mg/dL[‡]	73.5 M (31.7%)	29.4%	32.0%	30.7%	33.6%	38.8%	31.8%	N/A	N/A
HDL cholesterol <40 mg/dL[‡]	44.6 M (19.9%)	28.7%	10.2%	20.0%	10.3%	33.8%	12.8%	N/A	N/A
HBP									
Prevalence, 2012[†]	80.0 M (32.6%)	32.9%	30.1%	44.9%	46.1%	29.6%	29.9%	N/A	26.2%[*]
Mortality, 2011[§]	65,123	21,830	27,907	6610	6783	[‖]	[‖]	1667[‖]	326[‖]
DM									
Prevalence, 2012									
Physician-diagnosed DM[‡]	21.1 M (8.5%)	7.6%	6.1%	13.8%	14.6%	12.5%	11.8%	N/A	N/A
Undiagnosed DM[‡]	8.1 M (3.3%)	4.0%	1.7%	4.8%	2.3%	6.8%	5.0%	N/A	N/A
Prediabetes[‡]	80.8 M (35.3%)	43.0%	28.9%	36.3%	27.8%	43.0%	26.0%	N/A	N/A
Incidence, diagnosed DM[‡]	1.7 M	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mortality, 2011[§]	73,831	30,783	27,191	6048	6847	[‖]	[‖]	2035[‖]	927[‖]
Total CVD									
Prevalence, 2012[‡]	85.6 M (35.0%)	36.1%	31.9%	46.0%	48.3%	32.4%	32.5%	N/A	N/A
Mortality, 201l[§,¶]	786,641	331,751	340,803	46,081	47,130	[‖]	[‖]	17,050[‖]	3826[‖]
Stroke									
Prevalence, 2012[‡]	6.6 M (2.6%)	2.2%	2.5%	4.2%	4.7%	2.8%	2.0%	N/A	2.7%[*,#]
New and recurrent strokes[§]	795.0 K	325.0 K	365.0 K	45.0 K	60.0 K	N/A	N/A	N/A	N/A
Mortality, 2011[§]	128,932	43,264	65,278	7039	8814	[‖]	[‖]	3937[‖]	600[‖]
CHD									
Prevalence, CHD, 2012[‡]	15.5 M (6.2%)	7.8%	4.6%	7.2%	7.0%	6.7%	5.9%	N/A	4.5%[*,#]
Prevalence, MI, 2012[‡]	7.6 M (2.8%)	4.1%	1.8%	3.4%	2.2%	3.5%	1.7%	N/A	N/A
Prevalence, AP, 2012[‡]	8.2 M (3.3%)	3.4%	2.9%	3.3%	5.0%	3.2%	3.8%	N/A	N/A
New and recurrent CHD[**,††]	935.0 K	475.0 K	330.0 K	70.0 K	60.0 K	N/A	N/A	N/A	N/A
Mortality, 2011,CHD[§]	375,295	180,658	145,443	20,693	18,760	[‖]	[‖]	7828[‖]	1913[‖]
Mortality, 2011, MI[§]	119,905	58,447	45,576	6551	6228	[‖]	[‖]	2476[‖]	627[‖]

(*continued on next page*)

Table 17 (*continued*)

Diseases and Risk Factors	Both Sexes	Whites		Blacks		Hispanics/Latinos		Asians: Both Sexes	American Indian/Alaska Native; Both Sexes
		Males	Females	Males	Females	Males	Females		
HF									
Prevalence, 2012‡	5.7 M (2.2%)	2.2%	2.2%	2.8%	3.2%	2.1%	2.1%	N/A	N/A
Incidence, 2010§§	870.0 K	365.0 K	395.0 K	50.0 K	60.0 K	N/A	N/A	N/A	N/A
Mortality, 2011§	58,309	21,802	30,036	2371	3143	‖	‖	727‖	230‖

AP, angina pectoris (chest pain); BMI, body mass index; CHD, coronary heart disease (includes heart attack, angina pectoris chest pain, or both); CVD, cardiovascular disease; DM, diabetes mellitus; HBP, high blood pressure; HDL, high-density lipoprotein; HF, heart failure; K, thousands; LDL, low-density lipoprotein; M, millions; MI, myocardial infarction (heart attack); N/A, data not available; PA, physical activity.

*Age ≥18 years (National Health Interview Survey, 2013).

†Met 2008 full federal PA guidelines for adults.

‡Age ≥20 years.

§All ages.

‖Mortality data for the white, black, Asian or Pacific Islander, and American Indian/Alaska Native populations include deaths of people of Hispanic and non-Hispanic origin. Death rates for Hispanic, American Indian or Alaska Native, and Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific islander, and Hispanic decedents, as well as undercounts of these groups in censuses.

¶Total CVD mortality includes deaths from congenital heart disease.

#Figure not considered reliable.

**New and recurrent MI and fatal CHD.

††Age ≥35 years.

§§Age ≥55 years.

Taken from: Mozaffarian D, et al. *Circulation*. 2015;131:e29–e322.[256] Permission to reprint was obtained.

often in combination with type 2 diabetes mellitus and physical inactivity.

Furthermore, ASCVD (CHD plus stroke) is not only the leading cause of death for AAs, but also accounts for the largest proportion of inequality in life expectancy between whites and AAs, despite the existence of low-cost, highly effective preventive treatments.[503,505] In the Atherosclerosis Risk in Communities (ARIC) study, AA men and women had a higher incidence of first heart attack than did their white counterparts.[256] Additionally, the rate of premature CHD death among AAs surpasses that of whites.[506] AAs aged 45–74 years have a much higher proportion of CHD deaths than whites: 37.9% vs 19.4% in women and 61.5% vs 41.5% in men.[505] Nevertheless, in the Coronary Artery Risk Development in Young Adults (CARDIA) study, the prevalence of CAC in US adults aged 33 to 45 years was higher in white men and women than in their AA counterparts, despite higher rates of first MI in AAs, suggesting that CAC may be less reliable as an indicator of MI risk in AAs.[507,508]

The NCEP ATP III report in 2002 provided a concise description of unique non-lipid risk factors in AAs, emphasizing the impact of hypertension and left ventricular hypertrophy as more common and powerful predictors of mortality, and reporting that obesity is twice as common among AA women than white women.[12] Diabetes mellitus and multiple risk factor status were 1.5 times more frequent in AAs. The ATP III noted a similar relationship of total-C to CVD in both races, and slightly lower mean LDL-C levels in AA men than in white men. Also in the ATP III report, women were noted to have similar LDL-C levels among AAs and whites. In both sexes, HDL-C levels were noted to be higher among AAs than whites, whereas TG were lower and Lp(a) levels were higher in AAs.[12] The ATP III guidelines also suggested that the relatively high normal creatine kinase concentrations in AAs should be recognized before initiation of statin therapy.

Impact of race in ASCVD disparities

Increased ASCVD risk is associated with the social determinants of health (low income, lack of access to, or inadequate, health insurance, and low educational attainment) and geographic region.[503,509,510] Furthermore, "race" is a crude proxy for genetics and culture (shared values, beliefs, customs, and learned behavior) that impact disease burden.[510,511] Broad policy areas for addressing racial/ethnic health care disparities include raising public and provider awareness of racial/ethnic disparities in care and outcomes, expanding health insurance coverage, improving capacity and number of providers in underserved communities, and increasing the knowledge base on causes and interventions to reduce disparities. Data-driven performance improvement, provider education, cultural competency, team-based care, patient education, and increased community resources are all approaches with the potential

to reduce these disparities.[512] Low health literacy is particularly detrimental, and patients with less knowledge often miss essential health services.[513]

Recent advances in atherosclerotic risk assessment in AAs

The recent 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk includes AA status in its calculator to estimate 10-year ASCVD risk.[362] In addition, this new ASCVD risk calculator includes the prediction of both CHD and stroke risk, as it is notable that stroke disproportionately affects AAs.[256] Developed and supported by the National Heart, Lung, and Blood Institute, the 2013 ACC/AHA Risk Calculator utilized pooled cohorts with participants from several large, racially and geographically diverse populations with endpoint data from recent periods (up to the early 1990's) including the ARIC study, the Cardiovascular Health Study, and the CARDIA study, combined with applicable data from the Framingham Original and Offspring populations.[362] In a clinical vignette provided for illustration, a higher 10-year risk is calculated for AA vs white patients with the following characteristics: 55 years of age, nonsmoker, without diabetes, and with a total-C level of 213 mg/dL, HDL-C level of 50 mg/dL, and untreated systolic blood pressure of 120 mm Hg. With the 2013 ACC/AHA Risk Calculator, the predicted 10-year ASCVD risks for patients with this profile would be 2.1% and 3.0% for white and AA women, respectively, and 5.3% and 6.1% for white and AA men, respectively.

In view of the higher risk for ASCVD in AAs, there is a greater opportunity for risk reduction. A 2014 analysis of data from NHANES (1999–2000 to 2011–2012) examined trends in predicted 10-year ASCVD risk using the 2013 ACC/AHA Pooled Cohort Equations and calculated potential improvement in ASCVD risk by optimizing levels of all 5 modifiable cardiovascular risk factors—eliminate smoking, decrease systolic blood pressure to <120 mm Hg, decrease total-C to <200 mg/dL, raise HDL-C to >40 mg/dL (men) or >50 mg/dL (women), and eliminate diabetes.[514] The absolute change in mean predicted 10-year ASCVD risk declined by 3.3% overall, but by 6.4% among NHB (AA) men, and by 4.5% among NHB (AA) women.[514]

Dyslipidemia and CHD in AAs

In a sample of 14,812 asymptomatic subjects including 637 AAs, 1065 Asians, 13,345 Hispanics, and 11,776 NHWs, the prevalence of any CAC upon measurement in NHWs and AAs was 66% and 58%, respectively ($P < .0001$).[515] Among all racial/ethnic groups, the lowest survival during the 10-year follow-up was observed in AAs (83% of AAs, $P < .0001$ between ethnic groups), despite the lack of a difference between groups in the prevalence of hypercholesterolemia.[515]

In the Genetic Epidemiology Network of Arteriopathy Study (1286 NHB hypertensive subjects and 1070 NHW hypertensive subjects), the prevalence of dyslipidemia was significantly greater among NHWs than NHBs.[516] At baseline, mean LDL-C concentrations in NHB men and women were 118 and 123 mg/dL, respectively, and in NHW men and women were 123 and 119 mg/dL, respectively ($P = .06$ for ethnic comparison in both men and women). Among dyslipidemic subjects for whom treatment was indicated, treatment with lipid-regulating drugs was significantly more common among NHWs than NHBs (women 25.4% vs 16.4% [$P = .001$]; men 32.6% vs 12.8%, respectively [$P = .001$]).

The 2015 compilation of the National Heart Disease and Stroke Statistics from the AHA also suggest that hypercholesterolemia (elevated total-C and LDL-C) or dyslipidemia (elevated TG and low HDL-C) are not culpable for the excess CVD risk in AAs/NHBs (see Tables 15 and 18).[256] Mean levels and percentages of NHB (AA) adults with high levels of total-C and LDL-C were similar to those of NHWs. Mean levels of TG were lower and HDL-C higher in NHB (AA) adults compared to NHWs and the prevalence values for high TG and low HDL-C were also lower.

Importantly, the annual age-adjusted rates per 1000 population of first MI (2005–2011) from the ARIC study were 4.9 in black men, compared to 3.2 in white men, and 3.5 in black women, compared to 1.9 in white women (Unpublished data from ARIC Surveillance 2005–2011, NHLBI[256]) (Fig. 10). The 2015 AHA report also reinforces the higher ASCVD mortality in AAs/NHBs. CHD death rates per 100,000 were 146.5 for white males, but 161.5 for black males; for white females, the rate was 80.1, and for black females, it was 99.7. The decrease in CVD death rates in the United States has been slower in

Table 18 Mean levels of LDL-C, HDL-C, and triglycerides for adults aged ≥20 years according to race and/or ethnicity and sex from the 2015 AHA heart disease and stroke statistics[256]

	Non-Hispanic White		Non-Hispanic Black	
Lipid	Men	Women	Men	Women
LDL-C, mg/dL	113.8	116.8	113.4	115.5
HDL-C, mg/dL	47.7	58.5	51.9	57.4
TG, mg/dL	117.7	92.7	104.0	83.5

AHA, American Heart Association; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

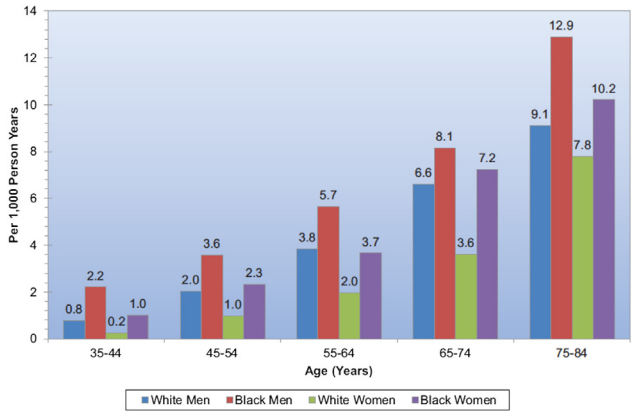

Figure 10 Incidence of myocardial infarction by age, race, and sex from the Atherosclerosis Risk in Communities (ARIC) Study. Incidence of myocardial infarction by age, sex, and race (ARIC Surveillance: 2005–2011; source, unpublished data from ARIC study, National Heart, Lung, and Blood Institute.) Taken from: Mozaffarian D, et al. *Circulation*. 2015; 131:e29–e322.[256] Permission to reprint was obtained.

blacks than whites, especially in those under 65 years of age.

Based on these results, it can be concluded that dyslipidemia is not the primary driver of the increased CVD mortality among AAs/NHBs compared to whites, but instead this increased risk appears to be explained by a higher prevalence of certain non-lipid risk factors such as hypertension, obesity, type 2 diabetes mellitus, smoking, and low physical activity (Table 17).[256] In addition, even when these risk factors are identified, their management may be suboptimal in AAs compared to whites because of issues related to socioeconomic status and reduced access to health care, as well as a lack of compliance with medication, in part due to the cost of medications.[517]

Dyslipidemia, insulin resistance and metabolic syndrome recognition in AAs

In Ford et al.'s[514] examination of NHANES data, AAs were found to have lower TG and higher HDL-C. Thus, the prevalence of metabolic syndrome was lower in AAs than whites, and this was more evident in men than women.[514]

There are distinctive features of lipoprotein metabolism in AAs, including increased post-heparin lipoprotein lipase activity.[518,519] AAs are more insulin-resistant than whites, insulin concentrations are higher, and there is greater inhibition of hormone sensitive lipase in adipose tissue, as well as less release of free fatty acids from peripheral adipose tissue. Activity of lipoprotein lipase to clear TG-rich lipid particles is higher in AAs than whites and is less inhibited by apo C3 and insulin resistance.[519,520] Obese AA women have a reduced whole-body adipose tissue lipolytic rate, less visceral adipose tissue, and lower intrahepatic TG content than do obese white women.[521] These differences in free fatty acid kinetics and body fat distribution could reduce substrate availability for TG-rich VLDL particle assembly and secretion from the liver in AA women.[521] Data suggest that lower VLDL-TG secretion is primarily responsible for the lower plasma TG concentration observed in AA women. Post-absorptive plasma free fatty acids and TG concentrations were lower in obese AA women with type 2 diabetes than in obese white women with type 2 diabetes mellitus who were matched for BMI, percentage of body fat, and insulin sensitivity, likely due to lower adipose tissue lipolytic activity and hepatic VLDL-TG secretion rates.[521] Thus, lower levels of TG and higher levels of HDL-C result in AAs having a lower prevalence of metabolic syndrome than whites, even though AAs are more likely than whites to be insulin resistant.[522]

Lp(a), variations in PCSK9, and unique aspects of lipids in AAs

Lp(a) consists of an LDL-like particle to which an apo B100 lipoprotein is covalently linked to apo(a). Lp(a) levels are nearly 2-fold higher in AAs than in whites. In the Jackson Heart Study, a panel of ancestry informative markers accurately estimated African ancestry and revealed the amount of African, compared to European, ancestry at the Lp(a) locus was strongly associated with Lp(a) level.[523] Newer data from ARIC indicate that Lp(a) levels were positively associated with CVD events, at least as strongly and with a larger range of Lp(a) concentrations, in AAs compared with whites.[524] This contradicts the previously suggested paradox for Lp(a) in AAs. More recent data from larger, long term studies provide further evidence that elevated Lp(a) concentration in AAs, as in whites, is associated with an elevated risk for ASCVD.[525] In general, elevated Lp(a) levels associate robustly and specifically with increased CVD risk. The association is continuous without a threshold and does not depend on high levels of LDL-C or non-HDL-C, or on the levels or presence of other cardiovascular risk factors. Therefore, if in an AA patient, premature CVD or CHD is not explained by conventional lipid levels and other risk factors, Lp(a) may be a factor.

PCSK9 is a serine protease that binds the LDL receptor, thereby targeting it for lysosomal degradation.[11] In the Dallas Heart Study (3543 subjects), among AAs missense mutations were associated with low plasma LDL-C levels and substantial protection from CHD.[526,527] Genetic variants of PCSK9 genes in AA men associated with lower LDL-C were also associated with lower carotid intima-media thickness and lower prevalence of measured CAC. Some loss-of-function PCSK9 mutations are relatively common in AAs (combined frequency, 2%) but rare in Americans of European descent (<0.1%), and are associated with ~40% lower plasma levels of LDL-C.[528,529]

Lipoprotein particle characteristics in AAs

The Studies of a Targeted Risk Reduction Intervention through Defined Exercise demonstrated unique aspects in lipoprotein subclass distributions among middle-aged AAs as compared to whites, controlling for a number of confounding risk factors and with no known history of

active smoking, CHD, or diabetes.[530] AAs of both sexes had larger HDL and LDL particle sizes than whites. Since TG elevation correlates strongly with reductions in HDL and LDL particle size, this may reflect the lower average TG level among AAs compared to whites. Group differences in the amount of visceral fat, lipoprotein lipase activity, and hepatic lipase activity may all be key mechanistic contributors to lipoprotein differences in AAs compared with whites. Despres et al.[518] reported that hepatic lipase levels were highest in white men, lowest in AA women, and intermediate in white women and AA men.

ApoL-I, the trypanosome lytic factor, has a pronounced association of 2 independent genetic variants within the *APOL1* gene with focal segmental glomerulosclerosis and with end-stage renal disease attributed to hypertension. The described variants are very common in AAs, but absent in chromosomes of European origin.[531] ApoL-I is a serum factor that lyses trypanosomes, but increased risk for CKD is the downside of having variants of this parasite-slaying protein and may thus contribute to the higher rates of renal disease in AAs.[532,533]

Statin use and efficacy in AAs

Various factors may contribute to lower frequencies of successful dyslipidemia management among AAs with dyslipidemia, including reduced awareness of lipid levels and poor long-term adherence. The frequency of LDL-C testing has been shown to be significantly less in AAs. In one study, less than 14% of those in urban settings recalled their cholesterol levels.[534] Even among hypertensive patients, over 50% did not have cholesterol measured in the prior year. ALLHAT-LLT was the first clinical outcome trial of the efficacy of statin (pravastatin) with substantial representation of black subjects.[347] In the main study results, there was no difference in all-cause mortality or CHD events in those treated with pravastatin vs usual care. However, AAs in the pravastatin group had significantly reduced risk for CHD events, possibly driven by underuse of statin in the usual care cohort. Nevertheless, the AHA 2015 report of data on CVD in America reported that screening now appears to be similar among NHWs (71.8% screened; 70.6% of men and 72.9% of women) and NHBs (71.9% screened; 66.8% of men and 75.9% of women).[256] In addition, the percentage of adults at least 40 years of age who used a prescription cholesterol-lowering medication in the United States from 2011–2012 was similar in blacks (28.2%) and whites (28.3%). However, data from a large Medicare Advantage plan showed that elderly blacks were still less likely to have their LDL-C controlled.[535] Also, data from a recent meta-analysis suggested that nonadherence to statins was greater in nonwhites than whites.[536]

In an examination of ethnic differences in LDL-C goal achievement in the NCEP Evaluation Utilizing Novel E-Technology II survey of 4885 patients receiving treatment for dyslipidemia, 79.7% were NHW and 8.4% were AA.[517] Frequencies of treatment success (defined as NCEP ATP III LDL-C goal attainment) were significantly lower among AAs than NHWs: 53.7% vs 69.0% ($P < .001$). Furthermore AAs were more likely to be in the highest risk category, but less likely to be using lipid drug therapy or taking high-efficacy statins. The gap in goal achievement between AAs and NHWs remained statistically significant after adjustment for these, as well as other, predictors of treatment success. Additional research is needed to examine the role that reduced compliance may have in the reduced treatment success reported among AAs.

A study on the phenotypic predictors of response to simvastatin therapy among AAs and Caucasians, the Cholesterol and Pharmacogenetics study, enrolled 944 AA and white men and women who completed an open-label, 6-week pharmacogenetics trial of 40 mg simvastatin.[537] Overall, simvastatin lowered LDL-C by 54 mg/dL or 41%. Compared with AAs, whites had a 3 mg/dL greater LDL-C reduction and a 1 mg/dL higher HDL-C elevation. These findings were independent of other variables, including baseline lipoprotein levels. Participants were required to demonstrate at least 90% compliance with pill counts at each 2-week clinic visit throughout the study. Therefore, reduced compliance was not likely the main contributor to reduced LDL-C lowering with the statin in AAs.

In JUPITER, subjects without hyperlipidemia but with elevated hs-CRP levels were assigned to placebo or 20 mg rosuvastatin daily. In JUPITER and other studies, black participants have been shown to have higher hs-CRP levels, particularly black women compared with women of other races.[344,497] Compared with placebo, blacks had somewhat smaller reductions than whites in hs-CRP (−22.2% vs −36.4%), LDL-C (−43.0% vs −51.4%), and apo B (−30.6% vs −38.7%) ($P < .001$ for all).[497] Rosuvastatin reduced the incidence of major cardiovascular events and first MI, stroke, arterial revascularization, hospitalization for unstable angina, and cardiovascular death in the overall study sample.[497] Rosuvastatin resulted in a 45% reduction in the primary end point among whites (HR 0.55; 95% CI 0.43–0.69), and a 35% reduction among blacks (0.65; 0.35–1.22). Rosuvastatin also resulted in a 55% reduction in stroke among whites (0.45; 0.27–0.77), and a 46% reduction among blacks (0.54; 0.19–1.60). Although differences in benefits were not statistically significant, the somewhat smaller responses to treatment for LDL-C and apo B may have contributed to the trend toward smaller benefits in blacks compared with whites.

Creatine kinase levels in AAs

Baseline creatine kinase levels are generally higher in AAs than in whites, SAs, and Hispanics/Latinos, and are also higher in men than in women.[538,539] The higher mean level in AAs is thought to be due to a proportional leak from normal tissues related to higher creatine kinase

activity, and is not reflective of tissue damage.[540] Clinicians should not withhold statin therapy from hypercholesterolemic patients with asymptomatic baseline creatine kinase levels that are >1.0 but <5.0 times the upper limit of normal. This would potentially deprive many AA men from receiving statin treatment, adding to the well-documented higher risk of cardiovascular problems caused by statin undertreatment. Recognizing the importance of promoting awareness of expected creatine kinase levels, the NLA Muscle Expert Panel recommended using normative upper limits for creatine kinase that are adjusted for age, race, and sex.[334]

Conclusions

Despite improvements in US health, life expectancy, and care, the distribution of ASCVD benefits has not been equitable, and there is a persistent mortality gap between AAs and whites, driven in part by disparate ASCVD outcomes. AAs are at higher risk for hypertension, diabetes mellitus, obesity, first MI, stroke, CKD, and cardiovascular mortality, especially premature cardiac death. As a group, the lipid profile in AAs is characterized by lower TG and higher HDL-C, leading to a lower prevalence of the metabolic syndrome despite higher prevalence of insulin resistance. Greater risk due to higher concentrations of Lp(a) in AAs is now recognized as important. In the past, AAs were under-represented in many landmark lipid trials and assumptions of treatment efficacy have been based on limited clinical data. Fortunately, the appropriate use of lipid-lowering drugs has become more equitable between AA and white populations in the United States in recent years. However, the rates of LDL-C control and adherence to medication regimens still differ materially, and therefore, increased efforts should be directed toward improving the persistent treatment gap between AAs and whites.

See Chart 8 for the Recommendations for African Americans.

South Asians (SAs)

Asian/SA population in the United States

The 2010 Census showed that the US population on April 1, 2010, was 308.7 million.[541] Out of the total US population, 14.7 million people (4.8%) were Asian alone (Table 19).[542] In addition, 2.6 million people, or another 0.8%, reported Asian ethnicity in combination with at least 1 other race/ethnicity. Together, these 2 groups totaled 17.3 million people. Thus, 5.6% of all people in the United States identified as Asian, either alone or in combination with 1 or more other races/ethnicities. The Asian population in the United States increased more than 4 times faster than the total US population from the years 2000 to 2010. The total US population grew by 9.7%, from 281.4 million in 2000 to 308.7 million in 2010, whereas the Asian alone population in the United States grew by 43%, from 10.2 million to 14.7 million.

Of the total Asian population in the United States, SAs totaled 3.86 million.[541] The SA community in the United States includes individuals who trace their ancestry to Bangladesh, Bhutan, India, the Maldives, Nepal, Pakistan, and Sri Lanka. The community also includes members of the SA diaspora–past generations of SAs who originally settled in other parts of the world, including Africa, Canada, the Caribbean, Europe, the Middle East, and other parts of Asia and the Pacific Islands. The 5 US states with the largest SA populations are California, New York, New Jersey, Texas, and Illinois. Metropolitan areas with the largest SA populations are New York City, Chicago, Washington DC, Los Angeles, and the San Francisco Bay area.[541]

Chart 8 Recommendations for African Americans

Recommendations	Strength	Quality
In general, AAs should be treated according to the NLA Recommendations for Patient-Centered Management of Dyslipidemia – Part 1[1] with the following special considerations.	A	High
Clinicians should be aware that AAs as a group are at increased risk for ASCVD.	A	High
Because attributable ASCVD risk in AAs is less driven by dyslipidemia than in NHWs, particular attention should be given to assessing non-lipid risk factors, such as hypertension, overweight and obesity, type 2 diabetes mellitus, and physical inactivity, when ascertaining ASCVD risk.	A	High
AAs have a lower incidence of metabolic syndrome than NHWs, due to lower prevalence of high TG and low HDL-C. However, the incidence of type 2 diabetes mellitus is higher in AAs.	A	High
Because AA race/ethnicity is included in the 2013 ACC/AHA Pooled Cohort Equations for estimating 10-year ASCVD risk, this may be the preferable risk calculator to use in patients of AA race/ethnicity.	B	Moderate
Because Lp(a) levels tend to be higher in AA patients, measuring Lp(a) for risk refinement may be considered in AA patients, particularly in those with a family history of premature ASCVD not explained by other risk factors.	E	Moderate
Clinicians should not withhold statin therapy from at risk AA patients with asymptomatic creatine kinase levels that exceed, but are <5.0 times, the standard upper limits of normal. When practical, normative upper limits for creatine kinase that are adjusted for age, race, and sex should be used.	E	Moderate

Table 19 Asian population by number of detailed groups from the US Census 2010

Detailed group	Asian alone		Asian in combination with one or more other races		Detailed Asian group alone or in any combination*
	1 Asian Group	2 or more groups	1 Asian group	2 or more groups	
Total†	14,327,580	346,672	2,429,530	217,074	17,320,856
Asian Indian	2,843,391	75,416	240,547	23,709	3,183,063
Bangladeshi	128,792	13,288	4364	856	147,300
Bhutanese	15,290	3524	442	183	19,439
Burmese	91,085	4451	4077	587	100,200
Cambodian	231,616	23,881	18,229	2941	276,667
Chinese‡	3,347,229	188,153	334,144	140,588	4,010,114
Chinese, except Taiwanese§	3,137,061	185,289	317,344	140,038	3,779,732
Taiwanese§	196,691	2501	15,781	468	215,441
Filipino	2,555,923	94,050	645,970	120,897	3,416,840
Hmong	247,595	4728	7392	358	260,073
Indonesian	63,383	6713	22,425	2749	95,270
Iwo Jiman	1	1	7	3	12
Japanese	763,325	78,499	368,094	94,368	1,304,286
Korean	1,423,784	39,690	216,288	27,060	1,706,822
Laotian	191,200	18,446	19,733	2751	232,130
Malaysian	16,138	5730	3214	1097	26,179
Maldivian	98	4	25	—	127
Mongolian	14,366	772	2779	427	18,344
Nepalese	51,907	5302	1941	340	59,490
Okinawan	2753	2928	3093	2552	11,326
Pakistani	363,699	19,295	24,184	1985	409,163
Singaporean	3418	1151	645	133	5347
Sri Lankan	38,596	2860	3607	318	45,381
Thai	166,620	16,252	48,620	6091	237,583
Vietnamese	1,548,449	84,268	93,058	11,658	1,737,433
Other Asian, not specified‖	218,922	19,410	366,652	18,777	623,761

For information on confidentiality protection, nonsampling error, and definitions, see www.census.gov/prod/cen2010/doc/sf1.pdf.

— represents 0.

Note: This table shows more detailed Asian groups and response types than tables in *2010 Census Summary File 1*. As a result, some numbers do not match those shown in *2010 Census Summary File 1*.

*The numbers by detailed Asian group do not add to the total Asian population. This is because the detailed Asian groups are tallies of the number of Asian "responses" rather than the number of Asian "respondents." Respondents reporting several Asian groups are counted several times. For example, a respondent reporting "Korean" and "Filipino" would be included in the Korean and the Filipino numbers.

†The total of 14,327,580 respondents categorized as reporting only one detailed Asian group in this table is higher than the total of 14,314,103 shown in Table PCT5 (US Census Bureau, *2010 Census Summary File 1*). This is because the number shown here *includes* respondents who reported "Chinese" and "Taiwanese" together as a single detailed group, "Chinese," whereas PCT5 *excludes* respondents who reported "Chinese" and "Taiwanese" together.

‡*Includes* respondents who reported "Chinese" and "Taiwanese" together.

§*Excludes* respondents who reported "Chinese" and "Taiwanese" together.

‖Includes respondents who checked the "other Asian" response category on the census questionnaire or wrote in a generic term such as "Asian" or "Asiatic."

Source: US Census Bureau, 2010 Census special tabulation. Accessed at: http://www.census.gov/prod/cen2010/doc/sf1.pdf on May 14, 2015.[542]

The heterogeneity of cardiovascular risk factors such as dyslipidemia, hypertension, obesity, and diabetes, as well as differences in the prevalence of ASCVD and cerebrovascular disease, among persons of Asian/SA ethnicity suggest a need to consider risk assessment and treatment strategies specific to these subgroups of the US population.

Prevalence of dyslipidemia, diabetes mellitus, and metabolic syndrome among Asians/SAs in the United States

The majority of studies of Asians have been conducted in their countries of origin. Data from the 2011–2012 NHANES provide a glimpse of current rates of hypertension, abnormal cholesterol levels, and high BMI among

non-Hispanic Asian Americans over 20 years of age.[543] About 1 in 4 (25.6%) surveyed Asian adults had hypertension (blood pressure ≥140/90 mm Hg or were taking antihypertensive medication), similar to the prevalence among Hispanics or whites, but less than the prevalence among blacks. About 1 in 10 Asian men and women had high total-C (≥240 mg/dL), similar to the prevalence in other groups. However, among non-Hispanic Asian adults, many more men than women—24.5% vs 5.1%—had low levels of HDL-C (<40 mg/dL), which was a greater sex difference than among other groups. In a 3-year cross-sectional study of 169,430 active primary care patients (≥35 years of age) from an outpatient healthcare organization in northern California, Asian Indians, Filipino, and Vietnamese women and Asian Indian men stood out as the Asian subgroups with increased risk of having the combination of high LDL-C (≥130 mg/dL or taking LDL-C lowering medication), low HDL-C (<40 mg/dL for men and <50 mg/dL for women), and elevated TG (≥150 mg/dL) compared to NHWs.[480] The Study of Health Assessment and Risk in Ethnic Groups from Canada showed greater prevalence of high LDL-C, increased small dense LDL, low HDL-C and higher TG levels among SAs compared to Chinese and European controls.[544]

Lipid abnormalities in SAs are closely intertwined with the prevalence of insulin resistance and diabetes. The prevalence of type 2 diabetes is growing worldwide with a projected rise in the total number of individuals with diabetes from 171 million in 2000 to 366 million in 2030 based on data from the World Health Organization Global Burden of Disease Study, which also predicted a particularly concerning 151% increase in prevalence of diabetes in the Indian subcontinent (from 31.7 million to 79.4 million).[545] The susceptibility towards developing insulin resistance may be partially explained by the "fetal origins hypothesis", which postulates that malnourished fetuses adapt to impaired nutrition by becoming relatively insulin resistant.[546] This adaptation may persist into adult life even when calories are abundant, thus leading to insulin resistance and type 2 diabetes mellitus. SAs have approximately 2- to 4-fold increased prevalence of diabetes compared to other native ethnic groups. Population-based studies that sampled SAs from different countries have reported an age-standardized adult diabetes prevalence of 15.7% in India, 21.0% in the United Kingdom, 12.8% in Singapore, 15.3% in Mauritius, 13.1% in Fiji, 9.8% in South Africa, 9.9% in Tanzania, and 15.3% in Canada.[547–555] Surveys in rural and urban India (including the India - Jaipur Heart Watch, and Chennai Urban Population studies) suggest that about one-third of the urban population in large cities in India have metabolic syndrome.[556–558]

A few studies have estimated diabetes and metabolic syndrome prevalence in SAs in the United States. In a community-based survey of 1046 Asian Indian immigrants living in and around the Atlanta, Georgia metropolitan area, 18.3% had diabetes based on self-report[553]; 17.4% of SA adults in a national US study were found to have diabetes based on self-report and fasting glucose levels[554]; and in a study from the Bay Area, California, 27% had diabetes based on an oral glucose tolerance test.[559] In a recent large population-based study from New York City, it was noted that the prevalence of diabetes among foreign-born SAs was nearly twice that of foreign-born other Asians (13.6% vs 7.4%, $P = .001$).[555] In multivariate analyses, normal-BMI foreign-born SAs had nearly 5 times the diabetes prevalence of comparable US-born NHWs (14.1% vs 2.9%, $P < .001$) and 2.5 times higher prevalence than foreign-born other Asians ($P < .001$).[555] The Diabetes in Indian American (DIA) Study of Asian Indian immigrants in 7 cities in the United States revealed an age-adjusted prevalence of metabolic syndrome of 33% in men and 32% in women; this was driven mainly by a high prevalence of low HDL-C (65%), high TG (45%), and increased waist circumference (32%).[554]

Clinicians should be aware when evaluating patients of Asian ethnicity of the need to interpret BMI values differently than in Caucasian patients. In the 2011–2012 NHANES data, only 38.6% of Asian adults had BMI ≥25 kg/m^2—much lower than previously reported rates for Caucasian (66.7%), NHB (76.7%), and Hispanic adults (78.8%)—but at a given BMI, Asian adults may have more body fat than white adults.[543] A large study (n = 43,507) from the Palo Alto Medical Foundation Research Institute examined the relationship between BMI and metabolic syndrome for Asian Americans and NHWs.[560] Metabolic syndrome prevalence was significantly higher in Asians compared to NHWs for every BMI category. A comparable prevalence of metabolic syndrome to that seen among NHW women and men with BMI of 25 kg/m^2 was observed among Asians with a BMI of 19.6 kg/m^2 for women and 19.9 kg/m^2 for men.[560] Because of this, screening for type 2 diabetes should be considered in all Asians and SAs with a BMI ≥23 kg/m^2. Furthermore, clinicians should be aware of the different waist circumference thresholds for defining abdominal obesity as a characteristic of metabolic syndrome in different populations (and from different organizations) (Table 20).[6]

The SA diet may predispose towards developing dyslipidemia and thus increases CHD risk. Use of clarified butter (ghee), deep frying, long cooking times, and reuse of the same oil multiple times may contribute to fatty acid oxidation and increased saturated and *trans* fat consumption. Furthermore, regular physical exercise is rare in this population, especially among women, and may also contribute to dyslipidemia.[561]

Treatment of dyslipidemia in Asians/SAs

There are few data available from large clinical trials or observational studies regarding the awareness, treatment, and control of dyslipidemia among Asians/SAs in the United States. However, available data suggest that similar to the overall population with dyslipidemia, and particularly those with metabolic syndrome, lifestyle modification

Table 20 Waist circumference thresholds for abdominal obesity by various international organizations

		Recommended waist, cm	
Population	Organization (reference)	Men	Women
Caucasian	WHO, 2000[112]	≥94 (increased risk) ≥102 (still greater risk)	≥80 cm (increased risk) ≥88 (still greater risk)
United States	AHA/NHLBI (ATP III*) (NCEP 2002)[26]	≥102	≥88
Canada	Health Canada (Health Canada 2003[113]; Khan et al 2006)[114]	≥102	≥88
European	European Cardiovascular Societies (Graham et al 2007)[115]	≥102	≥88
Asian	WHO (Hara et al 2006)[116]	≥90	≥80
Japanese	Japanese Obesity Society (Oka et al 2008)[117,118]	≥85	≥90
China	Cooperative Task Force (Zhou 2002)[119]	≥85	≥80
Middle Eastern, Mediterranean	IDF (Alberti et al 2005)[120]	≥94	≥80
Sub-Saharan African	IDF (Alberti et al 2005)[120]	≥94	≥80
Ethnic Central and South American	IDF (Alberti et al 2005)[120]	≥90	≥80
Europid	IDF (Alberti et al 2005)[120]	≥94	≥80
Asian (including Japanese)	IDF (Alberti et al 2005)[120]	≥90	≥80

AHA, American Heart Association; ATP, Adult Treatment Panel; IDF, International Diabetes Federation; NCEP, National Cholesterol Education Program; WHO, World Health Organization. The reference numbers in this table refer to the reference numbering from the original publication.

*Recent American Heart Association/NHLBI guidelines for metabolic syndrome recognize an increased risk for cardiovascular disease and diabetes at waist-circumference thresholds of ≥94 cm in men and ≥80 in women and identify these as optional cut points for individuals or populations with increased insulin resistance.[112,121]

Taken from Expert Dyslipidemia Panel, Grundy SM. *J Clin Lipidol*. 2013;7:561–565.[6]

including a diet low in saturated and *trans* fats, with weight loss if overweight/obese and increased physical activity should be the first-line and mainstay of treatment for the management of dyslipidemia in Asians/SAs.[1] When used, pharmacologic therapy should be directed at non-HDL-C and LDL-C targets as described in the NLA Recommendations for the Patient-Centered Management of Dyslipidemia–Part 1.[1] The higher prevalence of hypertriglyceridemia and small, dense LDL particles among some Asian subgroups (SAs) suggest that non-HDL-C, which includes the cholesterol carried by all atherogenic cholesterol particles, may be a particularly important consideration.[480,543,554]

Statins should generally be first-line drug therapy for patients of Asian/SA ethnicity, with consideration of the potential for side effects as discussed later in this document. The Investigation of Rosuvastatin in South Asians was a large randomized trial of statin therapy in 740 patients of SA origin and with hypercholesterolemia in the United States and Canada.[562] Subjects received 6 weeks of treatment with rosuvastatin 10 or 20 mg or atorvastatin 10 or 20 mg. LDL-C decreased by 45% and 40% with 10 mg rosuvastatin and atorvastatin, respectively, and by 50% and 47% with 20 mg rosuvastatin and atorvastatin, respectively. LDL-C goal (based on NCEP ATP III risk categories) was achieved by 76% and 88% of patients receiving rosuvastatin 10 and 20 mg, respectively, and 70% and 81% of patients receiving atorvastatin 10 and 20 mg, respectively.

Prevalence and incidence of CHD and ASCVD among Asians/SAs in the United States

The majority of studies of CHD and ASCVD risk in Asians have been conducted in their countries of origin. Compared to NHWs, Chinese generally have lower levels of LDL-C and TG, and Japanese have higher levels of HDL-C, which may help to explain the lower risk of CHD in these Asian subgroups.[563] Asian Indians and Filipinos have been shown to have higher prevalence of low HDL-C and high TG, and increased CHD risk.[563] Prevalence of CHD in rural South Asia is 3–4%, while the CHD prevalence among urban SAs and SA immigrants to the west approaches 10%.[564]

An assessment of CVD risk in a large multi-ethnic population study of 126,088 adults was performed in Northern California and included 13,448 (10.6%) Asian Americans with 5951 of them Chinese, 1676 Japanese, 4236 Filipino, 689 SA (mostly Asian Indian), and 896 other Asian.[563] The HRs and 95% CIs for CHD incidence among ethnic groups are shown in Table 21.[563] Increased risk among SAs was present in multiple strata, with the largest hazard in men, younger persons, heavy smokers, and persons with CHD events in the first 10 years of follow-up.

A study by Jose et al.[565] utilizing death records from 34 US states reported heart disease and stroke mortality rates for the 6 largest Asian-American subgroups. More than 10 million death records were examined and population data for 2003 to 2010 were derived. Standardized mortality ratios, relative standardized mortality ratios, and proportional mortality ratios for each sex and ethnic group

Table 21 Risk of coronary artery disease in a large multi-ethnic population study of 126,088 adults in Northern California

Group (Number With CAD)	HR	95% Confidence Interval	*P* Value
Adjusted* HR of various ethnic groups vs white			
White (4478)	1.0	–	–
African American (2055)	0.8	0.8–0.9	<.001
Hispanic (282)	0.9	0.8–1.0	.2
All Asian	1.0	0.9–1.0	.2
Chinese (262)	0.8	0.7–0.9	<.001
Japanese (95)	0.9	0.7–1.1	.18
Filipino (263)	1.2	1.0–1.3	.02
Other Asian (24)	0.8	0.5–1.1	.17
South Asian† (56)	2.4	1.9–3.2	<.001
Additional models for South Asian people vs white as referent			
Age- and sex-adjusted model	2.3	1.7–2.9	<.001
Added covariates‡	2.3	1.8–3.0	<.001
Adjusted* HR of CAD in South Asian people vs ethnicities other than white as referent			
African American	2.9	2.2–3.8	<.001
Hispanic	2.8	2.1–3.8	<.001
Chinese	3.3	1.4–3.3	<.001
Japanese	3.2	2.3–4.6	<.001
Filipino	2.3	1.7–3.1	<.001
Other Asian	2.8	2.1–5.6	<.001

CAD, coronary artery disease; HR, hazard ratio.

*Cox models in 7658 people with hospitalization for CAD vs 118,430 without hospitalization for CAD; controlled for age, sex, smoking, alcohol, body mass index, educational level, marital status, and cardiorespiratory composite. The cardiorespiratory composite was based on 27 questions about present or past history of possible diagnoses or symptoms including diabetes. It was a dichotomous (yes, no) marker considered positive if there was a "yes" response to any question.

†Mostly Asian Indian.

‡After correcting for age, sex, smoking, alcohol, body mass index, educational level, cardiorespiratory composite, and marital status, the following covariates were added to the model: systolic pressure, total cholesterol level, blood glucose level, and leukocyte count.

Taken from Hajra A, et al. *J Am Coll Cardiol*. 2013;62:644–645.[563] Permission to reprint was obtained.

compared to NHWs were assessed. The authors found that although NHW men and women had the highest overall CVD mortality rates when examined over the study period, standardized mortality ratios from all CVDs decreased each year. Except for Vietnamese women, the category of all other Asian women had an increased rate of hemorrhagic stroke compared to NHW women. While there has been a decrease in mortality rates for NHWs, the declines for ischemic heart disease and stroke have been less pronounced or absent in Asian populations.[565] Chinese Americans appear to have higher prevalence of hypertension, which may contribute to increased risk for stroke.[565,566]

ASCVD risk assessment in Asians/SAs

As described above, there are differences in the risk profile and in cardiovascular and cerebrovascular event rates among diverse groups of Asians. This heterogeneity of risk factors such as dyslipidemia, hypertension, obesity, and diabetes, as well as differences in the prevalence of ASCVD and cerebrovascular disease in the Asian subgroups, make it vital to accurately assess their risk. However, there is an absence of data from the United States and Asia to definitively guide risk assessment in these subgroups. Therefore, consensus recommendations by the experts must be adapted from US, British, and international recommendations and guidelines for the management of dyslipidemia for SAs. For the most part, both the Framingham Risk Score and the ACC/AHA Pooled Cohort Equations may be relevant in SAs with some adjustments.[3,362] As there are no outcome studies based on targeted therapeutic intervention or an adjusted risk scoring system in Asian and SA populations, the following recommendations regarding risk assessment were made by this NLA Expert Panel based on consensus:

1. The use of non-HDL-C concentrations in addition to LDL-C for screening purposes and for on-treatment assessment may be particularly important for SAs. Non-HDL-C includes the cholesterol carried by all atherogenic lipoproteins, including Lp(a) (which is elevated in Asian Indians compared to NHWs[567]) and VLDL (which is increased in SAs in association with a higher prevalence of elevated TG[480]).
2. Clinicians should be aware that risk assessment methods developed in other populations may underestimate risk in SAs living in the United States and should take this into account when making decisions about risk stratification and treatment.

The underestimation of CVD risk in SAs may be due to a high prevalence of non-traditional risk factors, notably high levels of Lp(a) and visceral adiposity with insulin resistance, despite comparatively low BMI.[543,560,567] Observed CHD morbidity and mortality rates among SAs have been substantially higher than those predicted by Framingham Risk Score and European System for Cardiac Operative Risk Evaluation, which led to the development of QRISK2 in the United Kingdom, a calculator that incorporates social deprivation and ethnicity.[568] The Joint British Societies Guideline uses QRISK2 lifetime risk, which uses a multiplier of 1.5 for Asian Indian men and 1.42 for Asian Indian women.[568] The calibration factors are even higher for Pakistanis (2.05 for men and 2.04 for women) and Bangladeshis (2.14 for men and 1.6 for women). Additional research is needed to establish appropriate risk scoring methods for Asians/SAs living in the United States. Therefore, the panel does not endorse a specific risk multiplier, but instead advises that clinicians should be aware of the increased risk in SAs, which may warrant classifying SAs into a higher risk category for a given number of major ASCVD risk factors, as a matter of clinical judgment.

ASCVD risk reduction with statins in Asians/SAs

In a Canadian study from British Columbia, investigators explored the associations between statin prescriptions and outcomes in a multiethnic population with diabetes using administrative data from 1993 to 2006.[569] Subjects had newly diagnosed diabetes and included 143,630 white persons, 9529 SAs, and 14,084 Chinese. White patients were older and had more comorbidity than the other groups. A statin prescription was associated with lower mortality compared with no prescription within each ethnic group, and to a similar degree: SA (HR 0.69; 95% CI 0.55–0.86; $P = .001$), Chinese (HR 0.60; 95% CI 0.49–0.72; $P < .0001$), and white (HR 0.65; 95% CI 0.63–0.67; $P < .0001$). These findings suggest that statin use is associated with lower mortality in white, Chinese, and SA patients with newly diagnosed diabetes, consistent with benefits of statins observed in other ethnic groups.

Side effects of statins in Asians/SAs

Statins are generally considered to be safe for use among Asians/SAs. Although not placebo-controlled, the Investigation of Rosuvastatin in South Asians, described previously, which was a large randomized trial of rosuvastatin 10 and 20 mg and atorvastatin 10 and 20 mg in patients of SA origin, showed that both statins were generally well tolerated.[562] There were no clinically relevant differences between statins in adverse events or the incidence of creatine kinase >10 times the upper limit of normal, alanine aminotransferase >3 times the upper limit of normal on 2 consecutive occasions, proteinuria, or hematuria. However, genetic variability in drug metabolism and increased prevalence of certain risk factors suggest the need for caution when prescribing statins to patients with Asian/SA ethnicity.

HPS2-THRIVE examined the cardiovascular outcomes of treatment with extended-release niacin/laropiprant or placebo added to simvastatin (with or without ezetimibe) in >25,000 patients with pre-existing CVD from the United Kingdom, several Scandinavian countries, and China (40% of patients).[570] Safety data indicated significantly greater incidence of myopathy in patients receiving the combination of niacin/laropiprant plus simvastatin compared to simvastatin alone (0.34%/year vs 0.08%/year of any myopathy, $P < .0001$). This appeared to be driven primarily by an increase in myopathy among Chinese patients (0.66%/year vs 0.13%/year for niacin/laropiprant plus simvastatin compared to simvastatin alone). Among patients in Europe, the incidence was 0.07%/year vs 0.04%/year, respectively. Therefore, the incidence of myopathy was elevated in Chinese patients in both treatment arms compared to Europeans. Although Chinese patients were the only Asians in HPS2-THRIVE, these results have led to a warning advising caution when prescribing simvastatin to Asian patients and instructions to use the lowest dose possible.

To date, the specific cause of the increased susceptibility of Chinese patients to myopathy has not been identified. Genetic variability in drug metabolism, especially with statins, among Asians through the CYP450 pathway and P-glycoprotein, as well as uptake via organic anion transporting polypeptides may play a role. Even if pharmacokinetics is not the explanation, a potential pharmacodynamic sensitivity justifies utilization of lower doses of statins during initiation in Asian patients with titration to goal as tolerated.[571]

Clinical trial data suggest a modest, but statistically significant, increase in the incidence of new-onset type 2 diabetes mellitus with statin use. In their review of the published evidence relating statin use to the hazard for diabetes mellitus or worsening glycemia, the Diabetes Subpanel of the NLA Expert Panel on Statin Safety concluded that the well-established benefits of statin therapy in primary and secondary prevention of cardiovascular events outweigh the risk of new-onset diabetes.[336] The Panel therefore did not recommend changes to clinical practice other than measuring glycated hemoglobin or fasting glucose prior to and within one year of statin initiation in those with diabetes risk factors. The risk for diabetes with statin use seems to be greater for intensive-dosage statin therapy, and to be most evident in those with major risk factors for diabetes.[572] Because SAs have increased risk for developing diabetes at a younger age, statin therapy and new-onset diabetes is a particular concern for this population, and clinicians should be vigilant in screening and monitoring for worsening glycemia in SA patients given statin therapy.

Conclusions

Heterogeneity of risk factors such as dyslipidemia, hypertension, obesity and diabetes, as well as disparities of ASCVD and cerebrovascular disease risks, among persons of Asian ethnicity make it important to address specific prevention and treatment strategies for this portion of the US population.[563] Among Asian subgroups, Chinese seem to have a higher prevalence of hypertension and stroke,[565,566]

and SAs have high TG, low HDL-C, increased visceral adiposity at lower BMI, and higher prevalence of type 2 diabetes and CHD.[566] These differences may be the result of both genetic and lifestyle factors. There are no prospective ASCVD outcome data in a randomized controlled trial of lipid-lowering therapy in an Asian population. A large interventional cohort study in SAs utilizing traditional and emerging risk factors and implementing strategies to reduce the burden of diabetes and ASCVD is needed.

NHWs. These include, obesity, metabolic syndrome, diabetes mellitus and cigarette smoking.[256,575] Prevalence values for hypertension and hypercholesterolemia appear to be comparable or slightly elevated in AIs/ANs compared to NHWs.[575] Additional factors that may contribute to ASCVD risk in AI/AN populations include low rates of achieving federal physical activity guidelines and high prevalence of low socioeconomic status.[256,576]

See Chart 9 for the Recommendations for South Asians.

Chart 9 Recommendations for South Asians

Recommendations	Strength	Quality
In general, patients of SA ethnicity should be treated according to the NLA Recommendations for Patient-Centered Management of Dyslipidemia – Part 1[1] with the following special considerations.	A	High
Clinicians should be aware that SAs (including individuals who trace their ancestry to Bangladesh, Bhutan, India, the Maldives, Nepal, Pakistan, and Sri Lanka; and also members of the SA diaspora–past generations of SAs who originally settled in other parts of the world, including Africa, Canada, the Caribbean, Europe, the Middle East, and other parts of Asia and the Pacific Islands) as a group are at increased risk for ASCVD.	A	Moderate
Patients of SA descent in the United States have a greater prevalence of insulin resistance than NHWs, and some of the metabolic disturbances that accompany this condition include high TG, low HDL-C, and dysglycemia.	A	Moderate
SAs have increased prevalence of metabolic syndrome compared to NHW Americans. Clinicians should be aware that Asians have different waist circumference cut-points for defining overweight/obesity for the definition of the metabolic syndrome than those recommended for Caucasian populations (≥37 inches [≥94 cm] for men and ≥32 inches [≥80 cm] for women).	A	Moderate
Clinicians should be aware that risk assessment methods may under- or over-estimate ASCVD risk when used in populations different from those in which they were developed. ASCVD risk equations may underestimate risk for SAs in particular, although the degree of underestimation is uncertain. Clinicians should consider this when making decisions about risk stratification and treatment.	B	Moderate
Due to the possibility of genetic variation in drug metabolism (as demonstrated mainly in studies of Chinese and Japanese patients), starting with a moderate intensity statin dosage and titrating upward to reach atherogenic cholesterol goals, or downward if intolerance occurs, is recommended for patients of Asian ethnicity.	B	Moderate
Because SAs are at increased risk for diabetes, vigilant monitoring for the potential of new-onset diabetes with statin treatment is warranted.	A	Moderate

American Indians (AIs) and Alaska Natives (ANs)

The US CDC defines AIs and ANs as people having origins in any of the original peoples of North and South America (including Central America), and who maintain tribal affiliation or community attachment.[573] According to the US Census Bureau, in 2013 there were roughly 5.2 million AIs and ANs living in the US, representing approximately 2% of the US total population.[573]

Relative to other US ethnic and racial groups, AIs/ANs have higher prevalence and incidence rates for certain medical conditions, including obesity, diabetes mellitus, and ASCVD. Average life expectancy is reduced by 5.2 years compared to the general US population, which is likely to be explained in part by elevated ASCVD risk.[574]

A number of ASCVD risk factors are clearly more common among AI/AN populations in the US than in

Dyslipidemia screening and management in AI/AN patients

In general, clinicians should screen for and manage dyslipidemia in AI/AN patients using the approach outlined in Part 1 of the NLA Expert Panel Recommendations for Patient-Centered Management of Dyslipidemia.[1] Because of the high prevalence and incidence rates for obesity, metabolic syndrome and diabetes mellitus in AI/AN populations, strong emphasis on lifestyle therapies, starting at an early age, is warranted, especially for patients who are overweight/obese or display metabolic syndrome.

ASCVD risk assessment in AI/AN patients

The NLA Expert Panel recommends that clinicians should be aware that ASCVD risk is elevated, on average, in AI/AN populations, which emphasizes the importance of controlling dyslipidemia and other modifiable risk factors.

Clinicians should generally assess risk in AI/AN patients using the risk assessment approach outlined in Part 1 of the NLA Expert Panel Recommendations for Patient-Centered Management of Dyslipidemia.[1]

When compared with NHWs, estimated 10-year risk of ASCVD is generally higher in AI/AN populations, although the degree to which this is attributable to differences in traditional ASCVD risk factors is uncertain. In primary prevention, for patients at moderate risk with 2 major ASCVD risk factors, and no conditions that would otherwise classify an AI or AN patient as high or very high risk, quantitative risk scoring may be used for risk refinement. The lack of specific risk assessment tools validated for use in AI/AN populations is an important gap, but development of such a tool would be a challenge due to blood quantum and multiracial composition of a significant portion of AI/AN patients. The ACC/AHA Guideline on the Assessment of Cardiovascular Risk[362] recommends that, although the development of algorithms specific to these groups is encouraged, in the interim, providers may consider using the Pooled Cohort equations for NHWs and for AI/AN patients. However, it is important to note that internal validation cohorts did not include AI or AN patients. Similarly, other quantitative risk assessment tools such as the Framingham Risk Score and the long-term Framingham Risk Score may be applied. However, this should be done with recognition that such tools may under estimate risk in groups, such as AI/AN populations that have higher average risk than the groups for whom the tools were validated.

See Chart 10 for the Recommendations for American Indians/Alaska Natives.

Chart 10 Recommendations for American Indians/Alaska Natives

Recommendations	Strength	Quality
Clinicians should be aware that AIs/ANs have higher prevalence and incidence rates for ASCVD, and that certain ASCVD risk factors (e.g., obesity, metabolic syndrome, diabetes mellitus, and cigarette smoking) are more common among AIs/ANs than NHWs, whereas prevalence values for hypertension and hypercholesterolemia are comparable or slightly elevated compared to NHWs.	A	Moderate
In general, clinicians should screen for and manage dyslipidemia in AI/AN patients using the approach outlined in the NLA Expert Panel Recommendations for Patient-Centered Management of Dyslipidemia – Part 1.[1] Because of the high prevalence of obesity, metabolic syndrome, and diabetes mellitus in AI/AN populations, strong emphasis should be on lifestyle therapies.	A	Moderate
Clinicians should generally assess risk in AI/AN patients using the risk assessment approach outlined in the NLA Expert Panel Recommendations for Patient-Centered Management of Dyslipidemia – Part 1.[1]	B	Low

High risk conditions and residual risk

Human immunodeficiency virus (HIV)-infected persons

The lifespan of patients with HIV infection and suppressed viral replication now approaches that of the general population. This prolonged survival is associated with an increased prevalence of co-morbidities, including CVD, presumably due in part to the inflammation, immune activation, and immune senescence associated with this viral infection. Results from observational studies support an increased CVD risk in the HIV population; however there is a paucity of data linking cardiovascular outcomes with lipid goals and no validated risk stratification schemes for this patient population. The NLA Expert Panel recognizes the paucity of data from RCTs with cardiovascular outcomes in patients with HIV infection to guide decisions on when to intervene using lipid-altering drug therapy. There is insufficient information available to make definitive recommendations at this time. However, given the strong data indicating that HIV infection is a risk factor for ASCVD, the Expert Panel believes that clinicians should have a frank discussion of risk with patients and consider HIV as an independent risk factor that should influence when to consider drug therapy for lowering atherogenic cholesterol.

While some experts suggest that it may be more difficult to achieve lipid goals in HIV-infected persons with current therapies, data from lipid-lowering trials suggest that the percent reductions in non-HDL-C, LDL-C, and TG with statins and fibrates are comparable to those achieved in the general population.[577,578] Not known is whether goals should be more aggressive in these patients, similar to those with other high risk features such as diabetes or known ASCVD. With no definitive data regarding lipid goals in HIV, following the NLA recommendations for the general population is a reasonable approach,[1] with the caveat that HIV infection can be considered an additional major ASCVD risk factor when counting risk factors for risk stratification. This recommendation is based on results from observational studies suggesting that the independent effect of HIV infection is similar to that of major, established ASCVD risk factors.[579–583] A multi-disciplinary panel of HIV experts reviewed the literature and has provided additional guidance on how the NLA recommendations on risk assessment and treatment may be applied to the HIV-infected population.

Cardiovascular risk in the HIV-infected population

HIV disease is associated with many of the risk factors for CVD. In persons not receiving antiretroviral therapy (ART), HIV infection clearly increases CVD risk.[584] Whether HIV infection itself causes atherosclerosis due to inflammation, immune activation, and/or another mechanism is unclear (Fig. 1).[585] Multiple cohort studies have demonstrated excess CVD risk among untreated HIV-infected patients and in ART-treated patients compared to those without HIV infection.[586,587] Patients infected with HIV and on ART often had a constellation of metabolic abnormalities including lipodystrophy (lipoatrophy and lipohypertrophy), insulin resistance, elevated TG, and low HDL-C. However, newer ART medications do not cause significant dyslipidemia and are associated with less risk of MI compared to prior regimens.[588] The importance of treating HIV infection with continuous ART cannot be overstated.[589]

Even with treatment of HIV, having a lower CD4 count is associated with increased risk of MI.[588] ART-associated lipodystrophy has been linked with cardiac and metabolic complications in patients similar to those observed in obese people.[590] This is of particular importance because patients with lipodystrophy often have normal body mass indices. Furthermore, patients with lipodystrophy have a greater prevalence of dyslipidemia and impaired glucose metabolism than patients without lipodystrophy.[591]

It is unclear what accounts for the association of CD4 count with CVD risk. Silverberg and colleagues[588] found that HIV-infected patients with recent or nadir CD4 count $\geq$500 cells/mm^3 had similar rates of MI compared to HIV-negative patients, whereas HIV-infected patients with recent or nadir CD4 count $<$200 cells/mm^3 had an increased risk. Viral load, prior ART use, and duration of therapy with protease inhibitors and nonnucleoside reverse transcriptase inhibitors were not associated with MI. Unsuppressed HIV viremia has been associated with MI[580] and stroke[592] in other studies. Both viral load and CD4 count are included as variables in the Veterans Aging Cohort Study,[582,593] one of the commonly used risk estimating equations in HIV (Table 22).[1,3,6,12,362,368,583,593–603] However neither viral load nor CD4 count are included in another HIV-specific risk calculator developed from the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) cohort.[595]

Special consideration of certain HIV subpopulations is warranted. Observational cohort data suggest that HIV-infected women have higher CVD risk than infected men.[582] Many patients with HIV infection are co-infected with hepatitis C. Hepatitis C infection increases CVD risk, but it is unclear whether the risks associated with HIV and hepatitis C virus are additive.[582] Other chronic viral infections, including cytomegalovirus infection, are more prevalent in HIV-infected persons and may also increase CVD risk.[604] Although the role of aging in HIV disease remains unclear, aging is associated with greater CVD risk. Increased attention to CVD risk in HIV-infected persons with advancing age is warranted.

Traditional CVD risk factors should not be overlooked. The prevalence of smoking is 2- to 3-fold higher among HIV-infected Americans compared with the general population.[605] Smoking increases mortality even in the presence of maximal viral suppression.[606] Furthermore, among HIV-infected individuals, the prevalence of dyslipidemia, diabetes mellitus, and hypertension is higher than in the general population.[582] The lipid profiles of HIV-infected patients are characterized by the "lipid triad" of hypertriglyceridemia, accompanied by an increase in small LDL particles and lower HDL-C.[607–609]

Although hs-CRP is valuable to discriminate individuals at higher risk of CVD events in the HIV seronegative population, the data are not as clear in those with HIV infection. Triant and colleagues[610] studied 70,357 patients in a single center database with hs-CRP measured. They found an increased risk of acute MI with elevated hs-CRP in HIV-infected individuals (OR 2.51). However, the bias of which HIV-infected persons were tested for hs-CRP (n = 487) vs not tested (n = 7099) and the lack of an absolute cut-off make these data difficult to generalize.[610] In the Multicenter AIDS Cohort Study, elevated CRP prior to initiation of ART was associated with a higher risk of progression to acquired immunodeficiency syndrome (AIDS).[611] The association between pre-ART elevation of CRP and HIV progression was also confirmed in a case-cohort study within the multinational Prospective Evaluation of Antiretrovirals in Resource-Limited Settings clinical trial.[612] Despite initiation of ART with efavirenz, CRP levels did not decline after 96 weeks with viral suppression.[613] In a randomized trial of pravastatin and fenofibrate for persons with HIV and combined hyperlipidemia there was no change in hs-CRP levels despite significant declines in LDL-C and TG levels.[614] Conversely, there are a number of studies demonstrating that hs-CRP declines with the use of statins in the general population.[615] In JUPITER, the 44% risk reduction with the use of rosuvastatin was associated with a decline in hs-CRP.[344] Thus, the biology of CRP levels in HIV infection is complicated and likely driven by multiple factors. It is possible that future randomized clinical endpoint trials of statins in persons with HIV may be able to address this question. However, until such time, the use of hs-CRP to adjudicate CVD risk in persons with HIV is not recommended.

Proposed mechanisms of atherosclerosis in HIV infection

Although data remain limited, chronic HIV infection appears to alter the morphologic characteristics and progression of atherosclerotic plaque. Plaques tend to have larger lipid pools with dystrophic calcification.[616] Patients with well-controlled HIV infection have modestly higher rates of subclinical vascular disease compared to uninfected controls—including worsened

carotid intima-media thickness,[617] abnormal endothelial function,[618] increased arterial inflammation,[619] higher prevalence of detectable CAC,[620,621] and greater burden of coronary plaque.[621,622] Carotid intima-media thickness may also progress more rapidly in HIV infection,[623] although this has not been confirmed in all studies.[624,625] Despite some attenuation in multivariable models, the HIV effect persists after adjustment for traditional vascular risk factors. HIV-infected persons are more likely to have non-calcified[626,627] and rupture-prone plaques that are highly associated with non-traditional risk factors, such as inflammation[626] and monocyte activation.[621,622] This suggests that chronic inflammation and immune activation are mediators of CVD risk in HIV (Fig. 11).[585]

Although antiretroviral drugs—particularly older protease inhibitors such as indinavir and lopinavir—were implicated as a cause of CVD in older studies,[627] newer drugs in this class (i.e., atazanavir or darunavir) do not appear to convey the same risk. Abacavir is a nonnucleoside reverse transcriptase inhibitor that has also been associated with higher CVD risk in some studies, although the association remains controversial.[628,629] Platelet activation may be worsened by abacavir[630] and ameliorated by switching to newer classes of drugs.[631] Most importantly, however, interruption of ART results in increased mortality and acute CVD events when compared to continued therapy.[587] The take-home message for the practicing physician and HIV-infected patient is that the benefits of ART greatly outweigh potential CVD risks.[632]

Role of inflammation in the pathogenesis of atherosclerosis in HIV-infected patients

Atherosclerosis is a chronic inflammatory process in which plaque formation is triggered by arterial wall injury, lipoprotein deposition, endothelial activation, and pro-inflammatory molecules.[633] An atherosclerotic lesion develops as focal thickening in the inner layers of the artery composed of vascular endothelial cells, smooth muscle cells, and immune cells (T cells, macrophages) that are prone to rupture and manifest as acute MI. In the setting of persistent systemic inflammation, the process of atherosclerosis is accelerated (Fig. 1).[585] HIV infection rapidly depletes CD4 cells, most notably from the gut, causing marked immune dysfunction and a chronic inflammatory state that accelerates end-organ diseases, and likely contributes to the development of atherosclerosis. Published data highlight the numerous pathways involved in HIV-associated atherosclerosis.[634]

Excess microbial translocation

Early depletion of CD4 cells from gastrointestinal-associated lymphoid tissue (GALT) is a signature feature of HIV infection.[635–637] GALT constitutes the largest immune compartment in the body. The profound depletion of CD4 cells from the GALT during acute HIV infection causes profound changes in the gut mucosal integrity, facilitating bacterial translocation, augmenting trafficking of inflammatory cells to the gastrointestinal tract, and promoting chronic systemic immune activation.[638,639] Activation of both the innate and adaptive arms of the immune system ensues and a state of chronic inflammation and immune activation is created.[634,638] Elevated inflammatory biomarkers can be measured, including markers of microbial translocation (e.g., lipopolysaccharide, lycium barbarum polysaccharide), pro-inflammatory biomarkers (e.g., interleukin [IL]-6, IL1β), monocyte activation (e.g., soluble CD14, soluble CD163), neutrophil activation (e.g., myeloperoxidase, neutrophil gelatinase-associated lipocalin), adhesion molecules (e.g., soluble intercellular adhesion molecule-1), coagulation markers, and fibrin degradation products (e.g., D-dimer).[638,640] Thus, changes in the GALT have profound ramifications for end-organ disease in the setting of HIV infection.

Cellular activation

With a massive depletion of CD4 cells, HIV-infected persons are left with a state of immune dysregulation manifested by low numbers of naïve T cells, an increase in terminally differentiated effector T cells, the generation of excessive pro-inflammatory cytokines, and altered T cell functional and proliferative profiles.[637,641,642] The chronically activated immune system generates excessive pro-inflammatory cytokines associated with end-organ disease such as atherosclerosis, diabetes, and renal injury.[622,643,644] Even with suppressive ART, T cell activation remains elevated above that seen in HIV-uninfected individuals. Recent data assessing non-AIDS events in persons on suppressive ART have suggested that the cells of the innate immune system play a more important role in the process of persistent inflammation and end-organ disease than the adaptive immune system.[645,646]

In HIV-negative persons with ASCVD, a shift in the monocyte phenotype has been demonstrated, consisting of a greater proportion of pro-inflammatory monocytes that target activated endothelial cells contributing to atheroma formation and resulting in acute MI.[617,647–649] In HIV infection, even with ART and viral suppression, these pro-inflammatory monocyte subsets are overrepresented and similarly contribute to excess vascular inflammation and hence atherosclerosis.[622,650,651]

Neutrophils, the most predominant immune cell population, are specifically geared for the rapid detection of invading pathogens. They have recently emerged as important contributors to atherosclerosis.[652–658] In the setting of HIV, neutrophil activation and degranulation is increased and remains elevated even with suppressive ART. The dysregulated neutrophil population in HIV is likely another immune mechanism driving accelerated atherosclerosis.

Additionally, the processes of coagulation and platelet function are dysregulated with HIV infection and likely also contribute to atherosclerosis.[659] Even with suppressive ART, markers of coagulation (e.g., D-dimer) remain elevated and are associated with end-organ disease,

Table 22 Risk scores and algorithms for assessing CV risk in the general population and among patients infected with HIV

Descriptor	Framingham Risk Score	SCORE	PROCAM	REYNOLDS
Population	General population from 1 geographic area: Framingham, MA, USA	European	European men	Men and women from USA, no known CVD (men were nondiabetic)
Age, y	30–74	19–80	35–65	Men, 57–80; women, ≥45
Data collection	1968–1971 Original Framingham cohort, 1971–1975, and 1984–1987; offspring studies	1967–1992	Recruitment 1979–1985 and followed for 10 y	Men, 1995–2008, followed for median of 10.8 y; women, 1992–2004, followed for a median of 10.2 y
Years risk prediction	10-y risk of CHD events; 30-y risk of CHD and stroke	10-y risk of CVD fatality	10-y fatal or nonfatal MI or sudden cardiac death	10-y risk for CVD
Variables	Sex, age, total-C, HDL-C, smoking status, systolic blood pressure (treated or not treated), diabetes	Sex, age, total-C or total-C/HDL-C, systolic blood pressure, smoking status	Age, LDL-C, HDL-C, TG, smoking status, diabetes, family history of MI, systolic blood pressure	Sex, age, smoking status, total-C, HDL-C, hs-CRP, parental history of MI <60 y of age, glycated hemoglobin (if diabetic)
Guidelines using score	NCEP ATP III[12]; Canadian Cardiovascular Society[468]; International Atherosclerosis Society[6]; National Lipid Association Recommendations[1]	European (ESC/EAS)[594]	None	None
Web site	http://cvdrisk.nhlbi.nih.gov/	www.heartscore.org	http://www.chd-taskforce.de/procam	www.reynoldsriskscore.com
Discrimination and calibration in HIV+	c-statistic[595–597]: 0.65, 0.71, 0.77; O/E[595–597]: 1.18, 1.51	c-statistic[597]: 0.57; O/E[597]: 1.20	Unknown	Unknown
Reference	[598,599]	[600]	[673]	[368]
Notes		Different versions applied to countries with low or high risk		Men were in the Physicians Health Study and women in the Women's Health Study

	Pooled cohort equations	D:A:D	VACS
Population	Population-based cohort studies funded by NHLBI	D:A:D cohort of HIV + men in Europe, Argentina, Australia, USA	HIV + USA veterans, men
Age, y		16–85	≥18
Data collection	Varied	1999–2008; followed for a median 4.8 y	2000–2007
Years risk prediction	10-y risk of ASCVD	5-y risk of CVD	5-y mortality
Variables	Sex, age, race (white or black), total-C, HDL-C, systolic blood pressure, treatment for high blood pressure (if systolic >120 mm Hg), diabetes, smoking status	Number of years on inidinavir, lopinavir, currently on indinavir, lipinavir, abacavir, sex, age, current cigarette smoker, previous cigarette smoker, diabetes, family history of CVD, systolic blood pressure, total-C, HDL-C	Age, CD4 count, HIV-1 RNA (viral load), hemoglobin, FIB-4, estimated GFR, hepatitis C infection status
Guidelines using score	2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults[3]; National Lipid Association Recommendations[1]	None	None
Discrimination and calibration in HIV+	c-statistic[596,597]: 0.65, 0.71; O/E[597]: 1.20; may be better than FRS at higher categories of predicted risk[596]	c-statistic[595,597]: 0.72, 0.77; O/E[595,597]: 1.33, 0.95	c-statistic[579] (for CHD death): 0.77; O/E: unknown
Web site	http://tools.cardiosource.org/ASCVD-Risk-Estimator/	http://www.cphiv.dk/tools/dadriskequations	http://www.vacohort.org/welcome/vacsindexinfo.aspx
Reference	[362]	[595]	[602]
Notes	Risk scores account for white and black race; eliminated targets for LDL-C[3]		Predicts mortality and CHD death for HIV + patients who have been treated with ART for at least 1 year[583,593,601,603]

ACC/AHA, American College of Cardiology/American Heart Association; ART, antiretroviral therapy; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; D:A:D, Data Collection on Adverse Events of Anti-HIV Drugs; eGFR, estimated glomerular filtration rate; ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; FIB-4, (years of age × aspartate transaminase)/(platelets × √alanine transaminase); HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; NHLBI, National Heart, Lung, and Blood Institute of the National Institutes of Health; O/E, observed-to-predicted events ratio; PROCAM, Prospective Cardiovascular Munster Study; SCORE, Systematic Coronary Risk Estimation; total-C, total cholesterol; VACS, Veterans Aging Cohort Study.

including atherosclerosis.[660–663] Chronic inflammation has been demonstrated to increase the production of procoagulant factors and down-regulate anticoagulants, leaving individuals at increased risk for thrombotic events.[664] Chronic viral infections, including HIV, activate the coagulation cascade by tissue injury and endothelial tissue damage with subsequent expression of tissue factor, which serves as a signaling molecule for activated T cells, monocytes, and neutrophils inducing atheroma formation.[665] Platelet activation is increased with HIV infection, even with suppressive ART, and the platelets express pro-inflammatory cytokines and tissue factor.[656,657]

Measuring inflammation or immune activation

There are no reliable clinically available markers of inflammation and immune activation to guide clinicians in the management of persons with HIV. There are many markers of inflammation and immune activation that correlate with chronic HIV infection, such as IL-6, D-dimer, and hs-CRP, but most are not measured routinely in clinical practice. Whether any of these markers can be altered in persons with HIV to reduce the risk for ASCVD is not known. The National Institutes of Health randomized trial Evaluating the Use of Pitavastatin to Reduce the Risk of Cardiovascular Disease in HIV-Infected Adults (REPRIEVE), which started in March 2015 and has an estimated completion date of April 2020, may shed some light on this issue by determining whether the use of statins is beneficial in HIV-infected patients who do not meet standard criteria for their use.[666] REPRIEVE is a large (N = 6500) multi-center randomized trial investigating the use of pitavastatin (4 mg) in HIV-infected patients on ART that do not qualify for statin therapy according to the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults.[666]

Statin use in HIV patients

Two mainstays of CVD prevention among HIV-infected patients are 1) treatment with ART to reduce HIV immune activation and inflammation, and 2) control of modifiable risk factors, including lipids.[653] Given that statins not only reduce LDL-C but also have anti-inflammatory properties, they may be beneficial in reducing the chronic inflammation associated with HIV infection.[652,667,668] Statins have been shown to be both safe and effective in HIV-infected persons.[669–671] However, the use of statins remains relatively low in HIV-infected patients.[580,672] The low use of statins in the HIV-infected population may reflect the relatively low prevalence of elevated LDL-C, their uncertain efficacy for CVD prevention, and the potential for adverse side effects and negative drug-drug interactions. REPRIEVE described above has been designed to help answer this question. Until these data are available, it is not clear whether statins should be used more aggressively in persons with HIV infection.

Assessing cardiovascular risk in the HIV-infected population

Risk scores and algorithms are used to determine intensity of lipid-lowering therapy to prevent disease. They have been used extensively for ASCVD, in particular to establish an LDL-C goal or to determine the percentage LDL-C reduction. Risk prediction in HIV-infected patients is an evolving science, because potential drivers of risk are present in HIV-infected patients that were not prevalent in the populations from which risk prediction equations were developed. Risk prediction schemes must also be easily employed and discriminate correctly.

The most widely used algorithm in recent years has been the Framingham Risk Score from the Framingham Heart Study. This score predicts 10-year risk for MI and CHD death.[598] Other established risk scores for the general population include: Systematic Coronary Risk Estimation,[600] Prospective Cardiovascular Munster (PROCAM),[673] Reynolds Risk Score,[368] and the 2013 ACC/AHA Pooled Cohort Equations.[362] The last, newest set of equations has been extensively debated. Some groups in the United States have recommended further validation prior to its adoption.[674–676] The risk prediction tools used in the NCEP ATP III guidelines (Framingham Risk Score) and the 2013 ACC/AHA Pooled Cohort Equations both underestimate the risk of CVD among HIV-infected individuals.[654,655,658] Although the NCEP ATP III Framingham equation and the 2015 NLA Recommendations risk stratification system[1] have not been validated in HIV-infected patients, the NLA Expert Panel agreed that either risk stratification scheme is acceptable for providing risk information for this patient population.

At this time there is no validated, 10-year risk score specifically for people infected with HIV. The D:A:D Study investigators[595] have published a risk equation for men that includes several antiretroviral drugs as well as traditional risk factors. Predictions were estimated for 5-year risk.[67] The Veterans Aging Cohort Study also published a mortality risk index that includes CD4 count and viral load. It is used for overall mortality prediction[602] but has also been used to assess cardiovascular mortality.[593] The risk scores noted above are summarized and compared in Table 22.[1,3,12,279,344,362,368,467,579,583,593–600,672]

There are differing opinions and data on how well the existing risk score tools predict risk among persons with HIV infection. Friis-Moller et al.[595] and Parra et al.[655] found that the Framingham Risk Score underestimated the presence of subclinical atherosclerosis and clinically manifest disease in HIV-infected patients. Falcone et al.[678] showed that increased Framingham Risk Scores predicted risk accurately and were associated with abnormal early and late surrogate markers (carotid intima-media thickness) in a group of 334 HIV-infected adults. Law et al.[679] compared the number of MIs observed among participants infected with HIV in the D:A:D Study with the number predicted by conventional risk factor

equations. They found that the Framingham Risk Score over-predicted rates in patients who did not receive ART and under-predicted rates in patients on ART. Nery and colleagues[680] assessed the agreement between Framingham, PROCAM, and D:A:D risk equations in HIV-infected patients in Brazil. The authors also used an expanded Framingham prediction tool for those with low or moderate 10-year Framingham risk by adding family history of CVD, metabolic syndrome, serum creatinine ≥1.5 mg/dL, hs-CRP >3.0 mg/L, or albuminuria >30 μg/mg. The PROCAM score placed the lowest proportion of patients into the high-risk group, while the Framingham with expanded risk indicators tool placed the highest proportion of patients into the high-risk group. Zanni and colleagues[658] used computed tomography angiography to assess the performance of the 2013 ACC/AHA Cholesterol Guideline in 108 HIV-infected individuals without known CVD. Thirty-nine participants had coronary atherosclerotic plaque morphology classified as high risk; however, statin therapy would not have been recommended for 74% of these individuals by the 2013 ACC/AHA guideline.

Risk for ischemic stroke had not been considered in most prior risk scores, although several, including the recent ACC/AHA Pooled Cohort Equations for 10-year risk, do include stroke risk. Fewer studies are available providing data on stroke in HIV-infected patients, but existing studies suggest an increase risk above what would be predicted from traditional risk factors.[592,681,682] Ovbiagele and colleagues[683] reported a 67% increase in HIV-infected patients hospitalized for stroke (hemorrhagic and ischemic) from 1997 to 2006 in the United States.[683] Mateen et al.[684] tested the accuracy of the Framingham Risk Score for prediction of stroke of any type in HIV-infected men compared to non-infected men in the Multicenter AIDS Cohort Study, and found that Framingham underestimated the long-term risk for stroke in HIV-infected men.

It does not appear that HIV itself directly increases risk for hypertension although there may be an increased prevalence of hypertension among older HIV-infected persons compared to age-matched uninfected individuals.[685] The prevalence of hypertension was reported to be 43% in one outpatient setting in New York City[686] and 31% in two HIV Naval Clinics.[687] Evidence for an association between use of ART and hypertension is not consistent; with some studies showing no association[687,688] and others showing that ART was associated with a higher prevalence of systolic hypertension.[689]

While it is clear that prolonged survival in HIV infection is accompanied by an increased prevalence of non-HIV related co-morbidities at all ages, it is less clear whether this increased prevalence may be attributed to the actual aging process or "accelerated aging".[690,691] A Kaiser-Permanente group reported that the overall incidence rates for MI for the HIV-infected population has steadily declined from 1996 to 2011 and this rate now approximates that of the general population.[692] An epidemiologic study of HIV-associated CVD mortality 2001–2012 in New York City showed that while the number of deaths due to ASCVD increased as a cause of death among those with HIV infection, the overall CVD mortality rate has steadily declined. Furthermore, the CVD mortality rates were significantly higher in the HIV-infected population under age 65 whereas CVD mortality after the age of 65 was essentially the same as the general population.[693] Nevertheless, it is likely that persistent underlying inflammation is contributing to the increased CVD morbidity, which is not captured in the current risk assessment tools leading to an underestimation of actual risk.[596,597]

Recommendations for assessing cardiovascular risk in the HIV-infected population

HIV-infected patients have a higher prevalence of CVD compared to the general population, which persists even after control of traditional risk factors.[581] This population also has higher rates of smoking and other behavioral and social factors that increase ASCVD risk.[677,686] HIV infection and its therapies may also produce a syndrome consisting of insulin resistance, lipodystrophy (lipoatrophy and fat accumulation including an increase in abdominal visceral fat), and abnormal lipids (elevated TG and low HDL-C).[653,694,695] The role of inflammation in the pathogenesis of atherosclerosis is well known in the general population and is believed to play a significant and unique role in the increased ASCVD risk in patients infected with HIV.[619,660,696] Taken together, these factors provide evidence that patients infected with HIV are at higher ASCVD risk, both from traditional and unique risk factors. This increased risk is not accurately assessed with existing risk scoring systems. There is a clear need to develop specific cardiovascular risk equations for people living with HIV. Established risk scoring systems are for short-term prediction, generally ten years. However, both the Framingham Risk Score and the ACC/AHA Pooled Cohort Equations provide lifetime risk estimates.[362,599] Most HIV cohort studies have followed patients for less than ten years; hence, there are no lifetime risk scores for patients infected with HIV.

At this time, the HIV Medicine Association of the Infectious Disease Society of America[697] and the European AIDS Clinical Society[698] both endorse use of the Framingham Risk Score, although it is not validated in patients with HIV.

This Expert Panel recommends estimating risk as outlined in the NLA Recommendations for the Patient-Centered Management of Dyslipidemia–Part 1.[1] This includes determining the number of risk factors, the use of risk prediction tools, such as the ATP III Framingham Risk Score or the ACC/AHA Pooled Cohort Equations if two risk factors are present, as well as clinical judgment. The Expert Panel consensus view is that it is reasonable to consider HIV a risk factor for ASCVD in risk factor counting. In primary prevention patients, for those with HIV infection plus 2 other major ASCVD risk factors, atherogenic cholesterol levels for non-HDL-C and LDL-C

goals are <130 mg/dL and <100 mg/dL, respectively. The NLA Part 1 document also states that "risk indicators" can be used for "risk refinement." These include strong family history of premature ASCVD and multipack per day smoking. Metabolic syndrome is not specifically listed as a risk criterion but can be considered for risk refinement, especially because this cluster of metabolic abnormalities (high TG, low HDL-C, insulin resistance, elevated waist circumference, and hypertension) is common in HIV-infected patients.

Current evidence suggests that HIV-infected patients are at higher risk for ASCVD, although whether it meets criteria for classification as an "ASCVD risk equivalent" similar to diabetes plus 2 major ASCVD risk factors is unknown. The importance of shared decision-making between the patient and provider about whether to initiate statin therapy is also a central principle of the NLA Part 1[1] and these Part 2 recommendations.

Treatment of dyslipidemia in HIV infection

HIV-infected patients should be treated similarly to the general population, with atherogenic cholesterol goals according to the NLA Part 1 Recommendations[1] with the caveat of considering the presence of HIV infection an additional major ASCVD risk factor. Challenges include understanding the risks attributable to HIV itself vs those induced by ART, as well as the complexities of selecting the specific lipid-lowering agents and adjusting their doses to reach maximal effectiveness without compromising safety. The current Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents and the International Antiviral Society-USA HIV treatment guidelines recommend that everyone infected with HIV should be offered ART, regardless of their absolute CD4 cell count, to reduce all-cause mortality, including that from CVD events, and to reduce transmission.[589,699] Although previous antiretroviral agents were associated with significant metabolic side effects, the more commonly prescribed and recommended regimens of today are not. It is also important to consider how many of these side effects are likely due to the current ART as opposed to traditional risk factors or HIV itself. In a patient who is otherwise tolerating ART with full virologic suppression, one must weigh the risks and benefits of switching ART. Many experts prefer treating with the appropriate lipid-lowering therapies rather than switching the ART regimen.

As with all patients with dyslipidemia, lifestyle interventions remain the cornerstone of therapy. Patients should be referred for nutritional counseling, smoking cessation, and weight management. Patients who are not virologically suppressed on ART should be referred for adherence counseling and managed with a goal of achieving full suppression. If dyslipidemia persists after maximizing HIV control and lifestyle interventions, patients should be treated according to the lipid abnormality present.

As in the general population, statins are the first-line drug class for treatment of dyslipidemia. The choice of statin is largely based on its drug interaction potential with the patient's ART as well as the intensity of the statin. The FDA recently issued updated recommendations concerning drug-drug interactions between drugs for HIV and statins and provided the statin dose limitations.[700] The reader is also referred to Kellick et al.[463] for a thorough review of statin drug-drug interactions by the NLA's Safety Task Force, as well as a systematic review of the use of statin therapy in patients with HIV by Feinstein et al.[701] The Expert Panel has provided a summary of the interactions between protease inhibitors (including cobicistat) and non-nucleoside reverse transcriptase inhibitors and statins (Table 23).[578] Nucleoside reverse transcriptase inhibitors and integrase inhibitors, except when boosted with cobicistat, do not have any significant drug-drug interactions with statins. In previous years, pravastatin was the preferred agent for patients with HIV, due to its limited interactions with most antiretroviral agents. However, in more recent years, atorvastatin and rosuvastatin have been prescribed more often because of their greater efficacy. Given the increase in certain statin blood concentrations due to HIV drug interactions, concerns exist for increased statin side effects such as myalgia or myopathy. As a result, it is generally recommended that lovastatin and simvastatin not be used in HIV patients despite being generic and inexpensive. In addition, some of the interactions are associated with a decrease in statin concentrations; caution should be used when prescribing statins so as not to under- or overdose. It should be noted that pharmacokinetic studies of ART and statins have been primarily conducted in HIV-uninfected subjects who may not adequately represent the metabolism of these medications in those with HIV infection, given the differences in gastric acidity and host-genomics-disease mechanisms. To date, pitavastatin is the only statin not known to have significant interactions with ART and does not require dose adjustments. Atorvastatin and rosuvastatin can also be used, but with dose adjustments depending on the type of HIV therapy used.

Monitoring of statin side effects in the HIV-infected patients is similar to monitoring in the general population. Questions about statin safety have been largely addressed by understanding the drug-drug interactions and relative plasma concentration of the statin compared to the dose prescribed. Routine monitoring of creatine kinase is not recommended. Some clinicians do order liver function tests approximately 1 month after prescribing statins, although the FDA does not recommend monitoring, suggesting that liver function be monitored only in patients with preexisting conditions that increase the risk of liver toxicity.

The most common lipid abnormality reported in persons with HIV is high TG with low HDL-C, presumably due to underlying inflammation and insulin resistance. Infections are known to increase TG by decreasing the clearance of circulating lipoproteins or by stimulating hepatic lipid synthesis or reesterification of fatty acids derived from

Table 23 Interactions between ART and statins*

Statin	Antiretroviral therapy drug class: Protease inhibitor, including cobicistat	Antiretroviral therapy drug class: Nonnucleoside reverse transcriptase inhibitor
Atorvastatin	• AUC ↑↑. • Use lowest starting dose and titrate carefully. • Do not exceed 20 mg daily with DRV/r, FPV/r, SQV/r. • AUC ↑↑ 488% with LPV/r. • ↑↑↑ 836% with TPV/r and should not be coadministered. • Start with the lowest recommended dose and titrate while monitoring for safety with all cobicistat containing regimens.	• AUC ↓ 43% with efavirenz. • ↔but C_{max} ↓ 37% with etravirine. • No data for nevirapine. • May need higher starting dose with efavirenz and etravirine. • No dose adjustments for rilpivirine.
Fluvastatin	• Use not recommended with nelfinavir.	• AUC ↑ with etravirine. • May require higher starting dose with etravirine.
Lovastatin	• Contraindicated with all PIs and cobicistat (AUC ↑↑↑).	• AUC ↓↓ with efavirenz. May require higher starting dose. • No adjustment needed for rilpivirine.
Pitavastatin	• Modest AUC ↑ with ATV/r (31%). • Modest ↓ AUC with DRV/r (20–26%) and LPV/r (20%). No dose adjustment required. • No dose adjustment with cobicistat.	• ↔ with efavirenz and no dose adjustment needed. • No dose adjustment needed for rilpivirine.
Pravastatin	• ↓ AUC of except with DRV/r and LPV/r which ↑ AUC by 81% and 33%, respectively. Use lowest possible starting dose.	• AUC ↓ 40% with efavirenz. • ↔ with etravirine. May need higher starting dose.
Rosuvastatin	• AUC ↑↑ 213% and C_{max} ↑↑↑ 600% with LPV/r. • AUC ↑↑ 108% and C_{max} ↑↑↑ 366% with ATV/r. • AUC ↑ 48% and C_{max} ↑ 139% with DRV/r. Do not exceed 10 mg daily. With DRV/r, use lowest necessary dose. • AUC ↔ and C_{max} ↑ 123% with TPV/r. • ↔ with FPV/r. Titrate dose carefully with LPV/r or ATV/r. • AUC ↑ 38% and C_{max} ↑ 89% with cobicistat.	• Allowed. ↔. No reported interactions.
Simvastatin	• Contraindicated with PIs and cobicistat (AUC ↑↑↑).	• AUC ↓ 58% with efavirenz and ↓ with etravirine. • No data for nevirapine. May require higher starting dose.

↑, some increase; ↑↑, moderate increase; ↑↑↑, large increase; ↓, some decrease; ↔, no significant change; ART, antiretroviral therapy; ATV/r, atazanavir/ritonavir; AUC, area under the concentration–time curve; C_{max}, maximum drug concentration; DRV/r, darunavir/ritonavir; FPV/r, fosamprenavir/ritonavir; LPV/r, lopinavir/ritonavir; PI, protease inhibitor; SQV/r, saquinavir/ritonavir.

*Nucleoside reverse transcriptase inhibitors and integrase inhibitors, except when boosted with cobicistat, do not have any significant drug–drug interactions with statins.

Table modified from Myerson M, Malvestutto C, Aberg JA. *J Clin Pharmacol*. 2015;55:957–974.[578] Permission to use adaptation was obtained.

lipolysis.[702,703] The derangements in TG metabolism reported in inflammatory conditions are thought to be secondary to cytokine responses. In HIV, circulating interferon alpha may induce increased TG in part by decreasing lipase activity and slowing the clearance of TG.[704] Furthermore, there are complex lipid metabolism pharmacogenomic interactions with ART as evidenced by differences in race and gender while on ART.[705,706]

TG must be determined in a fasting state. Repeated values ≥500 mg/dL that are unresponsive to lifestyle interventions should be treated with medications (see NLA Recommendations for the Patient-Centered Management of Dyslipidemia–Part 1[1]). Secondary causes of hypertriglyceridemia such as dietary characteristics (e.g., excess alcohol, high glycemic load) and other conditions (e.g., diabetes mellitus, hypothyroidism, CKD) that may elevate TG should also be considered, as described in the NLA Part 1 Recommendations.[1] Statins have a moderate effect on TG; fibrates, prescription omega-3 fatty acids, and niacin are frequently used pharmacologic therapies for very high TG.[153] In patients with hypertriglyceridemia ≥500 mg/dL, fibrates and certain omega-3 fatty acid preparations (those that contain DHA) may raise LDL-C. Niacin is generally the least well tolerated of the drugs that primarily lower TG and TG-rich lipoproteins, and high doses are necessary to achieve significant TG-lowering. Niacin also has the potential to induce insulin resistance and new-onset diabetes mellitus, thus it is generally reserved for patients that do not tolerate a fibrate or prescription omega-3 fatty acid agent.

Summary of treatment recommendations

All HIV-infected patients should be assessed for cardiovascular risk, including measurement of a fasting lipid panel with total-C, HDL-C, TG, LDL-C, and non-HDL-C, and should be counseled about lifestyle interventions,

Chart 11 Recommendations for HIV-infected persons

Recommendations	Strength	Quality
Clinicians should be aware that patients with HIV are at increased risk for ASCVD. The association between HIV infection and ASCVD risk is independent of the risk associated with major established ASCVD risk factors.	A	High
A fasting lipid panel should be obtained in all newly identified HIV-infected patients before and after starting ART.	A	Moderate
For primary prevention of ASCVD, HIV infection may be counted as an additional ASCVD risk factor for risk stratification.	B	Moderate
Risk stratification is based on the NLA Recommendations for the Patient-Centered Management of Dyslipidemia – Part 1[1] with initial risk stratification based on the number of major ASCVD risk factors (with the caveat that the presence of HIV infection may be counted as an additional risk factor), the use of risk prediction tools, such as the ATP III Framingham Risk Score or the ACC/AHA Pooled Cohort Equations if two risk factors are present, and the use of other clinical indicators to help inform clinical judgment, if needed.	B	Moderate
The non-HDL-C and LDL-C goals described in the NLA Part 1 Recommendations should be followed for HIV-infected patients.[1] Atherogenic cholesterol goals may not be attainable in all patients, but there is incremental benefit to lowering non-HDL-C and LDL-C to approach these goal levels.	B	Moderate
Elevated TG $\geq$500 mg/dL that is refractory to lifestyle modification or changes in ART (if an option) should generally be treated with either a fibrate (fenofibrate preferred) or prescription omega-3 fatty acids. After TG is lowered ($<$500 mg/dL), non-HDL-C and LDL-C should be reassessed for appropriate management.	B	Moderate
Statin therapy is first-line for elevated LDL-C and non-HDL-C; however, interactions between statins and antiretroviral agents and other medications must be considered prior to initiating lipid-lowering therapy. The NLA Expert Panel recommends using atorvastatin, rosuvastatin, or pitavastatin as the generally preferred agents in HIV-infected patients.	A	Moderate

including smoking cessation, diet, and exercise. At this time there has not been sufficient research to formulate comprehensive, evidence-based guidelines and validated risk stratification schemes for HIV-infected patients. Based on guidelines and recommendations for the general population with modification for this patient population, the NLA Expert Panel recommends the following.

See Chart 11 for the Recommendations for HIV-infected Persons.

Patients with rheumatoid arthritis (RA)

Heart disease is a leading cause of death in patients with RA.[707] Although RA is typically considered a disease of the joints, the systemic inflammation in RA has effects throughout the body, particularly in the vasculature. As a result, a leading cause of death in RA is CVD. CVD risk is 1.5- to 2-fold higher in RA compared to individuals from the general population with the same age and gender.[708,709] This elevated CVD risk in RA is attributed to chronic inflammation leading to accelerated atherosclerosis.[707,710] Currently no validated strategy exists for those in the United States that can integrate the burden of chronic inflammation with traditional risk factors to quantify cardiovascular risk in RA patients. Thus, a major challenge for physicians treating patients with RA and other inflammatory diseases is estimating their cardiovascular risk and identifying interventions to lower risk beyond managing traditional risk factors. In this section, we focus on topics surrounding the management of cardiovascular risk and dyslipidemia where adequate data exist for recommendations based on expert opinion. Our discussion focuses on RA because it is the most common inflammatory disease among the rheumatic diseases with the most data available on cardiovascular risk. CVD has been found to be elevated across the spectrum of inflammatory diseases including temporal arteritis[711] and with perhaps the highest risk among young women with systemic lupus erythematosus.[712,713]

Estimating cardiovascular risk in RA

No risk calculator has been validated for RA or other inflammatory diseases in the United States. A study that applied the 2013 ACC/AHA guidelines for the treatment of blood cholesterol,[3] to a cohort of RA patients with CAC scores found that a substantial proportion of RA patients with low CAC scores were classified as high risk and vice versa, i.e., RA patients with high CAC scores were classified as low risk.[714] The observed cardiovascular risk among RA patients was 2-fold higher than the calculated Framingham Risk Score[488] in women and 65% higher in men.[715] The Reynolds Risk Score[368] also underestimated cardiovascular risk in RA. The United Kingdom based QRISK2[716] is the only cardiovascular risk calculator that incorporates RA as a variable. While QRISK2 is a validated risk calculator for the general UK population, one study that examined its performance in RA showed that it overestimated cardiovascular risk.[717]

The European League Against Rheumatism published recommendations in 2009 for cardiovascular risk management in RA and other inflammatory diseases relying heavily on expert opinion.[718] These recommendations have not been adopted into clinical practice in the United States. They recommended multiplying a patient's Framingham Risk Score

or the European Systematic Coronary Risk Evaluation,[600] by 1.5 in RA patients who meet 2 of the following criteria: (1) RA disease duration >10 years, (2) rheumatoid factor or antibodies to cyclic citrullinated peptide positivity, or (3) presence of extra-articular manifestations such as bone erosions. Studies in the US population have found that multiplying the Framingham Risk Score by 1.5 does not improve how well the cardiovascular risk is estimated.[715]

There is evidence that assessment of cardiovascular risk factors may occur at a lower rate in RA patients than the general population.[719] Thus, this NLA Expert Panel recommends particular vigilance in ensuring that RA patients are routinely assessed for cardiovascular risk factors, e.g., hypertension, dyslipidemia, diabetes, family history of early-onset CVD, and smoking. In the NLA Recommendations for Patient-Centered Management of Dyslipidemia–Part 1, high-risk thresholds based on 3 commonly used risk calculators are ≥10% 10-year risk for a hard CHD event (MI or CHD death) using the ATP III Framingham Risk Calculator, ≥15% 10-year risk for a hard ASCVD event (MI, stroke, or death from CHD or stroke) using the ACC/AHA 2013 Pooled Cohort Equations, and ≥45% risk for CVD (MI, CHD death, or stroke) using the Framingham long-term (30-year) Risk Calculator.[1] For clinicians who routinely measure CRP, the Reynolds Risk Score, which incorporates CRP, was also identified as a reasonable option for estimating cardiovascular risk.[368] We note that despite the inclusion of CRP, the Reynolds Risk Score also significantly underestimates cardiovascular risk in RA similar to Framingham.[715] Statins are the first-line treatment for dyslipidemia in RA, but insufficient data are available to determine whether different treatment goals are warranted for patients with RA and other inflammatory diseases.[720]

Relationship between inflammation, treatment, and lipids

As in the general population, elevated non-HDL-C and LDL-C levels are associated with higher cardiovascular risk in RA. However, chronic inflammation adds to the complexity of this relationship.[721,722] RA patients have lower total-C and LDL-C levels than individuals of similar age and gender from the general population,[723,724] despite an overall higher risk of CVD. In addition, LDL-C levels may correlate with levels of inflammation. In a study of RA patients who experienced a reduction in inflammation, patients experienced an increase in their LDL-C levels.[725] Similarly, RA patients who received a tumor necrosis factor inhibitor as part of a clinical trial had a mean increase in their LDL-C level of up to 30%.[726,727] These data suggest that in an individual RA patient, LDL-C levels may increase when RA disease activity is controlled.[728,729] Although the overall reduction in inflammation is likely associated with reduced cardiovascular risk, the clinical significance of these lipid elevations with regards to cardiovascular risk has not been established.

Frequency of lipid assessments

Lipid levels, inflammation, and use of RA treatments are tightly linked. RA patients routinely experience a decreased response to their disease-modifying anti-rheumatic drugs over time, which requires treatment adjustments. If a patient has had lipid levels checked during an RA flare (e.g., swollen joints, high CRP), it is recommended that the lipids be re-checked when their disease is controlled, because the LDL-C level may have been artificially lower during the flare.

Of the RA treatments, only tofacitinib and tocilizumab have package inserts recommending a specific frequency of lipid measurements (Table 24).[730,731] Generally, patients should be referred to a preventive cardiologist or lipid clinic for issues such as high atherogenic cholesterol levels despite statin therapy (e.g., LDL-C ≥190 mg/dL and/or non-HDL-C ≥220 mg/dL), or for very high TG. Due to the higher cardiovascular risk in RA, it is reasonable to also consider referrals to a specialist for assessment of patients with lower LDL-C levels (e.g., 160 mg/dL).

RA treatments with known drug interactions with statins

Methotrexate (MTX), a folate antimetabolite, is the first-line agent for treatment of RA. In drug interaction databases, the recommendation is to monitor therapy with atorvastatin (Lexicomp Risk Rating C), because it can increase the serum concentration of MTX. The effects of this interaction have not been linked to increased side effects at the levels of MTX used for RA (maximum dosage of 25 mg once a week). In a trial of 30 subjects randomized to MTX plus prednisone vs MTX plus prednisone plus atorvastatin, there was no increase in adverse events in the atorvastatin arm. Specifically, no significant increases in

Table 24 RA treatments with manufacturer package inserts recommending frequency of lipid measurements

RA treatment	Rates of dyslipidemia (%)	Recommendations	Comments
Tofacitinib[730]	>10	4–8 wk after initiation	Increases in total-C, LDL-C, and HDL-C • Maximum increases within 6 wk of initiation
Tocilizumab[731]	>10	4–8 wk after initiation, then at ~24-wk intervals	Increases in total-C, LDL-C, HDL-C, and TG

HDL, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RA, rheumatoid arthritis; TG, triglyceride; total-C, total cholesterol.

liver enzyme abnormalities, mylagias, or myositis were observed.[732]

Tocilizumab, an IL-6 receptor blocker, also has a recommendation to monitor therapy (Lexicomp Risk Rating C) for atorvastatin, lovastatin, and simvastatin. In a clinical study of 12 RA patients on tocilizumab 8 mg/kg and simvastatin, tocilizumab increased metabolism of simvastatin.[733] Whether this interaction has a clinically significant effect remains to be determined. Because the recommendation for tocilizumab is to routinely measure lipids, the treating physician would be aware of it if the statin was not effective for lowering LDL-C.

Statin use may also be associated with a reduced clinical response to rituximab therapy.[734] Rituximab is a monoclonal antibody directed against the CD20 receptor on B-cells that eventually depletes the B-cells. The dosing for rituximab in RA is intravenous infusion at baseline, 2 weeks, and then every 24 weeks (the drug can be re-dosed at 16 weeks if RA symptoms recur). In an observational study of RA patients on rituximab and a statin, patients on a statin had a modestly higher mean RA disease activity score and required re-dosing of rituximab sooner than those not on a statin.[734] However, a subsequent study showed no association between statin use and the degree of B-cell depletion with rituximab,[735] suggesting that the clinical difference in response was not due to a reduced effect of rituximab.

In summary, although moderate interactions have been reported between statins and disease-modifying anti-rheumatic drugs, leading to recommendations to monitor therapy, there have been no contraindications for this combination. Furthermore, the effects between statins and disease-modifying anti-rheumatic drugs were not associated with an increased incidence of adverse events in the clinical studies to date.

Research directions

Improving the management of CVD in RA and other rheumatic diseases is a vibrant area of research. Research topics for which additional data are needed include the development and validation of a cardiovascular risk calculator specific for RA,[736,737] identifying biomarkers that can improve how cardiovascular risk is stratified in inflammatory diseases, and determining whether specific RA treatments may have beneficial effects for reducing CVD by targeting specific inflammatory pathways. In addition, although statins are first-line treatment for dyslipidemia in RA, there is a need to evaluate other lipid-altering therapies to assess whether treating to lower goals for a given risk category with statin add-on therapy would provide additional benefit for patients with RA and other inflammatory diseases.

See Chart 12 for Recommendations for Patients with Rheumatoid Arthritis.

Chart 12 Recommendations for patients with rheumatoid arthritis

Recommendations	Strength	Quality
Clinicians should be aware that patients with RA are at increased risk for ASCVD. The association of RA and systemic lupus erythematosus with ASCVD risk raises concern that other inflammatory conditions may also be associated with increased ASCVD risk. However, only RA has been studied sufficiently to accurately quantify the degree to which it increases ASCVD risk.	A	High
The association between RA and ASCVD risk is independent of the risk associated with major established ASCVD risk factors.	A	High
For primary prevention of ASCVD, RA may be counted as an additional ASCVD risk factor for risk stratification.	B	Moderate
Risk stratification is based on the NLA Recommendations for the Patient-Centered Management of Dyslipidemia – Part 1[1] with initial risk stratification based on the number of major ASCVD risk factors (with the caveat that the presence of RA may be counted as an additional risk factor), the use of risk prediction tools, such as the ATP III Framingham Risk Score or the ACC/AHA Pooled Cohort Equations if two risk factors are present, and the use of other clinical indicators to help inform clinical judgment, if needed.	B	Moderate
Clinicians should be vigilant in ensuring that RA patients are routinely assessed for cardiovascular risk factors, such as hypertension, dyslipidemia, diabetes, family history of early-onset ASCVD, and smoking. Calculation of lifetime ASCVD risk can be considered for patients age 20-59 years.	B	Moderate
Statins are generally the first-line treatment for dyslipidemia in RA.	A	Moderate
At this time, atherogenic cholesterol treatment goals for patients with RA and other inflammatory diseases are the same as described in the NLA Recommendations for Patient-Centered Management of Dyslipidemia – Part 1.[1]	B	Moderate
If an RA patient has had lipid levels checked during an RA flare, it is recommended that the lipids be re-checked when their disease is controlled.	B	Moderate

Patients with residual risk despite statin and lifestyle therapy

Meta-analyses from RCTs of statin therapy demonstrate that progressively more intensive lowering of LDL-C (and non-HDL-C) is associated with progressively greater risk reduction, which affirms the direct relationship between atherogenic cholesterol lowering and ASCVD event reduction.[738–740] A meta-analysis of 26 RCTs involving

approximately 170,000 patients has also shown a consistent proportional relationship between lowering of LDL-C and the reduction of major vascular events (nonfatal MI, CHD death, stroke, and revascularization).[355] By combining patient-level data from each of these studies, the investigators showed that for every 38.7 mg/dL (1 mmol/L) reduction in LDL-C with statin therapy, major vascular events were reduced by 22% (HR 0.78, 95% CI 0.76–0.80; $P < .001$) after approximately 5 years of statin therapy, compared with placebo or less intensive statin treatment. Reductions in LDL-C of 77.4 and 116.1 mg/dL would be expected to reduce the risk of a major vascular event by 40% (1 − [0.78 x 0.78]) and 53% (1 − [0.78 × 0.78 × 0.78]), respectively. Further support for the relationship between atherogenic cholesterol lowering and ASCVD event reduction is that other therapies that lower blood cholesterol levels through stimulation of LDL receptor activity, independent of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibition, including partial ileal bypass surgery, cholesterol absorption inhibition and bile acid sequestration in the gut by cholestyramine, also improve ASCVD outcomes.[370,383,384,741] Over a period of approximately 5 years, each 1% reduction in LDL-C or non-HDL-C is associated with a reduction of approximately 1% in risk for a CHD event.

The statin therapies currently available to lower blood cholesterol do not eliminate ASCVD events completely, which means that many patients receiving lipid-modifying treatment have residual risk, even if the treatment produces a robust response and the patient is fully adherent. The best average LDL-C reduction (∼50%) with high intensity statin therapy would be associated with ∼50% reduction in CHD events (CHD death and nonfatal MI) or ∼40% reduction in ASCVD events (assuming the individual has a mean untreated LDL-C of 150 mg/dL and achieves a 75 mg/dL reduction). As these estimates are drawn from clinical trials that generally lasted ∼5 years, it is possible that outcomes could be further improved if treatment is continued over decades, or if atherogenic cholesterol concentrations were maintained at even lower levels. Studies of individuals with genetic variants in the PCSK9 gene and polymorphisms in Niemann-Pick C1-like 1 protein that result in lower LDL-C levels throughout life suggest that the ASCVD risk reduction per 1% reduction in atherogenic cholesterol may be greater, with reductions of ∼3% per 1% lower LDL-C concentration over a period of decades.[7,11,742]

There are many clinical situations in which the patient's cholesterol level is not at goal on maximal tolerated statin therapy. In these cases, the NLA Expert Panel consensus is that it is reasonable to consider further atherogenic cholesterol lowering by adding lipid-altering therapy to ongoing statin therapy, as long as the patient has sufficient ASCVD risk to warrant it, and the expected treatment benefit outweighs the risk for adverse consequences. The following are considerations and recommendations of how to make these clinical decisions using the best available information.

Candidates for statin combination atherogenic cholesterol lowering therapy

The following are examples in which more intensive atherogenic cholesterol lowering may be indicated:

(1) High or very high risk patients with a less-than-desirable response to moderate or high intensity statin therapy;[740]
(2) Patients who have recurrent ASCVD events or progressive atherosclerotic vascular symptoms in spite of high intensity statin therapy;
(3) Patients with FH, especially with ASCVD or poorly controlled non-lipid risk factors, and less than optimal non-HDL-C or LDL-C levels;
(4) Patients after acute coronary syndromes on at least moderate intensity statin therapy.

Generally, if a patient in the categories above at high or very high ASCVD risk is not at non-HDL-C and LDL-C goals, strong consideration should be given to statin combination therapy (i.e., therapy with a statin in combination with an additional lipid-altering agent). Clinical ASCVD event benefits of combination therapy were demonstrated in a recent clinical trial of ezetimibe added to statin therapy,[370] and with investigational PCSK9 inhibitors added to statin therapy.[371,372] In these instances the clinician should determine whether statin combination therapies are indicated based on several considerations:

- Re-evaluation of the patient's risk factor status (including family history, smoking, metabolic syndrome criteria) and quantitative risk scoring (if needed);
- Reconsideration of the nature of the patient's history of vascular events;
- Reconsideration of the possible presence of genetic dyslipidemias (FH, as well as such conditions as familial combined hyperlipidemia and polygenic hypercholesterolemia);
- Examination of the affordability of therapy and possible risks associated with polypharmacy;
- Consideration of the patient's preferences.

If further assessment of ASCVD risk is desired in primary prevention situations to make the case for more intensive atherogenic cholesterol lowering, the presence of 1 or more of the following risk indicators may be considered:[1]

(1) CAC: A CAC score ≥300 Agatston units is considered an indication of high risk and should encourage optimal statin intensity and goal attainment.
(2) hs-CRP: An hs-CRP level ≥2.0 mg/L indicates the presence of inflammation, which may be related to atherogenesis and supports more intensive non-HDL-C and LDL-C lowering to recommended goals. There are currently no therapies available that specifically lower hs-CRP, nor is it recommended to follow hs-CRP levels after atherogenic cholesterol-lowering treatment.

(3) Non-HDL-C, apo B, or LDL particle concentration: Discordance may occur between the LDL-C level and 1 or more of these parameters, especially in patients with type 2 diabetes, the metabolic syndrome, or hypertriglyceridemia. If discordance exists, i.e., the non-HDL-C, apo B, or LDL particle concentration is higher than would be anticipated based on the LDL-C level, further lipid-lowering treatment to reach goal levels of non-HDL-C and apo B may be considered. (No specific goals have been recommended for LDL particle concentration.)
(4) Lp(a): Levels of Lp(a) ≥50 mg/dL using an isoform insensitive assay are indicative of increased ASCVD risk. An elevated Lp(a) is a reason to consider more intensive non-HDL-C and LDL-C lowering, since no outcome studies have demonstrated that reducing Lp(a) per se will reduce risk. Treatment options to lower Lp(a) are limited as well.
(5) Ankle brachial index: Peripheral artery disease (i.e., ankle brachial index of <0.90) is one of the strongest risk indicators of ASCVD. The NLA Recommendations for the Patient-Centered Management of Patient-Centered–Part 1 included it as a criterion for classification of ASCVD, and treatment goals in such patients are <100 mg/dL for non-HDL-C and <70 mg/dL for LDL-C.
(6) LDL-C ≥160 mg/dL and/or non-HDL-C ≥190 mg/dL: Presence of either of these in a patient at low or moderate risk may justify a higher level of treatment. Patients with genetic dyslipidemias resulting in elevated atherogenic cholesterol levels are also candidates for intensive lowering of non-HDL-C (and LDL-C), depending on their risk status.
(7) Severe disturbance in a major ASCVD risk factor, such as multipack per day smoking or a strong family history of premature CHD.
(8) CKD: Patients with stage 3B or 4 CKD (estimated glomerular filtration rate 15–45 mL/kg/1.73 m^2) are at high risk and warrant a lower treatment goal.

Based on this new risk assessment, consideration should be given for statin combination therapy if patients are not at their goal non-HDL-C and LDL-C levels, particularly patients whose ASCVD risk is high or very high and who are taking the maximally tolerated statin dosage.

Statin combination therapy for additional LDL-C lowering

Currently, 3 statin combination therapies that lower LDL-C are reasonable to consider: a cholesterol absorption inhibitor (ezetimibe), bile acid sequestrant (cholestyramine, colestipol, colesevelam), or a niacin product (crystalline niacin and extended release niacin) (Table 25).[370,743–752] These agents provide an additive, not synergistic, LDL-C lowering effect of 10–20% when added to statin therapy.

Cholesterol absorption inhibitor

The best tolerated of the 3 therapies is the cholesterol absorption inhibitor, ezetimibe; discontinuation of therapy due to adverse reactions occurs in about 5% of patients. The most common adverse effects are related to gastrointestinal symptoms; increases in liver enzyme tests and creatine phosphokinase levels with muscle symptoms are occasionally encountered.[370,747–750] Ezetimibe is administered in a 10 mg tablet once daily. In IMPROVE-IT, ezetimibe with a statin vs a statin alone was evaluated in 18,144 post-acute coronary syndrome patients (Tables 25 and 26).[370] The investigators of this 7-year outcome study reported that ezetimibe produced an additional 16.7 mg/dL (0.4 mmol/L) decrease in LDL-C (on treatment [1-year] levels of 69.9 and 53.2 mg/dL, respectively) and was associated with a statistically significant 10% reduction in a composite CVD outcome that most closely corresponds with the outcome used in the CTT analysis.[355,370] This degree of risk reduction is similar to the predicted effect based on the assumption that each 38.7 mg/dL (1 mmol/L) lowering of LDL-C will produce a reduction of 22% in ASCVD event risk (16.7 mg/dL ÷ 38.7 mg/dL = 0.4; 0.4 × 22% = 8.8%).

Bile acid sequestrants

These agents are administered as powders dissolved in water or other fluids (all 3 commercially available forms), or as tablets (colesevelam). The most common side effects reported with these agents are gastrointestinal, including constipation and bloating. Colesevelam appears to be better tolerated than the other agents and causes gastrointestinal adverse effects relatively infrequently (i.e., in <10% of patients).[745,746] The usual dosage is 8 to 16 g/day in divided doses for cholestyramine and colestipol, and 3.75 g/day for colesevelam (as powder or tablets). These agents reduce LDL-C by an additional 15–20% when added to a statin. Cholestyramine has been shown to reduce CHD events by 19% when used as monotherapy in 3806 adults without heart disease and an LDL-C concentration of ≥190 mg/dL over a 7.4 year observation period (Tables 25 and 26).[383,384,743,744] No outcomes data are available for bile acid sequestrant therapy use in combination with a statin or other lipid-altering agent. It should be noted that bile acid sequestrants can worsen TG levels, especially if the baseline is ≥200 mg/dL, and therefore should mainly be used to reduce LDL-C in patients with TG <200 mg/dL.

Niacin

Niacin products are difficult to tolerate due to a flushing side effect that requires the drug to be initiated with low dosages and slowly titrated up to a therapeutic dosage over weeks, as tolerated. The flushing is not harmful, but is bothersome. Extended release preparations reduce flushing symptoms, improve tolerability and have been used successfully by experienced lipidologists as statin combination therapies. Niacin reduces LDL-C by 8–14% when added to a statin and also reduces TG and increases HDL-C levels (Table 25).[751,752] Niacin has been frequently used for treating patients who have atherogenic dyslipidemia consisting of a high TG level (i.e., ≥200 mg/dL) and a

Table 25 Percentage reduction in LDL-C with statin alone and in combination

Study	Statin therapy	Combination drug	LDL-C reduction with statin alone (%)	LDL-C reduction with combination therapy (%)	LDL-C lowering attributed to the added drug (%)
Bile acid sequestrants plus statin combination therapy					
Ytre-Arne et al[743]	Simvastatin, 40 mg/d	Cholestyramine, 12 g bid	−40	−57	−18
Jacob et al[744]	Lovastatin, 80 mg/d	Cholestyramine, 8 g/d	−28	−40	−18
	Pravastatin, 40 mg/d	Cholestyramine, 8 g/d	−30	−39	−9
Knapp et al[745]	Simvastatin, 10 mg/d	Colesevelam, 3.8 g/d	−28	−42	−18
Hunninghake et al[746]	Atorvastatin, 10 mg/d	Colesevelam, 3.8 g/d	−38	−48	−10
Ezetimibe plus statin combination therapy					
Davidson et al[747]	Simvastatin various doses	Ezetimibe, 10 mg/d	−36	−50	−14
Ballantyne et al[748]	Atorvastatin various doses	Ezetimibe, 10 mg/d	−42	−54	−12
Gagne et al[749]	Various statins at various doses	Ezetimibe, 10 mg/d	−4	−25	−21
Gagne et al[750]	Simvastatin or atorvastatin with dose increased from 40 mg to 80 mg/d	Ezetimibe, 10 mg/d	−7	−27	−20
Cannon[370]	Simvastatin, 40 mg/d	Ezetimibe, 10 mg/d	−25	−44	−19
Niacin plus statin combination therapy					
Vacek et al[751]	Lovastatin, 20 mg/d	Niacin SR, 1200 mg/d	−23	−35	−12
Advicor Prescribing	Lovastatin, 20 mg/d	Niacin ER, 1000 mg/d	−24	−31	−7
Information[752]	Lovastatin, 40 mg/d	Niacin ER, 1000 mg/d	−29	−37	−8
	Lovastatin, 40 mg/d	Niacin ER, 2000 mg/d	−29	−43	−14

ER, extended release; LDL-C, low-density lipoprotein cholesterol; SR, sustained release.

low HDL-C level (i.e., <40 mg/dL), particularly if accompanied by an elevated level of non-HDL-C. Crystalline niacin has been shown to significantly reduce CHD events by 17% when used as monotherapy at a dosage of 3 g/day for 6 years in a high risk, male population (Table 26).[386,753] More recently, extended release niacin was tested as a statin combination therapy in 2 studies (AIM-HIGH and HPS2-THRIVE), and did not significantly reduce ASCVD events compared to statin monotherapy in very high risk patients.[388,389,755] However, in both of these studies, niacin was administered to patients with low average levels of atherogenic cholesterol during statin treatment, and therefore did not adequately test the potential benefits of administering statin plus niacin therapy to individuals in need of additional lipid lowering to achieve atherogenic cholesterol goals. It is important to consider the balance of risk to benefit with niacin added to statins since there were higher incidence rates for infections and gastrointestinal bleeds with niacin in the HPS2-THRIVE trial. *Post hoc* analyses of the AIM-HIGH study showed that the subgroup of subjects with both TG ≥200 mg/dL and HDL-C <32 mg/dL had a significant event reduction, suggesting that niacin might have benefit in a targeted population, such as those patients with residual high non-HDL-C plus concomitant low HDL-C.[755] An analysis from the HPS2-THRIVE study found that niacin (with laropiprant) was associated with a nominally statistically significant benefit in the subgroup of patients with higher baseline LDL-C levels (top tertile ≥77 mg/dL) and in the subgroup with higher baseline apo B levels (top tertile ≥70 mg/dL).[389]

Based on this information, the NLA recommends that statin combination therapies be considered for at-risk patients not at non-HDL-C and/or LDL-C goals while receiving maximally tolerated statin therapy. Furthermore, the NLA recommends that the following statin combination therapies be considered in the indicated order:

1. Ezetimibe 10 mg every day: Ezetimibe is recommended as a first-line statin combination therapy since it has been shown to reduce ASCVD events when added to a statin in a controlled clinical trial and because it has an important atherogenic cholesterol-lowering efficacy.
2. Colesevelam 625 mg 3 tablets twice a day (or 3.75 g powder form every day or in divided doses): This therapy is recommended as a second-line statin combination therapy because the drug class has been shown to reduce ASCVD events when used alone, it is better tolerated than the other resins, and it has an important atherogenic cholesterol-lowering efficacy.
3. Extended release niacin titrated to a maximum of 2000 mg, daily: Niacin in this dosage form is recommended as a third-line statin combination therapy for atherogenic cholesterol lowering because it has demonstrated lower ASCVD events when used alone, and may have benefit when given with a statin to patients with LDL-C or non-HDL-C not at goal. However, it provides

Table 26 Outcome trials with statin combination therapies

Study	Design	Patients	Treatment	Baseline LDL-C, beginning; end	LDL-C change (%)	Change in end point	Comment
Bile acid sequestrants							
LRC Coronary Primary Prevention Trial[383,384]	R, DB, PC, 7.4 y f/u	3806 adults without CHD and LDL-C >190 mg/dL	Cholestyramine 24 g/d	205 mg/dL; 159 mg/dL	−12.6	−19% in CHD[†]	−7% total mortality; −21% CVA
Ezetimibe							
IMPROVE-IT[370]	R, DB, simvastatin controlled, 7 y f/u	18,144 adults within 10 d of acute coronary syndrome	Simvastatin 40 mg/d vs simvastatin 40 mg/d + ezetimibe 10 mg/d	95 mg/dL; 69.5 mg/dL on statin vs 53.7 mg/dL on combo	−25 vs −44	−34.7% with statin vs −32.7% with combo in composite end point[‡]	−13% MI (P = .002); −21% Isch CVA (P = .008); −10% CV death, MI, CVA (P = .003)
Niacin							
Coronary Drug Project[386,753]	R, DB, PC 6 y f/u	3908 males with MI	Niacin, 3.0 g/d	NA	NA	−17% CHD[†] (P = .005); −29% MI (P = .005)	15 y f/u; −11% (P = .0004)
HATS[387] (The HDL Atherosclerosis Treatment Study)	R, DB, PC; 3 y f/u	160 men and women with CHD (MI, angina, coronary intervention) plus coronary stenosis of ≥30% and low HDL-C (<30 mg/dL males, <40 mg/dL females)	SR niacin up to 1000 mg bid or crystalline niacin up to 4 g/d to achieve defined HDL-C increase vs niacin 50 mg bid as control; stable background simvastatin	132 mg/dL; 75 mg/dL	−43	−70% of composite end point[§]	
FATS[754] Familial Atherosclerosis Treatment Study	R, DB, PC, 2.5 y f/u	146 males documented angiographic coronary artery disease, apo B >125 mg/dL	Lovastatin 20 mg bid + colestipol 10 g tid OR niacin 1 g qid + colestipol 10 g tid OR placebo for both therapies (colestipol was given for patients with LDL-C >90th percentile	189 mg/dL; 107 mg/dL L-C; 130 mg/dL N-C; 163 placebo	−7; −46; −32	−73% reduction in composite end point[¶] compared with placebo (HR, 0.73; 95% CI, 23%–90%; P = .001)	Angiographic studies before and after revealed coronary lesion progression in 21% of L-C pts, 25% of N-C pts, and 46% of placebo pts

AIM HIGH[388,755]	R, DB, PC, 3 y f/u	3414 with CVD	ER niacin 1500–2000 mg/d vs placebo added to simvastatin 40 mg or 80 mg/d and/or ezetimibe 10 mg/d	74 mg/dL; 65 mg/dL	−14	End point* not different (P = .80)	−36% end point in pts with TG >200 mg/dL and HDL-C <32 mg/dL (P = .032)
HPS2-THRIVE[389]	R, DB, PC, 3.9 y f/u	25,673 patients with occlusive arterial disease	ER niacin 2 g/d + laropiprant 40 mg/d vs placebo added to a stable background of statin therapy	63 mg/dL; 53 mg/dL	−16	−4% of primary end point‖ (P = .29)	−10% arterial revascularization; no difference in components of primary end point. Trend (P = .02) for subgroup with higher LDL-C levels
PCSK9 Inhibitors							
ODYSSEY LONG TERM[371]	R, DB, PC, 78 wk f/u	2341 men and women at high risk for CVD and with LDL-C ≥70 mg/dL and receiving statins at maximum tolerated dose with or without other lipid-lowering therapy	Alirocumab 150 mg or placebo as 1-mL subcutaneous injection every 2 wk	123 mg/dL; 48 mg/dL	61	HR, 0.52; 95% CI, 0.31–0.90 (P = .02)	
OSLER (2 trials)[372]	R, open-label, 11.1 mo f/u	4465 men and women who had previously participated in 12 shorter term parent trials of evolocumab	Evolocumab 140 mg every 2 wk or 420 mg monthly plus standard therapy vs standard therapy alone	120 mg/dL; 48 mg/dL	61	HR, 0.47; 95% CI, 0.28–0.78 (P = .003)	

ACS, acute coronary syndrome; CHD, coronary heart disease; CI, confidence interval; CVA, cerebrovascular accident; CVD, cardiovascular disease; DB, double-blind; ER, extended release; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; L-C, lovastatin + colestipol; MI, myocardial infarction; NA, not applicable; N-C = niacin + colestipol; PC, placebo controlled; PCSK9, proprotein convertase subtilisin/kexin type 9; pt, patient; R, randomized; SR, sustained release; TG, triglyceride; UA, unstable angina.

*First event of CHD death, MI, ischemic stroke, ACS hospitalization, coronary, or cerebral revascularization.

†CHD death or nonfatal MI.

‡CV death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 d), or stroke.

§CV death, MI, revascularization, hospitalized for UA.

‖First vascular event of CHD death, MI, stroke, or revascularization.

¶Death, MI, ischemic symptoms requiring revascularization.

only modest LDL-C lowering efficacy, and use of niacin in combination with a statin is not recommended for patients whose LDL-C is <70 mg/dL, based on RCT evidence for no benefit and possible harm in this group.

Special cases for statin combination and other combination therapies

In addition to further lowering atherogenic cholesterol in a patient not at treatment goal, other clinical situations can occur that require consideration of additional statin combination therapies. These include:

(1) Patients who require multiple LDL-C-lowering therapies (e.g., the patient who is intolerant to statin therapy or the FH patient who is unable to achieve optimal non-HDL-C and LDL-C levels with a high intensity statin and 1 other therapy): In these cases, combining statin and therapies with different mechanisms of action and in the order above is recommended, with careful consideration of the added cost and the potential for issues related to polypharmacy.

(2) Patients who have atherogenic dyslipidemia in which there are elevations in TG and VLDL-C (VLDL-C correlates closely with the TG level) plus low HDL-C (e.g., the patient with diabetes or metabolic syndrome, often with elevated non-HDL-C): These patients may benefit from evaluation of apo B or LDL particle concentration measurement because discordance may be present. Treatment options include additional atherogenic cholesterol lowering with statin combination therapies as described above, and/or other statin combination therapies that mainly lower TG and VLDL-C, such as fibrates and/or omega-3 fatty acids (prescription omega-3 fatty acids are currently only indicated for patients with TG ≥500 mg/dL). As stated previously, colesevelam may worsen TG, especially in those with levels ≥200 mg/dL at baseline, but it should also be noted that it might improve glucose control in patients with type 2 diabetes. Niacin may be used in patients with stable type 2 diabetes for lipid management, but monitoring of glucose control is advised.

Fibrate drugs

Of the currently available fibrates, gemfibrozil has been shown to reduce ASCVD events as monotherapy in primary prevention high risk males with elevated non-HDL-C[390] and for secondary prevention in males with below average HDL-C.[756] This class of drugs can reduce TG and non-HDL-C in patients with mixed dyslipidemia, and is considered a first-line choice for patients with severe hypertriglyceridemia (TG ≥500 mg/dL). The only outcomes trial of a fibrate (fenofibrate) added to a statin was the ACCORD Lipid study, which failed to demonstrate a benefit in the full study sample on ASCVD events compared to statin monotherapy in type 2 diabetes patients.[394] A predefined patient subgroup in this trial included those with TG in the top tertile (≥204 mg/dL) and HDL-C in the bottom tertile (≤34 mg/dL); these patients had a significantly lower ASCVD event rate with fenofibrate compared to placebo (−29%). Because of a drug-drug interaction with most statins that increases the risk for myositis, gemfibrozil should not be used with statins. Fenofibrate and fenofibric acid have not been found to have this adverse event when combined with statins. Fenofibrate has also been shown to reduce the progression of diabetic retinopathy and nephropathy, independent of ASCVD outcomes,[394,757] and has not been associated with incident diabetes. Fibrates should not be used in patients with stage 3B CKD or worse. Based on the limited available outcomes data, the main clinical situation in which fenofibrate or fenofibric acid could be considered as a statin combination therapy would be in type 2 diabetes patients with a non-HDL-C not at goal, who also have retinopathy and/or microalbuminuria, and do not have stage 3B or worse CKD.[757,758]

Omega-3 fatty acid preparations (EPA only or EPA + DHA)

These agents are effective for reducing TG, and are indicated for patients with very high TG (≥500 mg/dL). One outcomes trial, JELIS,[134] did show a significant reduction in ASCVD events (19% reduction) in 18,645 high risk Japanese patients who were treated with statins and were randomized to receive 1.8 g/day EPA or statin without EPA (placebo treatments are not allowed in Japan). The greatest benefit was found in those patients with TG ≥150 mg/dL and HDL-C <40 mg/dL. Until specific outcomes trials with this class of statin combination therapy in patients with elevated non-HDL-C levels are completed (the REDUCE IT[166] and STRENGTH studies[167] are ongoing), the NLA Expert Panel will not provide specific recommendations for their routine use except in patients with TG ≥ 500 mg/dL.

A new class for statin combination therapy: PCSK9 inhibitors

Monoclonal antibodies that inhibit PCSK9 (alirocumab and evolocumab) comprise a new class of statin combination therapy and have been approved by the FDA for use in addition to diet and maximally tolerated statin therapy in adults with heterozygous FH or with clinical ASCVD who require additional lowering of LDL-C. Two large, RCTs of PCSK9 inhibitors, including the Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) and the Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG TERM), study have demonstrated their effectiveness for reducing LDL-C and non-HDL-C levels by ~60% among patients at high cardiovascular risk and receiving maximum tolerated dosages of statins[371] and among patients at various degrees of cardiovascular risk receiving standard therapy.[372] Both these studies provided data over approximately 1 year. Both drugs lower Lp(a) by

~25%. Most adverse events occurred with similar frequency between PCSK9 and control groups, although neurocognitive events, injection-site reactions, myalgia, and ophthalmologic events were reported more frequently with PCSK9 inhibitors.[371,372] In a *post-hoc* analysis of the ODYSSEY LONG TERM trial, the rate of major adverse cardiovascular events was lower with the PCSK9 inhibitor than with placebo (HR 0.52; 95% CI 0.31–0.90; $P = .02$). A similar effect was reported by the OSLER investigators (HR 0.47; 95% CI 0.28–0.78, $P = .003$). Long term cardiovascular outcomes trials with both drugs, added to optimal statin therapy in very high risk patients, are ongoing (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab SAR 236553 [REGN727] and Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk).[759,760]

The PCSK9 inhibitor class has been approved by the FDA for use as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous FH, or clinical ASCVD, who require additional lowering of LDL-C. Cardiovascular outcomes trials with the PCSK9 inhibitors alirocumab and evolocumab are underway in ASCVD patients who are on maximally-tolerated statin therapy with LDL-C of 70–99 mg/dL. Until the results of those trials are available, a conservative approach would be to use PCSK9 inhibitors primarily in: 1) patients with ASCVD who have LDL-C ≥100 mg/dL (non-HDL-C ≥130 mg/dL) while on maximally-tolerated statin (±ezetimibe) therapy; and 2) heterozygous FH patients without ASCVD who have LDL-C ≥130 mg/dL (non-HDL-C ≥160 mg/dL) while on maximally-tolerated statin (±ezetimibe) therapy. The risks of this new class appear low based on the data available from the clinical development programs,[371,372] and the additional LDL-C reduction of ~60% when added to statin therapy will allow many patients to achieve goal LDL-C levels.

Finally, PCSK9 inhibitor use may be considered for selected high risk patients with ASCVD (e.g., recurrent ASCVD events) who have atherogenic cholesterol levels below the specified values listed, but above their treatment goals (i.e., LDL-C ≥70 mg/dL [non-HDL-C ≥100 mg/dL]). PCSK9 inhibitors may also be considered in selected high or very high risk patients who meet the definition of statin intolerance, as previously defined by the NLA Statin Expert Panel,[761] and who require substantial

Chart 13 Recommendations for patients with residual risk despite statin and lifestyle therapy

Recommendations	Strength	Quality
Fibrates and prescription omega-3 fatty acids are first-line drug choices for patients with TG ≥500 mg/dL, although consideration may be given to using statin therapy as a first-line drug in patients with TG 500-999 without a history of pancreatitis.	E	Moderate
In patients with elevated TG (200 to 499 mg/dL) on maximum tolerated statin therapy who are at their LDL-C goal but not their non–HDL-C goal, the addition of therapies that primarily lower TG and VLDL-C (fibrates, high-dose omega-3 fatty acids) may be considered to help achieve atherogenic cholesterol goals. Subgroup analyses from cardiovascular outcomes studies provide suggestive evidence of reduced ASCVD event risk with the addition of a TG-lowering agent to statin therapy, particularly in patients with the combination of elevated TG and low HDL-C.	B	Moderate
For patients not at goal levels for atherogenic cholesterol on maximally tolerated statin therapy, consideration should be given to adding non-statin lipid-altering therapy to ongoing statin therapy for further lowering of atherogenic cholesterol, as long as the patient has sufficient ASCVD risk to warrant it, and the expected treatment benefit outweighs the risk for adverse consequences.	B	Moderate
Recommended statin combination therapies to consider for further lowering of atherogenic cholesterol are, in the following order: first – ezetimibe 10 mg every day, second – colesevelam 625 mg 3 tablets twice a day (or 3.75 g powder form every day or in divided doses), and third – extended release niacin titrated to a maximum of 2000 mg, daily.	B	Moderate
Until cardiovascular outcomes trials are completed with PCSK9 inhibitors, these drugs should be considered primarily in: 1) patients with ASCVD who have LDL-C ≥100 mg/dL (non-HDL-C ≥130 mg/dL) while on maximally-tolerated statin (±ezetimibe) therapy; and 2) heterozygous FH patients without ASCVD who have LDL-C ≥130 mg/dL (non-HDL-C ≥160 mg/dL) while on maximally-tolerated statin (±ezetimibe) therapy.	B	Moderate
In addition, PCSK9 inhibitor use may be considered for selected high risk patients with ASCVD (e.g., recurrent ASCVD events) who have atherogenic cholesterol levels below the specified values, but above their treatment goals (i.e., LDL-C ≥70 mg/dL [non-HDL-C ≥100 mg/dL]). Such use would be based on clinical judgment, weighing the potential benefits relative to the ASCVD event risk and the risks and costs of therapy.	C	Low
PCSK9 inhibitor use may also be considered in selected high or very high risk patients who meet the definition of statin intolerance (as previously defined by the NLA Statin Expert Panel) and who require substantial additional atherogenic cholesterol lowering, despite the use of other lipid lowering therapies. Such use would be based on clinical judgment, weighing the potential benefits relative to the ASCVD event risk and the risks and costs of therapy.	C	Low

additional atherogenic cholesterol lowering, despite the use of other lipid lowering therapies. Such use for these selected cases would be based on clinical judgment, weighing the potential benefits relative to the ASCVD event risk and the risks and costs of therapy. In patients for whom the clinician is uncertain about the relationship of a statin with new or worsened muscle symptoms, the use of a statin myalgia clinical index score[334] may be helpful, but none have been validated.

See Chart 13 for Recommendations for Patients with Residual Risk Despite Statin and Lifestyle Therapy.

Improving patient outcomes

Patient adherence

Definition of adherence

In 2003, the World Health Organization defined adherence as the extent to which a person's behaviors, such as taking medication, following a diet, or making healthy lifestyle changes, corresponds with agreed upon recommendations from a healthcare provider.[762] Specifically, medication adherence refers to the patient's conformance with the provider's recommendation with respect to timing, dosage, and frequency of medication-taking for the prescribed length of time.[763,764] Adherence is not a single construct, but rather is a cluster of behaviors simultaneously effected by patient-, provider-, and healthcare system-related factors.[764,765] Poor adherence to medication may occur in the form of irregular or interrupted intake, and by lack of persistence. Persistence refers to the duration of time the patient takes the medication, from initiation to discontinuation of therapy.[763,764]

Prevalence and costs of non-adherence

Medication non-adherence is thought to account for 30–50% of treatment failures and a variety of adverse medical treatment outcomes, including increased hospitalization rates and institutionalization for the frail elderly as well as increased healthcare costs.[766] Bosworth et al.[767] reported that only half of the 3.2 billion annual prescriptions in the United States are taken as prescribed. Poor medication adherence or non-adherence is estimated to result in 33–69% of medication-related hospital admissions, and as many as 125,000 deaths per year in the United States.[767,768]

Much of non-adherence is found among patients with chronic diseases, such as hypertension, hyperlipidemia, diabetes, and asthma.[769] By the year 2020, the number of Americans affected by at least 1 chronic condition that will require medication therapy is expected to grow to 157 million. Patients with chronic conditions adhere only to 50–60% of medications as prescribed,[767] and rates of medication adherence to therapies for chronic conditions often drop after the first 6 months of therapy.[770]

Medication non-adherence ultimately costs an average of $2000 per patient in clinician visits annually, while the direct cost of non-adherence to the US healthcare system is estimated at $105.8 billion annually.[771,772] A substantial proportion of these costs may be preventable with the use of strategies targeting improved medication adherence. Moreover, research findings suggest that improved self-management of chronic diseases results in an approximate cost-to-savings ratio of 1:10.[768,773]

Adherence to lipid-altering medications

Medication non-adherence is particularly troublesome with cholesterol-lowering medications. Approximately 25–50% of patients discontinue statins within 1 year of treatment initiation, and persistence of use further decreases over time.[774,775] Results from studies have been mixed, but some have found that predictors of statin non-adherence include younger patient age, female sex, lower income, and non-Caucasian race.[536,776,777] Adherence to statins is improved when patients have a history of CVD and have multiple risk factors.[777,778]

Chi and colleagues[779] recently reported the results from a cross-sectional study of 67,100 CHD patients at Kaiser Permanente Southern California who were dispensed 2 or more statin prescriptions between May 2009 and May 2010. The purpose of this study was to determine the relationship between LDL-C goal attainment and adherence to statin medications. The medication possession ratio (ratio of sum of the days of supply divided by the total number of days between first and last dispensation dates, obtained through the pharmacy) was calculated to estimate adherence, and a ratio $\geq$80% was considered to represent adherence. LDL-C levels $<$100 mg/dL and $<$70 mg/dL were observed in 85.8% and 79.8% of patients, respectively. Almost 80% of patients were adherent to their statin medication. In this cohort of patients, LDL-C goal attainment was positively associated with statin adherence, male sex, Asian/Hispanic ethnicity, taking a larger number of prescriptions, having multiple comorbidities, and having hypertension.[780]

Factors associated with medication adherence

It is important to consider that adherence to medications relates to medication-taking behaviors that are influenced by the patient's beliefs about the medications, and by their trust in the provider who is prescribing the medications. Many providers are unaware that some of their patients have strong feelings about "chemical" medications vs natural therapies, the potential for side effects or interactions with other medications, and the relative efficacy of generic (vs brand name) medications. Table 27 is a list of the prevalence of self-reported reasons for primary non-adherence among patients with a newly prescribed statin medication.[780]

The provider-patient relationship and communication issues must be considered when addressing medication non-adherence. These provider-patient issues are often related

Table 27 Self-reported reasons for primary nonadherence from a telephone survey of patients with no record of redeeming a new statin medication among Kaiser Permanente Southern California members

Did not pick up cholesterol medication due to/because...	%Yes (n)
General concerns about medication	63.0 (46)
Decided to try lifestyle modification	63.0 (46)
Fear of side effects	53.4 (39)
Did not think medication was needed	38.9 (28)
Did not believe condition was life threatening	34.7 (25)
Fear of drug interactions	16.4 (12)
Already took too many medications and did not want to take any more	16.4 (12)
Financial hardship	12.3 (9)
Did not understand why provider prescribed medication	11.0 (8)
Did not understand purpose of medication	8.2 (6)
Did not think medication would be effective for condition	6.9 (5)
Inconvenient dosing regimen	4.1 (3)
Change in health insurance/drug benefit	2.7 (2)

Taken from Harrison TN, et al. *Am J Managed Care*. 2013;19: e133-e139.[780] Permission to reprint was obtained.

to a perceived lack of communication with the provider, a suboptimal provider-patient relationship, issues with care transitions between hospital and home, depression and cognitive impairment, and a low level of health literacy, which is found in approximately 90 million US adults.[781–783] Health literacy was defined in Healthy People 2010[783] as "the degree to which individuals have the capacity to obtain, process and understand basic health information and services needed to make appropriate health decisions." From a large survey administered in person to patients at 4 Veterans Administration medical centers, Chew et al.[782] reported answers to questions such as: "How confident are you filling out forms by yourself?"; "How often do you have someone help you read hospital materials?"; and "How often do you have problems learning about your medical condition because of difficulty reading hospital materials?" By their responses to these questions, 32.9% of patients were determined to have inadequate health literacy, 16.9% needed help reading medical material, 17.1% had problems learning about their medical condition, and 29.6% were not confident completing health forms alone.

It is important to consider the sequelae of inadequate health literacy, including increased annual health care costs for those with low literacy skills, which has been shown to be 4 times higher when compared to those with higher literacy skills.[784] Patients with low health literacy and chronic diseases have less knowledge of their disease and treatment, and fewer self-management skills than literate patients. Studies have further revealed that patients with low literacy skills have a 50% increased risk of hospitalization, compared with patients who have adequate literacy skills.[772,780]

Patients are often self-conscious and feel shame from their lack of understanding, which prevents them from seeking help and asking questions for clarification. Health care professionals need to be alert for clues of low health literacy from patient behaviors such as seeking help only when their illness is advanced, making excuses, becoming angry/demanding or quiet/passive, failing to complete intake forms, having difficulty explaining concerns or failing to ask questions, and frequently missing appointments or tests. Other indicators of a health literacy problem, suggesting that patients may not be able to read/understand a medication bottle, include statements, such as "I forgot my glasses" or "I'll bring this home so I can discuss it with my family".[772]

Lack of provider empathy, and failure to provide positive reinforcement to the patient have also been identified as contributors to inadequate adherence. Researchers report that approximately 70–90% of opportunities for a health care provider to express empathy to a patient are missed.[764,772,785,786] Patients often do not realize that there may not be an immediate benefit of therapy, which leads to their being frustrated and not adhering to, or failing to persist in taking their medication.[762,764,772] Providers must attempt to understand the patients' concerns and beliefs about their problems, which may not be in concert with the providers' understanding.

Medication cost/insurance coverage is traditionally thought to be a central limiting factor for medication adherence among those with low socioeconomic status.[787,788] Therefore, it is not surprising that reducing out-of-pocket costs has been shown to lead to both improved medication adherence and improved outcomes, without increasing total health care costs. These findings have important policy implications, suggesting that chronic disease pharmaceuticals are cost-effective for insurers.[764,772] Although cost is a major consideration, other contributors also play roles, including side effects (or fear of side effects), having a complex medication regimen, forgetfulness or inability to track medications, and a belief by the patient that the medication does not work or that he/she does not need it.[772,788] Queries about these issues will help the provider to identify and understand reasons for inadequate medication adherence, which may allow the development of tailored interventions that more specifically address the specific factors described by the patient.

In a nested case-control study, Kesselheim et al.[789] determined the implications of changing the generic pill appearance of medications for patients after an MI. Given that generic prescription drugs made by different manufacturers may vary in color or shape, the purpose was to determine whether use of generic drugs among post-MI patients was associated with inconsistent appearance of their medications. Cases had discontinued their index drug for at least 1 month while controls continued treatment. Controls and cases were matched for therapeutic class, number of dispensings before non-persistence, age, and sex. Results demonstrated that 29% of patients

(3286 of 11,513) had a change in pill shape or color. Statins had the most changes in appearance. The odds of non-persistence in case patients increased by 34% after a change in pill color and 66% after a change in pill shape.[789] These findings suggest that a change in medication appearance is a risk factor for non-adherence. Additional research is warranted to investigate strategies for minimizing the effects of changes in medication appearance on subsequent patient adherence.

Statin intolerance and non-adherence

In a cross-sectional, self-administered Internet-based survey of 10,138 US adult statin users conducted from September to October, 2011,[788] factors associated with adherence and reasons for switching medication or discontinuation were identified. Among the survey participants, 82.5% were current statin users who adhered to their prescribed statins (defined as taking at least 80% of their current prescribed statin dose in the past month) and 12% were former statin users (i.e., discontinuers). Of the former statin users, 60% cited muscle aches as the primary reason for discontinuation, followed by cost (16%) and perceived lack of efficacy (13%). Discontinuers expressed that they were less satisfied with their physician's explanation of cholesterol treatment, were more likely to research statins on the Internet, and were less likely to monitor cholesterol levels. Individuals who changed statins in the past, but were then adherent to their new statin, reported reasons for switching as muscle side effects (33%) and cost (32%). Results of the survey identified that lower income, muscle pain as a side effect, and taking other concurrent medications for CVD were predictors of statin non-adherence. Investigators concluded that better health care provider communication about the importance of statins and potential adverse effects is necessary for improved adherence and patient outcomes.

The NLA recently published assessments from an Expert Panel on Statin Safety regarding statin intolerance,[761] and issues of statin-related muscle complaints,[334] liver enzyme elevations,[790] cognitive complaints,[466] and diabetes risk.[336] Statin intolerance was defined by the panel 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 sleep, work/housework, or leisure-time activity), leading to a decision to stop or reduce statin therapy.[761] Myalgia, defined as muscle aches, soreness, stiffness or tenderness, with or without an abnormal creatine kinase level, is the most frequently reported side effect of statin use. Myalgia reports generally range from 1–5% of individuals among patients taking statins in controlled clinical trials to 11–29% in observational studies.[334]

The NLA Statin Safety Panel stated that patients should be told that if they feel that they have experienced a side effect (usually muscle aches) while taking a statin, whether to continue taking the statin is their decision, but it is best guided by advice from their health care provider.[761] Patients should be advised that before stopping a statin due to possible side effects, they should first speak to their health care provider. Even if statin intolerance is confirmed, in most cases the clinician and patient should attempt to maintain statin treatment in some form to reduce the patient's CVD event risk. Options for continuing statin therapy include a lower daily dosage of the same statin (which may still result in a clinically meaningful reduction in atherogenic cholesterol), less than daily dosages of the same statin (optimally with a long-acting statin, such as rosuvastatin or atorvastatin), or use of an alternative statin in daily or less than daily dosages. Patients who are initially intolerant to 1 statin can often tolerate a different statin. The highest tolerated dose of statin should be targeted, regardless of whether it will allow the patient to achieve the atherogenic cholesterol goal, because even modest cholesterol reductions will improve long-term cardiovascular outcomes. Other non-statin lipid-lowering drugs are options for patients with statin intolerance, with or without concomitant statin therapy, but with consideration of their potential for side effects, which may also lead to reduced adherence (e.g., flushing with niacin).

Strategies to improve medication adherence

Technology is helping with the collection of adherence information and bringing it to the desktop of the provider.[791] This information might come from the refill data in the electronic health record, the pharmacy, or the insurance carrier that is monitoring prescription claims. Advanced health systems frequently also have decision support tools including information on formularies and out-of-pocket costs to the patient that may inform the selection and prescribing of cardiovascular medications.[772]

Although patient self-report about medication adherence may suffer from social desirability bias, providers should ask the patient about adherence to lipid-lowering therapy if suboptimal adherence is suspected, such as when the response to therapy is poor. For example, the provider may ask, "In the last 2 weeks, you should have taken 14 doses of your statin medication. How many doses do you think you have taken?" As an alternative, a more formal strategy to measure self-reported medication-taking behavior may be used including an updated Morisky Medication Adherence Scale, now with an 8-item scale that was developed for use in patients taking antihypertension medications.[792,793] Use of a visual analog scale to measure patient adherence might also allow the provider to more accurately identify non-adherent patients.[772] If medication adherence is less than optimal, the provider can pursue the reasons for non-adherence and address barriers.

In very busy primary care or specialty practices, it may be difficult to find adequate time to review and value this apparent "flood" of information. New office designs or strategies are necessary to create a workflow that utilizes office staff to the fullest extent possible in collecting and

addressing adherence information, and that does not slow down the provider or practice. In the ideal Patient Centered Medical Home model, there are multiple providers and staff, including nurses and pharmacists that might help with these patients. Optimal strategies for practices will vary widely based on the type of patients treated and the staff available. Training staff in communication and redesigning roles and workflow to facilitate more provider and staff time with patients (e.g., face to face, phone, email, text, messaging via electronic record) will likely be beneficial for increasing adherence.[764,791,794]

In the era of the Patient Centered Medical Home, patient-determined goals and action steps are critical to positive outcomes. The goal is to help generate ideas (self-determined goals) to assist with medication adherence challenges. Open-ended questions such as "Tell me more about the trouble you are having?" or "What has helped in the past?" can be used. The providers need to work with patients to create realistic and actionable steps. Other questions such as "What do you want to do to address the problem?" or "When will you be ready to begin to make changes that will lead to increased adherence?" are also useful. A follow-through question is "May I call you next week to see how this is going?"

The role of health care providers begins with identifying the patient's problem, assessing the patient's level of understanding, and then providing necessary education including verbal explanations and written materials. The provider should emphasize that the patient is a partner in decision-making about the treatment regimen. When discussing therapeutic options, the provider will need to specifically relate the reason for prescribing medication to the patient's condition. For example, in a patient who is post-MI, the need for a high-intensity statin is paramount and has been shown to reduce subsequent cardiovascular events and mortality.[738,795] The provider will need to explain this to the patient in terms he/she will fully understand.

It is important to discuss the potential side effects of prescribed atherogenic cholesterol-lowering therapies, including statin therapy, with all patients, because they have usually heard or read about the side effects, and may be worried about taking certain medications based on rumor or misinformation. Items to discuss with the patient prescribed statins include the potential for muscle aches, as described previously.[334] The provider should specifically describe how the muscle ache might feel on statins. Also, the health care provider should reinforce that the provider/office staff needs to be contacted if the patient believes he/she is experiencing an adverse effect. Patients should be assured that safety labs are checked when the lipid panel is checked. The provider should also explain that although statins are 1 "class" of drugs, statins individually are very different drugs from one another—a problem with 1 does not usually mean that all statins need to be avoided.[334,761]

Shared decision-making is integral to the provider-patient encounter.[1,3,796] A statin prescription should not be an automatic recommendation for a patient with elevated cholesterol.[1,3] It is critically important to engage the patient in a discussion, review benefit vs risk of statin therapy, discuss all treatment options, and consider patient preferences as described in the NLA's Recommendations for the Patient-centered Management of Dyslipidemia–Part 1.[1]

Providers need to understand and be committed to the concept that communication is the key to preventing or overcoming medication adherence-related challenges. More conversation with the patient and repetition in the discussion can lead to enhanced adherence. The mnemonic "SIMPLE", described below, affords effective interventions to reduce medication non-adherence.[768]

S—Simplify the regimen

Providers should consider adjusting or simplifying the medication regimen when possible.[797] This can be accomplished by adjusting timing, frequency, amount, and dosage of medications. Once per day is always preferred, when feasible, as well as matching the regimen to the patient's activities of daily living, and recommending that all medications be taken at the same time of day if there are no interaction or food absorption issues. Whenever possible, the provider should avoid prescribing medications with special requirements such as those that need to avoid mealtime dosing.[798] Encouraging use of adherence aids such as pill organizers or alarms can also be useful.[762,764,772,799]

I—Impart knowledge

Providers should focus on provider-patient shared decision-making, discussing more within the health care team, involving the patient's family and caregivers in discussions, if appropriate, providing advice on how to cope with medication costs, and preparing clear written and verbal instructions for all prescriptions. Providers should consider limiting instructions to 3 or 4 major points, using plain language, as well as using written information or pamphlets along with verbal education at all encounters. Providers can suggest computerized self-instruction or legitimate websites if patients are interested in accessing health education information from the Internet. Discussions should be reinforced often, especially with low-literacy patients.[762,764,768,772]

M—Modify patient beliefs and behavior

To modify patients' beliefs and behavior, providers should empower patients to self-manage their condition. To do this properly, providers should create an open dialogue with each patient, verifying his/her needs, expectations, and experiences in taking medications. Providers should also verify what will help patients to become, and remain, adherent. It is important to ensure that patients understand that they will be at risk if they do not take their medications. This can be done by asking patients to describe the consequences of not taking their medications as well as having patients restate the positive benefits of taking their medications ("teach back"). The provider should address the patients' fears, concerns, and

perceived barriers. Adherence should be rewarded with praise, and, when possible, by arranging incentives such as coupons, certificates, and reduced frequency of visits.[762,764,772,800,801] Smith et al.[797] provided the following suggestions that providers can implement by involving their office staff to improve communication with their patients and, in turn, improve adherence:[764]

- Improve the convenience of scheduling appointments, referrals, and refills
- Remind patients to refill early
- Install interactive voice response systems
- Manage compliance-linked financial incentives
- Provide at-home self-management programs
- Provide counseling, repeated monitoring, and feedback
- Use automated telephone or computer-assisted patient monitoring
- Use manual telephone follow-up
- Deliver appointment and prescription refill reminders
- Send patient mailings that reinforce medication taking
- Teach behavioral strategies

P—Provide communication and trust

To provide communication and to develop trust with patients, providers should improve their interviewing skills, use brief motivational interviewing,[800] practice active listening, provide emotional support, use plain language to provide information, and elicit patients' input in treatment decisions.[762,764,766,768,772,787]

L—Leave the bias

In many cases, ethnicity, minority, and socioeconomic disparities are related to health outcomes and types of care, including preventive care. Patients from minority populations, or populations with lower socioeconomic status, often experience lower levels of patient-centered communication and display higher verbal passivity with health care providers compared to those with higher levels of education.[763] Providers should be aware of these issues and implement strategies to enhance the effectiveness of communication with these groups.

E—Evaluate adherence

There is no gold standard to evaluate a patient's medication adherence; however, providers are encouraged to use patient self-reporting to inquire about adherence at every patient encounter, and occasionally to ask the patient to do a "brown bag" for the next visit, i.e., bring all prescribed and over-the-counter medications to the visit. This will afford the provider the opportunity to review the medications for clarification and reinforcement of the rationale for particular medications, and to note renewal dates. The provider should ask direct questions about the level of adherence to cholesterol-lowering medications or administer medication adherence scales.[762,764,772] Technological intervention, such as automated phone calls if a prescription has not been filled, has been shown to reduce primary non-adherence of statin medications.[802]

Role of team-based collaborative care in improving adherence

Health care system changes have the potential to overcome challenges in improving medication adherence. Providers may work together with the patient by the introduction of team-based collaborative care (as described in the next section of these recommendations). In patients with demonstrated or admitted non-adherence to medication, it is sometimes helpful for other members of the provider's care team (nurse, pharmacist, behavioral health specialist, etc.) to spend more time with the patient exploring his or her views and how these might influence the perception of risk and medication-taking behavior. Such strategies optimize the patient's sense of the provider's concern for their view/welfare and allow for greater patient-provider dialogue in arriving at an acceptable treatment approach.[764,772] Team-based care should also improve the ability to educate patients on the advantages of adherence to the medication regimen and the purpose of their individual treatment regimen by improving access to providers when patients have questions or problems, and by utilizing reliable technologies to provide information and facilitate communication between the patient and health care team.[768,770,772]

Summary and recommendations

Medication non-adherence in patients with CVD risk factors is a common problem and is associated with worse outcomes and higher health system costs. Improving this situation will depend on actions that include early recognition of non-adherence and a sustained, coordinated effort by the entire health care team to prevent and address non-adherence. Central to adherence is the quality of the provider-patient relationship. Better communication has been empirically linked to positive outcomes of care, including patient satisfaction. An effective provider-patient dialogue provides increased opportunities for patients to understand their condition and be interactively involved with weighing the risks and benefits of therapies.[803] Providers can improve outcomes by focusing on public policy, outpatient practice redesigns that optimally leverage electronic health record capability, and patient-specific intervention strategies such as explaining the consequences of non-adherence, suggesting ways to improve adherence, introducing team-based care, and identifying roles and responsibilities in team-based care to deliver optimally improved patient-centered health outcomes.[772,804]

See Chart 14 for Recommendations for Patient Adherence.

Team-based collaborative care

Team-based collaborative care has emerged from the complexity of modern health care; that is, a given health care provider is responsible for a larger volume of patients, is held accountable for quality indicators based

Chart 14 Recommendations for patient adherence

Recommendations	Strength	Quality
The provider should assess adherence to both lifestyle and atherogenic cholesterol-lowering medications at every patient encounter.	E	Low
A multidisciplinary health care team (such as the patient's primary health care provider; nurses; nurse practitioners; pharmacists; physician assistants; registered dietitian nutritionists, including certified diabetes educators in some practices; exercise specialists; social workers; community health workers; and licensed professional counselors, psychologists, and health educators) is desirable to identify medication non-adherence and to facilitate strategies to improve adherence by helping patients overcome real (or perceived) barriers to adherence.	E	Low
The multi-faceted approach should be employed by clinicians to improve medication adherence, including: a) simplify the regimen; b) provide clear education using visual aids and simple, low-literacy educational materials; c) engage patients in decision-making, addressing their specific needs, values, and concerns; d) address perceived barriers of taking medication; e) identify suboptimal health literacy and use "teach-back" techniques to increase patient understanding of those behaviors needed to be successful; f) screen and eliminate drug-drug and drug-disease interactions leading to low adherence or drug discontinuation; and g) praise and reward successful behaviors.	E	Low

on a multitude of evidence-based clinical practice guidelines, must integrate new technologies to help patients prevent and manage illnesses, and must communicate with numerous other practitioners who are involved in the care of their patients. An effective health care team is widely recognized as necessary for a patient-centered and coordinated health care delivery system. Central to the success of team-based care is the expertise and reliability with which team members work together.[805] In 2012, the Institute of Medicine proposed a definition of team-based health care adapted from Naylor et al.:[806]

> Team-based health care is the provision of health services to individuals, families, and/or their communities by at least two health providers who work collaboratively with patients and their caregivers—to the extent preferred by each patient—to accomplish shared goals within and across settings to achieve coordinated, high-quality care.[805]

Recently, the Community Guide Branch of the CDC published a systematic review of the effectiveness of team-based care in improving blood pressure outcomes.[807] Results from this review can be applied to team-based care in the setting of lipid management.

Disciplines represented in "teams" and their roles

Several disciplines may be included in health care teams for optimal lipid management, including the patient; the patient's primary health care provider; nurses; nurse practitioners; pharmacists; physician assistants; registered dietitian nutritionists; certified diabetes educators; exercise specialists; social workers; community health workers; and licensed professional counselors, psychologists, and health educators. The patient should be recognized as an active partner in the health care team. The primary care provider may be a physician, nurse practitioner, or physician assistant, while other team members complement the activities of the primary care provider(s). For example, nurses provide process support and are often the first line of communication between the patient and provider for health issues when the patient is at home. Team members often share responsibilities for medication management, active patient follow-up, medication and lifestyle adherence, and self-care support. Pharmacists serve as important resources to health care providers such as assessing the potential for drug-drug or drug-disease interactions that could lead to poor outcomes and assessing the patient's ability to understand and adhere to complex medication regimens. Pharmacists are directly accessible to patients as a resource for health and medical information and can conduct preventive health testing—including services for cholesterol, blood glucose, and glycated hemoglobin levels. Lifestyle counseling and instructions are best provided by health care team members with expertise in these areas, such as registered dietitian nutritionists, exercise specialists, and licensed professional counselors or psychologists for purposes of dealing with life stressors, anger management and lifestyle coaching related to smoking cessation and eating disorders.

Team-based collaborative care and improved outcomes

The effectiveness of team-based care has been evaluated with respect to several outcomes: lipid levels and LDL-C goal attainment, medication and lifestyle adherence, behavior change, management of statin adverse effects, and cardiovascular risk reduction. In a 2-year prospective cluster RCT designed to evaluate the impact of remote physician-pharmacist team-based care on cholesterol levels in patients with diabetes, 6963 patients who received care from 68 physicians in 9 clinics were evaluated.[808] All clinicians had access to the health information technology tool CareManager, which provided point-of-care prompts, a registry, and performance feedback with benchmarking. Pharmacists evaluated the records of

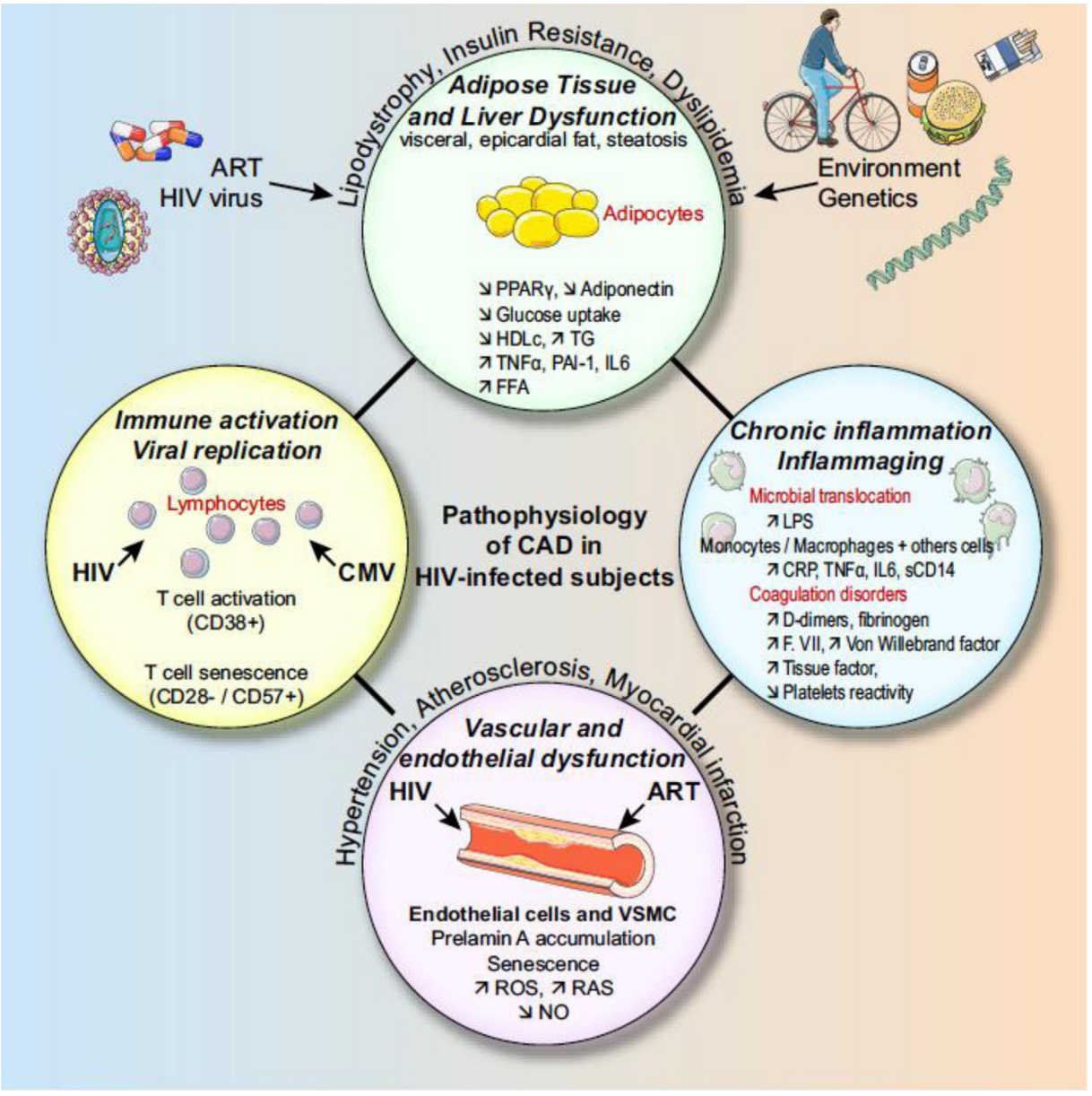

Figure 11 Hypotheses for the pathophysiology of atherosclerotic coronary artery disease in HIV-infected patients taking cART. Antiretroviral therapy (ART) and HIV itself could promote coronary heart disease (CHD) along with environmental and genetic factors. Adipose tissue and liver dysfunction have been associated with the accumulation of visceral fat, epicardial fat, and liver steatosis leading to metabolic disturbances (decreased adiponectin and glucose uptake, insulin resistance, dyslipidemia, and increased in situ and systemic inflammation). Both HIV and combined antiretroviral therapy (cART) have a deleterious effect on adipose tissue. Residual HIV replication even under potent cART and reactivation of other viruses (eg, cytomegalovirus [CMV]) could lead to permanent immune activation and to a degree of immune senescence that could favor atherosclerosis. Chronic inflammation could persist under cART potentially due to increased microbial translocation in the gut, associated with coagulation disorders. Adipose tissue dysfunction, immune activation, and chronic inflammation could result in vascular and endothelial dysfunction, leading to atherosclerosis and acute ischemic events. CRP, C-reactive protein; F VII, factor VII; FFA, free fatty acid; HDLc, high-density lipoprotein cholesterol; IL6, interleukin 6; NO, nitrogen oxide; PAI-1, plasminogen activator inhibitor type 1; PPAR, peroxisome proliferator-activated receptors; RAS, renin angiotensin system; ROS, reactive oxygen species; sCD14, soluble CD14; TG, triglyceride; TNF, tumor necrosis factor; VSMC, vascular smooth muscle cells. Taken from: Boccara F, et al. *J Am Coll Cardiol*. 2013;61:511–523.[585] Permission to reprint was obtained.

patients with elevated LDL-C, developed evidence-based treatment recommendations, and electronically sent treatment recommendations to physicians. Patients in the intervention arm were more likely to achieve goal LDL-C <100 mg/dL compared with controls (78% vs 50%; $P = .003$). Mean LDL-C was 12 mg/dL lower in the intervention arm compared to the control arm ($P < .001$). Additionally, patients in the intervention arm were 15% more likely to receive a prescription for a lipid-lowering medication ($P = .008$).

Several systematic reviews and meta-analyses have been conducted to assess the effects of pharmacist intervention on cardiovascular outcomes. Santschi et al.[809] identified 15 randomized controlled trials involving 9111 outpatients with diabetes in which the interventions in 8 of the studies were conducted exclusively by pharmacists and the remainder in collaboration with physicians and other health care team members. Compared to usual care, pharmacist involvement led to significant reductions in blood pressure, total-C, LDL-C, and BMI. Similarly, a systematic review was conducted to evaluate the effect of US pharmacists as team members on patient care.[810] A total of 298 studies with evidence of pharmacist involvement in direct care, a comparison group, and reported patient outcomes were included. Favorable results were reported for glycated hemoglobin, LDL-C, blood pressure, and adverse drug effects ($P < .05$) in pharmacists' direct care vs comparative services. In addition, medication adherence, patient knowledge, and quality of life/general health were improved ($P < .05$) with pharmacist involvement in direct care. The benefit of pharmacist involvement in disease management and education was also shown in a recent study evaluating simvastatin safety concerns.[811] Pharmacists reviewed the records of patients treated outside the revised statin labeling and then made recommendations to providers via the electronic health record. Results showed that providers accepted the recommendations by pharmacists 92% of the time without modification and 7% of the time with modification. Therefore, research indicates improved clinical outcomes with pharmacist involvement as a direct care team member as well as acceptance of pharmacist recommendations by primary providers.

In a nurse-led multidisciplinary intervention designed to improve the cardiovascular risk profile, 294 secondary prevention patients underwent a nurse practitioner-led lifestyle intervention program as well as medical treatment.[812] Other team members included a cardiologist and an internist. LDL-C and systolic blood pressure were significantly reduced ($P < .01$), as were the number of smokers ($P < .001$) and alcohol consumption ($P < .001$). Patients improved their healthy eating habits ($P < .001$), however physical activity did not change and BMI increased during follow-up.

In the Community Guide Systematic Review on team-based care and improved blood pressure control, lipid outcomes were evaluated in several studies.[807] Studies included in the systematic review were required to have a comparison group or an interrupted time-series design with at least 2 measurements before and after the intervention. Team-based care resulted in improvements in total-C and LDL-C. The authors noted that the essential features of interventions that improved outcomes other than blood pressure were a focus on multiple risk factors and the addition of nurse practitioners with the ability to prescribe medications.

Team-based collaborative care and improved patient satisfaction

The impact of team-based care on patient satisfaction remains inconclusive. The clinical trial by Pape et al.[808] on a physician-pharmacist team-based approach to cholesterol management showed no difference in patient satisfaction between study arms. A recent systematic review of RCTs evaluated whether team-based care improves patient satisfaction.[813] Twenty-six trials of over 15,000 participants were included. The pooled result of dichotomous data (10 studies) showed that team-based care improved patient satisfaction compared with usual care (OR, 2.09; 95% CI, 1.54 to 2.84), however in the 7 studies with combined continuous data, no difference was reported between team-based care and usual care (standardized mean difference, −0.02; 95% CI, −0.40 to 0.36).

Strategies for effective team-based collaborative care

The Community Guide Systematic Review on team-based care[807] offered several strategies for effective team-based care:

- Facilitate communication and coordination of care support among various team members;
- Enhance use of evidence-based guidelines by providers;
- Establish regular structured follow-up mechanisms to monitor patients' progress and schedule additional visits as needed;
- Actively engage patients in their own care by providing them with education about medication, adherence support, and tools and resources for self-management (including behavior change).

Incorporation of team-based collaborative care into the Patient Centered Medical Home model

The Patient Centered Medical Home is promoted as a component of the required changes needed to address health care quality, access, continuity and cost shortfalls in the United States. The Patient Centered Medical Home framework and financial incentives are framed around meaningful use of electronic health record technology to adopt a certified electronic health record and to have registry-like capabilities. The Agency for Healthcare Research and Quality defined the Patient Centered Medical Home by 5 attributes: a patient-centered orientation, comprehensive team-based care, coordinated care, access to care, and a systems-based approach to quality and safety.[814] Therefore, team-based collaborative care is central to the Patient Centered Medical Home model and can provide a structure to improve the efficiency of care delivery, support patient access to resources for self-management activities, and achieve a coordinated and comprehensive approach to treating lipid disorders, other risk factors, and chronic cardiovascular conditions.[807]

Chart 15 Recommendations for team-based collaborative care

Recommendations	Strength	Quality
Health care teams for optimal lipid and ASCVD risk management may include, where available: the patient; the patient's primary health care provider; nurses; nurse practitioners; pharmacists; physician assistants; registered dietitian nutritionists, including certified diabetes educators in some practices; exercise specialists; social workers; community health workers; and licensed professional counselors, psychologists, and health educators.	A	High
Health care team members should coordinate care support among various team members, use evidence-based guidelines/recommendations for dyslipidemia management, establish a structured plan for monitoring patient progress, and provide patients with a variety of tools and resources to improve their own care.	A	High
Team-based collaborative care may be incorporated into the Patient Centered Medical Home as a strategy to address shortfalls in patient health care quality, access, continuity, and cost.	E	Low

See Chart 15 for Recommendations for Team-Based Collaborative Care.

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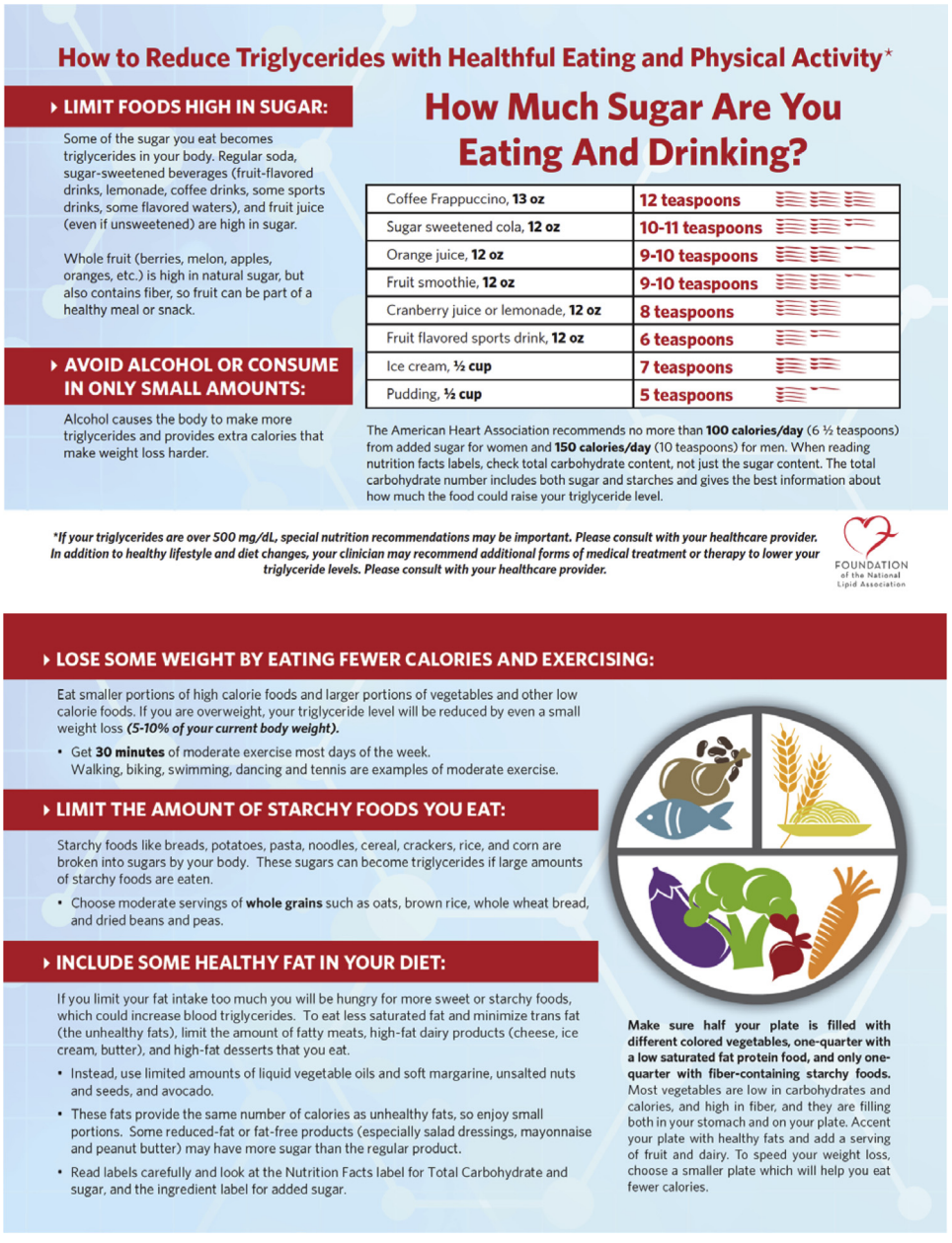

Supplemental Figure 1 Practical information for physicians to give patients regarding approaches to reduce triglycerides (NLA tear sheet). Taken from: National Lipid Association. How to Reduce Triglycerides with Healthful Eating and Physical Activity*. https://www.lipid.org/sites/default/files/NLA-Patient-Tear-Sheet-Healthy-Eating.pdf. Assessed December 1, 2014.[155]